The Spectrum of Alcohol Use Disorders: Implications for Health Care Providers

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Disclosure:
• The planners and presenter of this presentation have disclosed no conflict of interest, including no relevant financial relationships with any commercial interests

Objectives:
• Upon completion of the following discussion the participant should be able to:
  – Construct an appropriate benzodiazepine-based regimen for the management of acute alcohol withdrawal symptoms
  – Select drug regimens for prevention of ascites and spontaneous bacterial peritonitis
  – Differentiate pharmacologic strategies for secondary prevention of esophageal varices in

Pharmacology of Alcohol
• Acute: Dose dependent, Patient dependent

<table>
<thead>
<tr>
<th>Plasma concentration</th>
<th>Expected effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mg/dl</td>
<td>Normal</td>
</tr>
<tr>
<td>10 - 100 mg/dl</td>
<td>Anxiety, autonomic symptoms, tremors</td>
</tr>
<tr>
<td>100 - 200 mg/dl</td>
<td>Motor coordination, delirium, disorientation, delirium</td>
</tr>
<tr>
<td>&gt; 200 mg/dl</td>
<td>Seizures, coma, death, delirium</td>
</tr>
</tbody>
</table>

• Chronic:
  – Compensatory increase in excitatory pathways
    • Increase Epi, NE
    • Glutamate, NMDA alterations

Incidence Prevalence
• Alcohol abuse and dependence have a combined prevalence of 7.4 - 9.7% in the United States.
• This increases to 10 - 33% in intensive care unit (ICU) patients
  – 18% of these patients develop acute withdrawal symptoms during their hospitalization
• Alcohol withdrawal syndrome (AWS) is an abstinence syndrome characterized by autonomic hyperactivity, altered sensorium and severe hyperadrenergic state.
Stages of AUD

Characteristic organ system decline:

- Deficiencies:
  - Folate
  - B-12
  - Iron
  - Thiamine
- Warnecke's Nutritional Calories
- Protein Calorie Malnutrition
- Hypoalbuminemia
- Coagulopathies
- Acute Alcohol Withdrawal
- Chronic Alcohol Abstinence
- Adjunctive Medications
- Hepatic Dysfunction
- Acute Alcoholic Hepatitis
- Hepatic Encephalopathy
- Portal Hypertension
  - Variceal Bleeding
  - Gastric Bleeding
- Ascites
- Bacterial Peritonitis
- Hepato-Renal Syndrome
- Death

CIWA

- Scale to assess patients level of acute alcohol withdrawal
- Higher the number = worse withdrawal
- “Pick an organ system-dump on epinephrine”

How to relieve acute alcohol withdrawal symptoms:

- Alcohol
  - Give them a drink
  - 5:00 clockers
- Chloral Hydrate
- Benzodiazepines
- Sodium Channel Blockers
- Central alpha 2 agonists
  - Dexmedetomidine Precedex®- IV
  - Clonidine- Transdermal, PO

Acute Alcohol Withdrawal: Benzodiazepines

- Symptom Triggered
- Vs
- Scheduled
- Pros/Cons
- Long Acting Benzos
- Vs
- Short Acting Benzos
- Pros/Cons

Benzodiazepine Alcohol Withdrawal Recommendations Roger Heftinger, Pharm.D.

The chart shows Benzodiazepine Alcohol Withdrawal Recommendations for various schedules and dosages.
Benzo-metabolism:

Benzodiazepine Metabolism

- Provides Sedation
- Decreases BZDs
- Decrease Dopamine Antagonists
- LOS? ICU? Hospital?
- Need Intubation?
- Hypotension

Which would be an appropriate long acting scheduled benzodiazepine regimen?

A. Oxazepam 15 mg PO QID
B. Lorazepam 1 mg PO QID
C. Diazepam 10 mg PO QID
D. Alprazolam 1 mg PO QID

Liver Failure:

Stages of liver damage

- Healthy Liver
- Fatty Liver
- Liver Fibrosis
- Cirrhosis

Renal Function:
- Cr
- Liver metabolism:
  - Bilirubin
  - Synthetic function: INR

Acute Alcoholic Hepatitis

- Inflammation of the liver due to excessive intake of alcohol. It is usually found in association with fatty liver, an early stage of alcoholic liver disease, and may contribute to the progression of fibrosis, leading to cirrhosis.
- Signs and symptoms of alcoholic hepatitis include jaundice, ascites (fluid accumulation in the abdominal cavity), fatigue, and hepatic encephalopathy (brain dysfunction due to liver failure).
Severity Ratings with Outcomes

• Hepatic Discriminate Index (Maddrey Score)
  1992: if >32: 28 day mortality improved with
    – Prednisolone 40mg PO a day
    – Or Methyprednisolone 32mg IV a day

  \[ \text{Index} = 4.6 \times (\text{Prothrombin Time} - \text{Control Prothrombin Time}) + \text{bilirubin} \]

• MELD- Model for End Stage Liver Disease
  – Used for staging for liver transplantation

  \[ \text{MELD score} = \left( \frac{9.57 \times \text{Creatinine}}{1 - \text{Creatinine}} \right) + \left( \frac{0.378 \times \text{bilirubin}}{1 - \text{bilirubin}} \right) + \left( 1.12 \times \text{INR} \right) + 6.4 \]

What about corticosteroid “Non-Responders”

• Lille Score
  – Hepatology. 2007 Jun;45(6):1348-54
    – “The model was generated by logistic regression. The model combining six reproducible variables (age, renal insufficiency, albumin, prothrombin time, bilirubin, and evolution of bilirubin at day 7) was highly predictive of death at 6 months (P < 0.000001).”
  – The survival benefit was only statistically significant in those with a Lille score <0.56. The Lille score assesses improvement after one week of treatment, with lower scores indicating more improvement

Non-Responders may be considered for other therapies:

• Pentoxifylline Trental® 400 mg TID
  – Inhibits tumor necrosis factor (TNF) synthesis, which is increased in patients with alcoholic hepatitis.
  – Pentoxifylline has been considered as an alternative to glucocorticoids in patients with severe alcoholic hepatitis (DF ≥32), though the data supporting its use are much weaker than for prednisolone.
  – And subsequent years of data do NOT support use

Where are we in 2017?:

• Combining Data From Liver Disease Scoring Systems Better Predicts Outcomes of Patients With Alcoholic Hepatitis.
  – We compared the performances of 3 joint-effect models (Maddrey+Lille, MELD+Lille, and ABIC+Lille) to determine which combination had the best prognostic value, based on known patient outcomes:

Hepatic Encephalopathy

• Is the occurrence of confusion, altered level of consciousness, and coma as a result of liver failure.
  – In the advanced stages it is called hepatic coma or coma hepaticum. It may ultimately lead to death.
  – It is caused by accumulation in the bloodstream of toxic substances that are normally removed by the liver.
Hepatic Encephalopathy:
- The diagnosis of hepatic encephalopathy requires the presence of impaired liver function and the exclusion of an alternative explanation for the symptoms.
- Blood tests (ammonia levels) may assist in the diagnosis.
- Normal Ammonia: 15-45 ucg/dl

Treatment of HE
- Protein Restriction: < 1g/kg/day IBW
- Theory that there are higher levels of aromatic amino acids that may accumulate liver failure:
- Enteral and Parenteral nutritional solutions:
  - HepatAmine® provides a mixture of essential and nonessential amino acids with high concentrations of the branched chain amino acids isoleucine, leucine, and valine, and low concentrations of methionine and the aromatic amino acids phenylalanine and tryptophan, relative to general purpose amino acid injections

Hepatic Encephalopathy: Lactulose:
- **MOA-1:** Acidification gut
  - NH3- can cross
  - NH4- gets trapped
  - Pooped out
- **MOA-2:** Eradicates gut flora
  - 10g/15ml: 20g/30ml: 30 ml QID to 8 times a day
  - 2-3 loose stools a day
  - Rectal Retention Enema 300ml (10g/15ml) / 700 cc NS

Hepatic Encephalopathy: Non-Absorbable Antibiotics
- Neomycin
  - 500-TID-QID
- Metronidazole
  - 250-500 TID-QID
- Vancomycin
  - 125-250 TID-QID
- Xifaxan®
  - Fiduciary Concerns:
    - Metronidazole
      - 500 mg #120 2017 AWP- $86.40
    - Neomycin
      - 500 mg #120: 2017 AWP- $163.68
    - Vancomycin
      - 250mg #60: 2017 AWP- $3462.00
      - Actual acquisition- Compound IV for PO?
    - Xifaxan®
      - 550mg #60: 2017 AWP- $2328.01

Which will help with symptoms of hepatic encephalopathy?
A. Protein supplementation with high aromatic amino acids
B. Docusate Sodium 100mg BID
C. Polyethylene Glycol 17 grams PO Q Day
D. Lactulose 10g/15 ml 30 ml PO QID
Portal Hypertension

Diagnosis

- American Association for the Study of Liver Disease (AASLD)
- Recommends anyone with cirrhosis to have endoscopy to look for gastric and esophageal varices
- >5 mm should be noted as they are more likely to bleed in the future
  - Candidates for portal pressure lowering medications
- On-going surveillance 1-3 year intervals

Treatment before endoscopy:

- Intravenous access:
  - Blood products, Fluids
  - Hgb to 7-8
  - Not too aggressive
- Increase portal pressure
- Vasoactive agents:
  - Somatostatin inhibits the release of vasodilator hormones such as glucagon, indirectly causing splanchnic vasoconstriction and decreased portal inflow
- Prophylactic Antibiotics: Broad Spectrum
  - Quinolones:
    - Ciprofloxacin, Levofloxacin
  - “3rd Generation good gram positive no pseudomonas”
  - Cefotaxime Claforan®
  - Ceftriaxone Rocephin®
  - Carbapenems
    - Imipenem/Cilastin Primaxin®
    - Meropenem Merem®
    - Doripenem Doribax®

Prokinetic agents: clear the visual field

- Motilin Receptor Agonist: Erythromycin
  - Intravenous 250 mg 20-120 minutes prior to endoscopy
    - 48% erythromycin “empty stomach” vs 23% placebo
    - Shortens duration of initial endoscopy
    - Decrease need for second endoscopy
- Metoclopramide Reglan®
  - 10-20mg IV 30-120 minutes prior endoscopy
  - Lower Esophageal sphincter pressure
  - Lower Portal Venous pressure?
  - Improve gastric emptying
- Gastric Lavage

Octreotide: Sandostatin®

- Octreotide is a long-acting analog of somatostatin
- A recent meta-analysis of the 30 best studies demonstrates that the use of vasoactive agents is associated with a reduction in 7-day mortality, improved control of bleeding, lower transfusion requirements, and a shorter hospital stay when compared to placebo
- Comparison of 2 days versus 5 days of octreotide infusion along with endoscopic therapy in preventing early rebleed from esophageal varices: a randomized clinical study.

Conscious Sedation

- Fentanyl
- Midazolam

Treatment of Esophageal Varices

- Hemorrhagic:
  - Endoscopic variceal ligation (EVL)
  - Most effective
- Endoscopic sclerotherapy
- Sclerosants:
  - Sodium tetradecyl sulfate,
  - Sodium morrhuate,
  - Ethanolamine oleate,
  - Polidocanol,
  - Ethanol

Acid Suppression

- High Dose PPI or H2Blocker
  - Decrease acute re-bleed rates s/p ligation procedures?
  - Can/Should be considered adjunctive to ligation

<table>
<thead>
<tr>
<th>Generics</th>
<th>Brand</th>
<th>Product</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Prilosec®</td>
<td>G</td>
<td>No</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Provacid®</td>
<td>G</td>
<td>No</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Protonix®</td>
<td>G</td>
<td>No</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Fosaprin®</td>
<td>20, 40 mg</td>
<td>20-40 QD</td>
</tr>
<tr>
<td>Esmoprazole</td>
<td>Nexium®</td>
<td>2.5, 5, 10, 20, 40 mg</td>
<td>20-40 QD</td>
</tr>
<tr>
<td>Desflurane</td>
<td>Desfluran®</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Zepid®</td>
<td>2, 6, 10, 20, 40 mg</td>
<td>No</td>
</tr>
</tbody>
</table>

Primary Prevention: Secondary Prevention:

- Non Selective Beta Blockers
  - Propranolol Inderal®
  - Nadolol Corgard®
- Limited by HR reduction and tolerability
- Less Data:
  - Isosorbide Mononitrate
    - 30-60 mg BID
  - Isosorbide Dinitrate
    - 30-120 mg QD

Which has been shown to have primary and secondary prevention of esophageal varices?

A. Albuterol 4 mg PO QID
B. Salmeterol 50 mcg MDI BID
C. Nadolol 40 mg PO QD
D. Vilanterol 100 mcg PO QID
Treatment of Ascites

- Stick a needle in it:
- Paracentesis
  - Small Volume:
  - Large Volume:

- Prevent the Formation:
- Aldosterone Antagonists
- Spironolactone
  - 100-400 mg a day
  - Side Effects
- Eplerenone Inspra®
  - 25, 50mg
  - 100-200 mg a day
- Alpha 2 Agonists:
  - Clonidine 0.1-0.3 TID
  - Guanfacine 1-2 TID

Loops: “Water Wasters”

- Furosemide Lasix®
  - 10, 20, 40 80 mg Tablets
  - 10mg/ml Injection
- Bumetanide Bumex®
  - 0.5, 1, 2 mg Tablets
  - 0.25mg/ml Injection
- Torsemide Demadex®
  - 5, 10, 20, 100 mg Tablets
  - 20mg/2ml, 50mg/5ml Injection
- Ethacrynic Acid Edecrin®
  - 25 mg Tablets
  - Sodium Edecrin IV 50 mg

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

- A TIPS procedure involves creating a pathway through the liver that connects the portal vein (the vein that carries blood from the digestive organs to the liver) to a hepatic vein (one of three veins that carry blood from the liver to the heart).
- A stent placed inside this pathway keeps it open and allows some of the blood that would ordinarily pass through the liver to bypass the liver entirely, reducing high blood pressure in the portal vein and the associated risk of bleeding from enlarged veins.

Bacterial Peritonitis

- Acute: Spontaneous Bacterial Peritonitis SBP

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Percent of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>25</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>15</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>10</td>
</tr>
<tr>
<td>Other enterococci</td>
<td>5</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>5</td>
</tr>
<tr>
<td>Other gram-negative</td>
<td>5</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1</td>
</tr>
<tr>
<td>Proteus</td>
<td>1</td>
</tr>
</tbody>
</table>
| Acute SBP TXT:
  - Quinolones:
    - Ciprofloxacin
    - Levofoxacin
  - "3" generation good gram positive
    - Ceftazidime
    - Ceftriaxone
  - Carbapenems:
    - Imipenem/Cilastin
    - Meropenem/Marimastat
    - Doripenem/Zolimastat
Chronic Prophylaxis: Bacterial Peritonitis

- In patients with cirrhosis and ascites but no gastrointestinal bleeding, Abs can be justified if:
  - the ascitic fluid protein <1.5 g/dL and at least one of the following is present:
    - serum creatinine ≥1.2 mg/dL,
    - blood urea nitrogen ≥25 mg/dL,
    - serum sodium ≤130 mEq/L,
    - or Child-Pugh ≥9 points with bilirubin ≥3 mg/dL
- SMZ/TMP 1 DS QD (5-7 Days Week)
- Ciprofloxacin 500 mg Q day

When do we STOP Beta Blocker?

Gastroenterology 2014;146:1680–1690

Hepato-Renal Syndrome:

- Usually the “Terminal Event”
- Complex failure of the kidneys with failed liver
- Pharmacologic Goal:
  - Improve renal function
  - Improve Survival
  - Hours?
  - Days?
  - Weeks?
  - Months?

Rx Interventions:

- Octreotide: “Vasoactive Peptide”
  - Decrease portal pressures volumes
- Plus:
  - Midodrine: 5-20mg TID to QID
  - Peripheral Alpha 1 Agonist
  - Increases peripheral blood pressures
- Goal:
  - Decrease renal failure

Alcohol Poisoning

- Alcohol poisoning is a serious — and sometimes deadly — consequence of drinking large amounts of alcohol in a short period of time.
- Drinking too much too quickly can affect your breathing, heart rate, body temperature and gag reflex and potentially lead to a coma and death
- Usually alcohol naive patients
- “Holiday Heart”
  - Atrial Fibrillation secondary ETOH

Chronic Alcohol Abstinence Strategies:

- Disulfiram Antabuse®, G
  - 250-500 mg/day
- Naltrexone Revia®, G
  - 50 mg/day
- Acamprosate Campral®, G
  - 333 2 tabs TID
- Baclofen
  - 10-20mg TID
- Sodium Channel Blockers
  - Gabapentin
  - Topiramate
  - All of them?

For FDA Approval:

Duration to Relapse:

When Relapse amount consumed:

Non-FDA:

Reduction in Craving scores
Then End

Model for End Stage Liver Disease (MELD)

MELD score = 10(0.957 \times \log e (creatinine) + \log e (bilirubin) + 1.12 + \log e (INR)) + 6.43

3 month mortality according to MELD score

<table>
<thead>
<tr>
<th>MELD score</th>
<th>&lt;=9</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>&gt;=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized pt.</td>
<td>4%</td>
<td>27%</td>
<td>76%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Outpatient cirrhotic</td>
<td>2%</td>
<td>6%</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>