Interactive Case Presentation #3:
A Case of Acute-on-Chronic Liver Disease

Moderator:
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Texas Liver Institute
San Antonio, Texas
Case: Jocelyn

• A 55 year old Hispanic female presents on a routine physical exam with labs with the following findings

• Her exam is normal, with BMI of 28

• She has mild fatigue, no others symptoms

• Labs:
  – WBC: 4.6, Hb 13.8 g/dL, platelets 240k
  – Tbili: 1.0 mg/dL, alk phosphatase 128 U/L, AST 78 U/L, ALT 84 U/L
  – BUN: 38 mg/dL; Creatinine: 0.8 mg/dL
Case: Jocelyn

• She is referred to you for evaluation
• Her history is negative for prescribed or OTC medications
• Her PSH includes TAH/BSO
• Her PMH is positive for shingles at age 45, occasional urinary tract infections, and influenza at age 48
• I was the first consultant to see this patient.....
Biochemical markers, imaging, and patient presentation in acute hepatic injury

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San Antonio, Texas
Acute Hepatic Injury: Patient Presentation

• Symptoms:
  – Fatigue/Malaise
  – Lethargy
  – Anorexia
  – Nausea/Vomiting
  – Pruritus
  – Abdominal distention from ascites
  – Hypotension and tachycardia

• PE findings:
  – Hepatic Encephalopathy
  – Jaundice
  – RUQ pain and HMG
  – Ascites
  – Renal Failure
Biochemical tests in liver disease

• The true test of liver function
  – INR, PT, albumin, bilirubin (direct)

• Tests of hepatic injury/inflammation
  – Transaminases
    • Aspartate aminotransferase (AST): liver, heart, kidneys, brain, skeletal muscle
    • Alanine aminotransferase (ALT): liver specific? (heart, kidney, skeletal muscle)
  – Alkaline phosphatase (ALP)
  – Gamma-glutamyl transpeptidase (GGT)
  – Lactic dehydrogenase (LDH)

• Hepatocellular: AST/ALT elevation twice that of ALP
• Cholestatic – AST/ALT elevation less than twice of ALP
What main labs to look for in acute hepatic injury?

- Elevated AST/ALT
  - Can be elevated mildly to severely
- Bilirubin
  - Elevation means serious liver injury and dysfunction
- Prolongation of INR/prothrombin time (PT)
  - Help determine severity and prognosis
EVALUATION OF ABNORMAL LIVER TESTS

Suspected Liver Disease

Abnormal liver tests

Acute < 6 months

Hepatitis: ↑↑ALT
Mixed: ↑ALT, ↑AlkP

Diagnostic evaluation
1. IgM Anti-HAV
2. HBsAg
3. IgM Anti-HBc
4. Anti-HCV
5. ANA, SMA
6. Monospot, heterophile
7. Ceruloplasmin
8. Alcohol history
9. Drug history

Liver biopsy in acute liver disease:
Reserved for patients in whom the diagnosis remains unclear despite medical evaluation

Cholestatic:
↑↑AlkP,
↑↑gGT,
↑↑ALT

Diagnostic evaluation
1. AMA
2. Drug history
3. Ultrasound/MRI
4. MRCP/ERCP

Chronic > 6 months

Hepatitis: ↑↑ALT
Mixed: ↑ALT, ↑AlkP

Diagnostic evaluation
1. HBsAg
2. Anti-HCV
3. Fe saturation, ferritin
4. Ceruloplasmin
5. α, AT
6. ANA, SMA
7. Ultrasound
8. Alcohol history

Liver biopsy in chronic liver disease:
Often valuable for diagnosis as well as staging and grading liver disease

Cholestatic:
↑↑AlkP,
↑↑gGT,
↑↑ALT

Diagnostic evaluation
1. Drug history
2. AMA
3. P-ANCA
4. Ultrasound
5. MRCP/ERCP
Imaging and Pathology

• Ultrasound
  – Inexpensive, readily available, and noninvasive
  – Best place to start

• CT/MRI
  – More sensitive than U/S
  – Caution in renal patients

• Liver Biopsy
  – Almost always necessary in cases not leading to liver failure, except for acute hepatitis A and B
Acute liver injury is common
Acute liver failure is not
Etiology of Acute Liver Failure in the USA
Adult Registry (n = 2,224)

ALF Study Group, Jan 2015
Acute Liver Failure

- Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (jaundice) in a patient without preexisting liver disease.

- Acute liver failure can be subcategorized based upon how long the patient has been ill.
  - Hyperacute (<7 days)
  - Acute (7 to 21 days)
  - Subacute (>21 days and <26 weeks)
Take Home Message

• Many things can cause acute hepatic injury
• Do a good history and PE to help determine risk factors – viral? Recent meds?
• Eliminate causative factor for acute hepatic injury! – toxins, medications
• Do imaging to rule out obstructive causes
• Monitor LFTs to look for improvement!
Back to Angie
Jocelyn: Another Consultant

- A senior colleague is asked to advise on the case.
- A very detailed history is taken and a new bit of evidence comes to light.
- The patient had a urinary tract infection 6 weeks prior to presentation and it was treated for 5 days with an antibiotic.
Acute Drug Induced Liver Injury (DILI)

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University Medical Center Brackenridge
Brackenridge Specialty Clinics- Gastroenterology and Endocrinology
Austin, Texas
Acute Drug Induced Liver Injury (DILI)

• Drug-induced liver injury (DILI) has an estimated annual incidence between 10-15 per 10,000 to 100,000 persons exposed to prescription medications.

• DILI accounts for approximately 10% of all cases of acute hepatitis, and it is the most common cause of acute liver failure in the US.

• DILI is also the most frequently cited reason for withdrawal of medications from the marketplace.\(^1\)

# DILI: Intrinsic or Idiosyncratic

<table>
<thead>
<tr>
<th>Intrinsic DILI</th>
<th>Idiosyncratic DILI</th>
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<tbody>
<tr>
<td>• Hepatotoxicity w/ potential to affect all individuals to varying degrees.</td>
<td>• Unpredictably affects only rare susceptible individuals</td>
</tr>
<tr>
<td>• Typically stereotypic course, presentation, latency</td>
<td>• Less dose dependent</td>
</tr>
<tr>
<td>• Typically dose dependent (e.g. APAP)</td>
<td>• More varied in course and presentation</td>
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<tr>
<td></td>
<td>• Varies greatly in severity</td>
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<td></td>
<td>• Varying latency (days to year)</td>
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<td><strong>Most reactions to prescription drugs or HDS are considered idiosyncratic</strong>²</td>
</tr>
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</table>

Idiosyncratic DILI: Who Gets It?

Host factors: Age, pregnancy, gender, obesity, DM, malnutrition, co-morbidities including underlying liver disease, indications for therapy. May be genetic factors affecting DILI susceptibility w/ certain agents: ongoing research

Environmental factors: Smoking, ETOH, infection and inflammatory episodes

Drug factors: Daily dose, metabolic profile (including hepatic clearance, lipophilicity), class effect and cross-sensitization, drug-drug interactions, polypharmacy
DILI: How bad is it?

In general, outcomes of idiosyncratic DILI are good:
90% recover from the average instance of DILI

• ~ 10% develop ALF (coagulopathy and encephalopathy)

• Those with cholestatic injury generally fare better than those with hepatocellular injury

• DILI-ALF carries poor prognosis: 40% require liver transplantation; 42% die of the episode. Advanced coma grade and high MELD scores are associated with bad outcomes\(^1,2\)

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DILI : Common Culprits

- Acetaminophen (intrinsic DILI), amoxicillin/clavulanate, isoniazid, NSAIDs, antiepileptic medications (AEDs)
- **Antibiotics and AEDs** are most commonly reported and account for more than 60% of DILI overall\(^2\)
- Antibiotics: the most common class of drug responsible for acute liver failure (ALF) in DILI.
- Most common individual drugs: \(^3\)
  - Isoniazid
  - Sulfur antibiotics (TMP-SMX)
  - Nitrofurantoin

DILI Patterns and Associated Drugs

• Don’t forget: Certain herbal and dietary supplements (HDS) can be hepatotoxic, and a cause of DILI
  – This is increasingly a concern given HDS proliferation in a largely unregulated market without standardization.
  – Use of such substances must be investigated in history-taking.
“LIVERTOX® provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements. LIVERTOX also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LIVERTOX website provides a comprehensive resource for physicians and their patients, and for clinical academicians and researchers who specialize in idiosyncratic drug induced hepatotoxicity.”

http://www.livertox.nih.gov/
DILI Treatment

Stop offending drug (if not already done!)

Supportive measures for complications/symptoms, but no “silver bullet” or curative intervention.

- Some evidence for N-acetylcystine in adults with idiosyncratic DILI and early ALF
- DI-AIH can be treated with steroids

Avoid re-exposure to offending drug:

- Consider only if suspected drug was a lifesaving medication for which there are no other alternatives
- Proceed with caution under strict surveillance
Jocelyn recovers

• This patient was prescribed nitrofurantoin, an antibiotic that can lead to liver injury, particularly in older patients
• It can be the environmental trigger to also lead to autoimmune hepatitis
• Jocelyn did well and was instructed to not take that antibiotic again
• Her liver enzymes normalized after a few weeks and she was not heard of again until.....
Jocelyn

• 5 years later at age 60, Jocelyn is divorced, has had a bout of depression, and has gained weight, with a BMI of 33

• She has developed early signs of diabetes, with fasting glucose of 120 mg/dL

• She also has started drinking wine every night with her dinner, and occasional girls night out

• She is once again referred for elevated ALT of 109 U/L, AST of 108 U/L
Alcoholic Hepatitis

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Alcoholic Liver Disease

- A major cause of morbidity and mortality in the United States
- Encompasses a clinico-histological spectrum including
  - Fatty liver
  - Alcoholic hepatitis
  - Alcoholic cirrhosis
- The majority of people who abuse alcohol for an extended duration, DO NOT develop advanced alcoholic liver disease
  - 15-20% develop alcoholic hepatitis and/or cirrhosis
Why Don’t All Drinkers Develop Serious Alcohol Liver Disease?

• Women > men
• Family history
• >6-8 drinks/day
• Continuous drinking/binging
• Overweight/poor nutrition
• Genetic factors
How Does Alcohol Damage The Liver?

• Alcohol broken down in the liver
• Break down products lead to fatty liver, inflammation and scarring
Progression of Alcoholic Liver Injury

Normal Liver

Fatty Liver

Cirrhotic Liver
“Safe” Limit of Alcohol Intake

• Women=14 units per week=8 drinks per week
• Men=21 units per week=12 drinks per week

• Significant Alcohol Consumption (2012 Guidelines)
  – Women: >140 g of alcohol/wk = >10 drinks/week
  – Men: >210 g of alcohol/wk = >15 drinks/week
What Is A Unit Equivalent To?

1 standard drink = 14 grams of alcohol
1 unit = 8 grams of alcohol
CAGE Questionnaire

• Most widely used, easy to implement, short, simple and can be easily incorporated into clinical practice
• Asks 4 questions
  – Have you ever felt you should cut down on your drinking?
  – Have people annoyed you by criticizing your drinking?
  – Have you ever felt bad or guilty about your drinking?
  – Have you ever had a drink first thing in the morning to steady your nerves or to get ride of a hangover (eye-opener)?
• Item responses on the CAGE are scored 0 or 1, with a higher score an indication of alcohol problems
• A total score of 2 or greater is considered clinically significant
Physical Exam Findings

- Ascites
- Scleral Icterus
- Spider telangiectasia
- Jaundice
Long Term Management Strategies

• Always advocate **abstinence** from alcohol for these patients
• **Monitor** closely for recidivism and support counseling and behavioral changes
• **Address nutritional issues**, consider dietary consult
• **Liver transplantation**
  – Alcoholic liver disease is 2\(^{nd}\) most common indication for transplantation in Western World
  – Majority never referred due to concern for noncompliance, recidivism
  – Always safer to refer and let program decide if eligible
Algorithm for the Management of Alcoholic Hepatitis

Establish Disease Severity

Low Risk:
MDF <32 and 1st week decrease in bilirubin, or MELD <18 and 1st week decrease in MELD by 2 points

Nutritional Assessment / Intervention

Supportive Care & Close follow-up

Continue

Yes

Response by Lille model?

Prednisolone

No

High Risk:
MDF ≥ 32, presence of HE, or MELD ≥18

Nutritional Assessment / Intervention

Consider Liver Biopsy if Diagnosis is uncertain

If steroid contraindications or early renal failure

Pentoxifylline

Stop
Alcoholic Liver Disease Almost Always Ends in Death if Not Treated
Back to Angie
Jocelyn

• Jocelyn undergoes a liver biopsy since she now has possible features of alcohol liver injury

• The pathologist reviews the slides and says there is a tremendous amount of steatosis, but no evidence of inflammation or other features of alcohol injury

• Jocelyn swears she is drinking maximum of 2 drinks per night, and only 4-5 times per week

• So maybe she has another condition which can look like ASH....
Non-Alcoholic Fatty Liver Disease (NAFLD): Non-Alcoholic Fatty Liver (NAFL) and Non-Alcoholic Steatohepatitis (NASH)

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Texas Liver Institute
San Antonio, Texas
Clinical Clues of Fatty Liver Disease

- Right upper quadrant pain
- Obesity (most patients who are obese have NAFLD)
- Hepatomegaly
- Diabetes or signs of insulin resistance
- Elevated ALT
- Hepatic steatosis on an ultrasound
- Classic findings on liver biopsy
Diseases Associated with Visceral Obesity

NAFLD is Closely Associated with Visceral Obesity and Insulin Resistance

Visceral Obesity

- Dyslipidemia
- Hypertension
- Endothelial Dysfunction
- Atherosclerosis
- Insulin Resistance
- Type 2 Diabetes

- Polycystic Ovarian Syndrome (PCOS)
- Coronary Artery Disease (CAD)
- Non-alcoholic Fatty Liver Disease (NAFLD)
How Can Fat Affect the Liver?

NAFLD Spectrum

- Type 1 - NAFL, steatosis alone
- Type 2 - NAFL, steatosis plus inflammation
- Type 3 - NASH, steatosis plus hepatocyte injury (ballooning)
- Type 4 - NASH, steatosis plus fibrosis

NAFL - nonalcoholic fatty liver
NASH - nonalcoholic steatohepatitis
NASH Pathogenesis: A Perfect Storm

*Not all patients with NASH demonstrate insulin resistance.*
Evolution of NAFLD in the US

- NAFLD: Most common cause of chronic liver disease
- Disease burden from NAFLD will continue to increase
- Rise due to obesity or better identification by HCP

Prevalence rates (%)

NHANES Cycles

- ALD
- CH-B
- HCV(+)
- NAFLD


Younossi Z et al. *Clin Gastro and Hep* 2011
Increasing Burden of NAFLD Among Young Adults in the U.S.

- Prevalence rose from 9.6% in 1988-94 to 24% 2005-10
- Highest among Mexican Americans and those with BMI >40 kg/m²
- True prevalence of NAFLD probably higher than reported here (low BMI, normal ALT)
- Critical to target young adults for screening to prevent the development of cirrhosis at a young age.

Mrad, et al, Hepatology 13 May 2016
Which patients with NAFLD are at highest risk for NASH and how do we monitor?
Red Flags for NASH

- Age
- Gender
- Hispanic
- HT
- Obesity
- Diabetes
- ALT and AST level
- AST/ALT ratio
- Insulin level
- PNPLA3

No lab test or imaging study will be able to predict with 100% accuracy.

The more risk factors... the more concerned you should become.
Diagnosis of NASH

• Screening for NAFLD is not recommended
  – *But should it be?*
  – *Whom would be screened?*

• In cases of elevated ALT, *exclusion* of other liver disease must be done

• When NAFLD is suspected, *liver biopsy* is the gold standard for distinguishing NASH
  – Should be performed in those with the highest risk factors for NASH
# What Options Available Now?

<table>
<thead>
<tr>
<th>Weight Loss</th>
<th>Histological Improvement</th>
<th>Decrease in ALT</th>
<th>Major Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Yes(^1)/No(^2)</td>
<td>No(^2)</td>
<td>Yes(^1)/No(^2) Few studies</td>
</tr>
<tr>
<td>Metformin</td>
<td>Yes(^4)</td>
<td>No(^4)</td>
<td>No(^4) Limited Efficacy</td>
</tr>
<tr>
<td>Pio/Rosiglitazone</td>
<td>No- ↑(^4, 5)</td>
<td>Yes(^4, 5)</td>
<td>Yes(^4) Safety</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>No(^5, 6)</td>
<td>Yes(^5, 6)</td>
<td>Yes(^5, 6) ↑ mortality &amp; Pr Ca</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>No</td>
<td>No</td>
<td>Yes/No Limited Efficacy</td>
</tr>
<tr>
<td>Omega-3 FA</td>
<td>No</td>
<td>No</td>
<td>Yes Variable dosing &amp; source</td>
</tr>
<tr>
<td>&gt;5–7% Wt loss</td>
<td>Yes(^2, 3)</td>
<td>Yes(^2, 3)</td>
<td>Yes(^2, 3) Low compliance</td>
</tr>
<tr>
<td>Bariatric Surgery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes Surgical morbidity, weight regain</td>
</tr>
</tbody>
</table>

Yes/No = Conflicting studies.

# Emerging Small Molecules in NASH

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Mechanism of Action</th>
<th>Phase</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENFIT</td>
<td>GFT-505 (Elafibranor)</td>
<td>PPARα/δ agonist</td>
<td>2, completed</td>
<td>Reversal of NASH histology</td>
</tr>
<tr>
<td>Intercept</td>
<td>Obeticholic acid</td>
<td>FXR agonist</td>
<td>3</td>
<td>NAS Score</td>
</tr>
<tr>
<td>Gilead</td>
<td>Simtuzumab</td>
<td>Anti-LOXL2 Mab</td>
<td>2</td>
<td>Collagen</td>
</tr>
<tr>
<td>RAPTOR</td>
<td>RP-103</td>
<td>Cysteine-depleting agent</td>
<td>2, completed</td>
<td>NAS score</td>
</tr>
<tr>
<td>Tobira</td>
<td>Cenicriviroc</td>
<td>CCR2/5 inhibitor</td>
<td>2</td>
<td>NAS Score</td>
</tr>
<tr>
<td>Conatus</td>
<td>Emricasan</td>
<td>Caspase protease inhibitor</td>
<td>2, completed</td>
<td>Fibrosis (≥1 stage)</td>
</tr>
<tr>
<td>Galmed</td>
<td>Aramchol</td>
<td>Synthetic Fatty Acid / bile acid conjugate</td>
<td>2a, completed</td>
<td>Triglyceride level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2b/3</td>
<td>Triglyceride level/Safety</td>
</tr>
<tr>
<td>Galectin</td>
<td>GR-MD-02</td>
<td>galectin-3 inhibitor</td>
<td>1, completed</td>
<td>Safety/ALT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>Portal hypertension</td>
</tr>
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Final Thoughts: NAFLD

• Complex disease tied closely to insulin resistance, obesity and metabolic syndrome
• Genetic predispositions
• NAFLD can progress to NASH/cirrhosis
• *Personalized* treatment may be the best future option to treat NASH
Jocelyn

• Biopsy was consistent with NAFLD and she was enrolled in a clinical trial
• Will update her case next year......
Texas Liver Institute & UT Health Science Center

- Adult/Pediatric Liver Transplant
- Living donor transplant program
- Liver Cancer Center
- Clinics in Austin, Corpus Christi, El Paso, McAllen

Largest clinical liver research unit in the US

Phase 1-3 studies

Early phase testing ground for HCV, fatty liver and antifibrotic therapies

National Cancer Institute (NCI) designation
Roundtable Discussion/Q&A