

# An Overview of Alcohol and Your Liver

Alcohol Medical Scholars Program (AMSP) (Slide 1)

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February 22, 2010

## I. Introduction

A. Too much alcohol is bad for your liver

1. Features of a healthy liver are: (Slides 2 and 3)

a. Deeply penetrating blood supply

b. Portal triad

1'. Portal vein: Carries venous blood from the digestive tube, pancreas, and spleen (75%)

2'. Hepatic artery: Supplies oxygenated blood to the liver (25%)

3'. Bile duct: Bile secretion to gut

2. Features of a cirrhotic liver are: (Slide 4)

a. Scarring

b. Distorted portal triad architecture (Slide 5)

B. Alcohol can adversely affect the liver: How much is too much?

1. Some data show EtOH in moderation may be good <sup>1-3</sup>

2. Too much is bad, but where to draw the line?

C. This lecture reviews (Slide 6)

1. How a healthy liver metabolizes alcohol (Slide 7)
2. How alcohol damages the liver
3. How much alcohol is too much
4. How to help

## II. How a healthy liver metabolizes alcohol

### A. Enzymes involved in alcohol metabolism (Slide 8)

1. Starts with oxidation of ethanol to acetaldehyde
  - a. By alcohol dehydrogenase (ADH)
    - b. Byproducts include NADH and acetaldehyde
2. Acetaldehyde further oxidized by aldehyde dehydrogenase (ALDH)
  - a. Final byproducts are
    - 1'. CO<sub>2</sub>
    - 2'. Water
    - 3'. Acetic Acid
  - b. Through the citric acid cycle

### B. Time involved in alcohol metabolism<sup>4</sup> (Slide 9)

1. ↑Blood alcohol concentration (BAC) → ↑time for metabolism
  - a. Typical rate 10 grams (a standard drink)/hour
  - b. BAC after rapid consumption of different amounts<sup>5</sup>
    - 1'. BAC 50mg% = deterioration in driving skills
    - 2'. BAC 100mg% = intoxication in most States

## 2. Varies between individuals

### a. Rate faster if

- 1'. Male
- 2'. High Body Mass Index (BMI)
- 3'. Chronic heavy drinker
- 4'. Fast metabolizer (cytochrome P450 2E1)<sup>6</sup>

### b. Rate slower if

- 1'. Female
- 2'. East Asians (e.g. Chinese)
- 3'. Smaller, leaner
- 4'. Liver disease

## C. Genetic variants in alcohol metabolism<sup>7, 8</sup> (Slide 10)

### 1. Aldehyde dehydrogenase mutation (ALDH2\*2)

- a. 50% East Asians impaired function ALDH
- b. Drinking with ALDH2\*2 → increased acetaldehyde

- 1'. → Skin flush
- 2'. → ↑ pulse

### c. Homozygous vs heterozygous for ALDH 2\*2

- 1'. Homozygotes (ALDH 2\*2, 2\*2)
  - a'. Vomiting , diarrhea, etc.
  - b'. No alcoholics

- 2'. Heterozygotes

a'. Alcohol reaction but not ill

b'. Less alcoholism

2. Alcohol Dehydrogenase (ADH) mutations (Slide 11)

a. Faster ↓ EtOH

b. Faster ↑ acetaldehyde

c. Slightly ↓ alcoholic risk

**III. How alcohol damages liver (Slide 12)**

A. What is alcoholic liver disease (ALD)? (Slide 13)

1. Damage to liver by alcohol

2. Typically occurs in progression

a. Fatty liver and mild inflammation

b. → alcoholic hepatitis

c. → cirrhosis

B. Steps in metabolism leading to ALD (Slide 14)

1. First step (fatty liver) (Slide 14)

a. ADH metabolizes EtOH

b. Acetaldehyde/free radicals more toxic than alcohol

1'. → Mild inflammation

2'. → Fat cell proliferation

c. Image and natural hx. of fatty liver (arrow on fat vacuole)

<sup>12</sup> (Slide 15)

1'. Occurs in almost all heavy drinkers

2'. Usually asymptomatic

3'. Reversible with cessation/reduction of drinking

d. Image of healthy liver (left) and fatty liver (right) (Slide 16)

2. Second step (hepatitis; arrows on inflammatory cells) (Slide 17)

a. Alcohol affects gut bacteria

1'. Bacteria release endotoxins into blood

a'. Prototypical endotoxins = lipopolysaccharide (LPS)

b'. Found in outer membrane of gram-negative bacteria

2'. Cause disease by triggering immune cascade

b. Liver releases cytokines to counteract endotoxins<sup>9</sup>

1'. Specialized liver cell (Kuppfer cells) release cytokines

2'. Cytokines regulate inflammation

3'. Chronically elevated cytokines → less oxygen produced<sup>10</sup>

a'. → Liver cell death

b'. → Further inflammation

c'. → Further elevation of cytokines

4'. See ↑ “liver function tests” (e.g. ALT, AST)

c. Image and natural hx. of alcoholic hepatitis<sup>12</sup> (Slide 18)

1'. Seen in up to 35% of heavy drinkers

2'. Can occur suddenly

3'. Usually reversible if EtOH stopped/decreased

3. Third step (cirrhosis) (Slide 19)

a. Liver cell death → proliferation of stellate cells<sup>11</sup>

1'. Stellate cells = specialized liver cells

2'. Normal response to wound healing

b. Continued alcohol ingestion → further stellate cell proliferation

c. → Scarring

1'. Distorts normal liver architecture

2'. Impairs normal liver function

d. Image and natural hx. of cirrhosis<sup>12</sup> (Slide 20)

1'. ~ 20% alc's develop cirrhosis after 10 or more years of drinking

2'. 12<sup>th</sup> leading cause of death in adults (44% alcohol related)<sup>6</sup>

3'. Damage irreversible, but can stabilize with cessation of EtOH

C. Susceptibility to ALD<sup>13</sup> (Slide 21)

1. Genetic (researchers seeking factors to explain variations) <sup>6</sup>

- a. ADH mutation linked to cirrhosis but findings inconsistent
- b. ALDH2\*2 protective for alcoholic liver disease through ↓ AUD risk<sup>14</sup>
  - 1'. Aversive high levels acetaldehyde
  - 2'. Alcohol cirrhosis decreased 70% in ALDH 2\*2
- c. Cytochrome P450 variations
  - 1'. Affects liver and blood alcohol concentration (BAC)
  - 2'. People vary in ability to eliminate alcohol
  - 3'. Blood Alcohol Concentration (BAC) factor in ALD

## 2. Dietary

- a. Drinking without food, independent of quantity → ↑ risk ALD<sup>15</sup>
- b. High polyunsaturated fats → ↑ risk cirrhosis in animals<sup>16</sup>
- c. In alc's, obesity/hyperglycemia/ iron overload → ↑ risk cirrhosis<sup>6</sup>

## 3. Gender<sup>17</sup>

- a. Women more ALD after shorter EtOH careers
  - 1'. Lower ADH in stomach in women
  - 2'. → Higher BAC
  - 3'. ? Estrogen increases susceptibility to ALD?
- b. Mortality from cirrhosis 2x in women vs men

#### IV. How much alcohol is too much? (Slide 22)

##### A. Quantity x Frequency (Q/F)<sup>6</sup> (Slide 23)

1. Higher quantity x more time → ↑ risk ALD
2. Daily heavy drinking → ↑ risk cirrhosis<sup>18</sup>
3. > 2 drinks/daily → ↑ risk ALD
4. AUDIT-C score ≥ 5 → ↑ risk ALD

##### B. One standard drink (~10 grams ethanol)

1. 12 oz beer
2. 0.5 oz wine
3. 1.5 oz hard liquor (40% or “80 proof”)

##### C. Can measure Q/F with Time-Line-Follow-Back method (TLFB) (Slide 24)

1. Counting backwards from today, # standard drinks per day
2. Total # standard drinks in preceding week
3. Good validity and reliability

##### D. Q/F explored with AUDIT-C (Slide 25)

1. AUDIT-C questions validated as screening tool in many settings<sup>19</sup>
  - a. “How often have you had a drink containing alcohol in the last year?”
  - b. “How many drinks containing alcohol did you have on a typical day when you were drinking in the last year?”



c. "How often in the last year have you had 6 or more drinks on one occasion?"

2. AUDIT-C scoring

a. Possible scores 0-12

b. Reference range in literature for low-level drinking = AUDIT-C 1-4

c. Other groupings:

1'. AUDIT-C = 0 (non-drinkers)

2'. AUDIT-C = 5-8 (mild to moderate alcohol misuse)

A'. 1-2 drinks most days

B'. 6 or more drinks on some days in past year

3'. AUDIT-C = 9-12 (severe alcohol misuse  $\geq 5$  drinks most days)

3. Data EtOH amounts and liver toxicity (Slide 26)

a. Hazardous drinking  $\rightarrow$  increased risk of liver disease<sup>28</sup>

1'. Definition of hazardous drinking ("too much")

A'. Men: > 14 drinks/week or > 4 drinks on any occasion

B'. Women: > 7 drinks/week or > 3 drinks on any occasion

2'. Use TLFB method to deduce # drinks/week/  
occasion

- b. AUDIT-C scores 9–12 → 7x risk of new-onset liver disease in men<sup>29</sup>
- c. AUDIT-C scores 9–12 → 10x risk of new-onset liver dx in women<sup>29</sup>
- d. AUDIT-C scores > 5 → ↑ risk new G.I dx/G.I. hospitalization<sup>29</sup>

E. Some amount of alcohol healthier than not drinking? (Slide 27)

1. Data low-level EtOH → ↑ health compared to not drinking (controversial)

- a. ↓Mortality<sup>20, 21</sup>
- b. ↓G.I. illnesses<sup>22</sup>
- c. ↓Gastritis, cholelithiasis<sup>23</sup>
- d. ↓Cardiovascular disease<sup>24</sup>
- e. ↓Dementia (vascular and Alzheimer's) <sup>25</sup>

2. Protective effects may be overstated due to systematic study error <sup>26</sup>

- a. Data skewed by listing “sick quitters” as non-drinkers
- b. Many non-drinkers former heavy drinkers
- c. Many non-drinkers seriously ill
- d. Occasional drinkers as abstainers also biased

3. Meta-analysis on heart disease protection from low EtOh

- a. Controlling for lifelong abstainers, exdrinkers, and occ. drinkers
- b. No coronary disease protection for low EtOH use vs abstainers<sup>27</sup>
- c. No difference in overall mortality for low EtOH vs abstainers<sup>26</sup>

4. Regular light drinking more likely a marker of good health than a cause<sup>26</sup>

F. ↑Quantity associated with AUD and ALD

- 1. However, strict DSM-IV AUD diagnosis not reliant on quantity

(Slide 28)

a. EtOH abuse criteria: consequences

- 1'. Failure to fulfill role obligations
- 2'. Physically hazardous
- 3'. Legal problems
- 4'. Social/interpersonal problems

b. EtOH dependence criteria: control, compulsion, and consequences

- 1'. Tolerance and/or withdrawal
- 2'. Larger amounts than intended
- 3'. Unable to control use
- 4'. More time spent than intended

5'. Activities given up for use

6'. Continued despite persistent problems

2. Need quantity assessment to determine risk of ALD

## V. How to help (Slide 29)

A. Recognize heavy drinking and AUD's are common (Slide 30)

1. ~25% general population misuses alcohol

2. ~16% hazardous use

3. ~7% abuse or dependence

4. These patients have jobs, families, look like other patients

B. Screen for alcohol consumption (Slide 31)

1. Questionnaires focused on quantity and frequency

a. AUDIT-C (as described above)

b. Time-line-follow-back (TLFB)

2. Blood tests

a. Gamma-glutamyl transferase (GGT) (Slide 32)

1'.  $\uparrow$  Before damage to liver; GGT > 35 IU/L

2'. If GGT > 51, may signal liver damage

3'.  $\uparrow$  in 75% of chronic heavy drinkers

4'. Not specific to ALD (70% specificity)

b. Carbohydrate deficient transferrin (CDT) (Slide 33)

1'. Plasma protein that carries iron to bone marrow

2'.  $\geq 2.6\%$  suggestive of 5+ drinks/day regularly

3'. Sensitivity/specificity slightly > GGT

c. 'Liver function tests' (only after liver damage) (Slide 34)

1'. Alanine transaminase (ALT) (9–60 IU/L normal range)

2'. Aspartate transaminase (AST) (10–40 IU/L normal range)

3'. AST/ALT ratio > 2/1 → suggestive of ALD

C. Target treatment to level of severity (Slide 35)

1. If just hazardous use (not abuse or dependence) → “brief intervention”<sup>30</sup>

a. 15 minutes initial contact (5 A's of SBIRT) (Slide 36)

1'. Assess using a screening tool

2'. Advise to quit or reduce to healthy standards

3'. Agree on goals for reducing use

4'. Assist in motivating change

5'. Arrange follow-up or referral

b. At least one follow-up

c. Can reduce average # drinks/week by ~25%<sup>30</sup>

d. Refer to Moderation Management

1'. Mutual help group modeled on Alcoholics

Anonymous

2'. Goal is moderation in consumption, not abstinence

2. If abuse or dependence (Slide 37)

a. 12-step mutual help groups (Alcoholics Anonymous)

b. Referral to higher level of AUD care

1'. Day treatment

2'. Residential

3'. Clean and sober living environment

c. Consider medications

E. Meds for AUD's sometimes helpful (with psychosocial) (Slide 38)

a. Naltrexone 50–150 mg/daily

1'. Opioid blocker

2'. Thought to reduce cravings

b. Acamprosate ~ 2 mg/daily

1'. Antagonist to NMDA–glutamate receptor

2'. May decrease time to relapse

c. Antabuse: 250 mg/daily

1'. Blocks ALDH → nausea/vomiting if drinking concurrently

2'. Deterrent; issues of compliance

3'. Cannot use in ALD, diabetes, heart disease,

etc.

## F. Treating Alcoholic Liver Disease (Slide 39)

1. Stop drinking
2. Limit medications, including nonprescription drugs, e.g. acetaminophen
3. Low sodium diet
4. Reduce fluid build-up in the abdomen (ascites) (Slide 40)
  - a. Diuretic medications – eliminate fluid
  - b. Paracentesis – needle in abdomen to draw out fluid
  - c. Antibiotics – to fight infection in abdomen 2/2 ascites
  - d. Transjugular intrahepatic portosystemic shunt (TIPS) – divert fluid
5. Control variceal bleeding (leaky veins in G.I. tract) (Slide 41)
  - a. Vasoconstrictor medications
  - b. Shunts: redirect blood flow
  - c. Endoscopic variceal banding
6. Minimize encephalopathy (Slide 42)
  - a. Changes in mental function 2/2 liver not filtering poisons
  - b. Medication lactulose; prevents build-up of ammonia in gut
  - c. Low protein diet
6. Liver transplant
  - a. Indications

1'. When damage to liver is life-threatening

2'. No other serious medical conditions

b. Screening

1'. No EtOH or drug use x 6 months

2'. Good support system

3'. Can comply with complex post-transplant regimen

## VI. Conclusion

A. I've reviewed

1. How a healthy liver metabolizes alcohol
2. How alcohol can damage the liver
3. How much alcohol is too much: The evidence
4. How to help (Slide 43)
  - a. Screen
  - b. Intervene
  - c. Treat ALD

B. Take-home message (Slide 44)

1. Too much alcohol is bad for your liver
2. Screen and intervene
2. Too much means drinking in the hazardous range
  - a. AUDIT-C score > 5 for men and women
  - b. Men: > 14 drinks/week or > 4 drinks on any occasion
  - c. Women: > 7 drinks/week or >3 drinks on any occasion





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