Liver Disease in the Geriatric Patient

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Overview

• Changes in the aging liver
• Hepatitis C
• Non-alcoholic steatohepatitis
• Cirrhosis
  • TIPS
  • Liver Transplantation
• Hepatocellular carcinoma
The liver ages!

- Decrease in size of the liver due to decrease in number of hepatocytes
  - Liver size decreases by 25% from age 20 to 70
- Blood flow decreased by 1/3 in those over age 65
- No effect on liver tests
- Decrease in bile production and flow

Merck Manual online, accessed 8/22/2016

The aging liver

- Ability to metabolize decreases with decreased activity of hepatic cytochrome P450
  - Increased sensitivity to xenobiotics
  - Drug induced liver injury
- Pro-inflammatory state in elderly
  - Decreases ability to repair injury
- No age-related reduction in hepatic alcohol dehydrogenase
Drug induced liver injury in elderly

- Some data to suggest that incidence of DILI increases in the elderly
- Confounded by increased prescription number
- Elderly more likely to present with cholestatic pattern of liver tests
- Subacute presentation associated with worse prognosis


Overview

- Changes in the aging liver
- **Hepatitis C**
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- Cirrhosis
  - TIPS
  - Liver Transplantation
- Hepatocellular carcinoma
HCV Overview

- Discovered 1989
- Most common chronic blood borne infection in U.S.
  - Only 20% of HCV-infected persons in U.S. have been diagnosed
- May spontaneously resolve after acute infection (15–25%)
- Most often becomes a chronic disease that may lead to cirrhosis and liver cancer
- No vaccine available
- Treatment can result in viral eradication

Sources of Infection for Persons With Hepatitis C

- Injection drug use 60%
- Sexual 15%
- Transfusion 10% (before screening)
- Occupational 4%
- Other 1%
- Unknown 10%

* Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention
HCV Screening Guidelines

HCV Screening Guidelines From AASLD/IDSA/IAS-USA, CDC, and USPSTF

<table>
<thead>
<tr>
<th>Age-based</th>
<th>• One-time screening for adults born between 1945 and 1965¹-³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk-based</td>
<td>• Past or current injection drug use¹-³ or intranasal drug use¹-³</td>
</tr>
<tr>
<td></td>
<td>• Long-term kidney dialysis¹-³</td>
</tr>
<tr>
<td></td>
<td>• Recipients of: transfusion of blood or blood component, organ transplant before July 1992,¹-³ clotting factor concentrate before 1987,¹-² blood from a donor who later tested HCV-positive¹-²</td>
</tr>
<tr>
<td></td>
<td>• Healthcare worker exposed to HCV-infected blood¹-³</td>
</tr>
<tr>
<td></td>
<td>• Receipt of an unsterile/unregulated tattoo¹-³</td>
</tr>
<tr>
<td></td>
<td>• Children born to HCV-infected mothers¹-³</td>
</tr>
<tr>
<td></td>
<td>• Incarceration¹-³</td>
</tr>
<tr>
<td>Other medical conditions</td>
<td>• HIV infection¹-²</td>
</tr>
<tr>
<td></td>
<td>• Unexplained chronic liver disease, including persistently elevated ALT¹-²</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AASLD, IDSA, IAS-USA = The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society-USA; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; USPSTF = US Preventive Services Task Force.


HCV Tests:
What the Results Mean

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Acute or chronic HCV depending on the clinical context</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>False positive HCV antibody Resolved infection Low-level intermittent viremia</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>Early acute HCV infection Chronic HCV in setting of immunosuppressed state False positive HCV RNA test</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>Absence of HCV infection</td>
</tr>
</tbody>
</table>

Hepatitis C - Genetics

- Six genotypes, 1 through 6
- Subtypes, designated a, b, c, etc.
- Genotype 1 is the most common genotype in the United States

HCV Viral Load Independent of Fibrosis

- Genotypes and viral load distribution
- Log HCV RNA (copies/mL)
- No Fibrosis, Portal Fibrosis, Bridging Fibrosis, Cirrhosis

Source:
- Feroci, Semin Liver Dis 2003;23:13-16
Over 5.2 Million People Living With Chronic HCV in the US

Chak E, et al. Liver Int. 2011; 31:1090-1101

Hepatitis C Natural History

75% of patients exposed to HCV will not develop significant disease!
http://www.hepatitisc.uw.edu/page/treatment/drugs
Treatment of HCV in geriatric population

- In the interferon era, elderly were less likely to receive HCV treatment
- Patients with a life expectancy longer than 1 year can be considered for treatment HCV
  - Insurance authorization is the biggest barrier
- Receipt of curative antiviral treatment is associated with reduction in risk of cirrhosis, HCC and overall mortality, irrespective of age
- The key is identifying those who have HCV and link patients to care particularly those with CIRRHOSIS

El-Serag HB et al. J of Viral Hepatitis, 2016;23:687-696

I have a patient with HCV, what do I do?

- First ask, does the patient have cirrhosis?
  - Stay tuned
- If cirrhosis and life expectancy greater than a year, would treat HCV
  - Choice of regimen made in conjunction with a liver provider
  - There are many choices and variations based on patients prior history
  - Typically is approved by insurance
- If you do not suspect cirrhosis and life expectancy greater than a year, can treat HCV if insurance approval
- Pharmacy review of drug-drug interaction is critical**
- [http://www.hepatitisc.uw.edu/](http://www.hepatitisc.uw.edu/)
Overview

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- **Non-alcoholic steatohepatitis**
- Cirrhosis
  - TIPS
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The Metabolic Syndrome

- Insulin resistance
- Type 2 diabetes
- Heart disease
- Hypertension
- Lipid problems
- NAFLD
- Cancer
- Dementia
Burden of Non-alcoholic fatty liver disease (NAFLD)

- Diagnosis of NASH can ONLY be with biopsy, but biopsies rarely done unless ruling out another diagnosis (ie autoimmune hepatitis) or for staging
- Treatment for NASH is judicious weight loss!
- Clinical studies have shown that even 10% weight loss can reverse inflammation and fibrosis formation
- If patients are able to lose a more significant amount of weight (>10%), NASH can resolve
  - 90% in one study
- Medications that have been explored: vitamin E, pioglitazones
- Obeticholic acid- synthetic bile acid → decreases inflammation and fibrosis

**NASH and Cardiovascular disease**

- NASH associated with increased CV risk
- CV disease is the leading cause of death in NASH cirrhosis
- Comorbidities affect candidacy for liver transplantation, treatments for complications of cirrhosis


**NASH in the elderly**

- Adequate treatment of this condition is often limited by patient’s physical health and the ability to be active
- Medically optimize other components of the metabolic syndrome: DM, dyslipidemia
- Statins are not contraindicated in NASH
- Less open to lifestyle modifications?

Bertolotti M et al. *WJG* 2014
Overview

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Progression of fibrosis

- Normal
- Inflamed
- Fibrotic
- Cirrhotic

Healing

Repetitive injury

Staging according to Metavir Score

- **F1**
  - Portal fibrosis

- **F2**
  - Portal fibrosis with few septa

- **F3**
  - Septal fibrosis

- **F4**
  - Cirrhosis
Quick tips to spot cirrhosis

- Particularly in HCV/NASH, if AST>ALT
  - Main considerations are EtOH vs. cirrhosis
- Concomitant liver disease- esp hx. of EtOH dependence/abuse
- FIB-4
  - FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis
  - FIB-4 >3.25 would have a 97%
- Low PLT count
- Palmar erythema
- Splenomegaly
- Fibroscan (transient elastography) – proxy for liver biopsy
  - Need specific software package for NASH
Complications of cirrhosis

- Cirrhosis in older adults expected to increase due to rising incidence of NASH and aging of HCV population
- Comorbid conditions of the geriatric population often makes care of liver disease in this setting complex
- Identification of cirrhosis is the key initial diagnostic node when seeing any patients with chronic liver disease
  - EGD for variceal screening
  - HCC surveillance
  - Monitoring for other complications of cirrhosis

Decompensated liver disease/Portal hypertension
- Variceal bleeding
- Ascites
- Spontaneous Bacterial Peritonitis
- Hepatorenal syndrome
- Hepatic Encephalopathy
- Hepatopulmonary Syndrome
- Portopulmonary Syndrome
- Hepatocellular carcinoma

Impact of cirrhosis on older adults

Impact of cirrhosis on older adults

- Study in medicare population
- Individuals with cirrhosis had worse self-reported health status, more comorbidities
- Used significantly more health care services (hospitalizations, nursing home stays, physician visits)
- Greater functional disability for activities of daily living and instrumental activities of daily living
- Patients with cirrhosis received 2x the number of informal caregiving hours per week
- Comorbidities determine eligibility for many of the interventions and management recommendations in cirrhosis


TIPS: Transjugular intrahepatic portosystemic shunt
TIPS: Indications

• Common Indications
  • Refractory esophageal variceal bleeding
  • Gastric variceal bleeding
  • Refractory ascites
    • Ascites despite maximal diuretics
    • Renal insufficiency and electrolyte derangements on diuretics
  • Hepatic hydrothorax

Garcia-Tsao G. Sem Int Rad 2005

TIPS: Contraindications

• Absolute Contraindications
  • Congestive heart failure
  • Pulmonary hypertension
  • Sepsis

• Relative Contraindications
  • Age greater than 70 years
  • Refractory pre-existing hepatic encephalopathy
  • Child-Pugh Score >12, MELD 17
TIPS in Elderly

- Complications post-TIPS
  - Death
  - Acute liver injury/Ischemia
  - Encephalopathy
    - Impact of HE on patient and family
    - 20% risk of new onset HE after TIPS
- No statistical difference in adverse events in one study comparing patients younger 65 and older than 65

Parvinian A et al. J Vasc Interv Rad 2013

Can my patient with cirrhosis have surgery?

- Risks for any elective surgery increase once patient has a decompensation of liver disease
  - Most surgeries not recommended
- Even with Child’s A cirrhosis, risk of decompensation of liver disease after surgery
- “Clear patient for surgery”
- Post-operative mortality for patients with cirrhosis
Liver Transplantation in Older Adults

- In UNOS database, age >60 was associated with increased mortality
- Outcomes can be favorable for older patients, but only in highly selected candidates


Who should I refer for liver transplantation?

- No strict age cutoff for liver transplantation
- MELD>15 or have hepatocellular carcinoma
  - MELD-Na
- General rule of thumb: Candidates for LT are those age <65 with comorbidities or age <70 without comorbidities
  - DM, HTN
  - Severe CAD/PVD/CVD are contraindications
- Hepatologists at OHSU/VA are always available to discuss whether or not patients are candidates for liver transplantation
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Epidemiology of HCC

- 50-80% associated with cirrhosis
  - United States: Hepatitis C cirrhosis
- HCC in the absence of cirrhosis with chronic liver disease
  - Hepatitis B
  - Hemochromatosis
  - Non-alcoholic fatty liver disease
- 3:1 Male: Female
**Trends in US Cancer Mortality Rates**

- From 2003 to 2012, HCC continues to increase in incidence and mortality.
- HCC had the highest mortality rate increase of all cancers.
- Increase in incidence was second only to thyroid cancer.

**Annual Report to the Nation on the Status of Cancer, 1975-2012, Featuring the Increasing Incidence of Liver Cancer**

- Ryerson AB et al. Cancer 2016;122:1312–37
- El-Serag HB, Kanwal F. Hepatology 2014
Risk Factors for HCC

Fig. 1. Estimated 5-year cumulative risk (%) in cirrhosis
Caldwell S, Park SH. J Gastroenterol 2009;44(Suppl XIX):96-101
Risk Factors for HCC

75% of patients exposed to HCV will not develop significant disease!

Natural History of Hepatitis C

Caldwell S, Park SH. J Gastroenterol 2009;44(Suppl XIX):96-101
### Population Group - Surveillance Recommended

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for efficacy</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian male HBV carriers &gt; age 40</td>
<td>0.2</td>
<td>0.4-0.6%/year</td>
</tr>
<tr>
<td>Asian female HBV carriers &gt; age 50</td>
<td>0.2</td>
<td>0.3-0.6%/year</td>
</tr>
<tr>
<td>HBV carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
</tr>
<tr>
<td>African/North American Blacks with HBV</td>
<td>0.2</td>
<td>HCC occurs at younger age</td>
</tr>
<tr>
<td>Cirrhotic HBV carriers</td>
<td>0.2-1.5</td>
<td>3-8%/year</td>
</tr>
<tr>
<td>HCV cirrhosis</td>
<td>1.5</td>
<td>3-5%/year</td>
</tr>
<tr>
<td>Stage 4 PBC</td>
<td>1.5</td>
<td>3-5%/year</td>
</tr>
<tr>
<td>Genetic hemochromatosis and cirrhosis</td>
<td>1.5</td>
<td>Probably &gt;1.5%/year</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin def and cirrhosis</td>
<td>1.5</td>
<td>Probably &gt;1.5%/year</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Bruix J and Sherman M. AASLD Guidelines for HCC 2010

### AASLD HCC Guidelines 2010: Surveillance

- Ultrasound ONLY, every 6 months
- Data for this surveillance strategy is sparse
- Hepatitis B: RCT showing benefit of 6 month interval
- Most significant concern is the lack of utilization of surveillance
  - Only approximately 30%

Bruix J and Sherman M. AASLD Guidelines for HCC 2010
Surveillance of HCC - AFP

- AFP 20 ng/mL provides the optimal balance between sensitivity and specificity
  - Sensitivity is only 60%
  - If AFP cut-off 200 ng/mL, sensitivity 22%
- Role of AFP in diagnosis is de-emphasized in 2010 guidelines
- Remains controversial

Bruix J and Sherman M. AASLD Guidelines for HCC 2010

CT or MRI for surveillance?

- Role for CT and MRI in diagnosis of HCC
- Limited data for surveillance with cross sectional imaging modalities
- Issues with surveillance:
  - Radiation
  - Contrast administration
  - Expense

Bruix J and Sherman M. AASLD Guidelines for HCC 2005
LI-RADS: Liver Imaging Reporting and Data System

<table>
<thead>
<tr>
<th>Diameter (mm):</th>
<th>Arterial phase hypo- or iso-enhancement</th>
<th>Arterial phase hyper-enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>LR-3</td>
<td>LR-3</td>
</tr>
<tr>
<td>≥ 20</td>
<td>LR-3</td>
<td>LR-5</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>LR-3</td>
<td>LR-5</td>
</tr>
<tr>
<td>10-19</td>
<td>LR-4</td>
<td>LR-5</td>
</tr>
<tr>
<td>≥ 20</td>
<td>LR-4</td>
<td>LR-5</td>
</tr>
<tr>
<td>&quot;Washout&quot;</td>
<td>None</td>
<td>LR-4</td>
</tr>
<tr>
<td>&quot;Capsule&quot;</td>
<td>One</td>
<td>LR-4</td>
</tr>
<tr>
<td>&quot;Threshold growth&quot;</td>
<td>≥ Two</td>
<td>LR-5</td>
</tr>
</tbody>
</table>

Observations in this cell are categorized LR-4 except as follows:
- LR-5a, if there is ≥ 50% diameter increase in ≤ 6 months. These observations are equivalent to CPTN 5a-
- LR-5a., if there is both "washout" and visibility as discrete nodules at antecedent surveillance ultrasound, per AASLD HCC guidelines.

http://www.hitachimed.com/self-learning-activity/docs/AbdominalImagingModule/images/figure-43.jpg

pseudocapsule

http://www.hitachimed.com/self-learning-activity/docs/AbdominalImagingModule/images/figure-43.jpg
**BCLC Staging (Barcelona Clinic Liver Cancer)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Status</th>
<th>Performance Status</th>
<th>Liver Functional Status</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>Single or 3 tumors &lt;3cm</td>
<td>0</td>
<td>Child-Pugh A-B</td>
<td>50-75% 5 year</td>
</tr>
<tr>
<td><strong>Stage B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Large, multinodular</td>
<td>0</td>
<td>Child-Pugh A-B</td>
<td>50% 3 year</td>
</tr>
<tr>
<td><strong>Stage C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>Vascular invasion or extrahepatic spread</td>
<td>1-2</td>
<td>Child-Pugh A-B</td>
<td>50% 1 year</td>
</tr>
<tr>
<td><strong>Stage D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal</td>
<td>Any</td>
<td>3-4</td>
<td>Child-Pugh C</td>
<td>&lt; 3 months</td>
</tr>
</tbody>
</table>

Stage A and B: all criteria must be fulfilled  
Stage C: At least one criteria- Performance Status or Vascular invasion  
Stage D: At least one criteria- Performance Status or Stage/Child’s C


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**Child Pugh Score**

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin, μmol/L (mg/dL)</td>
<td>&lt;34 (&lt;2)</td>
<td>34-50 (2-3)</td>
<td>&gt;50 (&gt;3)</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.71-2.20</td>
<td>&gt; 2.20</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Grade I (or suppressed with medication)</td>
<td>Grade III-IV (or refractory)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>One year survival</th>
<th>Two year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>45%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Is it within the Milan Criteria?

- Single tumor, not > 5 cm
- Up to 3 tumors, none > 3 cm

Absence of macroscopic vascular invasion, absence of extrahepatic spread

- 5 year survival 71-75%

Bruix J and Sherman M. AASLD Guidelines for HCC 2010


Yao FY. Am J Transpl 2008;8:1-8

Slide courtesy of Dr. Joseph Ahn
Non-cirrhotic HCC

**TABLE 1: Summary of the Differences Between Hepatocellular Carcinoma (HCC) in a Cirrhotic Liver and HCC in a Non-cirrhotic Liver**

<table>
<thead>
<tr>
<th>Difference</th>
<th>HCC in Cirrhotic Liver</th>
<th>HCC in Non-cirrhotic Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Underlying viral hepatitis or alcohol abuse leading to cirrhosis</td>
<td>Underlying hereditary disorders, metabolic syndromes, viral hepatitis, or genotoxin exposure</td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td>Stepwise carcinogenesis: regenerative nodule → dysplastic nodule → HCC</td>
<td>De novo carcinogenesis</td>
</tr>
<tr>
<td>Major molecular alterations</td>
<td>Mutations or deletions of tumor suppressor genes such as p53, Rb, IGFBP2, and p16/INK4 and activation of protooncogenes such as β-catenin and ras-MAPK pathway; loss of heterozygosity is frequent</td>
<td>Lower rate of p53 mutation, higher prevalence of β-catenin mutation, p14 activation, and DNA mismatch repair; increased levels of V654—β-catenin in fibrolamellar HCC; loss of heterozygosity is infrequent</td>
</tr>
<tr>
<td>Multifocal or solitary</td>
<td>Usually multifocal</td>
<td>Usually solitary</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Variable size, often small</td>
<td>Large (mean size, 12.4 cm)</td>
</tr>
<tr>
<td>Demography</td>
<td>High male preponderance (male:female ratio, 8:1); common in elderly age group</td>
<td>Relatively lower male preponderance (male:female ratio, 2:1); bimodal distribution in 2nd and 7th decades</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Hepatomegaly, abdominal pain, jaundice, ascites</td>
<td>Hepatomegaly, abdominal pain, asthenia, malaise, fever, weight loss, and anorexia</td>
</tr>
</tbody>
</table>

Note—MAPK = mitogen-activated protein kinase.

**Treatment consideration:** more likely to be resection candidates given lack of cirrhosis

Gaddikeri S et al. AJR 2014

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**Summary**

- There are physiologic changes in the liver with aging that affect its susceptibility to injury
- Hepatitis C- we can treat older adults!
- Non-alcoholic steatohepatitis- the next epidemic in liver disease
- Both HCV and NASH are significant contributors to the burden of advanced liver disease/cirrhosis in the US
Summary

• Identifying cirrhosis is key due to risks of developing complications
• Cirrhosis can be difficult to manage in patients who are older with comorbidities
  • Education regarding complications of cirrhosis and what to expect
• Liver transplantation and TIPS: not typically recommended age > 70
• HCC
  • Many options for liver directed therapy for HCC
  • Non-cirrhotic HCC has a bimodal distribution with a peak in the 7th decade

Questions?

AASLD Guidelines
http://www.aasld.org/publications/practice-guidelines-o