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

<table>
<thead>
<tr>
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<th>Acute hepatitis</th>
<th>ALF</th>
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<tbody>
<tr>
<td>AST and/or ALT &gt; 400</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>INR</td>
<td>&lt; 1.5</td>
<td>≥ 1.5</td>
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<tr>
<td>Any Encephalopathy</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Pre-existing liver disease</td>
<td>Possibly</td>
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</table>

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


HBV

- 100 x more virulent than 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


HBV labs: Antigen = Disease

<table>
<thead>
<tr>
<th></th>
<th>Surface Antigen</th>
<th>Surface Antibody</th>
<th>Core Ab</th>
<th>DNA</th>
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<tr>
<td>Acute</td>
<td>Pos or neg</td>
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<td>Pos or Neg</td>
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<td>Chronic</td>
<td>Pos</td>
<td>Neg</td>
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<td>Exposed only</td>
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<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
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<td>Exposed + immune</td>
<td>Neg</td>
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<td>Immunized</td>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
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</tbody>
</table>

HCV

• United States - Estimated at 5 million people

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

- Injection drug use 60%
- Unknown 10%
- Transfusion (before screening) 10%
- Other (hemodialysis; health care work; perinatal) 5%
- Sexual 15%


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

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


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

**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

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**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

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**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

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**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

References

- Lucey MR. NEJM 2009; 360: 2758-2769
- Sources of Infection for Persons with Hepatitis C (CDC) US.png

Approach to Acute Liver Failure

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Division of Gastroenterology, Hepatology and Nutrition
The Ohio State University Wexner Medical Center

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
Educational Objectives
Understand common etiologies and prognosis
Execute early management steps
Discuss management of late complications

Disclosure
Salix pharmaceuticals

King’s College Criteria

Early Indicators of Prognosis in Fulminant Hepatic Failure

ALFSG

www.3lsoutheastmers.edu/beer
Targeting Acute Liver Failure in the 21st Century!
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

Etiology and prognosis

- 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 of Acute Liver Failure in the USA

Adult Registry (n = 1,696)

Acetaminophen cases as % of all cases

Comparison of Different ALF Etiology Groups

'Suicidal’ vs. ‘Accidental’ APAP cases

<table>
<thead>
<tr>
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<th>Intentional (n=251)</th>
<th>Unintentional (n=296)</th>
<th>p-value</th>
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<tr>
<td>Age</td>
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<td>39</td>
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<td>ACM dose(g)</td>
<td>38/38</td>
<td>477.5</td>
<td>NS</td>
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<tr>
<td>Coma (% &gt;3)</td>
<td>39</td>
<td>55</td>
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<td>ALT (IU/L)</td>
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<td>Alcohol use/abuse (%)</td>
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<td>50/17</td>
<td>NS</td>
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<tr>
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<td>34</td>
<td>NS</td>
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<tr>
<td>History of depression</td>
<td>45</td>
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<td>Narcotic cpd (%)</td>
<td>18</td>
<td>63</td>
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<td>Multiple preps</td>
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<td>38</td>
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<tr>
<td>Spont surv (%)</td>
<td>70</td>
<td>65</td>
<td>NS</td>
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Comparison of Different ALF Etiology Groups

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

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**“Subacute Phenomenon” in DILI Cases**

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**Prognosis in ALF: Etiology is a Main Determinant**

- 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

**Prognosis models**

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

- 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)
- Outcome benefit not established, data scarce

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

**BACKGROUND & AIM:** N-acetylcysteine (NAC), an antitoxic for acetaminophen poisoning, might benefit patients with non-acetaminophen-related acute liver failure. METHODS: In a prospective, double-blind, randomized controlled trial, patients with acute liver failure were randomized to NAC or placebo. RESULTS: NAC improved transaminase levels, liver synthetic function, and survival compared to placebo. CONCLUSIONS: NAC is an effective treatment for non-acetaminophen acute liver failure.
Primary/secondary outcomes in the NAC trial

- Overall survival
- Transplant-free survival
- Transplant-free 1 yr
- Transplant-free 2 yr
- Transplant-free 4 yr

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
- Herniation, ischemic, and hypoxic injury all potential contributors to CNS injury
- Pathophysiology poorly understood, likely involving multiple factors, including ammonia

Incidence

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

Grading of Encephalopathy

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

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

- 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\(^2,3\)


Management of Intracranial Hypertension

- Avoid over-resuscitation with fluids
  - 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

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

**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

**New updates on older recommendations**

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

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# 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