Welcome to Ask the Experts

Updates in the Management of Chronic Liver Disease
Welcome

**Host**

Veronica LaBeau  
Executive Director  
American Liver Foundation  
Northern California Division
Program Agenda

• Housekeeping
• Introductions
• Presentations
• Audience Q & A with speakers
• Wrap-up
Program Logistics

Orange button
• Collapses window
• Expands window

Asking questions
• Expand the window
• Type your question
• Hit “send”
Presenters

**Chronic Hepatitis B**
Eric W. Chak, MD, MPH
Assistant Professor of Clinical Internal Medicine
UC Davis Medical Center

**Chronic Hepatitis C: Diagnosis & Treatment**
Alicia Gonzalez-Flores, MD
Assistant Professor of Clinical Internal Medicine
UC Davis Medical Center

**Fatty Liver Disease**
Souvik Sarkar, MD, PhD
Assistant Professor, Director of Fellow Research, Division of Gastroenterology and Hepatology
UC Davis Medical Center

**Alcoholic Liver Disease**
Kidist Yimam, MD
Director, Autoimmune Liver Disease Program, Division of Hepatology and Liver Transplantation
California Pacific Medical Center
Chronic Hepatitis B
Eric W. Chak, MD, MPH
Assistant Professor of Clinical Internal Medicine
UC Davis Medical Center
Burden of Disease

- 240 million affected worldwide, mostly from Africa or Asia leading to 800,000 deaths worldwide.
- 850,000 Americans affected leading to 14,000 deaths.
- 340,000 deaths from cirrhosis and HCC/year (all etiologies of liver disease combined)
We are trying to prevent...

- Vertical Transmission
- Chronic Infection
- Liver cancer
- Cirrhosis
- Liver Transplant or Death
Natural History of CHB

- Immune-tolerant
- Immune-Active
- Inactive CHB
- Immune Reactivation

HBeAg+
HBeAg+
HBeAg-
HBeAg-
Caveat #1

In general, evidence of liver damage (either necroinflammation or fibrosis) is a prerequisite to treatment.

Caveat #2

Patients with cirrhosis should be treated even if HBV DNA < 2,000 IU/ml, regardless of ALT level.
Higher HBV DNA is associated with more HCC
Treatment Leads to Fibrosis

A

- Knodell score:
  - 10-14
  - 7-9
  - 4-6
  - 0-3

Baseline: 100%
Year 1: 90%
Year 5: 80%

B

- Ishak score:
  - 6
  - 5
  - 4
  - 3
  - 2
  - 1
  - 0

Baseline: 100%
Year 1: 90%
Year 5: 80%

C

- No histological improvement
- Histological improvement

1: (n=10)
2: (n=126)
3: (n=79)
4: (n=37)
5: (n=19)
6: (n=77)

D

Change in score from baseline:
-6 to 6
**FDA Approved HBV Therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Pregnancy</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN</td>
<td>180 μg/wk</td>
<td>C</td>
<td>Flu-like sx, psychiatric, autoimmune</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>100 mg/day</td>
<td>C</td>
<td>Pancreatitis, lactic acidosis (LA)</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>600 mg/day</td>
<td>B</td>
<td>CK elevation, LA, neuropathy</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5-1 mg/day</td>
<td>C</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10 mg/day</td>
<td>C</td>
<td>Renal Failure, Fanconi’s, DI, LA</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>300 mg/day</td>
<td>B</td>
<td>Renal failure, Fanconi’s, osteomalacia, LA</td>
</tr>
<tr>
<td>Tenofovir AF</td>
<td>25 mg/day</td>
<td>Untested</td>
<td>???</td>
</tr>
</tbody>
</table>
Finite HBV Therapy

• HBeAg-positive patients who seroconvert on therapy may stop therapy
• Must be on therapy for 12 months minimum with normal ALT and undetectable HBV DNA
• Non-cirrhotic

90% will have detectable HBV DNA
38% will flare ALT
Finite HBV Therapy

- HBeAg-negative patients without cirrhosis on therapy for at least 4 years may also be a candidate to stop anti-viral therapy
- At 144 weeks, 62% (13 of 21 patients) remained off therapy
- 4 patients in the TDF-stop group became HBsAg negative during the study
- Critique: Multi-center German study, mostly genotype D
Monitoring Plan

- Comprehensive panel (ALT), HBV DNA level every 6-12 months
- Other labs: HBeAg, HBeAb
- US Abdomen every 6-12 months
- Asian women over 50 years old
- Asian men over 40 years old
Tenofovir Alafenamide (TAF)
TAF may improve bone density and GFR

Agrawal et al. J Hepatol 68:672-681
Take Home Points

• Screen all patients from Asia or Africa (and family members) for CHB (HBsAg). Check ALT and HBV DNA level every 6-12 months

• Knowing the natural history of CHB will guide management (observation, entecavir, or tenofovir)

• Tenofovir disoproxil fumarate (TDF) has been shown to decrease fibrosis and may even decrease HCC, but has been associated with bone/kidney side effects

• Consider stopping therapy in HBeAg negative patients without cirrhosis after at least 4 years of treatment

• Tenofovir alafenamide may decrease bone and kidney side effects associated with TDF
Thank You
Chronic Hepatitis C: Diagnosis & Treatment

Alicia Gonzalez-Flores, MD
Associate Physician, Internal Medicine
UC Davis Medical Center
Orientation to the Presentation

- The following presentation is geared towards patients and caregivers.
- Slides marked with a stethoscope in the right upper corner contain more advanced information that might be useful for health care providers.
Objectives

By the end of this session, you will be able to:

• Understand who should be screened for Chronic Hepatitis C
• Understand how to diagnose Chronic Hepatitis C
• Understand the evaluation needed to treat
• Understand staging of liver disease
• Have a general sense of treatment options
• Understand the follow up of patients who have achieved cure.
• Know when a referral to a specialist is needed
Natural History of HCV

Adapted from Spach, DH: http://www.hepatitisc.uw.edu

60%
Awareness of HCV Infection Status

Screening for HCV
CDC + USPSTF HCV Screening Recommendations

Who should be screened?

- Persons who ever injected illegal drugs
- Persons with selected medical conditions, including
  - receipt of clotting factor concentrates produced before 1987;
  - ever on chronic (long-term) hemodialysis; and
  - persistently abnormal alanine aminotransferase levels
- Prior recipients of transfusions or organ transplants (before July 1992)
- Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
- Children born to HCV-positive women
- Adults born during 1945 to 1965 (Birth Cohort) should receive 1-time testing for HCV without prior ascertainment of HCV risk.
How Do We Test for the Hep C Virus?

Tourniquet is applied and area is disinfected.

Needle is introduced into vein, blood is drawn into vial and analyzed.

Test Patients Born from 1945 through 1965 for Hepatitis C

- Negative -
No hepatitis C virus infection

- Positive -
Hepatitis C virus infection

Follow-up RNA blood test for hepatitis C virus infection

- Negative -
No further action needed

- Positive -
No further action needed

SOURCE: CDC updated guidance, 2013
Recommended Testing Sequence for Identifying Current HCV Infection

1. **HCV Antibody**
   - **Non-Reactive**
     - **Stop**
       - *Repeat HCV Ab testing if HCV exposure within past 6 months*
   - **Reactive**
     - **HCV RNA**
       - **Detected**
         - **Current HCV Infection**
       - **Not Detected**
         - **No Current HCV Infection**

**Notes**:
- *Repeat HCV RNA testing if HCV exposure within past 6 months or recent HCV infection or has clinical evidence of HCV disease*

CDC 2013
HCV Genotype Distribution in the US

Total = 100
Stages of Liver Disease
Stages of Liver Damage

**STAGE 0**
Healthy liver

**STAGE 1**
Beginning of liver damage

**STAGE 2**
Moderate liver damage

**STAGE 3**
Significant liver damage

**STAGE 4**
Severe liver damage (Cirrhosis)

Ethological factors:
- Alcohol abuse
- Viral infections
- NAFLD
- Others

F0 (Without fibrosis) → Initial fibrosis (F1) → Intermediate fibrosis (F2) → Advanced fibrosis (F3) → Cirrhosis (F4)
Staging of Liver Disease

PHYSICAL EXAMINATION
LIVER FUNCTION TESTS
SERUM HYALURONATE
APRI OR OTHER “SIMPLE TEST”

ULTRASOUND
(FIBROSCAN®)
SERUM MARKERS & ALGORITHMS

FIBROSCAN®
MR-ELASTOGRAPHY*
ARFI*

HVPG

PRIMARY (GP)  SECONDARY  TERTIARY

LEVEL OF HEALTH CARE

HVPG = Hepatic Venous Pressure Gradient; ARFI = Acoustic Radiation Force Impulse Imaging. *These 2 techniques are promising but currently under investigation.

Castera and Pinzani, Gut, 2010
Transient Elastography

Dr. Marion Peters/Hepatitis Web Study
ABC’s of HCV Therapy

- Genotype
- Treatment naïve or experienced
- Staging/Cirrhosis or not
Who to Treat?

Who will benefit the most?

• Mostly everyone!
• Degree of liver fibrosis
• Risk for rapid progression (Co-infection, other liver disease present (NAFLD))
• Extrahepatic Manifestations
• High risk for transmission
Who Not to Treat?

Who will benefit the most?

• Unlikely to benefit if limited life expectancy (<12 months)...
• ...but use your clinical judgement
Evolution of HCV Therapy

1989: HCV identified
1995: IFN α-2b
2000: HCV replicons
2005: Peg-IFNα-2a in HCV/HIV
2010: Peg-IFNα-2b + RBV
2015: Sofosbuvir

Consensus IFN
IFN α-2a
BILN-2061 Phase 1b
In vitro HCV replication
Boceprevir
Telaprevir
IFN-free GT1 DAA regimens
Daclatasvir (EU)
Simeprevir (US)

SVR (%)

Relative misery

Dr. Davis Wyles, 2015 on Slideshare
Current HCV Drugs Class

- **NS5b**
  - "buvir"
  - Sofosbuvir
  - Dasabuvir

- **NS3 PI**
  - "previr"
  - Simeprevir
  - Paritaprevir
  - Asunaprevir
  - Grazoprevir
  - Glecaprevir

- **NS5a**
  - "asvir"
  - Ledipasvir
  - Ombitasvir
  - Daclatasvir
  - Elbasvir
  - Velpatasvir
  - Velpatasvir
  - Pibrentasvir
An American Liver Foundation Webinar Program

hcvguidelines.org
In General...

1. Treatment length is 8-12 weeks.
2. Most regimens are fixed doses (one pill) vs 3 pills
3. Cure rates are very similar for non-cirrhotic/tx naïve (~98% cure rates)
4. Monitoring is very similar for non-cirrhotic patients
5. Side effects are tolerable and rare
Most Common Treatment Options
Monitoring During Therapy

• Clinic visits or telephone contact to assess adherence
• The bare minimum (blood tests):
  – Start: CBC, CMP, INR
  – Week 4: VL
  – Week 24: VL=SVR check
• More frequent monitoring needed if using PIs, or if pt has cirrhosis or if using RBV.
Deciding Which Agent to Use

1. Side effect profile
2. DDI
3. Pill burden
4. Patient’s comorbidities

And everything else being equal:
1. Price
2. Insurance formulary
Following Up After Reaching SVR

- For patients who do not have advanced fibrosis (ie, those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV.

- Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection.
Following Up After Reaching SVR

• Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR.
When to Refer (Special Populations)

- Retreatment of patients who have failed multiple regimens
- Co-infected patients (HIV/HCV or HBV/HCV)
- Decompensated cirrhosis (CPT Class B or C)
- Renal impairment (ESRD, CKD III, renal transplant)
Thank You
Fatty Liver
Souvik Sarkar, MD, PhD
Assistant Professor, Director of Fellow Research, Division of Gastroenterology and Hepatology
UC Davis Medical Center
Fatty Liver Disease or Non-Alcoholic Fatty Liver Disease (NAFLD): A National Crisis

~75-100 Million individual have NAFLD

Approximately 30 million people have the more severe form of the disease, NASH

Almost 10% of all children

Image from Children’s Hospital Colorado
Development of NAFLD

Geneic factors
Epigenetic factors
maternal diet environment
Lifestyles
diet exercise

Cardiovascular disease
Insulin sensitivity
Type II diabetes
Endocrine dysfunctions

Obesity

NAFLD
Hepatic steatosis

The NAFLD Spectrum

Non-alcoholic fatty liver
~70-75% of NAFLD patients

Non-alcoholic steatohepatitis (NASH)
~20-25% of NAFLD patients

~20% of NASH patients
Progress to fibrosis and cirrhosis

Adapted from Rinella, JAMA, 2015
Mortality Risks of NAFL (simple fat) vs NASH

- Among those with NAFLD the major cause of mortality were:
  - Cardiovascular disease (30%)
  - Extrahepatic malignancies (28%)
  - Liver disease (19%)
Fibrosis is an Independent Predictor of Mortality and Liver-Related Morbidities

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Liver-related Events</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.6%</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>1</td>
<td>2.8%</td>
<td>2.4 (0.6-8.9)</td>
</tr>
<tr>
<td>2</td>
<td>7.1%</td>
<td>7.5 (2.3-24.9)</td>
</tr>
<tr>
<td>3</td>
<td>13.7%</td>
<td>13.8 (4.4-43.7)</td>
</tr>
<tr>
<td>4</td>
<td>23.5%</td>
<td>47.5 (11.9-188.6)</td>
</tr>
</tbody>
</table>

Diagnosis

Diagnosis of NAFLD incorporates

• Clinical history
  – Race, Age, Weight, BMI, Co-morbidities

• Laboratory data
  – LFTs (ALT), A1c, Lipid panel, serum markers for fibrosis

• Radiographic data
  – Ultrasound, Fibroscan, MRI

• Liver biopsy if available
Labs: ALT in Patients with NAFLD

- ALT level is not predictive of NAFLD disease severity
- ALT levels can be normal in patients with NASH inflammation or fibrosis

Maximos et al., Hepatology, 2015
## Labs: Selected Serum Markers for Fibrosis

<table>
<thead>
<tr>
<th>NAFLD</th>
<th>Components</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indirect</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIB-4</td>
<td>platelet, ast, alt, age</td>
<td>0.8</td>
</tr>
<tr>
<td>APRI</td>
<td>platelet, ast</td>
<td>0.85</td>
</tr>
<tr>
<td>FibroTest</td>
<td>age, sex, alpha-2 macroglobulin, alpha-2-globulin, gammaglobulin, apoA1, GGT, total bilirubin</td>
<td>0.81-0.9</td>
</tr>
<tr>
<td><strong>Direct</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELF</td>
<td>hyaluronic acid, TIMP-1, type III collagen</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Indirect</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| NAFLD Fibrosis Score | platelet, ast, alt, age  
BMI, glucose, platelet, albumin | 0.88  |
| BARD score     | BMI, ast, alt, DM                                                           |       |

Slide courtesy Dr. Sumeet Asrani
Current Imaging Tools for NAFLD

Can detect Steatosis and Fibrosis, not Inflammation

**Ultrasound**
- Can detect steatosis
- Useful for screening
- Sensitivity remains low (steatosis >20%)

**Fibroscan**
- Ultrasound based
- Fibrosis: Fibroscan
- Steatosis >10%: CAP
- Limited by BMI and significant ALT elevation

**MRI**
- Most sensitive
- Fibrosis: MR elastography (MRE)
- Steatosis: proton density fat fraction
- MR-PDFF-detect >4-5% Steatosis
- Expensive, limited availability
Stage-Based Approach to NAFLD

Suspected NAFLD
(Hepatic steatosis on imaging ± elevated serum ALT levels)

- Evaluate alcohol consumption
- Confirmation of NAFLD
- Exclude alternate causes of ↑ALT levels

Risk stratification for liver-related outcomes

Low-risk profile
- BMI < 29.9
- Age < 40 years
- No T2DM or metabolic syndrome features
- Noninvasive fibrosis estimation
  - FIB-4 < 1.30
  - APRI < 0.5
  - NFS ≤ -1.455
  - Fibroscan® < 5 kPa*

Intermediate-risk profile
- BMI > 29.9
- Age > 40 years
- Multiple features of the metabolic syndrome
- Noninvasive fibrosis estimation
  - FIB-4 1.30–2.67
  - APRI 0.5–1.5
  - NFS -1.455–0.675
  - Fibroscan® 6–11 kPa*

High-risk profile
- AST level > AST level
- Platelets < 150,000
- Noninvasive fibrosis estimation
  - FIB-4 > 2.67
  - APRI > 1.5
  - NFS > 0.675
  - Fibroscan® > 11 kPa*

- Follow and reassess patient as risk factors evolve
- Consider liver biopsy
- Consider liver biopsy or confirmatory testing for cirrhosis such as magnetic resonance elastography

Treatment Options

Weight Loss
- Diet
- Exercise

Medications for NASH
- Current
- Emerging
  - Bariatric Surgery
  - Gastric Balloon
Weight Loss

• Loss of at least 5% of body weight had improvement in liver fat
• ~7% body weight reduction was associated with steatosis and inflammation improvement
• ≥10% weight loss was associated with improvement in all features of NASH, including inflammation and fibrosis.
Diet

- Prospective trials comparing various diets in NAFLD patients are limited
- Decreasing caloric intake by at least 30% results in improvement in hepatic steatosis
- The Mediterranean diet showed significant improvement in steatosis

AASLD Guidance paper: Chalasani et al., Hepatology, 2018
Exercise

• The optimal duration and intensity of exercise remains undetermined.
• Data suggest that patients who maintain physical activity more than 150 minutes/week have improvement of ALT

AASLD Guidance paper: Chalasani et al., Hepatology, 2018
Alcohol Consumption in NAFLD Patients

- Heavy alcohol use should be avoided
- Insufficient data to make any definite recommendations
- NIAAA states >14 standard drinks/week for men and 7 drinks/week for women as heavy drinking

NIAAA AASLD Guidance paper: Chalasani et al., Hepatology, 2018
Current Regimens

No current FDA approved regimens

Below are AASLD Guidance Statements, based on available data:

• Metformin is not recommended for treating NASH
• Pioglitazone improves liver histology in NASH patients
  – Therefore, it may be used to treat these patients.
  – Benefits and risks should be discussed: weight gain, bone loss
  – Pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.

AASLD Guidance paper: Chalasani et al., Hepatology, 2018
Vitamin E

• Vitamin E at 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH

• Risks and benefits should be discussed: associated with increased risks of prostrate cancer, and increased risk for bleeding

• At this time, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy and NASH cirrhosis

2. AASLD Guidance paper: Chalasani et al., Hepatology, 2018
## Current Therapies in Phase III Trials

<table>
<thead>
<tr>
<th>Compound (company); MoA</th>
<th>Phase 3 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elafibranor (Genfit); PPAR-α and -δ agonist</td>
<td>RESOLVE-IT (<a href="https://clinicaltrials.gov/ct2/show/NCT02704403">clinicaltrials.gov, NCT02704403</a>)</td>
</tr>
<tr>
<td>OCA ( Intercept); farnesoid X receptor agonist</td>
<td>REGENERATE (<a href="https://clinicaltrials.gov/ct2/show/NCT02548351">clinicaltrials.gov, NCT02548351</a>)</td>
</tr>
<tr>
<td>REVERSE (<a href="https://clinicaltrials.gov/ct2/show/NCT03439254">clinicaltrials.gov, NCT03439254</a>)</td>
<td></td>
</tr>
<tr>
<td>Cenicriviroc (Allergan); CCR2/CCR5 antagonist</td>
<td>AURORA (<a href="https://clinicaltrials.gov/ct2/show/NCT03028740">clinicaltrials.gov, NCT03028740</a>)</td>
</tr>
<tr>
<td>Selonsertib (Gilead Sciences); apoptosis signal-regulating kinase 1 (ASK-1) inhibitor</td>
<td>STELLAR 3 (<a href="https://clinicaltrials.gov/ct2/show/NCT03053050">clinicaltrials.gov, NCT03053050</a>)</td>
</tr>
<tr>
<td>STELLAR 4 (<a href="https://clinicaltrials.gov/ct2/show/NCT03053063">clinicaltrials.gov, NCT03053063</a>)</td>
<td></td>
</tr>
</tbody>
</table>
Take Home Points

• NAFLD affects nearly a 3rd of the Nation’s population
• Cardiovascular disease is a major co-morbidity
• Advanced fibrosis may need specialty care
• Weight loss with healthy diet and exercise remain the mainstay of therapy in a majority
• Pioglitazone and vitamin E are potential therapies but come with associated risks
• New therapies are in the horizon
Thank You
Alcoholic Liver Disease
Kidist Yimam, MD
Director, Autoimmune Liver Disease
Division of Hepatology and Liver Transplantation
California Pacific Medical Center
San Francisco, California
Questions

• How much alcohol is “too much”?
• What is the natural history of alcoholic liver disease (ALD)?
• What is alcoholic hepatitis and what are the available treatment options?
• Is there a role for liver transplant in a setting of severe alcoholic hepatitis?
Epidemiology

- 52.2% of Americans aged ≥12 reported being current drinkers of alcohol in the 2013 survey, which translates to an estimated 136.9 million current drinkers.
- Heavy drinking was reported by 6.3% of the population aged ≥12, or 16.5 million people.
  - Heavy drinking is defined as binge drinking on at least 5 days in the past 30 days.
- Alcohol consumption accounts for ~3.8% of all global deaths and 4.6% of global disability-adjusted life-years.
- In Europe, this problem seems to be particularly relevant, with 6.5% of all deaths attributable to alcohol.
- Harmful drinking is responsible for one in seven deaths in men and one in 13 deaths in women aged 15 to 64 years.

Epidemiology

• In the US, alcoholic liver disease is the 8th most common cause of all cause mortality.

• According to UNOS, ALD accounted for up to 20% of transplants in the US, either alone or in conjunction with HCV, between 1988 and 2009.

• Percentage of new listing and transplants are rising for patients with ALD.

A standard drink contains 14 grams of alcohol
Excessive or Heavy Drinking

**Men**
- More than 4 drinks on any day
- More than 14 drinks/week

**Women**
- More than 3 drinks on any day
- More than 7 drinks/week

National Institute of Alcohol Abuse and Alcoholism

Courtesy of Dr. Chanda Ho
Recent Trends in the Epidemiology of Alcoholic Liver Disease

Abbreviation: SES, socioeconomic status
The progression for alcoholic liver injury to steatosis with scarring, inflammation and architectural distortion leading to cirrhosis

20-40% of cirrhotics may develop liver decompensation
Alcoholic Hepatitis (AH)

- AH is a serious form of acute decompensation of ALD that develops in heavy drinkers
  - Rapid onset of jaundice, malaise, anorexia, tender hepatomegaly, and features of the systemic inflammatory response syndrome (SIRS)
- Ranges from mild to severe
- Most patients with AH have underlying advanced liver disease
  - Approximately half of patients have cirrhosis
  - Severe AH (SAH): high short term mortality (30-50% at 3 months)
  - Patients with mild disease are at high risk for progressive liver injury

Making a Diagnosis

• Physical Examination
• Laboratory tests
  – AST:ALT ratio >2 (both usually less than 500)
  – Elevated bilirubin and Alkaline phosphatase
  – Leukocytosis with neutrophil predominance
  – Elevated INR, decreased albumin
  – Anemia with macrocytosis
• Rule out other causes of acute hepatitis
• Doppler Ultrasound to exclude vascular disorders and liver cancer
• History of recent alcohol use

Definition of AH

Consensus statement from the Alcoholic Hepatitis Consortium has provided a working definition of AH:

- Onset of jaundice within 60 days of heavy consumption (> 50 g/day) of alcohol for a minimum of 6 months
- A serum bilirubin > 3 mg/dL
- Elevated AST (50-400 U/L)
- AST:ALT ratio > 1.5, and no other obvious cause for hepatitis

Determining Disease Severity

Table I. Scores for assessing severity of AH

<table>
<thead>
<tr>
<th>Score</th>
<th>Calculator</th>
<th>Interpretation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discriminant Function (DF)</td>
<td>DF = 4.6 (patient’s PT – reference PT) + total bilirubin (mg/dL)</td>
<td>Prognosis poor when ≥ 32; threshold for corticosteroid therapy</td>
<td>Score longest and most frequently used</td>
</tr>
<tr>
<td>Model for End-Stage Liver Disease (MELD)</td>
<td>MELD = 3.8 x log(bilirubin (mg/dL)) + 11.2 x log(INR) + 9.6 x log(creatinine (mg/dL)) + 6.4</td>
<td>Prognosis poor when ≥ 18</td>
<td>Neglects kidney function</td>
</tr>
<tr>
<td>ABIC (Age, Bilirubin, INR, Creatinine)</td>
<td>(age x 0.1) + (serum bilirubin x 0.08) + (serum creatinine x 0.3) + (INR x 0.8)</td>
<td>Low risk ABIC ≤ 6.71 Intermediate risk when ABIC &gt; 6.71 and ≤ 9.0 High risk when ABIC &gt; 9.0</td>
<td>Designed for liver transplant allocation; performance equal to DF Not validated outside Spain Not designed to identify patients requiring corticosteroids</td>
</tr>
<tr>
<td>Glasgow Alcoholic Hepatitis Score (GAHS)</td>
<td>Age &lt;50  ≥50 - Leucocytes &lt;15  ≥15 - Urea (mmol/L) &lt;5  ≥5 - INR &lt;1.5  1.5-2.0  ≥2 - Bilirubin (mg/dL) &lt;7.3  7.4-14.6  &gt;14.6</td>
<td>Poor prognosis if score &gt; 8 (calculated on day 1 and 7 of hospitalization)</td>
<td>Requires more variables than the other scores</td>
</tr>
</tbody>
</table>

INR – international normalized ratio; PT – prothrombin time

Table II. The Lille model

Lille score = 3.19–0.101 x (age [years]) + 0.147 x (albumin day 0 [g/L]) + 0.0165 x (bilirubin day 1 [μmol/L] – bilirubin day 7 [μmol/L]) – (0.206 x presence of kidney failure y/n) – 0.0065 x (bilirubin day 0 [μmol/L]) – 0.0096 x INR

Allows stratification of patients with AH according to response to corticosteroid therapy: complete responders (Lille score ≤ 0.16), partial responders (Lille score 0.16–0.56) and null responders (Lille ≥ 0.56) (from ref. 55)
Treatment Options

- Abstinence
- Nutrition
- Corticosteroids
- Pentoxifylline
- Liver Transplantation
- Other (NAC, G-CSF)
Abstinence

• Most therapeutic intervention
  – Improve histologic features of liver injury
  – Reduce portal pressure
  – Decrease progression to cirrhosis
  – Improve survival

• Baclofen may be helpful- can inhibit ETOH craving
  – Other medications used include acamprosate, naltrexone
    (opioid antagonist), and nalmefene (opioid antag)

• Can still have progression of liver disease even if abstinence is achieved

• 1 year relapse rates range from 67-81%
  Abstain: 5 year survival: 75%
  Relapse: 5 year survival: 27%
Nutrition

- Protein calorie malnutrition common
- Enteral nutrition is encouraged with goal of 35–40 kcal/kg of body weight (BW) and a daily protein intake of 1.2–1.5 g/kg of BW
  - Confers potential benefit by preserving intestinal barrier, decrease risk of infection, decreased intestinal permeability, immune modulation
  - Prevent additional muscle loss
- Vitamin deficiency
  - Thiamine, folate, pyridoxine, zinc
  - Vitamins A and D
- Many studies show that nutrition improves liver function but not survival

Steroids

• The most studied pharmacological intervention in alcoholic hepatitis - evaluated in multiple RCTs and meta-analyses
• “Standard treatment” = Prednisolone 40 mg/day x 4 weeks, with or without a taper in patients with DF ≥ 32 (severe AH)
• To be used in patients without contraindication to steroid use - risk for infection
  - Active infection
  - Severe hyperglycemia, active GI Bleeding
• Those with DF <32 (mild-mod AH) should be monitored closely
28-Day Survival with Prednisolone vs. Control DF≥32

Meta-analysis of individual data from 5 RCTs

Mortality: 42% Relative RR in mortality
NNT = 7

Mathurin, Gut, 2011
Systematic review: glucocorticosteroids for alcoholic hepatitis – a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials

A. RAMBALDI*, H. H. SACONATO†, E. CHRISTENSEN‡, K. THORLUND*, J. WETTERSLEV* & C. GLUUD*

- 15 trials with 721 patients
- Steroids did not statistically reduce mortality compared to placebo
- Subgroup analysis:
  - Steroids decreased mortality in patients with DF ≥ 32 or encephalopathy (20% vs. 34%)

Alimt Pharmacol Ther. 2008
Lille Score Predicts 6-Month Survival in Alcoholic Hepatitis, with Prednisolone

Baseline: Age, albumin, bilirubin, creatinine, protime
Day 7: Change in bilirubin (vs. Day 1)

Lille score < 0.45
85% ± 2.6%

Lille score ≥ 0.45
24.4% ± 3.8%
What if my patients can’t take steroids?

- What has been recommended in the past: Pentoxifylline (PTX) 400 mg three times per day
- PTX serves as a phosphodiesterase (PDE) inhibitor which inhibit tumor necrosis factor (TNF) production. TNF plays a critical role in liver injury.
- RCT tested pentoxifylline in 101 patients with severe AH
- 40% decrease in mortality with most of the reduction related to decreased likelihood of hepatorenal syndrome (HRS)
- Subsequent meta-analyses concluded no differences in short-term mortality related to PTX
Primary Endpoint Analysis

Mortality at 28 Days

OR: 0.72 (0.52 – 1.01)  
OR: 1.07 (0.77 – 1.49)

P=0.056  
P=0.686

Mortality (%)

Prednisolone  |  No Prednisolone  |  Pentoxifylline  |  No Pentoxifylline

0  |  12  |  16  |  14

Thursz   NEJM 2015
Liver Transplantation (LT) in AH

- Because the short term mortality rate is so high, LT is a potential rescue therapy. Patients unresponsive to therapy have a 6 months survival of ~30%
- Highly controversial
  - Thought that patients with AH are responsible for their illness and are likely to resume ETOH use post transplant
  - How best to identify patients at low risk for recidivism?
    - “the 6 months rule”
- For carefully selected patients, transplant can confer an excellent survival advantage
Early LT for Severe Alcoholic Hepatitis

- French study: 26 patients listed for LT underwent LT after failing to respond to steroid therapy (Lille >0.45)
  - Case control study
- Patient selection
  - First episode of decompensation
  - Favorable psychosocial profile
  - No psychiatric disease
  - Agree to lifelong abstinence
  - Agreement by entire clinical team
    - RN/resident/fellow
    - Addiction medicine
    - Hepatology
    - Surgery and anesthesia

Mathurin, NEJM 2011
Early Liver Transplantation for Severe Alcoholic Hepatitis

Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

Mathurin, NEJM 2011
Early LT for Severe Alcoholic Hepatitis

- 6 deaths in the transplanted group
  - 5 deaths due to infection within 2 weeks
- 3/26 patients relapsed (15%)
  - 720, 740, and 1140 days after transplant
  - 2 remained daily consumers (30 g, >50g); 1 occasional alcohol (10g/week)
  - None with graft dysfunction
- 77% 6 month survival (vs. 23%)

Mathurin, NEJM 2011
Proposed Algorithm for management of acute AH

1. Rapid onset of jaundice
   Impaired liver function
   Active/recent alcohol abuse

2. Exclude other causes of acute liver dysfunction

3. Prognostic score (MDF, MELD, GAHS)

4. Risk low:
   MDF < 32; MELD < 18; GAHS < 8

   a. Malnutrition
   b. Nutritional status adequate

   c. Nutritional supplementation (35kcal/kg; 1.5g/kg protein)

   d. Supportive care, treatment of alcoholism, regular follow-up (screening for HCC)

5. Risk high:
   MDF ≥ 32; MELD ≥ 18; GAHS ≥ 8;
   hepatic encephalopathy

   a. Nutritional supplementation (35kcal/kg; 1.5g/kg protein)
   b. Prednisolone 40mg/day ± N-acetylcysteine
   c. Stopping rule: insufficient response within 7 days of treatment
   d. Consider pentoxifylline (2x400mg/day for 4 wks)

   e. Responders (Lille score <0.45)
   f. Treat for 28 days

   g. Non-Responders (Lille score ≥0.45)
   h. Consider LT

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Liver Transplant in ALD

- ALD is a major indication for transplant, ~20% of LTs
- Majority of centers (and payors) require 6 months of sobriety as well as enrollment in AA
  - Not a hard and fast rule but often used because earlier studies had suggested 6 months would decrease risk of recidivism although this has been debated
  - 6 months can also allow for some recovery from alcohol-related liver injury (and therefore transplant would not be needed)
- Recidivism: 16 to 49% return to some form of drinking
- A small percentage (5-7%) return to excessive drinking

Summary

• There is a significant health burden of alcohol use worldwide
• Prednisolone 40 mg/day x 30 days may represent the most viable treatment option for alcoholic hepatitis although STOPAH trial suggested that the survival benefit is modest at 28 days
  – Infection surveillance critical
  – Stop if Lille score >0.45
• Liver transplantation, while controversial, is a treatment option for selected patients with alcoholic hepatitis
• Decision to transplant is however center-dependent
Thank You
Q&A with Speakers

**Chronic Hepatitis B**
Eric W. Chak, MD, MPH
Assistant Professor of Clinical Internal Medicine
UC Davis Medical Center

**Chronic Hepatitis C: Diagnosis & Treatment**
Alicia Gonzalez-Flores, MD
Assistant Professor of Clinical Internal Medicine
UC Davis Medical Center

**Fatty Liver Disease**
Souvik Sarkar, MD, PhD
Assistant Professor, Director of Fellow Research, Division of Gastroenterology and Hepatology
UC Davis Medical Center

**Presentation TBD**
Kidist Yimam, MD
Director, Autoimmune Liver Disease Program, Division of Hepatology and Liver Transplantation
California Pacific Medical Center
Resources

ALF website... www.liverfoundation.org

ALF Northern California... www.liverfoundation.org/alf-northern-california

National Helpline... 1-800-GO-LIVER (1-800-465-4837)

Education Materials... www.liverfoundation.org/for-patients/resources/

Webinar recording will be posted at www.liverfoundation.org
Thank You