Pathophysiology: Hepatic Disorders and Drug-Induced Liver Diseases

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Hepatitis
inflammation of the liver

• Can have many causes
  – drugs
  – toxins
  – alcohol
  – viral infections (A, B, C, D, E)
  – other infections (parasites, bacteria)
  – physical damage
Common Locations of Gallstones
Introduction

• Hepatocytes represent 60% of total cell population of the liver
• Hepatocyte functions:
  – Synthesis
  – Metabolism
  – Storage
  – Catabolism
  – Excretion/clearance
Liver

• Functions
  – Stores sugar needed for energy
  – Absorbs good nutrients
  – Breaks down poisons (toxins) and drugs
  – Makes important proteins that help build new tissue and repair broken tissue
  – Produces bile, which helps remove waste from the body
Hepatic Disease

• ACUTE
  – Injury within 6 months in a previously normal liver

• CHRONIC
  – Progressive liver injury for >6 months leading to fibrosis and eventually cirrhosis

Liver Cell Injury

Bile duct damage
Hepatic Jaundice

Look for other evidence of end-stage chronic liver disease:

- Abdominal distention
- Ascites
- Fever
- SBP
- Confusion/coma
- Hepatic encephalopathy
- Melaena
- Oesophageal varices
- Any of above
- Hepatocellular carcinoma

Remember these 5 complications of cirrhosis
Clinical Manifestations of Cirrhosis

- Encephalopathy
- Esophageal varices
- Portal hypertension
- Cirrhosis
- Hepatorenal syndrome
- Tea-colored urine
- Clay-colored stool

INTERNAL SYMPTOMS
Patterns of Liver Damage

- **Hepatocellular damage**
  - Damage to hepatocytes themselves
  - Inflammation, infection, ischemia, toxin, etc

- **Cholestatic/Obstructive**
  - Blockage of bile ducts or impairment bile formation

- **Determination of Liver Function**
  - Indicators of residual hepatocyte function and usually indicative of chronic or fulminant liver damage
Liver ‘function’ test
Ground-rules

• There is NO PERFECT TEST
• Clinicians must use a battery of tests to give them an idea of “probable liver function”
• These tests can be used to monitor
  – Progression of injury
  – Recovery from injury
Because the liver performs SO MANY functions, a single laboratory test to assess liver function simply does not exist!

We must infer functional status by looking for evidence of obstruction and/or hepatocyte injury.
Is the liver synthesizing properly? Test for……

- Albumin
- Binding proteins for iron & copper
- Coagulation factors
  - prothrombin time
  - fibrinogen
Albumin

• 65% of serum protein
• ½ Life = 3 weeks
• Low levels can correlate with chronic liver dysfunction.
• Other reasons to be low?
  – Decrease production
    • Malnutrition
    • Chronic Inflammation
  – Increased Loss
    • Kidney – Nephrotic Syndrome
    • GI tract – Protein-losing enteropathy
    • Skin – Severe burn
Clotting Factors

- Most clotting factors are synthesized in the liver
- $\frac{1}{2}$ shorter than Albumin
- Prothrombin Time (PT) is a good functional test – but usually use INR to correct for lab variability
- PT/INR PROLONGED in liver disease
Clotting Factor

- Chronic cholestatic disease often have increased INR—Why?
  - Vit K def
  - Vit K Fat soluble
  - Cholestatic/obstructive so not enough bile secretion so not enough Vit K absorption

- How to differentiate Vit K def from Decreased synthesis?
  - Give Vit K (take 24-48 hours to correct)
  - Factor V NOT Vit K dependent so can check directly
If hepatocytes are not synthesizing properly then....

- Proteins which are directly measured will be LOW (albumin, iron binding proteins, fibrinogen)
- Prothrombin time will be abnormally LONG because you are measuring the ability to clot in seconds.
If hepatocytes have been directly injured ......then......

• Enzymes from the hepatocyte cytoplasm leak into the plasma and levels are abnormally HIGH
  – AST (SGOT)
  – ALT (SGPT)
  – LDH
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>T 1/2</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>10 hrs</td>
<td>Liver, heart, muscle, kidney</td>
</tr>
<tr>
<td>ALT</td>
<td>48 hrs</td>
<td>Liver, kidney</td>
</tr>
<tr>
<td>LDH</td>
<td>4 hrs</td>
<td>Liver, RBC, heart, muscle, kidney, tumors</td>
</tr>
</tbody>
</table>
Aminotransferase

• Typical ALT or AST Distribution

Direct Injury

Elevations of BOTH AST and ALT > 10 times the normal range ALMOST ALWAYS indicates severe hepatocyte damage.
Level of Elevation

Has there been an obstruction? (cholestasis ?) Test for ........

- Alkaline Phosphatase
- GGT (gamma glutamyl transferase)
- 5’ Nucleotidase (5-NT)
When biliary obstruction occurs, bile backs up and injury begins at the canalicular surface.

- Alk Phos, GGT and 5’-NT are all enzymes located at the canalicular surface.
- When obstruction occurs:
  - Surface tension increases
  - Surface enzymes are up-regulated
  - Enzymes leak into the plasma
Obstructive Biliary Disease

- In the absence of bone disease, elevated levels of alkaline phosphatase > 10 times the normal range are consistent with Extrahepatobiliary obstruction. (examples are Common Bile Duct Obstruction and pancreatic cancer)
Mechanisms of bilirubin excretion:

1. Haemoglobin → Haem
2. Haem → Unconjugated Bilirubin
3. Unconjugated Bilirubin → Conjugated Bilirubin
4. Conjugated Bilirubin → Bile
5. Bile → Urobilinogen in colon
6. Urobilinogen in colon → Urobilinogen in colon
7. Urobilinogen in colon → URINE
Bilirubin

- Direct Bilirubin
- Conjugated
- Soluble in H₂O
- 0-20% in plasma

- Indirect Bilirubin
- Unconjugated
- Insoluble in H₂O
- 80-100% in plasma
Three Categories of Jaundice

Hyperbilirubinemia (Jaundice)

- Prehepatic (Hemolysis)
  - Unconjugated Bilirubin
- Hepatic
  - Genetic defects, primary liver disease
  - Mixed
- Posthepatic
  - Bile Duct Obstruction
  - Pancreatic Head CA
  - Conjugated Bilirubin
Hyperbilirubinemia

• Markedly elevated Unconjugated bilirubin?  -----  Think Hemolysis!!!
• Markedly elevated Conjugated bilirubin?  -----  Think hepatic injury or post-hepatic obstruction!!!!
Remember these caveats of Liver ‘Function’ Tests

There is NO PERFECT TEST

A group of tests is needed in order to ‘infer’ functional liver status.

Mixed injury/obstruction patterns are common in REAL LIFE !!

DO NOT assume that a NORMAL test result indicates absence of liver disease.
(example: AST & ALT can be normal in End Stage Cirrhosis.)
Case # 1

- A 26 yo M IVDA presents with a 2 week history of worsening malaise, N&V & abdominal pain.
- PE: + mild fever; ?scleral icterus; +tender enlarged liver

- Labs: 
  - ALT: 1650 (N= 8-33 U/L) 
  - AST: 2200 (N= 4-36 U/L) 
  - Alk Phos: 700 (N= 20-130 u/L) 
  - Bilirubin 2.0 (N= 0.1-1.2 mg/dL) 
  - T Protein 6.0 (N= 6.0-7.8 g/dL) 
  - Albumin 2.8 (N= 3.2-4.5 g/dl) 
  - PT = 15 sec (N= 11-14.7 sec ) 
    » (INR=1.2)
Case # 1

- **Synthesis?** (Total protein & albumin on low side; PT normal.) is OK

- **Obstruction & Bilirubin Clearance?** (Alk Phos & Bilirubin are up, but not dramatically) Probably not a primary obstructive process.

- **Hepatocyte Direct Injury:** ALT & AST are DRAMATICALLY increased.

- **THE PRIMARY PROCESS IS DIRECT HEPATOCYTE INJURY**

- Could be Hepatitis B; Drug Toxicity...
Case # 2

- 47 yrF presents with Acute abdominal pain. Initially intermittent, but now is constant & increasing in intensity.

- PE: Abdominal tenderness, No organomegaly. Mild Scleral icterus

- Labs: 
  - ALT: 50 (N= 8-33 U/L)
  - AST: 62 (N= 4-36 U/L)
  - Alk Phos: 1800 (N= 20-130 u/L)
  - Bilirubin 2.9 (N= 0.1-1.2 mg/dL)
  - T Protein 6.8 (N= 6.0-7.8 g/dL)
  - Albumin 3.5 (N= 3.2-4.5 g/dL)
  - PT = 12 sec (N= 11-14.7 sec)
Case # 2

• Synthesis? (Total protein, albumin & PT normal.) is OK

• Obstruction & Bilirubin Clearance? (Alk Phos is up QUITE DRAMATICALLY; Bilirubin up modestly)
  PROBABLY A PRIMARY OBSTRUCTIVE PROCESS.

• Hepatocyte Direct Injury: ALT & AST are up a bit, but not dramatically.
  THE PRIMARY PROCESS IS OBSTRUCTIVE !!!

• Could be:
  common bile duct obstruction pancreatic cancer (esp. in head of pancreas)
Gall Stones
For every complex problem there is an answer that is clear, simple, and wrong.

H. L. Mencken
Liver Disease

Jaundice
Acute viral (A,B and E)

Jaundice
Biliary Obstruction
Hepatic causes
PBC
PSC
Drugs

Alcohol
Alcohol hepatitis/cirrhosis

Hepatitis
Chronic Viral (B and C)
Autoimmune disease
Alcohol
Progression to cirrhosis
Three Categories of Jaundice

Hyperbilirubinemia (Jaundice)

Prehepatic (Hemolysis)
- Unconjugated Bilirubin

Hepatic
- Genetic defects,
  primary liver disease
  (Mixed)

Posthepatic
- Bile Duct Obstruction
  Pancreatic Head CA
  (Conjugated Bilirubin)
Pre-hepatic

• **Gilberts**
  – Failure to conjugated
  – 2-5%
  – Autosomal recessive
  – Asymptomatic
  – Bilirubin (1.5-2.0)
  – Unconjugated
  – Normal ALT/ALP
  – Worse if infection

• **Haemolysis**
  – Excess bilirubin production
  – Unconjugated Bil ++
  – Normal ALP/ALT
  – Low Hb/retics++
  – Splenomegally
Post-hepatic Jaundice

• History
  – Pain Stones/Chronic pancreatitis
    • RUQ/back
  – Weight loss Carcinoma/ pancreatitis
  – Steatorrhoea Chronic pancreatitis
  – Fever/rigors Cholangitis

• Examination
  – Nil
  – Hepatomegaly Liver metastases
Post-hepatic

Cholangitis

Benign stricture
PSC
Chronic pancreatitis

Stones

Malignant stricture
Ampulla
Carcinoma pancreas
Cholangiocarcinoma

Liver metastases rarely cause jaundice
Jaundice and Weight Loss

• Anorexia
  – alcohol
• Malabsorption
  – Chronic pancreatitis
• Hypercatabolic state
  – Cirrhosis
• Malignancy
## Alcohol content in specific beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Amount</th>
<th>Alcohol %</th>
<th>gm/Drink</th>
<th>Drinks/50 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>12 oz. at 4%</td>
<td>11</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Wine</td>
<td>5 oz. at 11%</td>
<td>13</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Martini</td>
<td>3 oz. at 40%</td>
<td>28</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>
Ultrasound

**Hepatic**
Liver texture (cirrhosis/metastases)
Portal hypertension (splenomegaly/varices/ascites)

**Obstruction**
Dilated CBD
Intrahepatic duct
Stones (GB+ duct)
Pancreas
Scan demonstrating a mass in head of the pancreas
A perihilar cholangiocarcinoma in the common hepatic duct
Endoscopic retrograde cholangiopancreatography
Symptoms

- Abdominal discomfort
- Weight loss
- Anorexia and lethargy
- Itching
- Stool

- ✓ Hepatitis
- ✓ Cirrhosis
- ✓ Carcinoma
- ✓ Chronic pancreatitis
- ✓ PBC/PSC
- ✓ Pale or normal
History

- Presenting complaint
- Drugs
- Family history
  - Jaundice
  - Liver disease
  - Arthritis/thyroid
- PMH
  - NSAID/antibiotics/herbal
  - Haemochromatosis/Wilson
- SH
  - Alcohol
  - PBC/AICAH
  - Alcoholic hepatitis/cirrhosis
Ultrasound

**Hepatic**
Liver texture (cirrhosis/metastases)
Portal hypertension (splenomegally/varices/ascites)

**Obstruction**
Dilated CBD
Intrahepatic duct
Stones (GB+ duct)
Pancreas
Primary Biliary Cirrhosis

• Background
  – Small bile ducts damage
  – 90% Females

• Presentation
  – Itching
  – Abnormal liver tests
  – Complications of cirrhosis (rare)

• Investigations
  – ALP/GGT +++
  – Antimitochondrial Ab+
  – Liver biopsy

• Complications
  – Jaundice (late)
  – Progression to cirrhosis
  – 10-15yrs
Primary sclerosing cholangitis

• Immune damage to intrahepatic ducts (larger than in PBC)

• Presentations
  – Itching or Jaundice
  – Fever
  – Complications of cirrhosis
  – Abnormal LFTs

• Diagnosis
  – ERCP
  – Liver Biopsy

• Blood tests
  – High ALP/GGT
  – Bilirubin normal or increased

• Complications
  – Cholangitis
  – Stones
  – Benign strictures
  – Cholangiocarcinoma

• Associations
  – Ulcerative colitis >70%
HEPATOCELLULAR INJURY
- Hepatocellular injury (e.g., viral or alcoholic hepatitis)
- Drugs
- Pregnancy

BILE CANALICULUS
- Bile ductules
- Bile ductules (cholangiolitis)

PORTAL TRACT BILE DUCT
- Primary biliary cirrhosis
- Intrahepatic biliary atresia

MEDIUM AND LARGE INTERLOBULAR BILE DUCTS
- Sclerosing cholangitis
- Cholangiocarcinoma

Lumen of sinusoid
Classic cholangiographic appearance of sclerosing cholangitis
Haemochromatosis

- Excess iron absorption
- Autosomal dominant

### Presentation
- Age 40-50
- Women less Fe overload
- Abnormal LFT
- Lethargy
- Arthritis
- Screening of sibs

### Examination
- Grey-slate colour
- Hepatomegally

### Complications
- Cirrhosis and HCC
- Diabetes mellitus
- Joints
  - Arthritis
  - Chondrocalcinosis
- Cardiomyopathy
- Hypopituitarism
Haemochromatosis

• **Diagnosis**
  - Transferrin saturation +++ (>55%)
  - Ferritin > 1000
  - Liver iron content
  - HFE genotype
    • 90% C282Y mutation

• **Management**
  - Venesection
  - Screen family
  - If cirrhotic follow-up for complications

• **Outcome**
  - If non-cirrhotic normal life expectancy
A liver biopsy specimen shown at high power
WILSON’S DISEASE

An inborn error of copper metabolism – characterised by an increase in copper accumulation in tissues of the liver, brain, cornea, skin, joints and kidney as a result of decreased hepatobiliary excretion of copper.
Alcohol Use/Abuse - Prevalence

• 50-70% of population drinks alcohol
• 40-50% of population with h/o temporary EtOH problems (DUI, drunk..)
• There is a gender difference in the prevalence of alcoholism;
  – 10% male vs 3 % of the female
• 20-25% prevalence in medical inpatients.
Epidemiology

- > 10 million in the United States (1988 est)
- Ethnic Groups (↑ Irish & Native Americans)
- Social (↑↑↑ Separated > divorced > single)
- ↑ (!) with education-level & SEC
- ↑ In health professionals (Yep…PharmD too)
- “Hereditary” (4X ↑ in children of alcoholics)
- NOT more prevalent in slums
Honest…just one drink!!

- Alcohol content differs in every drink
- There is an equivalent 10 g EtOH in:
  - 12 oz Beer
  - 4 oz wine (none-fortified)
  - 1.5 oz 80 proof (40%) liquor.
Metabolism

• 2-10% of blood EtOH excreted in lungs, urine, sweat
  – Increased clearance with high blood levels
• 90% metabolism in liver
  – Alcohol Dehydrogenase Pathway (ADH)

\[
\text{EtOH} \xrightarrow{\text{ADH}} \text{Acetaldehyde} \xrightarrow{\text{ALDH}} \text{Acetate}
\]

– Microsomal ethanol oxidizing system (MEOS)
  Highly inducible, (Especially during chronic EtOH)
Compensation to Alcohol

Metabolic (Pharmacokinetic) Tolerance
• 30% ↑ in MEOS clearance p/1-2 wks EtOH

Cellular (Pharmacodynamic) Tolerance
• Neurohumeral changes, which lead to physical dependence (e.g. withdrawal if stop)

Behavioral Tolerance
• At same EtOH level, see improved coordination, cognition, skills
“Alcoholism”
Treatment for Alcoholism

• Recidivism!! - Very high relapse rate

• Individuals w/mod. dependence → TX program

• Address comorbid psychiatric/medical illness
Treatment for Alcoholism

• ↑ Successful treatment/cessation
  – Family, friends, & peers MUST be supportive & involved
  – Support groups
    • Al-Anon
    • Alcoholics Anon

• Pharmacologic intervention – “antabuse”
  – Best if linked to the above
Effects of Alcohol
## Alcohol Dose-Response

<table>
<thead>
<tr>
<th>Level (mg/dL)</th>
<th>Sporadic Drinkers</th>
<th>Chronic Drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-50</td>
<td>Congenial euphoria</td>
<td>No observable effect</td>
</tr>
<tr>
<td>“party”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Gregarious/garrulous</td>
<td>Often no effect</td>
</tr>
<tr>
<td>80-100</td>
<td>Legally intoxicated</td>
<td>Minimal effects</td>
</tr>
<tr>
<td></td>
<td>Uncoordinated</td>
<td></td>
</tr>
<tr>
<td>125-150</td>
<td>Unrestrained behavior</td>
<td>Congenial euphora or mild uncoordination</td>
</tr>
<tr>
<td>200-250</td>
<td>Lethargy</td>
<td>Effort required to maintain motor/emotional control</td>
</tr>
<tr>
<td>300-350</td>
<td>Stupor of coma, death(?)</td>
<td>Drowsy and slow</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>Death</td>
<td>Coma</td>
</tr>
</tbody>
</table>

* Toxicities significantly increased with concurrent benzodiazepines
## Alcohol Related Medical Disorders

<table>
<thead>
<tr>
<th>Organ</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>Deficiencies in folate, thiamine, pyridoxine, niacin, &amp; riboflavin, magnesium, zinc, calcium, phosphate, &amp; Protein</td>
</tr>
<tr>
<td>Brain</td>
<td>Hepatic encephalopathy, Wernicke-Korsakoff’s syndrome, Cerebral atrophy, Amblyopia, Central pontine myelinolysis Marchiafava-Bignami disease,</td>
</tr>
<tr>
<td>Nerve, muscle</td>
<td>Neuropathy, myopathy</td>
</tr>
<tr>
<td>Liver</td>
<td>Fatty liver, hepatitis, cirrhosis, hepatoma</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, cardiomyopathy, arrhythmia, strokes</td>
</tr>
<tr>
<td>Blood</td>
<td>Anemia, leukopenia, macrocytosis</td>
</tr>
<tr>
<td>GI</td>
<td>Esophagitis, gastritis, varices, pancreatitis</td>
</tr>
<tr>
<td>Metabolic-electrolytes</td>
<td>Hypoglycemia, hyperlipidemia, hyperuricemia, ketoacidosis, hypomagnesemia, hypophosphatemia</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Pseudo-Cushing’s syndrome, testicular atrophy, amenorrhea</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Oncology</td>
<td>10X ↑ Cancer (head &amp; neck, esophagus, stomach, liver, pancreas, breast)</td>
</tr>
</tbody>
</table>

Table 133-1, Andreoli
Major Organ Systems
Alcohol & the Liver

Normal liver
Just add alcohol…
Alcohol & the Liver

- Portal Hypertension

“Caput Medusa”
Alcohol & the Skin

• Rhynophyma (Acne rosacea variant)

Seen with EtOH & other vasodilatory substances
Alcohol & the Skin

• “Spider Angiomas”

(↓ estrogen clearance & testosterone production)
Alcohol & the Skin

• PALMAR ERYTHEMA

• (↓ estrogen clearance & testosterone production)
Treatment
Metabolism

• 2-10% of blood EtOH excreted in lungs, urine, sweat
  – Increased clearance with high blood levels

• 90% metabolism in liver
  – Alcohol Dehydrogenase Pathway (ADH)
    
    ![Metabolism Diagram]

  – Microsomal ethanol oxidizing system (MEOS)
    Highly inducible, (Especially during chronic EtOH)
DRUG
INDUCED
LIVER
INJURY
Drug-induced Liver Disease

- Hepatocellular
  - acetaminophen, INH, methyldopa, MTX
- Cholestatic
  - chlorpromazine, estradiol,
- Chronic Hepatitis
  - methyldopa, phenytoin, macrodantin, PTU
- Hypersensitivity Reaction
  - Phenytoin, Augmentin, allopurinol
- Microvesicular Steatosis
  - amiodarone, IV tetracycline, AZT, ddl, stavudine
• Acetaminophen has been approved for OTC use since 1960
• Although the drug is remarkably safe, toxicity can occur even with therapeutic doses.
• Alcoholics are particularly susceptible to hepatotoxicity
• Therapeutic dose of acetaminophen is 10-15 mg/kg/dose in children and 325-1000 mg/dose every 4-6 hours in adults, with a maximum of 4-8g/day.
Biochemical Basis of APAP Toxicity

• With normal doses, NAPQI is rapidly conjugated with hepatic glutathione, forming a nontoxic compound which is excreted in the urine

• With toxic doses, however, the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by CYP2E1

• NAPQI begins to accumulate once glutathione stores are depleted by about 70%
CLINICAL MANIFESTATIONS

• 2 to 12 hours after ingestion
  – nausea, vomiting, diaphoresis, pallor, lethargy and malaise are seen

• 24-48 hrs after ingestion
  – temporary symptomatic improvement
  – Signs of liver involvement begin at this time
    • right upper quadrant pain and hepatomegaly
    • elevations in the LFTs
    • prolongation of the PT

• 72 hours after ingestion
  – Signs of severe hepatic damage become apparent
  72 to 96 hours after ingestion
CLINICAL MANIFESTATIONS

- Systemic symptoms of the first stage reappear in conjunction with confusion, marked elevation in hepatic enzymes, hyperammonemia, and a bleeding diathesis.

- Signs of severe hepatotoxicity include plasma AST levels that often 10,000 IU/L, prolongation of the PT, hypoglycemia, lactic acidosis, and a plasma bilirubin concentration above 4.0 mg/dL.

- Acute renal failure may also be seen at this time, due primarily to ATN.
Severity of acetaminophen intoxication  Relationship between plasma acetaminophen concentration (in \( \mu \text{g/mL} \) or \( \mu \text{mol/L} \)), the time after drug ingestion, and the risk of hepatic toxicity. The thick diagonal line of possible hepatic toxicity represents a 25 percent likelihood of disease. A relatively low level (such as 10 \( \mu \text{g/mL} \)) is safe soon after ingestion, but associated with appreciable risk at 24 hours since it reflects a high initial load which has now distributed into the tissues. (Redrawn from Rumack, BH, Matthews, H, Pediatrics 1975; 55:873.)
The mainstays of the therapy of APAP intoxication include gastric decontamination with activated charcoal and the administration of N-acetylcysteine (NAC).

Activated charcoal avidly adsorbs APAP, reducing its absorption by 50 to 90%.

However, activated charcoal also adsorbs NAC and, by causing nausea and vomiting, may interfere with the administration of NAC.
TREATMENT

• NAC regimen is used in the United States
  – A loading dose of 140 mg/kg in a five percent solution is given either orally or via nasogastric tube
  
  – This is followed by 70 mg/kg every four hours for 17 doses; any doses vomited should be repeated
Liver transplantation

- Of patients meeting criteria for transplantation
  - 30 percent were too ill from multiple organ failure to be listed for transplantation
  - 30 percent deteriorated so rapidly after listing that they became ineligible for transplantation even though grafts became available for most patients within 24 hours
  - Only 35 percent of patients meeting initial criteria for transplantation had no contraindications to the procedure and did not deteriorate while on the waiting list
Clinical Manifestations

- Later Manifestations:
- Jaundice
- Skin Lesions
- Hematologic Problems
- Endocrine Disturbances
- Peripheral Neuropathy
- In advanced stage, liver becomes small and nodular
Cirrhosis of the Liver

- Progressive liver disease characterized by extensive degeneration and destruction of the liver cells (parenchyma)

- Liver cells attempt to regenerate, but process is disorganized leading to fibrous connective tissue which distorts the shape and lobes of the liver

- Ranked 5th leading cause of death and third among ages of 25 to 65 years of age
Cirrhosis
Complications

• Portal Hypertension:
  • Changes in the liver result in obstruction to the normal flow of blood through the portal system, resulting in the hypertension
Caput Medusa
Ascities

- Accumulation of serous fluid in the peritoneal or abdominal cavity

- Common manifestation of cirrhosis

- When blood pressure is elevated in the liver, proteins move from the blood vessels via the large pores of the capillaries into the lymph space

- When the lymphatic system is unable to carry off the excess proteins and H2O, they leak through the liver capsule into the peritoneal cavity and osmotic pressure of the proteins pulls fluid into the peritoneal cavity

- Other causes - Hypoalbuminemia and Hyperaldosteronism
Pathogenesis of Ascites

- Decreased oncotic pressure
- Increased hydrostatic pressure
Ascitis in Cirrhosis
Ascitis in Cirrhosis
Learn from the mistakes of others. You can't live long enough to make them all yourself...!
Peripheral Edema and Ascities

- Edema precedes ascities

- Edema results from decreased colloidal osmotic pressure from impaired liver synthesis of albumin and increased portal pressure

- Peripheral edema occurs as ankle and presacral edema
Management of Ascities

- Sodium restriction, diuretics and fluid removal
- Low sodium diet (250 to 500 mg per day)
- Diuretic Therapy - Aldactone, Amiloride, Dyrenium
- A paracentesis (needle puncture of the abdominal cavity) to remove ascetic fluid - reserved for patients with abdominal and respiratory impairment caused by severe ascities. Temporary and reaccumulates
- Peritoneovenous Shunt - provides continuous reinfusion of ascitic fluid into the venous system
Management of Ascities

- Accurate calculation of and recordings of intake and output
- Daily weights
- Measurement of extremities and abdominal girth for extent of edema
- Before paracentesis, must have patient void to prevent the puncture of the bladder
Summary: Ascite

- Initiated by altered hepatic and splanchnic hemodynamic
  - transudation of fluid into the interstitial space
  - intravascular volume deficit
  - initiates compensatory mechanism (aldosterone secretion)
- Indicator of advanced cirrhosis
- **Treatment**
  - 1) Medical management
    - dietary salt restriction
    - diuretic therapy- spironolactone 200-300 mg orally daily.
  - 2) Intermittent large-volume paracentesis
  - 3) Peritoneovenous shunt: significant morbidity
  - 4) TIPS : refractory ascite
Complications

- **Esophageal Varices:**
  - Common Complication
  - Collateral vessels are fragile and tolerate high pressure poorly
  - Likely to bleed
  - Patient with bleeding esophageal varices have high mortality rate
  - Recurrence is high
Esophageal Varacacies

**Intrahepatic causes**
- Esophageal varices
- Spleen markedly enlarged
- Azygos vein

**Infrarehepatic causes**
- Esophageal varices
- Cirrhotic liver
- Portal vein thrombosis
- Spleen decidedly enlarged
- Esophageal branches of left gastric vein
- Short gastric vein

**Radiographs**
- Esophageroscopic view (at cardia)
- Radiograph
- Splenogram
- Diaphragm
Upper GI Bleeding
VARICEAL HEMORRHAGE

- The single most life-threatening complication of portal hypertension

- 1/3 of all patients expirances Variceal Hemorrhage

- Mortality: 25 - 30 % (underlying hepatic functional reserve)
Management of Bleeding Varicies

- Must be observant of any signs of bleeding from the varicies, such as hematemesis and melena
- If bleeding occurs, patient is admitted immediately to the ICU
- Patient Airway is Very Important
Treatment for Esophageal Varicities

• **Esophageal Varicities:**
  – Goal is the avoidance of bleeding and hemorrhage. Patient should avoid ingesting alcohol, aspirin, and irritating foods

• **Bleeding Varicities:**
  – Emergency, Therapeutic and Prophylactic
Treatment of variceal bleeding

- Many available modalities (no single satisfactory therapy)
- Optimal therapy for long-term prevention
  : effective (low rebleeding rate) and minimally alter hepatic physiology
- Prophylactic therapy : minimal morbidity & mortality
Tx. of Acute Bleeding Episode

1) Resuscitation & Diagnosis
   - restoration of circulatory blood volume then endoscopy

2) Pharmacotherapy
   - Vasopressin (0.2 units/hr)
   - Somatostatin & Octreotide: fewer side effects than vasopressin

3) Balloon Tamponade (Sengstaken-Blakemore tube)
   - immediate cessation of bleeding (85%), widespread availability
   - frequent recurrent hemorrhage after balloon deflation
   - considerable discomfort, potentially lethal complication
     (esophageal perforation & ischemic necrosis, aspiration)
   - Consider sequential therapies (endoscopic therapy, operation, TIPS)

4) Endoscopic treatment (variceal sclerosis or ligation)
   - Most commonly used for
     - Tx. of acute bleeding
     - Prevention of recurrent hemorrhage
Treatment of Variceal bleeding

-Somatostatin, given IV by initial bolus (250-500 µg) followed by continuous infusion (250-500 µg/ h) controlling variceal bleeding in 60-80% of patients had no significant side effects associated with its use.

-Octreotide is synthetic somatostatin analog with longer half life. given IV by initial bolus (50 µg) followed by continuous infusion (25 µg/ h)
Treatment of Variceal bleeding

-Vasopressin given by continuous IV infusion 0.1-0.4 U/min control bleeding in 50% of patients.

-Significant side effect (myocardial and mesenteric ischemia) limit its use.

-Addition of nitroglycerin by continuous IV infusion 40-400 µg/ min ameliorates many of systemic side effects of vasopressin.
Endoscopic Banding
Prevention of Recurrent Bleeding

- Recurrent variceal bleeding rate > 70%
- **Aim**: recurrent bleeding
- **Definitive treatment**: Pharmacotherapy
  - Chronic sclerotherapy
  - Shunt, TIPS
  - hepatic transplantation
Prevention of Recurrent Bleeding

**Pharmacotherapy**:
Propranolol (Nonselective beta-adrenergic blocker)
- heart rate: 25%
- beta blocker + long-acting nitrate: effective than sclerotherapy
Prevention of recurrent bleeding III

Liver transplantation
variceal bleeding

end-stage hepatic failue

abstinent alcoholic cirrhosis with limited hepatic function reservoir (Child's class B, C)

poor quality of life secondary to encephalopathy, fatigue, bone pain

Limitation: high cost & limited donor supply
TIPS

Transjugular Intrahepatic Portocaval Shunt
Tips pre
Tips post
Complications Continued

- **Hepatic Encephalopathy**: May also be called coma, is a terminal complication in liver disease.

- Occurs when liver damage causes ammonia to enter the systemic circulation without liver detoxification. Source of ammonia is the bacterial and enzymatic deamination of amino acids in the intestines.

- When blood is is shunted past liver via the collateral circulation and bypasses the liver, the liver is unable to convert the ammonia to urea, which means remains systemic.
Clinical Manifestations of Hepatic Encephalopathy

• Changes in neurologic and mental responsiveness anywhere from lethargy to deep coma

• Early stages include euphoria, depression, apathy, irritability, memory loss, confusion, yawning and drowsiness to name a few

• Clinical manifestations of impending coma include disorientation X4 and flapping tremors
Clinical Assessment of Hepatic Encephalopathy

• Early
  – Neurological and mental manifestations
    • Changes in LOC, slurred speech, apathy, restlessness, short attention span, positive B Babinski sign, picking at bed clothing

• Impending Coma
  – Asterixis
    • Liver flap
    • Hepatic tremor
  – Disorientation
Management of Hepatic EncephaIopathy

• The goal is to reduce the ammonia formation
• Protein restriction and reduction of ammonia formation in the intestines
• Protein restriction may be as low as 0-40g per day
• Sterilization of the intestines with antibiotics - neomycin sulfate
• Lactulose (Cephulac) discourages bacteria
Management of Hepatic Encephalopathy

• Dietary
  – Reduction of protein
    • 15-40 g daily with sufficient CHO

• Administer Lactulose
  – 15-30 ml QID or 4-5 BM a day
  – Prevents diffusion of ammonia

• Bowel cleansing
  – Sterilization of the intestines with antibiotics
    • Decreases enteric organisms that produce ammonia
      – Neomycin 500 mg po qid
        » Orally or enema
      – rifaxmin 200 mg 3 times
Spontaneous Bacterial Peritonitis
Introduction

• Definition- an ascitic fluid infection without an evident intraabdominal surgically-treatable source

• Any patient with ascites is essentially at risk for developing SBP however it primarily occurs in patients with ascites secondary to cirrhosis.
SBP Clinical Manifestations

• There is a very wide array of symptoms and signs which patients can present with for SBP

• The key is HIGH INDEX OF SUSPICION in patients with known ascites

• The most common symptom is fever, found in about 80% of patients

• Abdominal pain in about 70%, which can range from frank peritonitis to a mild pain

• An acute change in mental status can be the presenting symptom in some cases
Causative Agents

- The usual agents are those that are gut flora
- E. Coli 50%
- Klebsiella 11%
- S. Pneumonia 19%
- Enterobacter 4%
- Staph 3%
- Psuedomonas 1%
- Taken from a series of 519 patients with SBP diagnosis
Treatment – who?

- Those with PMN counts greater than 250 should all receive a course of therapy regardless of culture results.
- The more tricky situation is the Monomicrobial fluid with <250 PMN’s. Given that most go on to develop SBP, those patients should receive a course of therapy.
Treatment – what?

• As mentioned previously most cases are gut flora so naturally the abx that would cover those bugs should be used.
• Many studies have been done with varying results as to what is the optimal choice
• Currently a third generation cephalosporin is being recommended -> cefotaxime