Definition of “liver function tests”
Abnormal serum liver enzymes in hospital setting
Systematic evaluation of abnormal liver chemistries
Acute liver failure
- Definition
- Etiology
- Diagnostic work-up
- Management
- Prognostic criteria

Often termed liver function tests (LFTs)
- Tests do not assess actual liver function
- Not solely of hepatic origin
- Normal values do not exclude disease
### Common Liver Chemistry Tests

<table>
<thead>
<tr>
<th>Liver Chemistry Test</th>
<th>Clinical Implication of Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>Hepatocellular damage</td>
</tr>
<tr>
<td>ALT</td>
<td>Hepatocellular damage</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Cholestasis, infiltrative disease, or biliary obstruction</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Cholestasis, impaired conjugation or biliary obstruction</td>
</tr>
<tr>
<td>Albumin</td>
<td>Synthetic dysfunction</td>
</tr>
<tr>
<td>Prothrombin Time / INR</td>
<td>Synthetic dysfunction</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase
ALT, alanine aminotransferase
INR, international normalization ratio

### Prothrombin Time / INR

- Prolongation of PT / INR
  - Significant hepatocellular dysfunction and/or
  - Vitamin K deficiency
    - Prolonged jaundice
    - Malabsorption
- Dysfunction vs. deficiency?
  - Administer *subcutaneous* vitamin K and assess response
    - No correction → liver dysfunction
    - Normalization → vitamin K deficiency

### Confirm Abnormal Liver Chemistries of Hepatic Origin

- **AST (ALT)** (Confirmatory test)
  - Cardiac (troponin)
  - Skeletal muscle (creatine kinase, aldolase)
  - Erythrocytes (CRP, LDH, haptoglobin)
- **Alk Phos** (GGT, S’nucleolidase, isoenzymes)
  - Pregnancy (preg test)
  - Bone
  - Intestina
- **Albumin**
  - Protein losing enteropathy (stool alpha-1 anti-trypsin)
  - Neoplastic syndrome (urine protein)
Abnormal Serum Liver Chemistries in Hospitalized Patient

1. Associated with initial reason for admit
   - Acute hepatitis, cholecystitis, heart failure

2. Secondary to chronic liver disease
   - Alcohol, HCV, non-alcoholic steatohepatitis

3. De novo – developing in hospital
   - Accounts for minority

De Novo Abnormal Liver Chemistries in Hospitalized Patient

- Drug induced - antibiotics most common
- Disseminated infection
- Ischemic hepatitis ("shock liver")
  - Most common in those with cardiovascular disease
- Post-operative jaundice
  - Most common in cirrhatics
  - Impaired liver perfusion
    - Perioperative hypotension/hypoxia
    - Blood transfusion
    - Medication reaction
    - Occult sepsis

Elevated Serum Liver Chemistries in Acute Medical Setting

- Retrospective review July 1 – Dec 31, 2006
- Acute medical admission in Scotland, UK
- Abnormal LFTs
  - AST and ALT >100 U/L
  - Alk phos >250 U/L
  - Bilirubin >2.9 mg/dL
- 4,816 admissions
  - 378 (8%) had abnormal LFTs
4,816 admissions
- 378 (8%) had abnormal LFTs
- 100/378 (26%) died <30 days of admit
  - 42% sepsis
  - 27% malignancy
  - 22% decompensated liver disease

Viral (classical)
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E

Viral (other)
- CMV
- EBV
- HSV

Medications
- Prescription
- Illicit
- Herbal

Biliary
- Choledocholithiasis
- Cholestasis (NASH/NAFL)
- Wilson's disease
- Hemochromatosis
- Pregnancy
- Alcohol
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing choangitis

Ischemic
- Arterial thrombosis
- Budd-Chiari syndrome
- Veno-occlusive disease
- Ischemic hepatitis

Malignancy
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Metastatic disease

Diagnosis in 378 patients with abnormal LFTs

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial sepsis</td>
<td>123</td>
<td>33%</td>
</tr>
<tr>
<td>Alcohol-related elevated liver enzymes (without decompensation)</td>
<td>32</td>
<td>22%</td>
</tr>
<tr>
<td>Decompensation chronic alcoholic liver disease</td>
<td>48</td>
<td>13%</td>
</tr>
<tr>
<td>Tumors (primary and secondary)</td>
<td>39</td>
<td>10%</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>19</td>
<td>5%</td>
</tr>
<tr>
<td>Drugs-related abnormal LFT parameters (antibiotics, hepatitis and sepsis)</td>
<td>10</td>
<td>5%</td>
</tr>
<tr>
<td>Drug overdose (prescribed)</td>
<td>13</td>
<td>3%</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>7</td>
<td>2%</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>7</td>
<td>2%</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>Paracoccidioides</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>Miscellaneous (renal, primary, biliary cirrhosis, primary sclerosing choangitis, sepsis of unknown etiology and hemochromatosis)</td>
<td>10</td>
<td>3%</td>
</tr>
</tbody>
</table>
### Initial Evaluation of Abnormal Liver Chemistry Values

- **Careful history**
  - Did patient have pre-existing abnormal LFTs before recent illness or hospitalization?
- **Risk factors for liver disease - viral hepatitis, alcohol**
- **Drug toxicity**
  - Prescribed
  - Illicit
  - Herbal
- **Concomitant medical problems**
- **Physical exam**
  - Evidence of chronic liver disease

---

### Examine the liver

**“One good feel of the liver is worth any 2 LFTs”**  
- *F.M. Hanger Jr., 1971*

- **Pulsatile**
  - Heart failure
- **Tender**
  - Congestion
  - Hepatitis
  - Cholangitis
- **Size**
  - Small – cirrhosis, acute necrosis
  - Large – viral hepatitis, malignant infiltration, heart failure, venous outflow obstruction
Non-Invasive Radiographic Imaging

- US +/- Doppler
  - Masses
  - Gallstones
  - Biliary duct dilation
  - Fatty infiltration
  - Vessel patency
- CT Scan w/ contrast
  - Confirm masses
  - Extent of vessel thrombosis
  - Cirrhosis and portal hypertension
  - Splenomegaly
  - Varices

Do Abnormal Liver Chemistries Predict Inpatient Imaging Yield?

- Retrospective study at Brigham and Woman’s March 1995-March 1998
- Reviewed imaging for abnormal LFTs
  - Positive – explained abnormal LFTs
  - Abnormal and unrelated
  - Abnormal and clinically unimportant
  - Unknown clinical importance
  - Normal
- Labs < 5 day of imaging

Do Abnormal Liver Chemistries Predict Inpatient Imaging Yield?

- 89,450 admissions
- 3,995 inpatients who underwent imaging
- 1,080 were for abnormal LFTs
  - 627 US, 429 CT, 33 MRI
- Excluded
  - 233 – imaging request not matching report
  - 97 – no liver tests <5 days
- 759 images in 604 patients
**Abdominal imaging results for indication of abnormal liver enzymes**

<table>
<thead>
<tr>
<th>Imaging result code</th>
<th>CT</th>
<th>US</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive, abnormal and related to the abnormal LFT*</td>
<td>108 (36)</td>
<td>96 (33)</td>
<td>106 (36)</td>
</tr>
<tr>
<td>Abnormal and unrelated to the abnormal LFT*</td>
<td>101 (35)</td>
<td>362 (124)</td>
<td>464 (151)</td>
</tr>
<tr>
<td>Clinically important but unrelated to the abnormal LFT*</td>
<td>70 (24)</td>
<td>15 (5)</td>
<td>85 (29)</td>
</tr>
<tr>
<td>Clinically significant*</td>
<td>40 (14)</td>
<td>166 (55)</td>
<td>206 (69)</td>
</tr>
<tr>
<td>Clinical importance unknown*</td>
<td>37 (13)</td>
<td>85 (29)</td>
<td>122 (41)</td>
</tr>
<tr>
<td>Exclusion findings*</td>
<td>25 (9)</td>
<td>31 (11)</td>
<td>56 (19)</td>
</tr>
<tr>
<td>Normal*</td>
<td>8 (2)</td>
<td>72 (25)</td>
<td>80 (27)</td>
</tr>
</tbody>
</table>

| Total | 207 (72) | 472 (159) | 679 (228) |

CT: computed tomography; US: ultrasonography; LFT: liver function tests.

* Chi-square test comparing imaging results between CT and US examinations, P < 0.001.

**Most common diagnoses:**
- Biliary obstruction (CT 19%, US 29%)
- Cholecystitis (CT 12%, US 32%)
- Malignancy (CT 30%, US 9%)
- Cirrhosis (CT 15%, US 16%)

**Relationship between severity and positive findings:**
- Individual AST and alk phos
- AST & ALT class

**Severity of LFTs and yield of abdominal imaging**

Liver function test classes:
- Normal
- Abnormal results abnormal LFT
- Abnormal results normal LFT
- Abnormal results normal LFT
Patterns of Liver Chemistry Abnormalities

- Hepatocellular Injury or Necrosis
- Cholestatic Pattern
- Mixed Pattern

Predominantly AST & ALT elevation
Predominantly alk phos elevation

Patterns of Liver Chemistry Abnormalities

<table>
<thead>
<tr>
<th>Hepatocellular</th>
<th>Bilary</th>
<th>Infective &amp; Inflammatory Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic &amp; Tissue</td>
<td>Viral Hepatitis</td>
<td>Alcohol Complete Partial</td>
</tr>
<tr>
<td>AST &amp; ALT</td>
<td>5x-10x</td>
<td>2-3x</td>
</tr>
<tr>
<td>alk phos</td>
<td>1.5x</td>
<td>1.5x</td>
</tr>
<tr>
<td>bilirubin</td>
<td>1.5x</td>
<td>1.5x</td>
</tr>
<tr>
<td>ALT</td>
<td>Prolonged and unresponsive to vitamin K in severe disease</td>
<td></td>
</tr>
<tr>
<td>Response to SQ vitamin K</td>
<td>Usually normal</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>Decreased in chronic disease</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>Usually normal</td>
<td></td>
</tr>
</tbody>
</table>

Serum Aminotransferase Levels in Various Liver Diseases
Toxic injury
- AST>ALT; rapid decrease after initial peak
- History of medication/toxin

Acute viral hepatitis (A-E, herpes)
- Slow decrease in transaminases
- Risk factors for viral hepatitis

Autoimmune hepatitis
- Other autoimmune diseases

Ischemic Injury
- Similar to toxic injury
- Comorbid condition

Acute viral hepatitis (A-E, herpes)
- Slow decrease in transaminases
- Risk factors for viral hepatitis

Autoimmune hepatitis
- Other autoimmune diseases

Ischemic Injury
- Similar to toxic injury
- Comorbid condition

Marked elevated in AST & ALT in absence of other potential causes
- Histologic evidence of centrolobular necrosis
- Pathogenesis presumed to be anoxic hepatocellular injury
- Cardiac disease (right sided heart failure) almost always present
  - Venous congestion may predispose hepatocytes to hypoxic injury resulting from hypotension

Hepatic
- Chronic HBV and HCV
- Acute viral hepatitis (A-E, EBV, CMV)
- Steatohepatitis
- Alcohol-related liver injury (AST predominant)
- Hemochromotosis
- Autoimmune Hepatitis
- Alpha1-antitrypsin deficiency
- Wilson’s disease
- Celiac disease
- Cirrhosis

Non-Hepatic
- Hemolysis
- Myopathy
- Thyroid disease
- Strenuous exercise
**History and PE**

- **Alk phos**, bilirubin, INR, albumin, viral hep serologies, iron studies
- **Lifestyle modification?**
  - Alcohol cessation
  - Stop hepatotoxic medications
  - Weight loss
  - Diabetes control

**Ultrasound, ANA, anti-smooth muscle antibody, ceruloplasmin, α1-antitrypsin**

**Repeat liver chemistries**

**Liver Biopsy**

- Yes and asymptomatic
- Abnormal
- 3-6 months

---

**Causes of Elevated Alkaline Phosphatase**

- **Hepatobiliary**
  - Bile duct obstruction
  - Primary biliary cirrhosis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Medications
  - Hepatitis
  - Cirrhosis
  - Infiltrating disease of liver (next slide)

- **Nonheptic**
  - Bone disease
  - Pregnancy
  - Chronic renal failure
  - Lymphoma and other malignancies
  - Congestive heart failure
  - Infection and inflammation

---

**Infiltrating Diseases of Liver Causing Elevation in Alkaline Phosphatase**

- Sarcoidosis
- Tuberculosis
- Fungal infection
- Other granulomatous diseases
- Amyloidosis
- Lymphoma
- Metastatic malignancy
- Hepatocellular carcinoma
### Bilirubin

- **Unconjugated (indirect) hyperbilirubinemia**
  - Gilbert’s syndrome
  - Hemolysis (increased heme breakdown)
  - Crigler-Najjar syndrome

- **Conjugated (direct) hyperbilirubinemia**
  - Extrahepatic obstruction of bile flow
  - Intrahepatic cholestasis
  - Hepatitis
  - Cirrhosis

---

### Elevated Bilirubin

**History and PE, liver chemistries**

- Unconjugated bilirubin, nml
- ALT and alkaline phosphatase

- Gilbert’s syndrome, hemolysis studies

- Conjugated bilirubin, abnormal ALT and alkaline phosphatase

- RUQ ultrasound to assess for ductal dilatation
  - Present
  - Absent

- ERCP or MRCP

*See AST & ALT <5x nml algorithm.

AMA, anti-mitochondrial antibody; positive in primary biliary cirrhosis

ERCP, endoscopic retrograde cholangiopancreatography

MRCP, magnetic resonance cholangiopancreatography
Initial Laboratory Testing

- Urine and blood toxicology screen in ER or HD#1
- Viral
  - HAV IgM
  - HBsAg, HBeAb, HBsAb
  - HCV Ab
- Viral (optional)
  - HBsAg (+)
  - HCV Ab (+)
  - HCV RNA and genotype
  - Immunosuppressed
    - CMV IgM and/or PCR
    - EBV IgM and/or PCR
    - HSV IgM and/or PCR
- Autoantibodies
  - Antinuclear Ab (ANA)
  - Antismooth Muscle Ab (SMAb)
  - Antimitochondrial Ab (AMA)
- Metabolic
  - Ceruloplasmin (serum), urine for 24-hour urine
  - Ferritin, total iron-binding capacity
  - Lipid profile, HbA1c

Summary of Approach to Abnormal Serum Chemistries

- History and physical exam
- Characterize into either:
  - Hepatocellular (AST and ALT predominant)
    - Severe elevation (>15x nml)
    - Mild elevation (<5x nml)
  - Cholestatic (Alk phos predominant)
- In hospital most abnormal liver chemistries
  - Associated with reason for admission
  - Secondary to chronic liver disease
- De Novo liver enzymes in hospital
  - Drugs, infection, ischemia

Acute Liver Failure
**Case**

- ID/CC: 60 y/o admitted with new jaundice
- PMH: Hypothyroidism
- Meds: Synthroid
- ROS: Treated for UTI in past month with Bactrim

---

**Case (con’t)**

- AST 800
- ALT 1000
- ALK 125
- TB 6.6
- Creat 0.9
- INR 1.3
- Pits 136
- WBC 10.4
- Hct 38
- TSH 0.40
- HAV IgM – neg
- HBsAg – neg
- HBCAb – neg
- HBsAb – neg
- HCV Ab - neg
- ANA – strong pos. 1:320
- ASmAb – Neg
- AMA - Neg
- HSV PCR – Neg
- US Doppler - Normal

---

**Case (con’t)**

- Discharged and readmitted week later
- Transferred to UCH
- Labs:
  - TB 22, AST 481, ALT 688, INR 2.2, MELD 26
- Liver biopsy confirms autoimmune hepatitis
- Mentating well
  - Beating her children in Gin Rummy!
- Started on IV steroids
- Evaluated for liver transplant
Majority of patients with AIH respond to steroids
- Those presenting with jaundice have 25% chance of death or transplant
- Study of 72 consecutive, treatment-naïve AIH pts treated with steroids
- Treatment failure associated with
  - Higher bilirubin
  - Higher INR
  - MELD score
  - Δ MELD at day 7

- Rare condition
  - 2,000 cases/yr
- Rapid deterioration liver function
  - Altered mental status
  - Coagulopathy
- High mortality
- Difficult to study
  - Very few controlled trials
- Standards of ICU care for this condition have not been established
- Advances in critical care medicine has greatly impacted management of these challenging patients
**ALF - Definition**

- Most widely accepted definition:
  - Coagulopathy (INR >1.5)
  - Encephalopathy
  - Illness <26 weeks
  - No pre-existing cirrhosis

  **Exceptions:** Wilson’s disease, HBV, autoimmune hepatitis if recognized <26 weeks

---

**Etiology of ALF in the US**

![Bar chart showing etiology of ALF in the US](chart.png)

*Data from the ALF Study Group Registry 1998-2007*

- APAP, acetaminophen
- AIH, autoimmune hepatitis
- BCS, Budd-Chiari syndrome

---

**Unrecognized Acetaminophen Toxicity As Cause of Indeterminate ALF**

![Diagram showing unrecognized acetaminophen toxicity](diagram.png)

- Predominance female
- Very high AST and ALT
- Low bilirubin levels

*Hepatology 2011:53:S67*
**Diagnosis**

- **History**
  - Risks for viral hepatitis (HAV, HBV, HSV)
  - Drugs (acetaminophen, antibiotics)
  - Toxins
  - Risk factors for chronic liver disease

- **Exam**
  - Careful mental status exam
  - Stigmata of chronic liver disease
  - Jaundice – often not seen at presentation
  - Inability to palpate/percuss liver can indicate massive hepatocyte loss
  - Hepatomegaly
    - Viral hepatitis, malignant infiltration, heart failure and acute Budd-Chiari syndrome

**Initial Labs**

- INR – definition and prognostic significance
- CMP – glucose, total bilirubin
- CBC
- ABG – pH <7.3 poor prognosis in acetaminophen toxicity
- Lactate
- Toxicology screen
- Acetaminophen level
- Viral serologies (anti-HAV, HBsAg, HSV IgM, HCV Ab)
- Ceruloplasmin
- Pregnancy test
- Autoimmune markers (ANA, smooth muscle Ab, immunoglobulins)
- HIV test (for listing)
- Amylase/lipase (pancreatitis seen in HAV and acetaminophen)

**Liver Biopsy**

- Not necessary for diagnosis, however may be helpful in following cases:
  - Autoimmune hepatitis
  - Metastatic liver disease
  - Lymphoma
  - Herpes simplex hepatitis
  - +/- Budd-Chiari syndrome
Early Management

- Admit to ICU for frequent monitoring
- Early communication with transplant center
  - UCH Hepatology Direct Physician Line: 303-993-9998
- Further evaluation for etiology
  - Provides best indicator of prognosis
  - Dictates specific management
    - Acetaminophen → N-acetylcysteine (NAC)
    - Autoimmune → steroids
    - Hepatitis B → antiviral medication
    - Herpes → acyclovir
    - Lymphoma → chemotherapy
    - Budd-Chiari syndrome → TIPS

Acetaminophen Toxicity

- Dose related toxin
  - Factors influencing toxicity
    - Excessive intake acetaminophen
    - Excessive P450 activity due to induction by alcohol or other drugs
    - Decreased capacity for glucuronidation or sulfation
    - Depletion of glutathione stores due to malnutrition or chronic alcohol ingestion

- Most cases of ALF exceed 10gm/day, however can rarely occur with 3-4gms/day
- Low or undetectable acetaminophen level does not exclude diagnosis
  - Nomograms only helpful if knowledge of single large dose
- Activated charcoal up to 3-4 hours from ingestion
- Antidote: N-acetylcysteine (NAC)
  - May still be of value up to 48 hours
  - Load: 140mg/kg in D5 over 15 minutes
  - Maintenance 70mg/kg over 4 hours
**NAC in Non-APAP ALF**

- Primary Endpoint – Survival at 3 weeks
  - NAC 70%
  - Placebo 67% (p=0.57)

<table>
<thead>
<tr>
<th>Encephalopathy Grade at Admission</th>
<th>Spontaneous Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>1-2</td>
<td>17/56 (30%)</td>
</tr>
<tr>
<td>3-4</td>
<td>8/36 (22%)</td>
</tr>
<tr>
<td>Total</td>
<td>25/92 (27%)</td>
</tr>
</tbody>
</table>

Chest 2006;134;1092-1102

**Idiosyncratic Drug Reaction**

- Isoniazid
- Sulfonamides
- Phenytoin
- Statins
- Propylthiouracil
- Halothane
- Isofuranone
- Disulfiram
- Valproic acid
- Amiodarone
- Dapsone
- Didanosine
- Efavirenz
- Metformin
- Ofloxacin
- PZA
- Lisinopril
- Nicotinic acid
- Imipramine
- Gemtuzumab
- Labeliol
- Amphetamines
- Etoposide
- Flutamide
- Tolcapone
- Quetapine
- Nefazodone
- Allopurinol
- Methldopa
- Keconazole
- Troglitazone
- Diclofenac
- Ecstasy

**Herbal Products / Dietary Supplements Associated with Hepatotoxicity**

- Kava kava
- Skullcap
- Pennyroyal
- Heliotrepe
- Comfrey
- Senecio
- Greater celandine
- He Shon Wu
- LipoKinetix
- Chaparral
- Germander
- Jin Bu Huan
- Rattleweed
- Sunnhemp
- Impila
- Gum Thistle
- Ma Huang
- Bai-Fang herbs
**Acute Viral Hepatitis**

- Infrequent cause in US
  - 12% HBV
  - 4% HAV
- HEV in pregnant female from Russia, Pakistan, Mexico or India
- HBV from reactivation in setting of chemotherapy or immunosuppression
- Herpes simplex virus (HSV)
  - Pregnant women or immunosuppressed
  - Rapidly fatal without treatment (acyclovir)
  - Treat empirically with acyclovir if suspected
  - Skin lesions often present (50%)
  - Liver biopsy helpful in diagnosis

**Other Etiologies of ALF and Treatment**

- Autoimmune Hepatitis
  - Serological testing (ANA, ASMAb, globulins)
  - Liver biopsy often diagnostic
    - Massive hepatic necrosis
    - Lymphoid aggregates
    - Central Perivenulitis
    - Plasma cell enrichment
  - Therapeutic trial of prednisone 40-60mg daily

- Acute fatty liver disease of pregnancy and HELLP syndrome
  - Expeditious delivery with good prognosis

- Acute ischemic injury
  - Treat underlying process

- Acute Budd-Chiari syndrome
  - TIPS

**Mechanism of Multiorgan Dysfunction in ALF**

[Image of diagram showing various mechanisms and pathways related to ALF]
ICU Care of ALF Patient

- Cerebral edema
- Infection
- Coagulopathy
- Hemodynamics support
- Renal failure
- Metabolic issues

Cerebral Edema

- Etiology multifactorial and incompletely understood
- Hyperammonemia leads to toxic level of glutamine in astrocytes leading to osmotic swelling
- In cirrhosis, osmotic balance maintained by slower rate of glutamine accumulation offset by export of organic osmolytes from astrocytes

Basic Maneuvers to Minimize Risk Intracerebral Hypertension

- Elevate HOB 30 degrees
- Maintain neutral neck position
- Avoid or minimize painful stimuli
- Maintain mild respiratory alkalosis
- Intracerebral pressure (ICP) monitor
ICP Monitor Goals

- No consensus among experts and centers
  - Only indicated in liver transplant candidates
- May lengthen survival time awaiting transplant, but no data to demonstrate overall survival benefit
- Goals of therapy:
  - ICP > 20 mm Hg
  - CCP > 50 mm Hg
    - CCP < 40 mm Hg > 2 hrs associated with poor neurological outcome

Cerebral perfusion pressure (CPP) = MAP – ICP

Treatment Strategies for Cerebral Edema and ICH in ALF

- Hypertonic saline solution
- Mannitol
- Steroids
- Plasma
- Mannozyl
- Hypertonic saline
- Hypothermia
- Vasopressors
- Other

Infection

- Infection most common cause of death
- Infection precipitates MOSF
- SIRS risk for cerebral edema and intracranial hypertension
- Data for prophylactic antibiotics is lacking
  - Reduce risk of infection by not survival
- Our program advocates prophylactic antibiotics and antifungals for patients awaiting LT
**Coagulopathy**

- INR prognostic indicator!
- Vitamin K okay
- Don't give FFP unless bleeding, invasive procedure, INR >7 (?)
- Don’t forget stress ulcer prophylaxis

---

**Liver Transplantation**

- In pre-LT era, survival from ALF was 15%
  - Survival now ≥60%
- Spontaneous recoveries (mostly acetaminophen) previously 15%
  - Now ~40% with improved critical care
- Death rates for those awaiting LT 25-40%
- Post-LT survival rates ~80-90%
  - Accurate long-term data not yet available.

---

**Interactions Determining Outcomes.**

Spontaneous survival

- Host factors
  - Age
  - Nutritional
  - Comorbid conditions

- Host genetics
  - HLA
  - Polymorphisms

- Hepatic microenvironment
  - LPS
  - Chemokines
  - IFN

- Death

Liver transplant

Absolute contraindications

Etiologies Associated with Poor Transplant Free Survival

- Idiosyncratic drug reaction
- Non-Hepatitis A viral infections
- Autoimmune Hepatitis
- Mushroom poisoning
- Wilson Disease
- Budd-Chiari syndrome
- Indeterminate cause
  - Unrecognized and untreated acetaminophen?

Arch Intern Med 2003

King’s College Criteria

- Acetaminophen-induced ALF
  - Arterial pH <7.3 (after resuscitation) irrespective of coma grade  
  - INR >6.5 and serum creat >3.4 in patients with grade III/IV coma

- Non-acetaminophen induced ALF
  - INR >6.5 irrespective of degree of encephalopathy
  - Any three of the following, irrespective of coma grade:
    - Drug toxicity, indeterminate cause of ALF
    - Age <10 years or >40 years
    - Jaundice to coma interval >7 days
    - INR ≥3.5
    - Serum bilirubin >17.5 mg/dL

Gastroenterology 1989

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Overdose Pattern in Acetaminophen-Induced ALF

- Unintentional overdose independently associated with reduced survival
  - Older, more alcohol use

- Unintentional overdose should be treated as high risk; low threshold for NAC
  - Sicker, less spont. survival

- King’s College Criteria have reduced sensitivity in unintentional overdose

Other Poor Prognostic Signs in ALF

- Grade III/IV coma on admission
- Non-acetaminophen ALF
  - MELD score

Summary

- LFTs do not assess liver function
- Two primary patterns of abnormal liver chemistries:
  - Hepatocellular injury (↑ AST and ALT)
  - Cholestatic (↑ alkaline phosphatase)
- Acute liver failure defined as severe liver injury with
  - Coagulopathy (INR >1.5)
  - Encephalopathy
- Determining etiology in ALF provides best indicator of prognosis and specific management
- Most widely accepted prognostic criteria in ALF if King’s College Criteria