Microvesicular Disease

DILI  
- Aspirin (Reye’s Syndrome)  
  - Aspirin use in pediatric pt w/ febrile viral infection esp Chicken Pox or Influenza  
  - Sx: after 3d there is abrupt onset of intractable N/V, delirium, stupor, seizure, coma, death (50% mortality)  
  - Tx: supportive care  
  - NB very uncommon these days as most mothers are taught by their pediatricians to never give aspirin to children  
- HAART  
- Valproic Acid

Acute Fatty Liver of Pregnancy
Jamaican Vomiting Syndrome
Congenital Defects of Metabolism

Macrovesicular Disease

More Suggestive of AFLD vs NAFLD: malnourished, AST>ALT, high GGT, no metabolic syndrome, less severe steatosis, greater iron deposition, more cholestasis, Mallory Bodies

Alcoholic Fatty Liver Disease (AFLD)  
- Mechanism  
  - Increased TGL synthesis, reduced lipid transport proteins, decreased beta oxidation, damaged proteasome function, abnormal methionine metabolism which subsequently affects the methylation of a variety of compounds used to make DNA/RNA/protein, etc  
  - TNF mediated inflammation by Kupffer Cells  
- General Alcohol Metabolism  
  - Alcohol Dehydrogenase (ADH, stomach) converts ethanol (drunk state) to acetaldehyde (sick state w/ flushing, tachycardia, N/V)  
    - NB CYP-2E1 (liver) also converts ethanol to acetaldehyde and is upregulated several fold in chronic alcoholics  
    - NB some alcohol makes its way to the colon where colonic bacterial ADH breaks it down making acetaldehyde which acts as a cathartic causing “beer shits”  
  - Aldehyde Dehydrogenase (ALDH, liver) converts acetaldehyde to acetate (no effect)  
    - NB ALDH polymorphisms with variable activity levels exist (eg. Asians have 50% activity leading to accumulation of acetaldehyde (“Oriental Flush Syndrome”))  
    - NB disulfiram (Antabuse) inhibits ALDH  
  - Acetate Kinase (brain) converts acetate to adenosine (dilates blood vessels causing a migraine like headache)  
  - HOW TO TREAT A HANGOVER? slowly raise sugar w/ oatmeal and drink lots of water the night before and the next morning sip caffeinated coffee to constrict blood vessels  
- Effect of Ethanol  
  - Interpolates into Cell Membranes resulting in increase fluidity which...  
    - results in the effect of “drunkenness”  
    - can cause cerebellar degeneration  
  - Converted to Acetaldehyde which... (this is the metabolite that is dangerous to the liver)  
    - increase NADH and thus less need to make glucose and thus hypoglycemia  
    - converts into acetyl-CoA which increases FA synthesis leading to steatosis  
    - binds proteins, DNA, etc. which causes hepatitis  
    - depletes antioxidants  
    - decreased methionine, SAM, folate w/ increased homocysteine  
  - Thiamine Deficiency resulting in Wernicke-Korsakoff Syndrome  
  - Testicular Atrophy  
  - Mallory-Weiss Syndrome  
  - Dilated CM  
  - Aspiration PNA  
  - Pancreatitis  
  - Anorexia, Malabsorption, Catabolic State  
- Epidemiology  
  - 12th most common cause of death w/ ½ due to liver disease  
  - RFs: female (generally do worse)  
- S/S  
  - Amount of alcohol needed to begin causing changes to the liver  
    - >80-80g/d = 4-8drinks/d ×5yrs F-M  
    - 1 drink = 12oz beer = 5oz wine = 1.5oz 80 proof liquor = 10g of ethanol  
    - Legal BAL: 80mg/dL = 0.08% (decreases by 20% Qhr)  
  - Acute Alcohol Intoxication/Withdrawal
- Alcohol Fatty Liver Disease – AFLD (usually asymptomatic but sometimes mild pain/HM, mild increases in LFTs with just hepatomegaly, reverses quickly w/ abstinence) 75% 5yrs survival
  - Can resolve w/ abstinence after a few weeks
- Chronic-to-Acute Alcoholic Steato Hepatitis – ASH (highly variable from asymptomatic w/ features of chronic liver dz w/ malaise, anorexia, etc to fulminant dz w/ Sx of pain, fever, N/V, jaundice w/ cholestatic LFTs, etc, always characterize as chronic or acute and if acute then use DF to characterize how bad, refer below for immediate survival) 65% 5yrs survival
  - Major Increase in LFTs
    - <500mg/dL
      - Why low levels? alcoholics are deficient in VitB6 which is needed to make AST & ALT thus if higher levels then other coexisting liver dz must be investigated esp concurrent Tylenol intoxication
    - AST/ALT >2
      - Why >L? b/c there is selective damage to mitochondria which hold AST
    - High GGT
    - Leukemoid Leukocytosis
      - NEVER called ALF b/c EtOH is always chronic therefore always call it “decompensation” nevertheless it looks just like ALF w/ HE, high INR, very high TB
- Laennec’s Cirrhosis 40% 5yr survival
  - ONLY 20% of men drinking >120g/d will develop cirrhosis at 10yrs (the big question is why???)
  - Some pts p/w cirrhosis w/o any clear h/o AFLD/ASH

- Risk Factors for Progression
  - Dose, Duration, Gender, Female, Obesity, Iron Overload, Viral Hepatitis, PNPLA3 Genotype
- Bx
  - Alcohol Fatty Liver Disease: Macrovesicular Steatosis
  - Acute on Chronic Alcoholic Hepatitis: Mallory Hyaline Bodies, Hepatocellular Disarray, Perivenular Neutrophilic Infiltration, Ballooning Degeneration
  - Alcoholic Cirrhosis (refer)
- Treatment
  - Acute Intoxication/Withdrawal
    - <24hr post last drink tremulousness/irritability/hyperadrenergic state “The Shaker”
      - Place pt in calm environment w/ sitter
      - Chlorodiazepoxide (Librium) 25mg PO TID and then taper
      - Thiamine 100mg IV/IM x1 then 100mg PO QD
      - Folate 1mg SC x1 then 1mg PO QD
      - MVI 1tab PO QD (pts are low in multiple vitamins)
      - Haldol if psychotic features
      - Correct Electrolytes esp Mg/Phos/K
      - some just give Banana bag (add thiamine 100mg, folate 2mg, one MVI to each 1L bag of IV fluids)
      - Boost w/ each meal but watch for refeeding syndrome
      - Naltrexon/Acamprosate can help reduce EtOH cravings
    - ½-2d post-last drink: mix b/t above and below “Rum Fits”
    - 2-7d post-last drink: seizure/AMS/autonomic instability “Delirium Tremens” (20% mortality if unTx)
      - Ativan (Lorazepam) 1-4mg IV Q4-6hrs p/r agitation
      - No AEDs
      - Medical emergency as 50% mortality
  - Alcoholic Fatty Liver Disease (AFLD)
    - Encourage abstinence or even reduction as has been shown to be helpful
    - Good Enteral Nutrition
    - Chemical Dependency (CD) Consult
    - Disulfiram (Antabuse) inhibits aldehyde dehydrogenase resulting in accumulation of acetaldehyde thus precipitating the same reaction that is seen in Asians (flushing, N/V), it can be aborted by VitC and antihistamines
- Other Drugs: Balcofen (improves abstinence decreasing likelihood of recurrence)
  - Chronic-to-Acute Alcoholic Steato Hepatitis (ASH)
    - Maddrey and Bolintii’s Discriminant Function (DF) = 4.6(PT-Control) + Total Bilirubin
      - If <32 (20% 1mo mortality) then pentoxifylline (Trental) 400mg PO TID x1mo which inhibits TNF production
      - If >32 (60% 1mo mortality) or encephalopathy, MELD >18, Glasgow Alcoholic Hepatitis Score >9, then Methylprednisolone 32mg PO QD x4wks followed by a taper (20mg QD x7d, 10mg QD x7d), at 7d check TB and if still increasing then stop (prednisolone is recommended b/c it does not require hepatic metabolism for activation) decreased 1mo mortality to 5%
        - Exceptions: GI, pancreatitis, renal failure, active infection (must rule out with cultures before why? b/c excluded in the studies)
  - NB it was found that TNF/TGFBeta from Kupffers cells was integral in inflammatory process so studies looked at anti-TNFs but it was found that those pts had a higher mortality 2/2 increased infections b/c TNF is also needed to regenerate hepatic tissue hence not used therefore just a general anti-inflammatory like prednisolone is most effective
  - Always r/o Budd-Chiari Syndrome b/c they can look very similar w/ hepatomegaly and failure to visualize hepatic veins on US and rapid course!!!
  - Nutrition is VERY IMPORTANT always place an NGT and give TF
  - The Lille Model (based on age, bili on Day 0 and 7, Cr, Alb, PT) generates a number and when it is >0.45 then risk of survival at 6mo is 25% vs 85% if >0.45

  - Laennec’s Cirrhosis
    - Liver Transplant only if pt has been abstinent x6mo and must be involved in ongoing alcohol cessation program before even being considered for transplant
    - Pts can have labs that look like hemochromatosis
    - Decompensation is sometimes precipitated by viral infection (Influenza, HAV/HBV/HCV)
    - Faster progression w/ HCV, obesity, smoking
    - Antioxidants (VitE, Silymarin, SAM) were looked at but not effective

Non Alcoholic Fatty Liver Disease aka NAFLD
- History
  - “Lardaceous Degeneration” of the liver described in 1879 but first well characterized by Ludwig at Mayo Clinic in 1980 coined the term NASH
- Mechanism
  - Metabolic Syndrome → Insulin Resistance, High Leptin, Low Adiponectin → First Hit: Fat Deposits in Liver (NAFLD) → Second Hit: Mitochondrial Oxidative Stress and Cytokine Alterations esp High IL-6 and TNF-Alpha → Inflammation (NASH) → Fibrosis (Cirrhosis)
  - New RFs for NAFLD
    - Alteration in gut flora (increase in proteobacteria) with resultant formation of endotoxins
    - Polymorphism of adiponutrin (PNPLAS)
- Epidemiology
  - NASH is the most common liver disease in the US affecting ¼ of all adults b/c of the multitude of causes
  - Ethnicity: Hispanic > White > AA
- Etiology
  - 1ª Metabolic Syndrome (Abdominal Obesity w/ Waist >102/88cm for M-F, Impaired Fasting Glucose >110-126mg/dL, Hypertriglyceridermia >150mg/dL, HDL <40/50 mg/dL for M/F, HTN >135/85)
  - DILI: Amiodarone (asympt abnl LFTs to steatohepatitis to ALF, chronic dz to cirrhosis, importantly liver dz progression can occur despite discontinuation b/c amio concentrates in the liver, hyperdense liver on CT), Cytotoxic Chemo, Estrogens/Tamoxifen, Glucocorticoids, HAART, Certain Metals, Work-Exposure Agents, Diltiazem, Tetracycline
  - Liver Diseases: Genotype 3 HCV, Wilson’s/Hemochromatosis, Budd-Chiari Syndrome, Inborn Errors of Metabolism
  - Surgeries: Jejuno-Ileal Bypass, Gastropasty, Biliopancreatic Diversion, Extensive Small Bowel Resection
  - Other: Acute Starvation w/ Rapid Weight Loss, TPN, Bacterial Overgrowth, Celiac Disease, HIV or other Lipodystrophy, Abetalipoproteinemia, Pregnancy, PCOS, Hypothyroidism, Any Chronic Inflammatory Disease
  - *** high risk of NASH after liver transplant b/c of prednisone, increased weight, DL from cyclosporine/sirolimus, DM from tacrolimus ***
- S/S
  - Non Alcoholic Fatty Liver Disease – NAFLD (Steatosis)
    - 20% of the general population
    - 75% Asymptomatic vs 25% Mildly Symptomatic (fatigue, malaise, RUG pain, hepatomegaly)
    - Mild increase in LFTs (ALT>AST as opposed to alcoholic liver disease)
    - No increase in M&M aside from comorbid conditions
    - 20% of NAFLD pts develop NASH at ~10yrs
    - Risk Factors for Progression: Older Age, Obesity, Female, AST, HOMA-IR, Superimposed HCV
    - NAFLD Score (www.nafldscoore.com) may be helpful in separating those who are developing fibrosis
- CK-18 may be helpful in separating NAFLD w/ NASH w/o Bx
  - **Acute Non Alcoholic Steato Hepatitis – NASH (" + Zone 3 hepatocellular ballooning, inflammation)
    - 3% of the general population
    - 50% Asymptomatic vs 50% Moderately Symptomatic (similar Sx as NAFLD just a little more intense)
    - Moderate increase in LFTs
    - Increase in M&M w/ questionable increased r/o HCC even if not cirrhotic
    - 10% of NASH pts develop cirrhosis at ~5yrs (higher compared to ALFD)
    - Risk Factors for Progression (same as above)
  - **Cirrhosis
    - consider in cryptogenic cirrhosis aka “burnt-out” NASH
    - often steatosis goes away making dx confusing

- **Dx**
  - Imaging: CT (hypodense consistent during non-contrast phase), US (hyperechoic), MRI (T1 hypointense)
  - NB all imaging are not sensitive
  - NB sometimes steatosis can be focal looking like malignant lesions dx
  - Labs: ALT>AST (however as the dz becomes more advanced w/ scarring the ratio can switch), labs consistent w/ RFs above, Cytokeratine-18 as a marker for NASH
  - Pts have can have elevated ANA, IgA and iron studies w/ + iron staining (likely reflects inflammation rather than contributing to pathogenesis but some studies suggest that depleting iron may have a therapeutic role)
  - Bx: do not so much for Dx but for distinguishing steatosis from NASH/cirrhosis
  - To say non-alcoholic the pt must drink <3-2 drinks/d for M-F

- **Tx (these decrease steatosis/inflammation but not fibrosis)**
  - Reduce RFs above esp stop smoking
  - **Weight Loss via Diet and Exercise**
    - not too quick weight loss b/c can actually make steatosis worse therefore the recommended goal is to lose 1lbs/wk w/ the goal 10% of body weight loss that is all that is actually needed
    - interestingly significant weight loss w/ RYGB does not cause NAFLD
  - **Meds**
    - VitE 400IU PO BID <2yrs for non-diabetic pts (tackles the second hit, long term safety and efficacy unclear, increased r/o all cause mortality with high doses, prostate cancer)
    - Pioglitazone 45mg PO QD <2yrs for diabetic pts (tackles the first hit, long term safety and efficacy is unclear, increased r/o CV events, bladder cancer, fracture, weight gain, not any better/safer than VitE = therefore consider only if very advanced dz and some don’t use it at all)
    - Questionable Helpful: URSO, Statins, Coffee, L-Carnitine, Pentoxyfilline, VitD, Fish Oil
  - Not Helpful: Metformin

- **Other**
  - Iron Depletion

- **Complications**
  - Higher r/o CV disease and cholangiocarcinoma along w/ HCC