Updates in Chronic Liver Disease

Bertus Eksteen, MBChB PhD FRCP(Lond)
Aspen Woods Clinic, Calgary, Alberta

Disclosures: I will work with any company that improves outcomes for my patients but I will not allow them to dictate the contents of my talk or slides.
Learning Objectives:
1. Develop understanding of the development of cirrhosis, portal hypertension and hepatocellular carcinoma in patients in whom active hepatitis C virus has been eradicated by current drug treatments.
2. Understand the role of sarcopenia in cirrhosis, how to intervene, and the role of biomarkers in cirrhosis.
3. Recognise Primary Biliary Cirrhosis in non-Caucasian populations.

CanMEDS:
Collaborator, Health Advocate, Scholar, Professional, Medical expert
**CSIM Annual Meeting 2018**

**Conflict Disclosures**

**Definition:** A Conflict of Interest may occur in situations where the personal and professional interests of individuals may have actual, potential or apparent influence over their judgment and actions.

“I have the following conflicts to declare

<table>
<thead>
<tr>
<th>Category</th>
<th>Company/Organization</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory Board or equivalent</td>
<td>Gilead, Janssen, Abbvie, Takeda,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobira, Astellas, Lupin, Shire,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ferring, Intercept, Pfizer</td>
<td></td>
</tr>
<tr>
<td>Speakers bureau member</td>
<td>Abbvie, Takeda, Lupin, Intercept,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>Grant(s) or an honorarium</td>
<td>Abbvie, Pfizer, Intercept</td>
<td></td>
</tr>
<tr>
<td>Participating or participated in a clinical trial</td>
<td>Gilead, Shire, Tobira, Takeda, Abbvie,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pfizer</td>
<td></td>
</tr>
</tbody>
</table>
Some of the drugs, devices, or treatment modalities mentioned in this presentation are:

Besafibrate and fenofibrate

I intend to make therapeutic recommendations for medications that have not received regulatory approval.
What about Measles?
1/2000 cost
ION Phase 3 Program (ION-1, ION-2, ION-3) Efficacy Summary

- 97% (1886/1952) overall SVR rate
- 3% (66/1952) did not achieve SVR
  - 1.4% (28) LTFU
  - 0.1% (2) virologic breakthrough (both due to non-adherence)
  - 1.8% (36) relapsed. Patients may be rolled over to a retreatment study
Treatment Aims and Rationale for Patients With HCV and Cirrhosis

Mortality over time in patients with HCV and cirrhosis according to treatment and SVR

SVR is associated with reduced risk of mortality

Beneficial effect of treatment even in the absence of SVR

SVR, sustained virologic response

Reduction in all-cause mortality in patients with SVR

Norah Terrault et al. Management of the patient with SVR. J Hepatology 2016 vol. 65 j S120–S129
Reduction in all-cause mortality in patients with SVR

Norah Terrault et al. Management of the patient with SVR. J Hepatology 2016 vol. 65 j S120–S129
HCV case (Bob 64 year old man)

- Referred to liver transplant 2012.
- Hemophilia B and had a single hemarthrosis in 1980s requiring a blood transfusion.
- Hepatitis C positive and relapsed after interferon and ribavirin therapy
- 2012 – Compensated cirrhosis with esophageal varices undergoing banding
- 2012 – Considered for transplant as a back up for triple therapy with first generation oral antivirals (Telaprevir, IFN and RBV)
- 2012 – Decompensated after 2 weeks with hepatic encephalopathy (Lactulose) and ascites (Lasix/Spironolactone)
- 2012 – Failed to clear HCV virus
- 2012 – Listed for transplant but low MELD
HCV case (Bob 64 year old man)

- Considered transplant at the Mayo clinic due to organ shortages
- Multiple esophageal variceal banding
- 2014 – Sofosbuvir/ledipasvir (Harvoni) and Ribavirin clinical trial with HCV clearance
- 2014 – Re-compensating liver disease with ascites controlled with diuretics and HE controlled on lactulose and rifaximin
- 2014 – Much more energy. Delisted from transplant given improvement.
HCV case (Bob 64 year old man)

What’s next? Discharge?
HCV case (Bob 64 year old man)

- Ongoing varices that require therapy in 2018

- Does still need to take Lasix and Rifaximin but more stable
HCV case (Bob 64 year old man)

Is Bob just unlucky?
Not all fibrosis can be cured by HCV eradication

38 cases with cirrhosis 5 years post SVR – 61% regression
97 cases 5 years post SVR – 45% regression, 48% unchanged and 6% progression

Norah Terrault et al. Management of the patient with SVR. J Hepatology 2016 vol. 65 j S120–S129
HCV eradication in advanced cirrhosis

Factors associated with poor outcomes

Norah Terrault et al. Management of the patient with SVR. J Hepatology 2016 vol. 65 j S120–S129
Hepatic Venous Pressure Gradient (HPVG) and Portal Hypertension post HCV eradication

.... And does not correlate with Fibroscan readings

Hepatic Encephalopathy and Portal Hypertension post HCV eradication

J Romano et al. Journal of Gastroenterology and Hepatology 2018
Variceal bleeding

Some cases can still develop varices but at a lower rate.
SVR Does Not Eliminate Long-term Risk of HCC

Survival outcomes for hepatocellular carcinoma in patients with chronic HCV and advanced fibrosis ± SVR

SVR is associated with reduced incidence of HCC but patients with cirrhosis and SVR still remain at risk for HCC

Cirrhotic patients who achieve SVR should remain under surveillance for HCC

Lifestyle and liver fibrosis

Factors associated with hepatic fibrosis progression in HCV

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-time cannabis use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>1.2</td>
<td>0.5-3.2</td>
<td>.67</td>
</tr>
<tr>
<td>Daily</td>
<td>3.4</td>
<td>1.5-7.4</td>
<td>.005</td>
</tr>
<tr>
<td>Age at contamination (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-40</td>
<td>2.4</td>
<td>1.2-4.8</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;40</td>
<td>10.5</td>
<td>3.0-37.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Metavir activity grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;A2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥A2</td>
<td>5.4</td>
<td>2.9-10.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HCV genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>0.3-3.1</td>
<td>.95</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>1.5-7.7</td>
<td>.005</td>
</tr>
<tr>
<td>4/5</td>
<td>1.2</td>
<td>0.4-3.6</td>
<td>.69</td>
</tr>
<tr>
<td>Disease-time alcohol intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 g/d</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 g/d</td>
<td>2.2</td>
<td>1.1-4.5</td>
<td>.03</td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent to mild</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>2.0</td>
<td>1.0-4.1</td>
<td>.05</td>
</tr>
</tbody>
</table>

Cannabis
- Non and occasional users
- Daily

Alcohol < 30 g/day
- P = .02

Alcohol ≥ 30 g/day
- P = .34

Fibrosis stage ≥ F3 (%)

Age at biopsy:
- 6/55 ≤ 40
- 7/33 > 40
- 11/94 8/13
- 1/10 5/23 10/21 12/20

HE´ZODE ET AL. HEPATOLOGY, July 2005
Assessing severity of liver disease

Fibroscan – ultrasound-based elastography
Assessing severity of liver disease

Fibroscan with Controlled Attenuation Parameter CAP for steatosis

Meta-analysis of individual patient data (n = 2735) comparing histology and controlled attenuation parameter (CAP)

Relevant covariates:
etiology, BMI, diabetes
Assessing severity of liver disease
MR elastography

Accuracy of Predicting Composite Outcomes (Hepatic Decompensation, HCC, CCA, Listing or Receiving LT) in Patients with PSC (N=69)

MRI Elastography

ROC Curves for Comparisons

Kidist Yimam et al. DDW 2016

Accuracy of predicting composite outcomes (Hepatic decompensation or liver transplant listing in patients with PSC (N=69)}
Assessing severity of liver disease

- **Stage 5**: SBP, Bacteremia (49-66% 1-year Mortality)
- **Stage 6**: Renal failure (70% 1-year Mortality)

**Fibrosis Stages**:
- **F1**: Fibrogenesis and Angiogenesis
- **F2**: Scar and X-linking
- **F3**: Thick Scar & nodules
- **F4**
  - **Compensated**: Insoluble scar
  - ** Decompensated**: Stage 3

**HVPG** (Portal Vein Pressure):
- Low
  - **None**
- High
  - >6
  - >10
  - >12
  - >20

**Symptoms**:
- None
- Ascites
- Varices
- Rec VH
- HE
- HRS, SBP, HE

**1-year Mortality**:
- 1%
- 3.4%
- 20%
- >50%

Adapted from Eksteen, B (BADGUT) and D'Amico G, Garcia-Tsao G, Pagliaro L. J Hepatol 2006; 44: 217-231
Assessing severity of liver disease

**Child Pugh Score**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1 (None)</th>
<th>2 (Controlled)</th>
<th>3 (Uncontrolled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Controlled</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>$\leq 33$</td>
<td>34-50</td>
<td>$\geq 51$</td>
</tr>
<tr>
<td>Albumin</td>
<td>$\geq 36$</td>
<td>28-35</td>
<td>$\leq 27$</td>
</tr>
<tr>
<td>INR</td>
<td>$\leq 1.6$</td>
<td>1.7-2.2</td>
<td>$\geq 2.3$</td>
</tr>
</tbody>
</table>

**Survival by Child Pugh Class**

- **CP class A**
- **CP class B**
- **CP class C**

Pooled analysis on prognosis from 118 studies (n=23,797)


**MELD** = Bilirubin & INR & Creatinine

**MELD-Na** = Bilirubin & INR & Creatinine & Sodium

**5vMELD** = Bilirubin & INR & Creatinine & Sodium & Albumin
Assessing severity of liver disease - MELD

Three-month waiting list mortality risk by MELD score.
Assessing severity of liver disease

The frequency of malnutrition in cirrhosis is highly variable and affects between 50%-90% of patients.

Subjective global assessment (SGA) – Physical exam and degree of weight loss
Imaging-based body fat composition
Pulmonary function tests
Sarcopenia and muscle health
Sarcopenia and cirrhosis

Objective measurements of sarcopenia
Sarcopenia and cirrhosis

- Nausea and satiety
  - Ascites
  - Delayed gastric emptying
  - Impaired gut

- Loss of appetite
  Up-regulation of:
  - TNF-α
  - Leptin

- Taste alteration
  - Zinc deficiency

- Hypermethabolic state
  - Systemic inflammation in cirrhosis

- Physical inactivity, Obesity and other endocrine factors

- Alcoholism
  - Poor feeding
  - Low socioeconomic status

- Anorexia and dietary restriction
  - Sodium restriction
  - Reduced protein intake

- Small intestinal bacterial overgrowth
The L3 skeletal muscle index (L3 SMI) is expressed as cross sectional muscle area/height$^2$. Sacropenia is L3 SMI: $\leq 38.5 \text{ cm}^2/\text{m}^2$ for women and $\leq 52.4 \text{ cm}^2/\text{m}^2$ for men.
Sarcopenia and cirrhosis

Cirrhosis

Cirrhosis and HCC

Sarcopenia and cirrhosis

Management:
1. Recognition of sarcopenia
2. Assessment of all cirrhotics for sarcopenia
3. Dietician/ malnutrition clinic assessments
4. 1.5g protein/ kg body weight per day but low sodium
5. Leucine rich amino acids
6. Physical exercise but careful with varices
7. Address barriers to eating – nausea, ascites and NPO!
8. Enteral feeding
Start eating yourself out of cirrhosis!

1 egg = 6g

Half a cup = 14 g

4oz steak = 30g

Chicken breast = 27g

Daily total = 77gram

80kg patient needs 120gram
Need additional 43gram

Protein drinks 2x/day

Vegetarians and Vegans at high risk
Spectrum of immune mediated biliary disease

Primary biliary cholangitis (PBC)
Primary sclerosing cholangitis (PSC) ± raised IgG4
IgG4 disease

Common final result of cholestasis of toxic bile
What is Primary Biliary Cholangitis (PBC)?

- Immune mediated destruction of small bile ductules.
- Mostly affect woman 40-60 years old
- Likely environmental triggers leading to immune mediated biliary inflammation
- Leads to cholestasis (Increased ALP/GGT) and biliary cirrhosis
PBC: Diagnostic markers

- PBC can be confirmed when at least 2/3 criteria are confirmed:
  - Elevated serum alkaline phosphatase level (of liver origin) for at least 6 months
  - Presence of anti-mitochondrial antibodies (AMA) in serum (titer ≥1:40)
  - Liver histology compatible with PBC on liver biopsy (focal bile duct destruction with granuloma formation)

PSC, primary sclerosing cholangitis
PBC, primary biliary cirrhosis
AnkS, ankylosing spondylitis
CAD, coronary artery disease;
CelD, celiac disease;
CholM, cholesterol metabolism;
CroD, Crohn’s disease;
GD, Grave’s disease;
GS, gall stone disease;
IBD, inflammatory bowel disease;
MS, multiple sclerosis;
PID, primary immunodeficiency syndromes;
Ps, psoriasis;
RA, rheumatoid arthritis;
SLE, systemic lupus erythematosus;
SS, systemic sclerosis;
T1D, type 1 diabetes;
TrigM, triglyceride metabolism;
UC, ulcerative colitis;
Viti, vitiligo.
PBC in Calgary

Incidence

Prevalence

Fig. 2. Annual age/sex-adjusted incidence of PBC in the CHR between 1996 and 2002.

Fig. 3. Annual age/sex-adjusted point prevalence rates of PBC in the CHR as of March 31 of each fiscal year between 1996 and 2002.

Myers et al. HEPATOLOGY, Vol. 50, No. 6, 2009
PBC and Mortality

The graph shows the proportion of patients surviving over time based on gender and diagnosis.

- **Canadian females**: Solid line
- **PBC females**: Dotted line
- **Canadian males**: Dashed line
- **PBC males**: Dotted and dashed line

**No. at risk**

<table>
<thead>
<tr>
<th>Gender</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>114</td>
<td>101</td>
<td>96</td>
<td>60</td>
<td>33</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>18</td>
<td>15</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Alberta cases

- 56 year old female
  - Fatigue
  - ALP 550 ALT 120
  - GGT 470
  - Bili 27
  - AMA +
  - ASMA –
  - IgM 6.7

- 48 year old female smoker
  - Obese with BMI 39
  - ALP 80 ALT 55
  - GGT 370
  - US fatty liver
  - AMA +

Classical PBC

Modern PBC
UDCA: Effect on survival (combined data)

- 3 clinical trials; French (n=146), American (n=180), Canadian (n=222)

Graph showing the probability of survival over time for UDCA and placebo. The graph is divided into double-blind and open-label phases.UDCA 13–15 mg/d and Placebo→UDCA are indicated.

Table: UDCA vs Placebo

<table>
<thead>
<tr>
<th>Months</th>
<th>UDCA</th>
<th>Placebo→UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>236</td>
<td>220</td>
</tr>
<tr>
<td>24</td>
<td>273</td>
<td>275</td>
</tr>
<tr>
<td>36</td>
<td>116</td>
<td>87</td>
</tr>
</tbody>
</table>
**FXR agonist - Obeticholic acid (OCA)**

- **FXR agonist**
- **Cholesterol**
- **Primary bile acids (e.g. CDCA)**
- **Hepatocyte**
- **Bile canalicus**
- **Bile acid synthesis**
- **Lipogenesis**
- **Gluconeogenesis**
- **Regeneration**

**FXR agonist**

- **CDCA**
- **NTCP**
- **BSEP**
- **FGF4**
- **FGFR4**
- **OSTα/β**

**OCA (6E-CDCA)**
- Close analog to bile acid CDCA but **100x more potent on FXR**
- Metabolic stability
- First-in-class with novel mechanism of action

**CDCA**
- Endogenous FXR agonist
- Only product approved for PBC
- Displaces more detergent bile acids in pool
- **No FXR activity**

**UDCA**
- Ursodeoxycholic acid
- Epimer of CDCA
- No activity
POISE (OCA in UDCA non-responders): Treatment responders (primary endpoint)

- ALP <1.67xULN and >15% reduction from baseline, and total bilirubin ≤ULN


![Bar chart showing treatment responders for Placebo (n=73), OCA 5-10 mg (n=73), and OCA 10 mg (n=70).]

*P<0.001 vs placebo*

2 year double-blind, randomized, placebo-controlled trial of bezafibrate used off-label in conjunction with ursodeoxycholic acid (UDCA). They randomized patients to either receive UDCA with placebo (n = 44) or UDCA with bezafibrate (n = 48).

- Complete biochemical response placebo 0% and bezafibrate 30%
- ALP decrease placebo 0% and bezafibrate 60%
PPARα agonists (Fenofibrate 160mg)

- Ursodiol 1.5g/day
- Fenofibrate 160mg/day
- GP stopped drugs

Graph showing ALP U/L levels over time:
- 20-Feb-2015
- 20-Feb-2016
- 19-Feb-2017
Case 1

- 36 year old First Nations female
- Admitted with alcoholic hepatitis
- ALT 105, Bili 75, ALP 350
- Family history PBC and Sjogrens
- AMA –
- ANA weak positive, ASMA -, IgG 12
- Liver biopsy – alcoholic hepatitis and PBC
Years of life lost in female BC First Nations

Potential Years of Life Lost Standardized Rate, Females, Status Indians and Other Residents, BC, 1995-2004

Cause of Death
- Accidental Poisoning
- Motor Vehicle Accidents
- Chronic Liver Disease/Cirrhosis
- Suicide
- Cerebrovascular
- Ischemic Heart
- Female Breast Cancer
- HIV Disease
- Homicide
- Lung Cancer
- Pneumonia/Influenza
- Diabetes
- Colorectal Cancer
- Accidental Falls
- Cervical Cancer
- Chronic Lung Disease
- Fire and Flames
- Tuberculosis
- Arteries
- Asthma

PYLLSR Per 1,000 (with 95% CI)


Indications for liver transplantation in British Columbia's Aboriginal population: a 10-year retrospective analysis.

Disproportionate amount of cases with PBC and AIH

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Number of recipients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary biliary cirrhosis</td>
<td>8 (53.33)*</td>
</tr>
<tr>
<td>Autoimmune hepatitis*</td>
<td>4 (26.67)*</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>2 (13.33)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 (6.67)</td>
</tr>
<tr>
<td>Total</td>
<td>15 (100)</td>
</tr>
</tbody>
</table>

\*P<0.001 compared with all liver transplant recipients; \*Includes one patient with autoimmune cholangitis and autoimmune hepatitis overlap syndrome; \*\*P=0.017 compared with all liver transplant recipients

Liver disease in native populations in North America

PBC in Pacific Canada

- Liver Biopsy consistent with PBC 100%
- AMA negative 18%
- Family history PBC 33%
- 5x higher incidence than caucasions
- PBC occurrence in first degree relatives 4%
  (10% woman)
- Other autoimmune 79% - arthritis (60%), thyroid (16%) and SLE (12%)

PBC global prevalence / million

227-402

58-251

62-233

NA

51

78-492

NA

Carlo Selmi. Journal of Autoimmunity 2012
Case 2

- 40 year old Filipino female
- Nurse
- Pemphigus Vulgarus
- HBcAB IgG + and being considered for immunosuppression
- GGT 180, ALP 330
- US – mild steatosis
- AMA –
- ANA +
- Next step?
Summary

• Modern Direct Acting Antivirals cures hepatitis C and saves lives but does not cure cirrhosis and its complications.

• Sacropenia is an important biomarker in cirrhosis – search for it and treat it actively.

• PBC occurs in high rates in aboriginal and Asian populations and is masked by perceptions substance abuse.
  • AMA negative 20% and prominent family histories of PBC or other autoimmunity
# PBC in Calgary

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Data</th>
<th>Reference Range in Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMA/anti-pyruvate dehydrogenase-positive (n = 92)</td>
<td>78% (72)</td>
<td>—</td>
</tr>
<tr>
<td>AMA titer</td>
<td>1:640 (1:160-1:640)</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunoglobulin M (g/L) (n = 70)</td>
<td>3.94 (2.38-6.66)</td>
<td>0.4-3.0</td>
</tr>
<tr>
<td>Liver histologic stage III/IV (n = 39)</td>
<td>28% (11)</td>
<td>—</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L) (n = 83)</td>
<td>274 (157-415)</td>
<td>30-145 (women), 30-150 (men)*</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L) (n = 83)</td>
<td>65 (40-96)</td>
<td>1-40 (women), 1-60 (men)</td>
</tr>
<tr>
<td>Total bilirubin (umol/L) (n = 79)</td>
<td>12 (8-23)</td>
<td>0-20 (women), 0-24 (men)</td>
</tr>
<tr>
<td>Albumin (g/L) (n = 77)</td>
<td>37 (34-40)</td>
<td>33-48</td>
</tr>
<tr>
<td>International normalized ratio (n = 80)</td>
<td>0.9 (0.9-1.0)</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>Creatinine (umol/L) (n = 61)</td>
<td>68 (57-85)</td>
<td>35-100 (men), 50-120 (men)</td>
</tr>
</tbody>
</table>