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

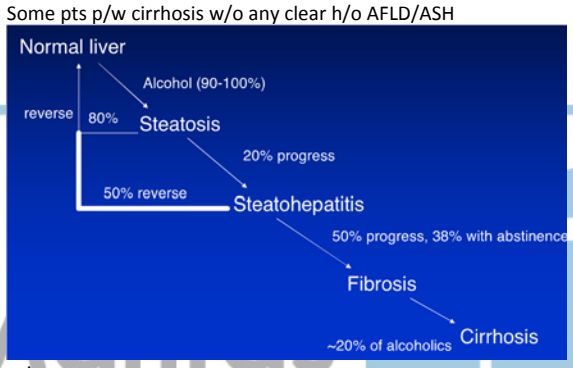
Macrovesicular Disease

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
    - >40-80g/d = 4-8drinks/d x5yrs F-M
    - 1 drink = 12oz beer = 5oz wine = 1.5oz 80 proof liquor = 10g of ethanol
    - Legal BAL: 80mg/dL = 0.080% (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/ cholestasis LFTs, etc, always characterize as chronic or acute and if acute then use DF to characterize how bad, refer below for immediate survival) 65% 5yr 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 S>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
    - <1/2d post-last drink: tremulousness/irritability/hyperadrenergic state "The Shakes"
      - Place pt in calming environment w/ sitter
      - Chlorodiazepoxide (Librium) 25mg PO TID and then taper
      - Thiamine 100mg IV/IM x1 then 100mg PO QD
      - Folate 1mg IV/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 "Delerium Tremens" (20% mortality if unTx)
      - Ativan (Lorazepam) 1-4mg IV Q4-6hrs prn 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 Boitnott'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: **GIB, pancreatitis, renal failure, active infection** (must rule out with cultures before) why? b/c excluded in the studies
            - NB it was found that TNF/TGF-beta from Kupffer 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 coining 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 (PNPLA3)
- Epidemiology
    - NAFLD 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
    - **1° Metabolic Syndrome** (Abdominal Obesity w/ Waist >102/88cm for M-F, Impaired Fasting Glucose >110-126mg/dL, Hypertriglyceridemia >150mg/dL, HDL <40/50 mg/dL for M/F, HTN >130/85)
    - DILI: **Amiodarone** (asymp 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, Gastroplasty, 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, RUQ 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.nafldscore.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 lesionsdx
    - 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 cholangiocarcinona along w/ HCC