Core Curriculum In Hepatology And Liver Transplantation 2012-13

Acute Liver Failure
October 30th, 2012

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Acute Liver Failure - Outline
- Incidence
- Definition
- Etiology
- Diagnosis, Specific Therapies
- Prognosis
- Treatment
  - Current
  - Future
- Complications
- Prevention

Acute and Chronic Liver Disease

- Acute Liver Failure
- Chronic Liver Disease
  - resolution
  - compensated
  - decompensated (ESLD)
  - liver transplantation

ALF: Incidence

USA ~ 2-4,000 cases/year
UK ~ 1-6/ million per year
Affects younger patients, often otherwise healthy, with high morbidity and mortality

Acute Liver Failure: Definition

FHF - “a potentially reversible condition, the consequence of severe liver injury with an onset of encephalopathy within 8 weeks of appearance of the first symptoms of the disease and in the absence of pre-existing liver disease”

Trey and Davidson, 1970

Critical Points:
- A liver-related illness of short duration (absence of chronic liver disease – exceptions)
- “ALF”: encompasses all durations up to 26 weeks
Acute Liver Failure: Definition

**Critical Points:**
- Coagulopathy (INR > 1.5)
- Any degree of alteration in Mental Status (presumed not due to sedation alone)
  - **Stage I**
    - May be subtle – change in behaviour w/ min change in LoC
  - **Stage II**
    - Lethargy, gross disorientation, inappropriate behaviour – (asterixis, dysarthria)
  - **Stage III**
    - Confusion, incoherent, arousable (asterixis, hyper-reflexia)
  - **Stage IV**
    - Coma – unresponsive to pain, decorticate/decerebrate

Acute Liver Failure: Expanded Definitions

Popular…but no prognostic significance distinct from the etiology of the ALF.....

O'Grady, Lancet 1993

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- Aetiology
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Acute Liver Failure: Aetiology

- **Vascular**
  - Ischemic (shock)
  - Budd-Chiari syndrome
  - Veno-occlusive disease

- **Metabolic**
  - Wilson’s Disease, AFLP/HELLP, Reyes Syndrome

- **Miscellaneous**
  - Autoimmune hepatitis
  - Malignant infiltration
  - Primary non-function
  - Septicaemia
  - Hyperperfusion

Acute Liver Failure: More Common Etiologies

- **Drugs**
  - Paracetamol (Acetaminophen, APAP)
  - Isoniazid

- **Viral**
  - Hepatitis A, B, D (superinfection)
  - Hepatitis E (most common in China, India)
  - Hepatitis C (very rare)
  - Herpes viruses (HSV-1, HSV-2, EBV, CMV, HHV-6)
  - Others (e.g., adenoviruses, Cox B, parvovirus B-19)

- **Toxins**
  - Amanita phalloides
  - Herbal remedies
  - Industrial solvents

Etiology Of ALF In USA

Data courtesy W. Lee
ALF and OLTx Due To DILI (non-APAP) in US 1987-2006

Increasing Incidence Of Paracetamol-Related ALF In US

Paracetamol-Related ALF In US Suicidal Vs. Accidental APAP Cases

Paracetamol Toxicity

Clinical Features:
- Intentional or inadvertent ingestion
- Sustained elevated ALT/AST after 4gm/day x 4 days – unclear if increased ALF
- First 24 hours - nausea and vomiting, subsides → delayed medical attention
- 72 hours: confusion, RUQ pain, jaundice
Paracetamol Adducts

![Bar chart showing paracetamol adducts](image)

Occult Paracetamol Toxicity

- Approximately 20% of indeterminate ALF cases appear to be related to occult APAP toxicity
- Approximately 4% of all ALF cases appear to be related to occult APAP toxicity

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ALF: Initial Testing

- INR, Biochemistries, ABG, lactate, CBC, Type, Glucose

SEEK PRECISE ETIOLOGY TO GUIDE SPECIFIC MANAGEMENT

- Tox, Paracetamol level
- Viral Hepatitis esp. HAIgM, HBcIgM
- Ceruloplasmin (slit lamp exam)
- Autoimmune (ANA, ASMA, IgG)
- βHCG, Ammonia, HIV
- US w Doppler
- Liver biopsy +/-

ALF: Diagnosis, Specific Therapies

- Evaluate acute hepatitis → INR: if > 1.5, admit
- Evaluate MS: if altered → admit to ICU and contact a Transplant centre (early is ALWAYS better) given potential for rapid progression
- Transfer if Stage I or II encephalopathy
- Early transfer as risks increase or may preclude later transfer if Stage III or IV encephalopathy
- At Transplant Caner, begin expedited evaluation ASAP
- Social considerations, potential contraindications common, complex and potential may preclude OLTx

ALF: Diagnosis, Specific Therapies

- Administer NAC in any case of suspected paracetamol ingestion, irrespective of nomogram, as early as possible, even if doubt, and likely of benefit at least up to 48 hours after ingestion – PO or IV
- Non-paracetamol ALF - transplant-free survival better in pts. with coma grades I-II who received NAC (52% vs. 30% for placebo)

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

*William M. Lee, Linda S. Hyman, Lorenzo Resio, Robert J. Pendergrass, Robert F. Strayhorn*

*AMERICAN JOURNAL OF HEPATOLOGY 2009;57:956–966*
ALF: Diagnosis, Specific Therapies

- *Amanita phalloides* - PenG and silibinin
- Non-paracetamol DILI - corticosteroids not indicated unless DRESS syndrome
- Viral hepatitis -
  - hepatitides A-E – no proven Rx (but treat HBV)
  - HSV/VZ – acyclovir
- Wilsons - low AP, high BR/AP (>2), KF in 50%, high Ur Cu++ …. uniformly fatal without OLTx
- AIH – corticosteroids, biopsy

ALF: Diagnosis, Specific Therapies

- *AFLP/HELLP* – expedite delivery
- Acute ischemic injury – CV support
- Budd-Chiari Syndrome – decompression not usually successful
- Malignant infiltration – rapidly fatal (days)
- Indeterminate aetiology – poor outcomes

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ALF: Prognosis

- Heterogeneous etiologies but consistent clinical features
  - Acute loss of hepatocellular function, SIRS, MOF
- Prior to OLTx, survival estimated previously at 15%
- Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers (n=308) in US
  - 73% of patients were women; median age was 38 years.
  - Overall patient survival at 3 weeks was 67%.
  - 29% had OLTx 10% death while waiting
  - 43% survived *without* OLTx (reflects more APAP)
- Short-term LT-free survival
  - 68% for pts. with APAP ALF
  - 25% & 17% for other DILI and indeterminate ALF respt.
- Coma grade at admission was associated with outcome

Survival After OLTx For ALF

- Quickly identify those most likely to benefit from emergent OLTx
- Spontaneous survival with ICU care has improved 10-20% → 40%
- Models ideally should predict survival
  - Challenging given variety of aetiology, unpredictable complications
  - Allows judicious use of organs, avoids lifelong IS
  - Severity of HE, age, aetiology, worse renal function (non-paracetamol), predict worse outcome
  - Many models, most methodologically flawed....
- FV level < 20% in pts. < 30 y/o or < 30% in pts. with HE III or IV predicted mortality with PPV 82% and NPV 98%
ALF: Predictors of Poor Prognosis - King’s College Criteria

Paracetamol-induced ALF:
- pH < 7.3 (s/p hydration and irrespective of grade of HE)
- Or Grade III+ HE and:
  - INR > 6.5
  - Creat > 200

Survival if:
- If pH < 7.3:
  - 5%
- If INR > 6.5:
  - 28%

Non-Paracetamol-induced ALF:
- INR > 6.5 (any grade of HE)
Or any three of following:
- Indeterminate or drug-related
- Age < 10 or > 40
- > 7 d of jaundice prior to HE
- Bilirubin > 300
- BUN > 35

Survival if:
- One adverse predictor:
  - 20%
- Two:
  - 6%

ALF: Prognostic Scores

- Pooled meta-analysis: 68% sens, 86% spec
- King’s College Hospital (KCH) criteria are reasonably specific for predicting poor outcome but identify only 50-60% of patients who will ultimately die or need OLTx

<table>
<thead>
<tr>
<th>Group</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-APAP</td>
<td>91</td>
<td>32</td>
<td>123</td>
<td>78.0%</td>
<td>73.7%</td>
</tr>
<tr>
<td>APAP</td>
<td>77</td>
<td>10</td>
<td>87</td>
<td>24.4%</td>
<td>92.4%</td>
</tr>
<tr>
<td>Overall</td>
<td>168</td>
<td>42</td>
<td>210</td>
<td>38.3%</td>
<td>65.7%</td>
</tr>
</tbody>
</table>

Liver Transplantation For ALF

- OLTx is the only definitive therapy
- Long-term outcomes better than OLTx
- Commits to lifelong IS, medical follow-up
- Listed as Status IA (US), “superurgent” (UKELD)
- Our prognostic scales are imperfect...
- The decision is difficult...

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ALF: Clinical Features

- Whole body
  - Systemic inflammatory response
  - High energy expenditure and catabolism
- Liver
  - Loss of metabolic function
  - Decreased gluconeogenesis leading to hypoglycemia
  - Decreased lactate clearance leading to lactic acidosis
  - Decreased ammonia clearance leading to hyperammonemia
  - Decreased synthetic capacity leading to coagulopathy
- Lungs:
  - Acute lung injury
  - Adult respiratory distress syndrome
- Adrenal gland
  - Inadequate glucocorticoid production contributing to hypotension
- Bone marrow
  - Frequent suppression, especially in viral and seerogenic disease

ALF: Clinical Features

- Circulating leukocytes
  - Impaired function and immunosuppression contributing to high risk of sepsis
- Brain
  - Hepatic encephalopathy
  - Cerebral oedema
  - Intracerebral hypertension
- Heart
  - High output state
  - Frequent subclinical myocardial injury
  - Pancreatitis
- Particullary in paracetamol-related acute liver failure
- Kidney
  - Frequent dysfunction or failure
  - Portal hypertension
  - Might be prominent in subacute disease and conflated with chronic liver disease
**Key Points In Caring For The Patient With ALF**

- Requires multidisciplinary team
  - Transplant hepatologists, surgeons, RN coordinators
  - ICU physicians and nurses
  - Nephrologists
  - (Neurosurgeons)

- Rapidly assess for contraindications (medical, psych/social) to liver transplant
- List ALF patient for transplant as soon as eligible (barring contraindications)
- Anticipate/prevent/manage complications of ALF
- Support patients to allow/facilitate hepatic repair/regeneration

“Orphan disease - large clinical trials impossible, much of its management is based on clinical experience only”

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**“NAC Is TPA For The Liver”**

- NAC should be given ASAP to patients with suspected paracetamol overdose
  - Always be suspicious
  - Paracetamol levels are unreliable
- IV NAC is safe and more reliable than oral NAC in patients with ALF
- Treat patients with cryptogenic ALF and high aminotransferases with NAC
- Late administration of NAC appears to be ameliorate APAP toxicity
- Role for non-APAP-related ALF – appears to improve spontaneous survival in early ALF

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**ALF: Elevated Intracranial Pressure**

- Poorly understood pathogenesis
- Arterial NH3 (>200) appears to be predictive of complications (rare when < 75)
  - Role of lactulose and enteric antibiotics undefined
- Difficult to diagnose accurately on clinical grounds
- CT insensitive and impractical (exclude bleed)
- Avoid sedation if at all possible
- Grade III HE – 35% ↑ ICP, Grade IV HE – 65% ↑ ICP
- Intubate and ventilate for Grade III/IV HE

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**Overall survival: n = 695 (67%)**

<table>
<thead>
<tr>
<th>Spontaneous survivors</th>
<th>Transplanted</th>
<th>Died (Not Transplanted)</th>
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<tr>
<td>n = 483 (45%)</td>
<td>n= 262 (25%)</td>
<td>n= 306 (30%)</td>
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At 1 year

**ALF: Elevated Intracranial Pressure**

- Frequent neuro monitoring (exclude hypoglycemia)
- Choice of sedation and paralysis not studied
- Non-depolarizing neuro-muscular blocking e.g. cis-atracurium may be preferable (less muscle contraction)
- Low dose propofol often used
- Control seizures quickly (DPH, SA BDZs) – prophylaxis unproven

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**Lee AASLD PG 2011**
ALF: Elevated ICP (ICH)

- Goals: ICP < 20 mm Hg, CPP > 50-60 mm Hg to avoid hypoperfusion → hypoxia
  (CPP by ICP = MAP - ICP)

Preventive strategies
- Avoid volume overload (→ early CVVHD)
- Avoid/treat factors that may increase ICP
  - Fever, seizures, hypertension, vasodilating drugs (e.g. nitroprusside), agitation, jugular venous compression, neck flexion, unnecessary stimulation/suctioning
- Elevate head of bed to 30 degrees
- ? Role of ICP monitoring in intraoperative period

Cerebral Edema In ALF

8 HOURS LATER

ALF: Elevated ICP Treatment

- Administer osmotically-active agents or vasopressors to maintain CPP
  - Mannitol (20%) 0.5 to 1 gm/kg over 5 min; repeat Q 4-6 hours as necessary until serum osmolarity > 310-20 mOsm/L – transient benefit, recommended as ‘first-line’
  - Not effective with renal failure (→ consider renal support early) or when severe ICH ( > 50 mmHg)
  - Hyperventilation to Pa CO2 of 25-30 mmHg
  - Effect short-lived and often spontaneous anyway...
  - No survival benefit shown in one trial
  - No role for prophylactic hyperventilation

ALF: Elevated ICP Treatment

- Barbiturates for severe ICH – but hypotension and slow clearance
- Corticosteroids – single trial did not show efficacy
- Prophylactic hypertonic saline (Na 145-155) may reduce ICH but no effect on survival

ALF: Elevated ICP Treatment

Moderate Hypothermia
- 32-33 °C
- Reduces systemic production and cerebral uptake of ammonia
- Decreases ICP in uncontrolled studies
- Side effects - shivering, infection, platelet dysfunction, impaired hepatic regeneration, arrhythmias?
- Moderate hypothermia as a bridge to OLTx
- ALFSG study planned
ALF: Infection

- 504/887 (57%) manifest SIRS
- Magnitude of SIRS correlated with mortality
- Infected patients more often developed SIRs, and greater magnitude
- Associated with progressive HE
- Prophylactic antimicrobials given...but with survival benefit data
- Periodic surveillance

ALF: Coagulopathy

- Impaired synthesis, increased consumption
- Despite elevated INR, most patients with ALI/ALF maintain normal hemostasis by TEG (dynamics and physical properties of clot formation in whole blood)
- Don’t correct INR unless bleeding / ICP monitor / IV access
- Potential for volume overload with FFP, reduced with rFVIIa and FFP
- Spontaneous bleeding uncommon (intracranial < 1%)
- PPIs administered though without specific ALF data

ALF: Hemodynamics & Renal Failure

- Low SVR, less splanchic pooling than cirrhosis
- Initial adequate volume resus:
  - NS to ½ NS, include Dextrose (→ D20 for hypoglycemia)
- No studies to define optimal pressor
  - Consensus US/UK – norepinephrine → vasopressin
  - Goals: MAP > 75mmHg, CPP > 60mmHg
- AKI common, multifactorial – continuous modes of RRTx preferred
- PA pressure measurement rarely indicated

Novel Medical Therapies Are Desperately Needed

- We need better medical therapies aimed at limiting liver injury and enhancing liver repair/regeneration
- We need better therapies to prevent and treat cerebral edema

“...a potentially reversible condition, the consequence of severe liver injury with an onset of encephalopathy within 8 weeks of appearance of the first symptoms of the disease and in the absence of pre-existing liver disease.”

ALF: Liver Support Systems

‘Life On MARS’...or elsewhere

- While awaiting regeneration/bridge to OLTx
- None thus far has been proven to unequivocally improve outcomes, and expensive...
- Artificial support – sorbent based, acellular e.g. MARS
- Bioartificial – hepatocyte columns e.g. HepAssist, ELAD
- Studies difficult to perform, very expensive, heterogeneous,
- No proven benefit
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Is ALF Preventable?

- Mass vaccination for viral hepatitis A and B
- Appropriate food handling and preparation
- Education for mushroom pickers

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- Mass vaccination for viral hepatitis A and B
- Appropriate food handling and preparation
- Education for mushroom pickers
- Safer drugs
  - Drug Induced Liver Injury Network (DILIN)

Magnitude Of DILI Problem

- DILI is most common cause of ALF in US
- DILI is the most common reason for drug withdrawal or restriction of prescription
  - Enormous fiscal implications for pharmaceutical and regulatory industries
  - Many patients may be denied access to “good drugs”
- “Primum non nocere”
  - DILI is iatrogenic
- Mediocolegal implications

Is ALF Preventable?

- Mass vaccination for viral hepatitis A and B
- Appropriate food handling and preparation
- Education for mushroom pickers
- Safer drugs
  - Drug Induced Liver Injury Network (DILIN)
- Limitation of package size for paracetamol (UK/Irl)
Acute Liver Failure - Summary

- ALF is a rare but important syndrome
- Multiple aetiologies cause ALF but paracetamol toxicity is most common
- Aetiology is at all in doubt, treat with NAC, quickly
- Prognostic models for ALF are imperfect
- Early referral to an OLTx center and listing of the patient with ALF is potentially life-saving
- Better medical therapies needed aimed at limiting liver injury and enhancing liver repair/regeneration