Starting Line

Top GI Topics for 2013
- Nonalcoholic fatty liver disease
- Probiotics
- Hepatitis C
- Celiac Disease
- Clopidogrel and PPI's
- GERD updates
NAFLD
- Steatosis w/o secondary cause
- Without significant inflammation/fibrosis
- Most common liver disease
- Prevalence 20-51% in the US
- Increasing over time

NASH
- Hepatic inflammation
  - Ballooning hepatocytes
- With or without fibrosis
- Difficult to distinguish from ETOH on path
- Prevalence 3-5%
- Cirrhosis 20%
- Leading cause of cryptogenic disease

Secondary Causes
- Macrovesicular steatosis
  - ETOH
    - >21 drinks per week in men
    - >14 drinks per week in women
  - Hepatitis C genotype 3
  - Wilson’s disease
  - Starvation
  - TPN
  - Lipodystrophy
  - Abetalipoproteinemia
  - Medications
    - Amiodarone, MTX, tamoxifen, corticosteroids
Secondary Causes
- Microvesicular
- Reye’s
- Antiretroviral meds
- AFLP
- HELLP
- Inborn errors of metabolism

NASH Pathology
- NASH
- NASH with fibrosis

NASH Cirrhosis
Associated Disorders
- Metabolic syndrome
- Obesity elevated BMI and visceral fat are risk factors for fibrosis
- Hypertension
- Dyslipidemia- prevalence of 50%
- High TG > 150 and low HDL < 40 in men
- Insulin resistance
  - 69% prevalence found on US
  - 67% with fatty infiltration had histologic confirmation
- Metabolic syndrome is associated with increased risk of fibrosis
  - Odds ratio of 3.5
- Increased prevalence of fibrosis also seen in:
  - Male, older, hispanic

Pathogenesis of Steatosis
- Primary cause is insulin resistance
- Excessive TG accumulation
- Second hit hypothesis
  - Additional oxidative injury leads to necroinflammatory component
  - Iron deposition
  - Antioxidant deficiencies
  - Intestinal bacteria
- Visceral adipose tissue associated with inflammation and fibrosis
  - Independent of insulin resistance

Clinical Manifestations and Physical findings
- Fatigue
- Malaise
- RUQ abdominal discomfort
- Hepatomegaly
  - 18%
Who to evaluate

- Hepatic steatosis detected on imaging
- Abnormal liver biochemistries
- Screening is not recommended in high risk individuals
  - Obesity, diabetes or hyperlipidemia
  - Including family members
    - 18% risk of affected first degree relative

Laboratory Findings

- AST and ALT elevations
  - 2-5 times upper limit of normal
  - AST/ALT ratio < 1
- Transaminases may be normal in NAFLD
- Degree of elevation doesn’t reflect severity
- Alkaline phosphatase may 2-3 times abnormal
- Albunin and bilirubin typically normal
- Serum Ferritin > 1.5 x normal
  - NASH and advanced fibrosis
- Elevated autoantibodies ANA >1:160, SM>1:40
  - 21% present, not associated with advanced histology

Diagnosis

- Diagnosis requires all 3 criteria
  - Steatosis by imaging or biopsy
  - Exclusion of significant ETOH consumption
  - Exclusion of other causes
- Biopsy is required
  - Diagnosis questioned
  - Determine the degree of fibrosis
  - Only way to differentiate NAFLD and NASH
Diagnosis
- Exclude other disorders
  - Viral hepatitis serologies
  - Iron studies
  - Mildly elevated ferritin is common
  - Consider checking HFE gene study
  - Autoimmune serologies elevations are common
- ANA > 1:160 or SMAB > 1:40
- Consider further evaluation if high transaminases and globulin
- Consider testing if history indicates
  - Wilson’s disease
  - Thyroid d/o and Celiac disease
  - A1AT
  - Budd-Chiari

Radiographic Diagnosis Ok
- Imaging consistent with fatty infiltration
- Exclusion of other causes
- No signs or symptoms of cirrhosis
- Patient is not at an increase risk for advanced fibrosis
  - Younger
  - Nondiabetic
  - Normal ferritin

Diagnosis Imaging
- Ultrasound hyperechoic
  - Sensitivity 85%
  - Specificity 94%
- CT has poor sensitivity
  - Noncontrast 33%
  - Contrast 50%
  - Specificity 100% and 83%
- MRI low specificity 63%
  - Sensitivity 88%
Who to Biopsy
- Liver biopsy is the gold standard
- Unclear Diagnosis
- Evidence of Cirrhosis or degree of fibrosis
- Risk for advanced fibrosis
  - Evidence of cirrhosis
    - Cytopenias, splenomegaly, decompensation
    - Serum ferritin > 1.5 x normal
    - >45 years with obesity or DM
    - Metabolic syndrome

Histologic Findings
- Steatosis
- Inflammation
- Cellular injury
- Fibrosis
  - Minimum Criteria >5% steatotic hepatocytes
  - Typically macrovesicular
  - May be indistinguishable from ETOH

Natural History
- NAFLD may progress to cirrhosis
  - Steatosis
  - Steatohepatitis
  - Fibrosis
  - Simple Steatosis low risk for fibrosis
    - Overall increase in mortality
    - Cardiovascular disease most common cause of death
    - NASH higher risk for significant fibrosis
      - Increase liver mortality rate
      - 10 year survival rate 81.5%
Risk Factors for Progression

- No inflammation: 17% developed advanced fibrosis
  - Developed in 13.4 years
- Inflammation: 49%
  - Developed in 4.2 years

Risk Factors for Progression

- Age > 45
- Diabetes mellitus
- Aminotransferase levels > 2 x uln
- Ballooning + Mallory hyaline or fibrosis
- BMI > 28
- Coffee consumption associated lower risk
- Heavy ETOH consumption

Management

- Weight loss is the primary treatment
- Recommended overweight and obese
- Shown improvement in:
  - LFT's
  - Histology
  - Serum insulin levels
- Goal 5-10% weight loss
  - 1-2 pounds per week, avoid rapid weight loss
  - Exercise 140 minutes per week
- Increased exercise without diet can reduce steatosis without significant change in weight
**Management Weight Loss**
- RCT 31 overweight and obese with biopsy proven NASH
- Randomized wt loss and exercise 200 minutes/week vs education
- Weight loss program after 1 year higher weight loss 9.3% vs 0.2% counseling arm
- Histologic improvement in NASH (not fibrosis)
  - 72 vs 30%
  - Primarily in those who lost 7%
- Weight loss of 10% may be required to reduce necroinflammation
- *Hepatology 2010; 51 (1): 121  Randomized controlled trial testing the effects of weight loss on NASH*

**Other Management Recs**
- Hepatitis A and B vaccination
- Treatment for DM and Hyperlipidemia
  - Statins are safe in patients with NASH
  - May improve biochemistry and histology
- Vitamin E 400 IU daily in patients with advanced fibrosis
  - Excluding patients with DM and CADz
- ACG guidelines 800 IU/day with NASH
- Avoid heavy ETOH consumption
  - <1 drink per day possibly beneficial

**Vitamin E**
- 247 pts with NASH w/o DM
- Randomized to Pioglitazone 30 mg, Vit E 800 IU/day, or placebo for 96 weeks
- Vitamin E more likely to have improvement in histology index
  - 43% vs 19% placebo
- E-Associated with improved AST/ALT
- Concern of increased overall mortality
  - RCT showed increased risk of prostate cancer
- *NEJM 2010;362(18)  Pioglitzone, vitamin E or placebo for NASH*
Pioglitazone
- Resolution of NASH in the study was seen
  - 47% of patients receiving Pioglitazone
  - 21% in the placebo group
- Associated with weight gain
  - 4.7 kg increase
- Recent meta-analysis of 5 RCT showed improvement in steatosis and inflammation
- Safety concerns: CV disease, CHF, bladder CA
- ACG guidelines can be used for biopsy proven cases

First Finish

Probiotics
- Microorganisms with beneficial properties to the host
  - Live nonpathogenic
- Derived from food sources and supplements
  - Primarily milk
  - Lactobacillus
  - Bifidobacterium
  - Saccharomyces boulardii
- Numerous disease states linked to alteration of flora
- Gut flora altered by
  - Antibiotics
  - Prebiotics dietary components promote growth
  - Probiotics
  - Fecal transplant
Probiotics Slide

Single-organism probiotics

- Escherichia coli 1917 Nissle
- Lactobacillus salivarius UCC-4331
- Lactobacillus reuteri
- Lactobacillus plantarum 299v
- Lactobacillus acidophilus
- Bifidobacterium infantis 35624
- Bifidobacterium longum
- Lactobacillus casei
- Lactobacillus rhamnosus GG
- Bifidobacterium animalis DN-173001
- Saccharomyces boulardii

Composite probiotics

- VSL #3: Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus
- Lacteol Fort: Lactobacillus, lactose monohydrate, anhydrous lactose

Probiotics MOA

- Suppression of epithelial binding by pathogenic bacteria
  - Lactobacillus prevent adhesion or colonization
- Improvement of intestinal barrier
  - Saccharomyces boulardii strain of yeast
  - Inhibits pathogenicity of bacterial toxins
- Modulation of the immune system
- Lactobacillus produces acetic acid lowering pH
  - Inhibits growth of E. Coli and Clostridium spp
- Modulation of pain perception

Probiotics Pouchitis

- Pouchitis occurs after proctocolectomy for UC
  - It is the most frequent complication of IPAA
    - 20% at one year and 50% at five years
- Microflora are altered
  - Increased C. perfringens
  - Fusobacteria are present
  - Lack of Streptococcus
- Antibiotic therapy is beneficial
Probiotics Pouchitis

- VSL #3 (Bifidobacterium, Lactobacillus and Streptococcus)
- 40 patients RCT with chronic pouchitis
- VSL #3 6 gm per day vs placebo
- After 9 months on treatment
  - 15% relapsed vs 100%
  - After stopping treatment
  - All patients relapsed

P Gionchetti Gastroenterology 2000; 119:305

Probiotics Pouchitis

- VSL #3 3 grams (9 billion bacteria) per day for IPAA vs placebo
- 40 patients
- Immediately after ileostomy for 1 year
- VSL group had 10% incidence of acute pouchitis
- Placebo group 40%
- Improvement in quality of life

P Gionchetti Gastroenterology 2003; 124:1202

Probiotics Ulcerative Colitis

- Meta-analysis of RCT in adults with UC
- Compared probiotics vs. mesalamine or placebo
- 578 patients
- No significant difference
- Overall insufficient evidence to support use
- Observational studies were not included with probiotics as adjunctive therapy

K Naidoo Cochraine Daabase Syst Rev 2011:12
Probiotics Crohn’s
- 75 children with Crohn’s in remission
- Treated with Lactobacillus GG vs Placebo
  - In addition to standard therapy
  - Time to relapse was 9.8 months with tx
  - Placebo time to relapse 11 months
- Overall data does not support the use
- Clinical trials varied results

A Bousvaros Inflamm Bowel Dis 2005; 11:833

Probiotics Infectious Diarrhea
- Data is limited
- May reduce the duration and possibly complications
- Meta-analysis of 63 RCT
  - 8014 adults and children with acute diarrhea
  - Reduced stool frequency and duration
    - Duration was reduced by 25 hours
    - Decreased diarrhea lasting >4 days by 59%
  - Lactobacillus and Saccharomyces boulardii
  - Reduced stool frequency on day 2
  - SJ Allen Cochrane Database Syst Rev 2010; 11

Probiotics IBS
- Meta-analysis RCT using Lactobacillus GG vs Placebo
  - Children with abdominal pain
    - Probiotics reduced intensity and frequency of the pain
      - A Horvath Aliment Pharmacol Ther 2011; 33:1302
  - Meta-analysis 16 RCT
    - Most studies had methodologic limitations
    - Bifidobacterium infantis more effective than placebo
      - 362 patient showed significant relief at 4 weeks
    - Modest reduction in symptoms with little risk
    - Overall there is no clear benefit however
Probiotics and Antibiotics
- Preventing antibiotic associated diarrhea
- 9 Studies upon review
  - Odds ratio in favor of active intervention
  - 0.39 with 95% CI with S. boulardii
  - 0.34 for Lactobacilli
- Meta-analysis 2010 of 10 RCT
  - Odds ratio in favor for S. boulardii
  - 0.47 with 95% CI
- Overall evidence supports the use of probiotics
  - de Roock S Clin Exp Allergy 2010:40;103-110

Probiotics and C. difficile
- C. difficile colitis is a further complication
- C. difficile colitis prospective study 150 inpatients
  - Received L. acidophilus and Bifidobacterium
  - C. difficile toxin was positive
  - 2.9% Probiotic group vs 7.25% placebo group
  - All patient regardless of developing diarrhea
  - 46% toxin positive vs 78% of the placebo group
- Supports the use of Probiotics in reducing colonization

Probiotics Adverse Effects
- Side effects: Gas, diarrhea, bloating and hicups
- Infectious Complications
  - Highly immunosuppressed or critically ill
  - Septic Lactobacillus Casei
  - Fungemia S. boulardii
  - Liver abscess Lactobacillus GG
Probiotics Take Home Points
- Definite indication for Pouchitis VSL#3
- Recommended for prevention for C diff.
- Recommended for antibiotic associated diarrhea
- Recommended in infectious diarrhea
  - Lactobacillus species and Saccharomyces boulardii
- Not indicated for IBD
- Consider in IBS patients

Coming In

Hepatitis C Overview
- 180 million people are infected
- Prevalence of 1.6%
- 20-30% will develop cirrhosis
- Primary cause of death in liver disease
- Leading indication for liver transplant
- Mortality will continue to increase
- Most patients with chronic infection are asymptomatic
Hepatitis C Screening
- CDC recommends all people born between 1945 and 1965
- Illicit drug use or intranasal cocaine
- Blood transfusions prior to 1992
- Hemodialysis patients
- Exposure to HCV
- Sexual partner of HCV infected person
- Incarcerated individuals
- Elevated ALT

Hepatitis C Testing
- HCV ELISA testing is 95% sensitive
- May remain positive for years after treatment
- RIBA used for confirmation only
  - If positive check HCV RNA
  - If negative then it is a false positive
  - No further testing is needed
- Check HCV RNA in immunocompromised pts
  - HIV, dialysis, transplant recipients
  - Consider checking at risk patients even if anti-HCV is negative
- If HCV RNA is positive check a genotype

Hepatitis C SOC
- Current SOC for genotype 1
  - Boceprevir or telaprevir
  - Peg-IFN and RBV
  - SVR is 70-75%
  - IL-28B genotype CC 80-90% vs TT 50-66%
- Adverse events
  - Anemia 35-40% on triple therapy
  - Rash 50% with telaprevir
  - GI side effects 25%
Hepatitis C New Treatments
- Fission Study 12 week treatment for chronic hepatitis C
- Treatment naïve Genotype 2 or 3
  - 20% had compensated cirrhosis
- Sofosbuvir once daily HCV polymerase inhibitor with RBV
- Versus standard tx peg-Inf and RBV for 24 weeks
- SVR 67% in both groups
- Side effects higher in peg-inf group
  - Fatigue, HA, nausea, insomnia and dizziness
  - INF arm 11% stopped treatment vs. 1%

Hepatitis C New Treatments
- Neutrinot study genotype 1, 4, 5 or 6
  - 17% compensated cirrhosis
- Sofosbuvir with RBV and peg-inf for 12 weeks versus standard therapy
- 90% SVR with Sofosbuvir treatment
  - 80% SVR in cirrhotic patients
- 60% SVR with standard treatment
- Overall shorter duration & increased SVR
- Expected to be available by mid 2014
Hepatitis C New Treatments
- Ledipasvir with sofosbuvir and ribavirin
- Genotype 1
  - Majority had high viral load
  - 25 noncirrhotic treatment naïve
  - 9 null responders
  - SVR at 12 weeks was 100%
  - No viral breakthrough at end of tx
- Safe and well tolerated
  - Anemia 20%, depression 8% and HA 4%

Hepatitis C
- Treat Now
  - Hepatitis C genotype 2 and 3
  - Genotype 3 more rapidly progressive
  - Easier to treat
  - Genotype 1 with advanced fibrosis or compensated cirrhosis
  - Not a treatment candidate after decompensation
  - Number needed to treat 4-6 for mortality and HCC

Celiac Disease
- Autoimmune disorder
  - Genetically predisposed individuals
    - 46% of the population has HLA-DQ 2&8
    - 99% of celiac patients have the haplotype
  - Immunologic response to gluten antigens
  - Occurs at rates approaching 1% of the population
  - 50% diagnosed under the age of 2
  - Adults typically diagnosed in the 4-6th decade
Celiac disease

Celiac Disease Who to Test
- Gastrointestinal symptoms
  - IBS, bloating, diarrhea, malabsorption
  - IDA, folate or B12 deficiency, elevated LFT's, short stature, infertility, recurrent aphthous stomatitis, recurrent migraines, idiopathic peripheral neuropathy
- Diabetes Mellitus Type 1
- Autoimmune disorders
- First and Second degree relatives of patients dx with CD
- Turner, Down or Williams syndromes

Celiac Disease Testing
- Serologic antibodies used to dx celiac:
  - IgA and IgG anti-gliadin antibodies
  - Second generation AGA tests
  - IgA endomysial antibodies
  - IgA and IgG tissue transglutaminas antibodies
  - Anti reticulin antibodies (not used)
Celiac Disease Testing

- Anti-gliadin antibodies lower sensitivity and specificity
  - Sensitivity 80-90%
  - Specificity 85-95%
- High false positive results 15-20%
- Leads to unnecessary endoscopy with biopsy
- Anti-gliadin test is no longer recommended
- It is included in most celiac panels
- Second generation AGA tests available DGP
  - IgA Sensitivity 94%, Specificity 99%
  - IgG Sensitivity 76-83%, Specificity 97-99%

Celiac Disease Testing

- Tissue transglutaminase
  - Sensitivity 90-98%
  - Specificity 95-97%
- Less costly and easier to perform than EMA
- TIG IgA is my preferred assay
- IgG TIG 40% sensitive and 95% specific
- TIG, DGP and EMA are considered the best screening markers

Celiac Disease IgA Deficiency

- More common in Celiac patients 1:40
  - 2-5%
  - General population 1:400 or <0.5%
- IgA deficient = False negative serologies
- Total serum IgA must be ordered
- If IgA deficiency exists perform IgG assay
Celiac Disease Gluten Free
- Initial step is baseline antibody testing
- If antibody testing is positive- HLA testing
- If antibody testing is negative- HLA testing
- If antibody testing is negative then proceed with a gluten challenge
- If HLA is positive then proceed with a gluten challenge
- 3 grams of gluten for 8 weeks
- Followed by a small bowel biopsy
- Check serology at the end of the challenge
- If negative repeat in 2-8 weeks

Clopidogrel and PPI's
- Conflicting data regarding PPI's potential to reduce the effectiveness of Plavix
- Prodrug requires metabolism P450 enzymes
- PPI's are known inhibitors of enzymes required for the conversion to the active metabolite
- Not all PPI's inhibit CYP2C19 to the same extent

Cogent Study
- 3,873 patients randomly assigned to receive clopidogrel with ASA
- In combination with omeprazole or placebo
- 51 patients had a GI event
  - 1.1% with omeprazole and 2.9% with placebo
- 109 patients had a CV event
  - 4.9% with omeprazole and 5.7% with placebo
- Prophylactic use of omeprazole reduced GI bleeding
- There was no apparent CV interaction with PPI
- Study was terminated early however
**Clopidogrel and PPI’s**
- Systematic review of 10 laboratory studies and 33 clinical studies
- Involving the interaction of PPI’s and Clopidogrel
- 70% of the lab studies in healthy volunteers showed reduction in platelet inhibition
- Same occurred in 61% of patients in studies
- Clinical studies showed marked imbalances leading toward variability in results
- Conclusion that, “an adverse effect of PPI use on clinical outcome in patients on clopidogrel cannot be substantiated.”

**Clopidogrel and PPI’s**
- Randomized clinical trail assessing the affects of dexlansoprazole, lansoprazole, esomeprazole and omeprazole
- 160 healthy subjects
- Less reduction noted in active metabolite and platelet inhibition with dexlansoprazole and lansoprazole
  - Overall, no clinically important impact on antiplatelet activity
  - Frelinger, Andrew JACC, 2012, Vol 59
- Current evidence does not support that PPI’s are associated with adverse CV events

**ACG GERD Updates**
- PPI therapy is a risk factor for C. diff
  - Use with care in high risk patients
- PPI can be used in patient’s with known osteoporosis
  - Hip fracture risk was only present with one additional risk factor
  - Should not influence the decision to treat
- B12 deficiency does not develop in chronic PPI users
  - Except possibly in chronically elderly institutionalized patients
ACG GERD Updates
- Reflux laryngitis should not be diagnosed solely upon findings from laryngoscopy
- Weight loss is recommended for obese patients or those who recently gained weight
- Sulcralfate should not be used in nonpregnant patients
- Screen patients for Barrett’s esophagus
  - Found in 5-15% of patients screened for GERD
  - Risk factors
    - >50 years, male, greater than 5-10 years of symptoms, and caucasian

Summary
- **NASH**
  - Weight loss is the primary treatment
  - Consider Vitamin E and Pioglitazone
  - Statins are safe
  - Probiotics
  - Useful in pouchitis, infectious and antibiotic-associated diarrhea
- **Hepatitis C**
  - New treatment emerging within one year
  - Treat patients now with evidence of significant fibrosis or genotype 2 or 3

Summary
- **Celiac disease**
  - Preferred screening exam is TIG with an IgA level
  - Check HLA DQ 2 and 8 on patient with a gluten-free diet
  - PPI therapy is not contraindicated with Clopidogrel
  - PPIs are safe in patient’s with osteoporosis
  - Screen patients for Barrett’s with appropriate risk factors