Revised Objectives…

• Review of the clinically relevant/common liver conditions in primary practice
  – Swiss cheese vs Kraft single approach
• Work up and investigations prior to GI/Hepatology referral
• Management of the sequelae of chronic liver disease
The Basics…

• Liver enzymes vs liver function tests
  – Bilirubin, INR, Albumin, Glucose

• Pattern recognition
  – Cholestatic  AP/GGT > AST/ALT
  – Hepatocellular  AST/ALT > AP/GGT
  – Mixed
  – Infiltrative AP/GGT with normal bili

• Trend of enzyme abnormality
  – Persistent vs peak and valley
Case 1.

- 54 year old male with history of hypertension, dyslipidemia referred with elevated liver enzymes x 6 months (normal synthetic function, ferritin 330/150, AST 85/45, ALT 54/40, N GGT/AP). Meds - simvastatin, HCTZ. Exam N/ BMI 30. What’s on the differential?

- Viral hep, NAFLD, Drug induced, Hemochromatosis,
Non Alcoholic Fatty Liver Disease (NAFLD)

- Encompasses fatty liver, non-alcoholic steatohepatitis (NASH), NAFLD-related cirrhosis
- Globally the most common liver disease affecting 15-25% of general population
- Most commonly seen in 4th-6th decade
- M=F
NAFLD

• Although can be due to a variety of drugs and toxins, vast majority of cases are due to METABOLIC ABNORMALITIES
• NAFLD is the hepatic manifestation of the metabolic syndrome
• Reproducible correlation between waist-hip ratio, BMI and degree of hepatic steatosis
  – Insulin resistance, dyslipidemia, elevated BMI
NAFLD - Clinical Features

- Usually incidental diagnosis
- Usually asymptomatic, although some may describe dull RUQ pain
- Hepatocellular enzyme elevation (1.5 - 4x ULN with ALT>AST) seen in 50% with steatosis and 80% with NASH
- Serum ferritin elevated in 30-50%
NAFLD

• Imaging helpful - U/S, CT, MRI
• Unable to distinguish steatosis from NASH
  – Histology critical for differentiation
• Natural history largely unknown
  – Benign disease in many patients
  – Progressive in some
  • BMI>28, age>50, AST/ALT ratio>1, ALT>2xULN
  • Hypertriglyceridemia

Likely accounts for most cases of cryptogenic cirrhosis
NAFLD - who to biopsy

• Diagnosis unclear

• Multiple risk factors with persistent significant enzyme abnormalities

• Synthetic dysfunction
NAFLD - Treatment

• Aggressive risk factor modification
  – Diet, exercise, optimal glycemic control etc

• Clinical follow up at 6 and 12 months with assessment of BMI, fasting glucose (HbA1C), chol panel, liver enzymes and function studies

• Consider dietician referral
Case 1. continued…

• Your 54 year old patient returns at 12 months and his liver enzymes are unchanged. BMI now 27. His cholesterol panel has normalized. What next?

• Options include: GI referral and Start vitamin E
Role of Vitamin E

• Pioglitazone, Vitamin E, or Placebo for NASH

• 247 non-diabetic patients with NASH randomized to pioglitazone 30mg OD, Vitamin E 800 IU OD, or placebo for 96 weeks

• 1° outcome - histologic improvement
• 2° outcome - changes in AST/ALT, lipid profile, BMI
Role of Vitamin E

• 1° outcome
  – Vitamin E > placebo (43% vs 19%) - NNT 4
  – Pioglitazone ≈ placebo (34% vs 19%) - ns

• Similar results in 2° outcome measures with both agents meeting statistical significance

• Significant weight gain (average - 4.7kg) with pioglitazone, sustained post discontinuation
Vitamin E - conclusions

• Significant evidence supporting use in non-diabetic NASH patients (along with other measures)

• Excellent safety profile
Alcoholic Liver Disease

- AST>ALT usually >2 (rarely >400-500)
- Increased GGT
- Variable AP
- Increased ferritin
- Variable abnormalities in synthetic function
Hepatitis A

- Fecal oral transmission
- Never chronic
- Member of the 1000+ club
  - Drugs (acetaminophen)
  - Acute biliary obstruction
  - Acute Viral Hepatitis
  - Ischemic hepatitis
- Need to request IgM if acute Hep A suspected
Hepatitis B

- Highly endemic regions - Southeast Asia (excluding Japan), China and much of Africa
  - 8-10% carrier risk
  - 70-80% lifetime risk of infection
- Globally, the major cause of cirrhosis and HCC
Hepatitis B

• Age of infection is the principal determinant of the clinical outcome
  – Neonatal infection - 95% chronic
  – Adult infection - 1-5% chronic

• 25-30% of chronic carriers will have progressive liver disease
Hepatitis B - Natural History

<table>
<thead>
<tr>
<th>Immune tolerance</th>
<th>Immune clearance</th>
<th>Immune control</th>
<th>Immune escape</th>
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</thead>
<tbody>
<tr>
<td>HBeAg+ve</td>
<td></td>
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<tr>
<td>HBV-DNA</td>
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<td></td>
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<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HBeAg +ve chronic hepatitis</td>
<td></td>
<td>Inactive (carrier) state</td>
<td>HBeAg −ve/+ve active chronic hepatitis</td>
</tr>
</tbody>
</table>

< < HBeAg−ve >
Hepatitis B

- Important parameters to follow
  - Liver enzymes
  - Liver function studies
  - HBV DNA
  - Hep Be Ag/ Hep Be Ab

- Early screening for HCC, in the absence of cirrhosis
  - >40 years
  - >30 years, if African
Hepatitis B

• Multiple treatment options
  – Goal is not cure but sustained viral suppression (similar to management of HIV)

Family members should be screened and vaccinated if non-immune.
Hepatitis C

• Need to identify risk factors as majority unaware of infection

• Risk Factors:
  – IVDU, incarceration, PRBC prior to 1992, hemodialysis, tattoos, intranasal cocaine, high risk sexual activity, needlestick injury
Heptitis C - Natural History

100 acute HCV infections

- 20% clearance (HCV+/RNA-)
- 80% chronic infection (HCV+/RNA+)

- 30% severe progressive hepatitis
- 40% variable progression
- 30% chronic nonprogressive
Hepatitis C

• 6 genotypes
  – 1a - 57%
  – 1b - 17%
  – 2 - 14%
  – 3 - 7%
  – 4, 5, 6 < 5%
Hepatitis C

• Treatment
  – Pegylated Interferon and Ribavirin

• SVR (HCV RNA negative 6 mo post Tx)
  rates:
  – G1 - 40-45% with 48wks
  – G2 - 90% with 24 wks
  – G3 - 80% with 24 wks

SVR - sustained virologic response
Hepatitis C

• Pharmacare criteria for approval:
  – ALT > 1.5xULN on 2 occasions 3 months apart
  – Advanced fibrosis on biopsy
  – G2 or 3
Hepatitis C - Promising advances

• New class of protease inhibitors
  – Telaprevir
  – Boceprevir
• Studies reveal increased SVR rate in G1 patients of ~80%
• Realistically still 2-3 years away in Canada
Hepatitis C - Who to treat?

• G2 or G3
• G1
  – If advanced fibrosis, significant hepatitis
  – Otherwise, probably best to monitor and await protease inhibitors
Hereditary Hemochromatosis

• What is the 1st line screening test?

• fasting transferrin saturation
Hereditary Hemochromatosis

- Elevated ferritin (but also seen in viral hepatitis, NAFLD, AFLD)

- Screening test - fasting transferrin saturation
  - If 2 values >0.45, should have genetic testing
Management of Chronic Liver Disease

• The referral package

• Dealing with the sequelae
  – Ascites
  – Encephalopathy

• Prevention of complications
  – Spontaneous Bacterial Peritonitis (SBP)
  – Variceal Bleeding
  – Hepatocellular Carcinoma (HCC)
  – Vaccinations
The Referral Package

• Generic
  – Recent liver enzymes, liver function studies
  – Viral serology - HAV Ab, Hep BsAg, cAb, sAb, HCV Ab
  – Fasting transferrin saturation
  – Abdominal ultrasound
  – Accurate medication profile (including over the counter)
  – ETOH use
• HCV Ab +
  – HCV RNA, genotype
• HepB sAg+/ cAb+
  – HBV DNA, HepB eAg/ eAb
Ascites

- Low salt diet is critical (<2g/day)
- Diuretics
  - Spironolactone:Furosemide (100:40)
  - Amiloride 2.5 - 10mg (also K-sparing but no gynecomastia)
- Monitor lytes and GFR 1-2 wks following any changes and q3 months
- Refractory ascites
  - Large Volume Paracentesis (use albumin support)
  - TIPS

Do not free water restrict unless Na<130 or symptomatic
Encephalopathy

- Early features: day night reversal, mild apraxia, incoordination
- Asterixis suggests more advanced - grade 2
- Treatment:
  - Lactulose (titrate to achieve 2-3 loose BMs/d)
  - Oral antibiotics (metronidazole, rifaximin)
- Identify the precipitant
  - Electrolytes, Constipation, Volume depletion, Protein load, GI bleed, Infection
- Should not be driving
# Child Pugh Score - Prognosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin micromol/L (mg/dL)</td>
<td>&lt;34.2 (&lt;2)</td>
</tr>
<tr>
<td>Albumin g/L (g/dL)</td>
<td>&gt;35 (&gt;3.5)</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>&lt;4</td>
</tr>
<tr>
<td>CPT classification:</td>
<td></td>
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<tr>
<td>Child A: score 5-6 (well compensated)</td>
<td></td>
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<tr>
<td>Child B: score 7-9 (significant functional compromise)</td>
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<tr>
<td>Child C: score 10-15 (decompensated)</td>
<td></td>
</tr>
</tbody>
</table>

1 year survival:

A(5-6pts) - 92%; B(7-9pts) - 70%; C(10+pts) - 35%
SBP

• Fever, abdominal pain
• Rebound tenderness
• Diagnosis confirmed with diagnostic paracentesis
• Secondary Prophylaxis
  – Cipro 750mg OW
  – TMP-SMX 1 DS 5 days per week
Esophageal Variceal Bleeding

• High morbidity and mortality rate
• Secondary prophylaxis
  – Variceal banding
  – Non-selective β-blockade with target of reducing baseline HR by 25%
    • Propanolol, Nadolol, Bisoprolol
HCC Screening

• Start early for Hep B - pre-cirrhosis
  – ?family history
• All Cirrhotics (1-2% annual risk)
  – Abdominal imaging and alafetoprotein
  q6 months

  Do not request radiologically guided liver biopsy unless HCC definitely excluded
Vaccinations

- HAV /HBV
- Influenza
- Pnemovax
Questions