ALCOHOLIC LIVER DISEASE (ALD)

Pathophysiology

- ALD is associated with the ingestion of 60 – 80 g/d of ethanol for more than 12 years.
- Alcoholic liver disease is the major cause of liver disease in Western countries.
- 1 out of 12 patients are at risk of cirrhosis with alcohol abuse.
- Likelihood depends on individual susceptibility.
- Increased risk if have poor nutritional status.
- Female gender is at increased risk because of different first pass.
- ALD is characterized as a progressive and chronic condition having 4 stages (steatosis/fatty metamorphosis, alcoholic hepatitis/steatonecrosis, fibrotic changes of cirrhosis, and hepatic failure and death).
- Alcohol is metabolized by the liver, intestinal lumen and pancreas via alcohol dehydrogenase to acetaldehyde then to acetic acid via mixed function oxidase.
- The production of acetaldehyde and mixed function oxidase system require NADH – NAD+.
- An increase in the ratio of NADH:NAD+ leads to increase in fatty acid synthesis, and accumulation in cells. This leads to an increase in lactic acid, and increase collagen formation (decreases pH, decreases uric acid excretion).

Sign and Symptoms

- Scleral icterus
- Spider angiomata
- Palmer erythema
- D tosted liver
- Palpable spleen
- Gynecomastia
- Increased bilirubin
- Increased Alt/AST
- GGTP increases, specific for liver disease
- Decreased serum albumin (as low as 2 g)

Complications of ALD

- Steatosis: seen in biopsy – hepatocytes (and surrounding central vein – centrilobular) are filled with lipid containing vesicles.
- Steatonecrosis: lysis – necrosis of fatty cells which causes an immune response.
- Alcoholic hyaline/Mallory bodies – intracellular eosinophilic perinuclear inclusion bodies as seen in severe cases.
- Cirrhosis – complication of terminal ALD: occurs because of fibrotic changes decreasing the integrity of the liver and decrease in parenchymal mass and decreased liver function. It is destruction of hepatocytes and normal cells, which get replaced with fibrates.
- Portal hypertension: occurs because of increased mechanical resistance to blood flow through liver. With damage there is increased pressure in the liver, spleen and GIT. Portal hypertension increases fibrotic tissues which increase resistance, as a result ascites occurs. Increased pressure in esophagus leads to esophageal varices (build up fluid can cause varices throughout the body).
- Esophageal/Gastric Varices: Because of hypertension there is a pooling of blood in the spleen/mesenteric vein and artery which leads to increased blood in the small capillaries along the GI. Breakdown of the gastric mucosa leads to increased damage from acid and pepsin in the stomach and esophagus due to the toxic effects on the mucosal surface.
- **Decreased liver functions**: Occurs because of decreased parenchymal mass, loss of basic hepatocyte function, decreased protein synthesis, and decreased liver ability to handle drugs and endotoxins. Decreased albumin production occurs, thus decreased drug binding and decreased oncotic pressure. Leads to increased bleeds because of decreased production of vitamin K. Decreased detoxification of ammonia occurs.

- **Hepatic Encephalopathy (HE)**: is a complex neuropsychiatric syndrome with signs and symptoms of neurologic impairment that occurs in cirrhotic patients. The symptoms are thought to result from an accumulation of gut-derived nitrogenous substances in the systemic circulation. These substances then enter the CNS and result in a loss of consciousness and behavior. Serum ammonia levels are poorly correlated with grade of HE. There are three forms, acute, chronic, and subclinical.

- **Coagulation Defects**: Complex coagulation derangements can occur in cirrhosis. These include the reduction in the synthesis of coagulation factors and the clearance of activated clotting factors. There is a decrease in platelets. The net effect of these events is the development of bleeding diathesis.

- **Ascites**: is the pathologic accumulation of lymph fluid within the peritoneal cavity. It is one of the most signs of cirrhosis. The development of ascites is related to systemic arterial vasodilatation which triggers baroreceptors and then finally activation of rennin – angiotensin system with sodium and water retention.

- **Spontaneous Bacterial Peritonitis (SBP)**: Patients with documented or suspected SBP should receive broad spectrum antibiotic therapy to cover E. coli, K. pneumonia and S. pneumonia.

### Goal and Treatment outcome
- Clinical improvement or resolution of acute complications such as **variceal bleeding**, and resolution of hemodynamic instability for an episode of acute variceal hemorrhage.
- Prevention of complications, achieving adequate lowering of portal hypertension with medical therapy using β blockers, or supporting abstinence from alcohol.
- Identify and eliminate the cause of cirrhosis (e.g., alcohol abuse). The treatment of ascites secondary to portal hypertension includes abstinence from alcohol, sodium restriction, and diuretics. NaCl should be restricted to 2 g/d.
- Assess the risk of variceal bleeding and begin pharmacologic prophylaxis where indicated.
- HE is a common complication of cirrhosis and requires clinical vigilance and treatment with dietary restriction, elimination of CNS depressants, and therapy to lower ammonia levels.
- **Cefotaxime**, 2 g IV q 8 h or similar third generation cephalosporin is the drug of choice for SBP.
- **Ofloxacin 400 mg PO q 12 h** is equivalent to intravenous cefotaxime in terms of resolution of infection as well as survival.
- In patients with acute HE, **limit protein intake to 10 – 20 g/d** while maintaining total caloric intake. Lactulose is initiated at **45 ml q 1 hr** until catharsis begins. The dose is then decreased to 15 – 30 ml 4 times daily and titrated to produce two to four soft, acidic stools per day.
- With chronic HE, initiate lactulose at 30 – 60 ml/d with titration to the same end point. Neomycin and metronidazole is reserved for those patients who have not responded to diet and lactulose.

### Pharmacological Therapy

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<tr>
<td><strong>Propranolol (Inderal)</strong></td>
<td>Nonselective β adrenergic blocker, mainstay of primary prophylaxis, prevention of re – bleeding, and treatment of variceal hemorrhage. Dosed as 10 mg PO TID Titrated to a reduction in resting HR of 20 – 25%, absolute HR of 55 – 60 bpm or development of adverse effects. Onset is 1 – 2 hours and duration of 6 hours. Blocks adrenergic dilatory tone of mesenteric arterioles, decrease portal inflow and portal pressure. Therapy should be life long unless not tolerated.</td>
<td>Bleeding can occur when abruptly discontinued. Bradycardia Bronchospasm. Vivid dream Impotence Mask</td>
<td>Extreme caution in asthmatic patients. Heart rate decreases when used with digoxin, verapamil and diltiazem.</td>
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<td>Drug</td>
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<td>Nadolol (Corgard)</td>
<td>Reduces mortality. Nadolol dosed as 20 mg PO once daily. Onset of action is 2 – 4 hours and duration is 17 – 24 hours.</td>
<td>hypoglycemia</td>
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<td><strong>MANAGEMENT OF ACUTE VARICEAL HEMORRHAGE</strong></td>
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<td>Somatostatin</td>
<td>Vasoactive drugs used in early stage to stop bleeding. In GIT, inhibits glandular secretion, neurotransmission and smooth muscle contractility, producing mesenteric vasoconstriction. Stops or slow bleeding early in patient management, allow stabilization and permit endoscopy. Decrease splanchnic blood flow, decrease portal and variceal pressures. Given by IM and PO route. Onset IM is 15 minutes and PO is 30 – 60 minutes. Octreotide is more potent than somatostatin. IV bolus is 50 – 100 mcg followed by continuous infusion is 25 mcg/h up to max. 50 mcg/h. Onset is 2 – 3 weeks and time to peak is 1 – 3 hours.</td>
<td>Not significant. Monitor hypo or hyperglycemia when injecting octreotide.</td>
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<td>Octreotide (Sandostatin)</td>
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<td>Terlipressin (Glypressin)</td>
<td>Glycl residues are enzymatically cleaved in vivo, slow conversion into lysine vasopressin. Synthetic prodrug of vasopressin, has intrinsic vasoconstrictor activity, greater decreased measured variceal pressure and maintained ↓ed variceal pressure. Onset is 2 – 3 weeks and time to peak is 1.5 – 3 hours.</td>
<td>Sedation</td>
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<td><strong>MANAGEMENT OF Portal HYPERTENSION AND ASCITES</strong></td>
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<td>Spironolactone (Aldactone)</td>
<td>Inhibits aldosterone, decrease fluid retention, and blood pressure. Weak K+ sparing effects. Used for prevention of re-bleeding in combination with β blockers in patients who fail to achieve sufficient decrease in portal pressure with β blockers alone. Starting dose is 100 – 200 mg/d with gradual increase up to maximum 400 mg/d q 5 – 7 days. Time to peak is 1 – 3 hours.</td>
<td>Drowsiness Lethargy Headache Hyperkalemia Gynecomastia Caution with K+ sparing diuretics.</td>
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<td>Furosemide (Lasix)</td>
<td>Increase Na+ excretion to 20 – 25% of filtered load of Na, enhance free water clearance, maintain efficacy unless renal function is severely impaired (CrCl &lt; 5 ml/min). 40 mg daily, then increase daily by 20 – 40 mg until diuresis is achieved up to maximum 160 mg/d in divided dose. Goal is 0.5 kg maximum daily weight loss.</td>
<td>Electrolyte depletion Hypotension and azotemia. Dose related rash and ototoxicity. Hypokalemia may predispose to digoxin toxicity. May have increased risk for lithium toxicity.</td>
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