Managing the Patient with Acute Liver Failure

Pennsylvania Society of Gastroenterology
September 21, 2014

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Acute Liver Failure

- The abrupt loss of liver function characterized by:
  - 1. Hepatic Encephalopathy
     - Any degree
  - 2. Coagulopathy
     - INR 1.5 or >
  - Within 26 weeks of the onset of symptoms
    - (classically jaundice)
  - In a patient without previous liver disease

Many authorities further subdivide ALF based on Jaundice-Encephalopathy Interval

- 1. Hyperacute (< 7 days)
  - APAP
  - HAV
- 2. Acute (8-28 days)
- 3. Subacute (> 28 days)
  - DILI

Incidence/Prognosis

- ~ 2,000 cases per in the United States

- Although the outcomes have improved over the last 3 decades
- Mortality still remains high at 40-50%
  - Minus Liver Transplant
First Step in the Management of ALF

• Must include an effort to identify ETIOLOGY

• No question is more important to answer IMMEDIATELY:
  1. Is Acetaminophen involved?

Acetyl-Para-AminoPhenol (APAP)

• 60K cases/year
  • 1% ALF

• More commonly seen unintentionally
  • Therapeutic misadventure

• Dose dependent
  • 150mg/kg

• Chronic alcohol use, malnutrition and concurrent narcotics
  • Can lower threshold
  • ? Gastric Bypass

JAMA: Whitcomb/Block 12/1994

‘Typical’ Acetaminophen ALF

• TBr 1, AST 12000, ALT 16000, AP 222
• INR 4.8

1. Exclusively Hepatocellular
2. Initially normal to only mild elevation in TBr
3. AST/ALT usually > 3,500
4. RF ~ 10% (ATN)
5. Hyperamylasemia in up to 80%

• BUN 28, CR 2.8
• Amylase 590
After APAP, most common cause of ALF in the US is Indeterminate

- Most common causes of 'indeterminate' (explant)
  - APAP
  - AIH
  - Malignancy

- Is there a role for liver biopsy?

Role of Liver Biopsy in ALF

- Retrospective analysis of 71 ALF patients
- All underwent TJ Liver Biopsy
- Adequate specimens obtain in 95%+
- Confirmed diagnosis in 82%
- Altered the diagnosis in 18%
- There was some prognostic information obtained
  - In regards to % necrosis
    - 75% is fatal

After APAP and Indeterminate: Other Drugs

- Antimicrobials
  - Augmentin, Bactrim, Rifampin-INOH Combo, Nitrofurantoin
- Neurologic/Psych
  - Phenytoin, Valproic Acid
- Amiodarone, Cocaine, PTU
- NSAIDs
- Herbals
  - Kava Kava, Hydroxycut, Ma Huang (Ephedra)
Viruses

- HAV: food-borne; fever, diarrhea; supportive
- HBV > HAV
  - Especially re-activation HBV in setting of ls/immunosuppressed patient
- HCV does not cause ALF
  - 10-12% of HCV presents acute/severe
- HEV: Russia, Pakistan, India, Mexico: supportive
  - Especially in context of pregnancy
- Herpes: immunosuppressed, pregnant, skin lesions in 50% of cases
  - Acyclovir 5-10mg/kg q 8 x 7 days

? Other Viruses, Limited to Case Reports

- EBV
- Adeno
- CMV
- Varicella
- Parvo B19
- Yellow Fever
- Hemorrhagic Fever

ALF Study Group 1999-Present

- 60+ Publications:
- ALF BMI
- ALF in Elderly
- AFL Racial, Ethnic
- False + Acetaminophen
- EBV ALF
- AMA & ALF
- Troponin & ALF
- ParvoB19 and HEV were not in ALF

72 patients ALF from AIH Stravitz et al. Hepatology 2011

- All patients biopsied
- Mean age 41
- 58% Females; 67% Caucasian
- Tbr17, AST 1100, ALT 1200, AP 205
- Mean Globulins 3.4
  - IgG hallmark of AIH
- 50% ANA
- 64% Smooth muscle

AIH 5% of ALF
Vascular

- Budd-Chiari – is a very rare cause of ALF
  - When it does present with ALF prognosis is very poor
- RUQ pain, +++ HM and ascites: TRIAD
- Imaging with ultimately venography being gold standard
- Must r/o underlying malignancy prior to liver tx

Ischemia

- Hypotension
  - Septis, cardiac arrest, heart failure, heat stroke, niacin, cocaine
- Hypoxia
  - COPD, heart failure
- Marked elevation in LFTs
- LDH
  - Almost always with concomitant renal failure (ATN)
- Ischemic liver injury typically only causes ALF in setting of
  - chronic advanced liver disease or
  - advanced underlying heart disease (esp R sided failure)
- Treatment is supportive

Transaminases 10K + ?

- The differential is tiny
- Most commonly:
  - APAP
  - Ischemia

Wilson

- 6-12% of all patients with ALF
- Acute Wilson predom in young females (4:1)
- Disproportionate TBr > 20 (to other LFTS) and low Alk phos (sometimes UD)
  - Largely in part to Coombs negative hemolytic anemia (uncon hyperbili)
  - KF rings in 50% of cases
  - Ceruloplasmin normal in 15%
  - On Flip side ceruloplasmin is low in 50% of cases of acute liver injury
Wilson

- Urinary Copper, Hepatic Copper (on biopsy) can confirm
- Renal failure, Low Uric Acid levels
- Bil/Alk Phos > 2 is a rapid, reliable indicator
- Most patients have unrecognized cirrhosis at time of their presentation
- Uniformly fatal without liver transplant

Acute Fatty Liver of Pregnancy

- Can be difficult to distinguish from HELLP
- Increased risk of fetal and maternal mortality
- Confined to 3rd trimester
- Early recognition is crucial

AFLP

- Clues: jaundice, coagulopathy, low platelets, steatosis on imaging
- Hepatic rupture/intrahepatic hemorrhage can be a rare manifestation
- Treatment is prompt delivery

Malignancy

- Hepatomegaly
- Marked cholestasis (infiltration)
- Breast, Small Cell Lung, Lymphoma, Melanoma, Myeloma, Prostate
- Biopsy is Key
- Transplant in Contraindicated
Mushroom Poisoning

- Amanita Genus
- Death cap
- Should be suspected in patients with severe GI sx within hours of ingestion
- Mortality approaches 30%
- Penicillin G and Silibinin (milk thistle) may ameliorate hepatic injury
- ? Role for NAC

Specific Therapy Based On Etiology
N-Acetylcysteine (NAC) for APAP

- No debate
- Initiate even if the slightest suspicion for acetaminophen
- Most effective when administered within 10 hours of overdose, but likely still of benefit in patients who present > 24 hours later

Administration of NAC

- 21 hour IV and 72 oral regimen are both efficacious
- Studies suggest lots of errors with administration
- One study evaluated IV (306 patients) versus PO (145)
  - N/V more common with oral administration (23 versus 9%)
  - Anaphylactic reactions more common with IV (6 versus 2%)
  - IV route may be cheaper

OTHER THAN LTX & NAC:
NAC for NON APAP ALF

• Prospective, double-blind trial
• ALF patients without APAP were randomly assigned to NAC or placebo infusion x 72 hours
• Non APAP ALF: relatively equally divided
  • DILI, HBV, AIH and Indeterminate

NAC Non APAP

• 173 patients
• Survival at 3 weeks: NS
  • 36% NAC
  • 38% placebo
• Transplant free survival: p=0.043
  • 40% NAC
  • 27% placebo
  • Benefit of transplant free survival was confined to those with grade I/II encephalopathy (52% NAC versus 30% placebo; p=0.01)
  • In grade III/IV difference was not significant

NAC Non APAP ALF (In a center without LTx)

• 47 patients with ALF
• Majority of patients with HAV/HBV/HEV
• Survival 47% NAC cohort versus 27% in Controls
• p<0.05
### NAC in Pediatric Patients with Non APAP ALF


- Birth – 17 years of age
- 184 patients randomized to NAC versus placebo
- No difference in 1 year survival
  - 73% NAC
  - 82% Placebo
- 1 year LTx free survival was significantly lower in those who received NAC
  - 35% NAC
  - 53% Placebo (p = 0.03)

### Anti-Virals for HBV ALF

- One retrospective study using LAM in patients with severe and ALF HBV suggested an improvement
- A larger randomized, placebo study found no benefit
- There may be some role for anti-viral in patients with acute severe (de novo) HBV (TBr > 10, INR 1.5)
  - Acute severe and ALF are two very different entities
- The best measure for ALF from HBV however is liver transplant

### Steroid use in ALF (AIH, Indeterminate, Drug)


- Drug induced and indeterminate ALF might be due to an AI like hepatitis and may benefit from corticosteroid administration
- 62 ALF patients treated with steroids
- Steroid use was not associated with improved overall survival in any diagnosis category
- It was associated with diminished survival in certain subgroups (MELD > 40)

### Steroids Specifically for Autoimmune Hepatitis ALF

- Initiation of steroids therapy may be considered in ‘early stage ALF’ (i.e. without multiorgan failure; ensure to rule out infection)
- 40-60 mg daily
- But LTx should not be delayed while awaiting a ‘response’
- Liver biopsy should be considered
**Complications of ALF**

- Infection
- Cerebral Edema & Intracranial HTN
- Bleeding

**Infection**

- Most common cause of death in patients with ALF is multi-organ system failure (MOSF)
- Which is usually driven by infection/sepsis

**Incidence of Infection**

- PNA 50%
- Urosepsis 22%
- Line related bacteremia 12%
- Spontaneous bacteremia 16%

- 90% of patients with ALF will develop an infection at some sort
  - Emphasizes that these patients are immunocompromised

**The Use of Prophylactic Antibiotics**

- Relatively limited data
- Although there may have been a decreased incidence of infection, there was not an improvement in survival
- At this time, no strong evidence to support the routine use of prophylactic abx

- Common sense stuff
  - Minimize IV lines
  - Aseptic technique
  - Daily cultures/frequent surveillance
It is reasonable to administer Prophylactic Antibiotics to:

- Patients with rapid clinical deterioration
- High grade PSE
- Renal failure
- SIRS
- Those listed for liver transplant

Cerebral Edema and ICH

- Long been recognized as the most serious complications of ALF
  - Closely linked to sepsis/infection
  - The development of uncal herniation as a result is almost always fatal
  - 22% of deaths in Kings College Liver Unit were attributed to cerebral edema

Ammonia; NH3

- Increasing evidence that ammonia plays a role in the pathogenesis of cerebral edema/ICH
- Preliminary report found an increase survival in patients with ALF who received lactulose versus those who did not (matched controls)
  - May infer the use of rifaximin

Cerebral Edema

- The occurrence of cerebral edema is related to severity of hepatic encephalopathy
  - Rare in grade I/II
  - And increased to 33% in grade III
  - And up to 75% in grade IV
Hepatic Encephalopathy in ALF

- Grade I - quiet ward, avoid agitation
- Grade II - Transfer to ICU
  - avoid sedation if possible
- Grade IV - Intubate/Mechanical ventilation
- CTH not unreasonable to exclude other causes, although admittedly low yield

Treating Cerebral Edema and ICH

- Several measures have been proposed to monitor and treat cerebral edema and ICH
- These interventions are supported by scant evidence and no uniform protocol has been established

ICP Monitoring

- Its use is controversial
- Rational of insertion of these monitors is to improve the early recognition of ICH so that corrective therapy can be initiated
  - Most literature sites an ICP > 20 - 25 mm Hg as indication for treatment
- Clinical signs of increased ICP (systemic htn, bradycardia and irregular respirations - Cushing triad) are not uniformly present
- CTH does not reliably demonstrate evidence of edema, especially in early stages

ICP Monitors

- Major reluctance to insertion is bleeding and infection
- In a study of 262 patients who underwent placement of ICP Monitor (epidural catheter)
  - complication rate 3.8%
  - 1% fatal hemorrhage
ALF Study Group

- Reports of ICP monitors do not reliably demonstrate survival benefit compared to patient managed without.
- Despite this the US ALF Study group endorses the use of ICP monitoring.
  - Citing improvement in the management of ICH in ALF patients.
  - Two interventions to treat ICH recommended by ALFSG:

Mannitol

- If ICH develops.
  - Most literature cites an ICP of > 20-25 mm Hg as indication for treatment.
  - Mannitol is transiently effective in decreasing cerebral edema.
  - Have to watch for volume overload.

Hypertonic Saline

- In patients with ALF and severe hepatic encephalopathy.
- Prophylactic induction of hypernatremia with hypertonic saline.
- (To serum sodium of 145-155) suggested a lower incidence of ICH.
  - But no survival benefit.

Hypothermia

- Therapeutic hypothermia (32-33 C).
- In experimental models of ALF induction of hypothermia has been shown to be neuroprotective.
- In small studies there appears to be promise.
- More studies are needed.
Management of BLEEDING Diathesis

- INR prolongation is a requisite for ALF
- Despite this clinically significant bleeding is reported in only 5% of cases

INR

- INR does not correlate well with bleeding risk in patients with liver disease
  - Acute and chronic
- In the absence of bleeding, it is not advisable to correct the INR with plasma, since clinically significant blood loss is rare and
- Correction obscures trends in INR – an important measure of prognosis

Vitamin K (5-10mg subcu) should be administered routinely, since
- Vitamin K deficiency has been reported in patients with ALF

Recombinant factor VII (7) may be considered prior to high risk procedures to help treat clotting factor deficiency. Barriers to its use:
- Include high (very high) cost
- and reports of thromboembolism (MI/PVT)
Platelets

- Use of prophylactic platelet transfusion is also discouraged
- Typically use threshold of 10,000 before prophylactic administration
- Most experts do recommend platelets transfusion of > 50K prior to invasive procedures

Bleeding & ALF

- Spontaneous bleeding is rare
- When it does occur: stomach, lungs, GU
- Variceal bleeding almost never occurs
- Spontaneous Intracranial bleeding less than 1%
- The prophylactic use of H2 blockers has been shown to decrease transfusion requirements
  - Can infer the same with PPI

Invasive Procedures

- There does appear to be a slight increase risk of bleeding with invasive procedures
- Transjugular liver biopsy is preferred to US guided percutaneous

Risk of bleeding with ICP monitors

- Correlates directly with depth of insertion
  - Epidural 4%
  - Subdural 20%
  - Intraparenchymal 22%
- Fatal hemorrhage 1, 5 and 4% respectively
When to transplant?

- The decision and timing of liver transplant is crucial
- As many patients will eventually (usually very quickly) develop contraindications to liver transplant as the natural course of the disease progresses

PROGNOSIS AND LIVER TX

- Multiple **prognostic models** have been proposed
- Factors implicated:
  - Phosphate, Factor V levels, AFP, Ammonia
  - Gc globulin, MELD score
- None are satisfactory in predicting outcome and determining candidacy for transplant

Kings College

- Most widely applied prognostic system is King’s College
  - APAP and non-APAP
  - Developed from a retrospective cohort of nearly 600 patients
- In a meta-analysis of studies using KCH
  - Pooled sensitivity and specificity was 70 and 90%
Liver Transplant

- Overall 1 year survival following liver transplant for ALF is less than those with chronic disease
  - But long term survival is superior
- The majority of deaths occur within the first 1-3 months are usually secondary to
  - Neurological complication
  - Sepsis

Live Donor

- Live donor liver transplant
- Accounted for 2% (between 1988 and 2010)
  - Its use remains controversial
- One year survival in this cohort is 75%

Status 1A Listing: UNOS Criteria

- No Pre-existing liver disease
- Encephalopathy
- Must be in ICU and must have at least 1 of the following 3:
  - INR > 2
  - Mechanical Ventilation
  - RRT

ALF & LT

- ALF accounts for less than 10% of all transplant performed in the US
- Of those listed 35% will recover spontaneously
- MANY patients will have psych/social contraindications to liver transplant
Liver Support Systems

- Artificial support - detoxify only employ charcoal or albumin
  - Plasmapheresis
  - MARS
  - Prometheus albumin dialysis
  - None have shown survival benefit

Liver Support Systems

- Bioartificial Support - Hepatocytes (human or other mammalian) used in cartridges in extracorporeal circuits
  - HepatAssist
  - ELAD
  - MELS
  - BISS
  - AMC-BAL
  - None are FDA-approved
    - We are currently evaluating the use of ELAD in patients with AAH

Liver Support Systems

- A recent meta-analysis considering all forms of devices together
  - showed no efficacy for artificial or bioartificial liver devices for the treatment of ALF
Management Recommendations in ALF

1. Identify patient has ALF
2. Transfer to Transplant Center
3. Try to determine Etiology
4. APAP?
5. NAC
   a. Non APAP?
   b. NAC may be of utility early in course

Management of ALF

6. Lactulose
7. Vigilant about Infection
8. NO FFP
   a. Vit K and Platelets prior to procedures
9. Advanced Encephalopathy
   a. Intubate
10. ICP Monitoring
    a. Mannitol
    b. Hypertonic saline