Management of Patients with Cirrhosis: Dispelling Myth and Avoiding Common Pitfalls

Jody C. Olson, M.D., FACP
Assistant Professor of Medicine and Surgery
Hepatology and Transplant Critical Care

Kansas ACP Chapter Meeting
October 13, 2017
Learning Objectives

• Describe epidemiology and basic clinical definitions in advanced liver disease
• Describe common myths and errors in management of cirrhosis
• Review basic management of common complications of cirrhosis
Prevalence of Cirrhosis in the US

- 0.27% corresponding to 633,323 adults
- 69% were unaware of having the disease
- 30,000 diagnoses per year at tertiary referral centers

Scaglione et al., *J Clin Gastroenterol* 2015 Sep;49(8):690-6
### 20 leading causes of death worldwide

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>Deaths (000s)</th>
<th>% deaths</th>
<th>Deaths per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>All Causes</td>
<td>55859</td>
<td>100.0</td>
<td>789.5</td>
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<tr>
<td>1</td>
<td>Ischaemic heart disease</td>
<td>7356</td>
<td>13.2</td>
<td>104.0</td>
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<tr>
<td>2</td>
<td>Stroke</td>
<td>6671</td>
<td>11.9</td>
<td>94.3</td>
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<td>3</td>
<td>Chronic obstructive pulmonary disease</td>
<td>3104</td>
<td>5.6</td>
<td>43.9</td>
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<td>4</td>
<td>Lower respiratory infections</td>
<td>3052</td>
<td>5.5</td>
<td>43.1</td>
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<tr>
<td>5</td>
<td>Trachea, bronchus, lung cancers</td>
<td>1600</td>
<td>2.9</td>
<td>22.6</td>
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<td>6</td>
<td>HIV/AIDS</td>
<td>1534</td>
<td>2.8</td>
<td>21.7</td>
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<td>7</td>
<td>Diarrhoeal diseases</td>
<td>1498</td>
<td>2.7</td>
<td>21.2</td>
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<td>8</td>
<td>Diabetes mellitus</td>
<td>1497</td>
<td>2.7</td>
<td>21.2</td>
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<td>9</td>
<td>Road injury</td>
<td>1255</td>
<td>2.3</td>
<td>17.7</td>
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<td>10</td>
<td>Hypertensive heart disease</td>
<td>1141</td>
<td>2.0</td>
<td>16.1</td>
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<td>11</td>
<td>Preterm birth complications</td>
<td>1135</td>
<td>2.0</td>
<td>16.0</td>
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<tr>
<td>12</td>
<td>Cirrhosis of the liver</td>
<td>1021</td>
<td>1.8</td>
<td>14.4</td>
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<tr>
<td>13</td>
<td>Tuberculosis</td>
<td>955</td>
<td>1.7</td>
<td>13.2</td>
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<tr>
<td>14</td>
<td>Kidney diseases</td>
<td>864</td>
<td>1.6</td>
<td>12.2</td>
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<tr>
<td>15</td>
<td>Self-harm</td>
<td>804</td>
<td>1.4</td>
<td>11.4</td>
</tr>
<tr>
<td>16</td>
<td>Birth asphyxia and birth trauma</td>
<td>744</td>
<td>1.3</td>
<td>10.5</td>
</tr>
<tr>
<td>17</td>
<td>Liver cancer</td>
<td>740</td>
<td>1.3</td>
<td>10.5</td>
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<tr>
<td>18</td>
<td>Stomach cancer</td>
<td>733</td>
<td>1.3</td>
<td>10.4</td>
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<tr>
<td>19</td>
<td>Colon and rectum cancers</td>
<td>724</td>
<td>1.3</td>
<td>10.2</td>
</tr>
<tr>
<td>20</td>
<td>Alzheimer's disease and other dementias</td>
<td>701</td>
<td>1.3</td>
<td>9.9</td>
</tr>
</tbody>
</table>

Worldwide burden of liver disease

Underestimation of Liver-Related Mortality in the United States

SUMEET K. ASRANI,¹,² JOSEPH J. LARSON,³ BARBARA YAWN,⁴,⁵,⁶ TERRY M. THERNEAU,³ and W. RAY KIM¹,⁴

Asrani et al., Gastroenterology (2013);145:375–382
Total number of cirrhosis hospitalizations

Total hospital charges associated with cirrhosis hospitalizations in billions of dollars

Costs associated with critical care of advanced liver disease in billions of dollars

Data from Dr. W. Ray Kim
Mortality Trends: Cirrhosis and ICU

Data from Dr. W. Ray Kim
Leading Causes of Cirrhosis in the US

- Chronic hepatitis C infection
- Alcohol related liver disease
- Non-alcoholic fatty liver disease (NAFLD)
Definitions

• Cirrhosis
  • Final common pathway for chronic liver disease

• Compensated disease
  • Median survival 10+ years

• Decompensated disease
  • Median survival ~2 years
Diagnosis of Cirrhosis
Quiz:

What is the first lab abnormality often present in cirrhosis?

A) Elevated AST and or ALT
B) Elevated bilirubin
C) Thrombocytopenia
D) Elevated INR
Quiz:

What is the first lab abnormality often present in cirrhosis?

A) Elevated AST and or ALT
B) Elevated bilirubin
C) Thrombocytopenia
D) Elevated INR
Diagnosis
Diagnosis
Diagnosis
Cirrhosis should be suspected

1. Patient with chronic liver disease
   a. Variceal bleeding
   b. Ascites
   c. Hepatic encephalopathy

2. Physical examination:
   a. Splenomegaly
   b. Spider nevi
   c. Palmar erythema
   d. Parotid enlargement
Cirrhosis should be suspected

3. Labs
   a. Thrombocytopenia (often the first lab abnormality)
   b. AST> ALT (in non-alcoholic liver disease)
   c. Low albumin or elevated INR

4. Abdominal imaging:
   a. Nodular liver
   b. Collaterals
   c. Splenomegaly
   d. Varices
Role of Biopsy

- Not required in decompensated disease
- In compensated disease may aid in diagnosis of cirrhosis and etiology
- Expensive
- Procedure related complications
- Requires expertise
  - Procedure
  - Pathology
Algorithm to Assess Presence of Cirrhosis

- Variceal hemorrhage, ascites, encephalopathy
  - AND/OR
    - Plt < 100,000/µl + AST > ALT
    - Cirrhotic liver on imaging
    - Varices on endoscopy
  - Patient has cirrhosis
  - No need for biopsy

- History + physical exam
  - CBC
  - Liver profile
  - Imaging

- Fibrosis assessment by liver stiffness and/or fibrosis serum scores
  - Reliable/Agree
    - Patient has cirrhosis
    - No need for biopsy
  - Disagree, unreliable, unavailable, or diagnostic uncertainty
    - Liver biopsy

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Medication Safety in Cirrhosis
Myth: Acetaminophen is unsafe in cirrhosis
Etiology of Acute Liver Failure in the USA
Adult Registry (n = 2,000)

ALF Study Group, Jan 2013

- APAP: 916 (46%)
- Drug: 220
- Hep B: 142 (11%)
- Hep A: 36
- Autoimm: 137
- Ischemic: 112
- Wilson's: 25
- Budd-Chiari: 15
- Pregnancy: 18
- Other: 134
- Indeter: 245

KU Medical Center
The University of Kansas
The Metabolism of Acetaminophen and the Synthesis of Glutathione.

OTC analgesics

• Acetaminophen is safe (preferred)
  • Consider dose reduction in alcohol use and more severe disease (2 G/ day)

• NSAIDs are contraindicated in decompensated disease
  • High risk of renal injury
  • Reduced renal perfusion (inhibition of prostaglandin synthesis)
  • Gastrointestinal side effects

Gines et al., J of Hepatology (2010) 53:397-417
ACEi and ARBs

• Induction of arterial hypotension
• Renal failure
Myth: Statins are unsafe in cirrhosis
Statins may offer benefit

Statins and NAFLD

Fig. 4 - Effects of statins on cardiovascular events and on the liver in patients with nonalcoholic fatty liver disease.

Tziomalos et al. Metabolism (2015) 64:1215-1223
Statins Take Home

• Safe
• May offer benefit in all liver disease
• Probable benefit in NAFLD
• Benefit in post-OLT patients

Tziomalos et al. Metabolism (2015) 64:1215-1223
Benzodiazepines in cirrhosis: NO
Plasma concentration of free triazolam (ng/ml) over time (hours).
Effect of triazolam on cognitive performance

What do we know:

- Sedation can have prolonged effects in cirrhosis
- Sedation may be effectively achieved with intermittent doses of narcotics
- Alternative agents:
  - Dexmedetomidine
  - Propofol
Take home message-Medications

- Acetaminophen is safe
- Statins safe
- Avoid
  - NSAIDs
  - Sedatives
  - Aminoglycosides
  - ARBs and ACEi in *decompensated* disease
Treatment of Encephalopathy
Treatment of HE

- Lactulose is the cornerstone of therapy
  - Titrated to 2-3 soft bowel movements/day
  - Can be used as an enema
  - Rectal tube 500 mL/day
- Rifaximin—a non-absorbed macrolide antibiotic has improved treatment of HE
Rifaximin Treatment in Hepatic Encephalopathy

Nathan M. Bass, M.B., Ch.B., Ph.D., Kevin D. Mullen, M.D., Arun Sanyal, M.D., Fred Poordad, M.D., Guy Neff, M.D., Carroll B. Leevy, M.D.,* Samuel Sigal, M.D., Muhammad Y. Sheikh, M.D., Kimberly Beavers, M.D., Todd Frederick, M.D., Lewis Teperman, M.D., Donald Hillebrand, M.D., Shirley Huang, M.S., Kunal Merchant, Ph.D., Audrey Shaw, Ph.D., Enoch Bortey, Ph.D., and William P. Forbes, Pharm.D.

ABSTRACT
Findings: Rifaximin added to lactulose reduced breakthrough encephalopathy over a six month period (22% vs. 46 % p<0.001) and decreased hospitalizations 14% vs. 23% p=0.01)
A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy

Barjesh Chander Sharma, MD, DM¹, Praveen Sharma, MD, DM², Manish Kumar Lunia, MD¹, Siddharth Srivastava, MD, DM¹, Rohit Goyal, MD, DM¹ and S.K. Sarin, MD, DM²

Am J Gastroenterol 2013; 108:1458–1463
Results: Significant difference in the primary endpoint of complete reversal of HE (76% vs. 51%, p<0.04). Also significant difference in the secondary endpoints of hospital mortality (24% vs 49%, p<0.05) and length of stay 5.8 vs 8.2 days, p=0.001)
Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution for Treatment of Overt Hepatic Encephalopathy: The HELP Randomized Clinical Trial

Robert S. Rahimi, MD, MS; Amit G. Singal, MD, MS; Jennifer A. Cuthbert, MD; Don C. Rockey, MD

Published online September 22, 2014.
HELP trial outcomes:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 50)</th>
<th>Lactulose (n = 25)</th>
<th>PEG (n = 25)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h HESA score change, mean (SD)</td>
<td>1.1 (0.8)</td>
<td>0.7 (0.8)</td>
<td>1.5 (0.8)b</td>
<td>.002</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>6 (9)</td>
<td>8 (12)</td>
<td>4 (3)</td>
<td>.07</td>
</tr>
<tr>
<td>6- to 24-h Ammonia, mean (SD), μmol/Lc</td>
<td>(n = 33)</td>
<td>(n = 15)</td>
<td>(n = 18)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>159 (73)</td>
<td>175 (70)</td>
<td>146 (75)</td>
<td>.19</td>
</tr>
<tr>
<td>After study</td>
<td>103 (51)</td>
<td>82 (29)</td>
<td>120 (60)</td>
<td>.049</td>
</tr>
<tr>
<td>Difference</td>
<td>56 (88)</td>
<td>93 (71)</td>
<td>26 (90)</td>
<td>.03</td>
</tr>
</tbody>
</table>

a: values in parentheses are P values.
Measuring ammonia: Don’t

• Very limited role
• Clinical diagnosis
• Potential errors (not stored on ice, venous samples)
• In patients in whom diagnosis is uncertain
  • Normal ammonia should prompt search for alternate diagnosis
Coagulopathy in Liver Disease
Standard tests of coagulation:

• Measure certain portions of the coagulation cascade
• Do not capture the “complete picture”
• Have intrinsic flaws in certain disease states e.g. cirrhosis.
Standard tests in liver disease

- PT (INR) and aPTT are typically abnormal in liver disease
  - These abnormalities are not necessarily associated with increased risk of bleeding
  - In fact patients may be HYPERcoaguable
Myth of INR as a predictor of bleeding risk in cirrhosis:

• Leads to artificial requirements for “safe” INR
• Significant overuse of FFP in cirrhosis without an evidence basis for support
• Failure to treat patients at risk for DVT when hospitalized

INR is a test of liver function not bleeding risk
(Exception: Pts. on warfarin)
Cardiac Catheterization in the Evaluation of 240 Liver Transplant Candidates: MUSC Data

Cardiac Catheterization: Right 157, Left ± Right 83

No catheter-related bleeding complications at all


Slide courtesy of Dr. Adrian Reuben
Coagulopathy Does Not Fully Protect Hospitalized Cirrhosis Patients from Peripheral Venous Thromboembolism

Patrick G. Northup, M.D., M.H.E.S.,1 Matthew M. McMahon, M.D.,2 A. Parker Ruhl, M.D.,2 Scott E. Altschuler, M.D.,1 Agata Volk-Bednarz, M.D.,3 Stephen H. Caldwell, M.D.,1 and Carl L. Berg, M.D.1

1Division of Gastroenterology and Hepatology, 2School of Medicine, and 3Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia
Viscoelastic Testing

• TEG® or ROTEM®
• At or near bedside test of coagulation
• Provides a comprehensive view of coagulation pathways
• Proven evidence based benefit in liver transplantation and cardiac surgery
Coagulation abnormalities

Take Home Message:

• **Do not treat unless bleeding or for major proc.**
• Do not correct for routine procedures*
  • Small bore thoracentesis/paracentesis
  • Bronchoscopy without biopsy
  • Central venous (IJ) or arterial line placement
• *Consider correction for pts with renal failure
• When correction necessary use viscoelastic testing for guidance (TEG®/ROTEM®)
Ascites
Uncomplicated Ascites: management

Sodium Restriction

- 2 grams sodium (5.4 grams of dietary salt) / day
- Fluid restriction is generally not necessary
- Goal is to achieve a net negative sodium balance

Side effect: unpalatable diet
Uncomplicaed Ascites: management

Diuretic Therapy

- Spironolactone is preferred to furosemide
- Combination therapy common
  - Ratio spironolactone/furosemide 5:2

Side effects: Hyponatremia, renal dysfunction, encephalopathy, gynecomastia, hyperkalemia
Diagnostic Paracentesis

Indications:
- New onset ascites
- Admission to the hospital
- Symptoms or signs of SBP
- New renal dysfunction
- Unexplained encephalopathy
- Fever

Contraindications:
- None
Refractory Ascites: definition

True refractory ascites occurs in 10-20% of cirrhotic patients

Diuretic-intractable ascites 80%
Therapeutic doses of diuretics cannot be achieved due to diuretic-induced complications.

Diuretic-resistant ascites 20%
No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide daily)
Safety of paracentesis

- 1100 patients undergoing paracentesis at Mayo Clinic
  - Platelets to 19K and INR as high as 8.7
  - No transfusions
  - No bleeding events
- 4729 patients undergoing paracentesis
  - 8 of 9 bleeding events in patients with renal failure

Therapeutic paracentesis:

- For large volume (5 L or more)
  - Albumin mandatory
  - Dose 8 g 25% albumin / liter of ascites
  - Safe procedure
AVOID Permanent Drains

• Chest tubes
• PleurX catheters
• Peritoneal drains

• Exception—Palliative care/Hospice
Post-Paracentesis Circulatory Dysfunction (PCD) Depends on the Type of Plasma Volume Expander and the Amount of Ascites Removed

LVP Without Albumin Leads to Increases in Renin, Renal Failure and Hyponatremia

Before

After

Albumin
No albumin

Plasma renin activity (ng/mL/h)

12
8
4
0

p<0.01

ns.

Renal failure / Hyponatremia

20
15
10
5
0

Post-paracentesis circulatory dysfunction (PCD)

p<0.01

Gines et al., Gastroenterology 1988; 94:1493
Infections in Cirrhosis
Infections:

• Infection may be the single most common cause of acute decompensation of cirrhosis
• Precipitates encephalopathy, renal failure, and increases portal pressure and leads to bleeding
Epidemiology of infections in cirrhosis

• Prevalence of infection in a multi-center Italian study
  • 34% of hospitalized patients with Childs B/C cirrhosis
  • 60% of infections were community acquired
  • 40% were nosocomial
    • Urinary tract 41%
    • Ascitic fluid 23%
    • Blood stream 21%
    • Respiratory tract 17%

Epidemiology of infections in cirrhosis

- US Multi-center study (NACSELD) of 207 patients
  - 85% hospitalized in prior 6 months
  - 51% experienced at least one infection
    - Urinary tract 25%
    - Ascitic fluid 23%
    - Blood stream 21%
    - Skin 13%
    - Lower respiratory tract 8%
    - *Clostridium difficile* 5%

First infections

Infections in hospitalized cirrhotics

• 23.6% of patients died during hospitalization or within 30 days of discharge
• Case fatality rate for first infections with C. difficile 40%
• 24.1% of patients developed a second infection while hospitalized

Second infections

Second infections

Table 5. Final Predictive Model Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>OR</th>
<th>OR 95% CI</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-4.9689</td>
<td>1.5511</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>MELD</td>
<td>0.1169</td>
<td>0.0281</td>
<td>1.124</td>
<td>(1.064, 1.188)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Albumin</td>
<td>-0.6863</td>
<td>0.3341</td>
<td>0.503</td>
<td>(0.262, 0.969)</td>
<td>0.0399</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.0279</td>
<td>0.0120</td>
<td>1.028</td>
<td>(1.004, 1.053)</td>
<td>0.0202</td>
</tr>
<tr>
<td><strong>Second infection</strong></td>
<td><strong>1.4852</strong></td>
<td><strong>0.4022</strong></td>
<td><strong>4.416</strong></td>
<td><strong>(2.007, 9.713)</strong></td>
<td><strong>0.0002</strong></td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval.
**SBP: Early diagnosis**

**Table 2. Clinical outcomes**

<table>
<thead>
<tr>
<th></th>
<th>EP, N=141</th>
<th>DP, N=98</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>18 (13%)</td>
<td>25 (27%)</td>
<td>0.007</td>
</tr>
<tr>
<td>AKI</td>
<td>61 (43%)</td>
<td>47 (48%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Intensive care days</td>
<td>1.3±4.1</td>
<td>4.0±9.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospital days</td>
<td>8.4±7.4</td>
<td>13.0±14.7</td>
<td>0.005</td>
</tr>
<tr>
<td>3-Month mortality</td>
<td>21/98 (21%)</td>
<td>28/76 (37%)</td>
<td>0.03</td>
</tr>
<tr>
<td>1-Year overall survival</td>
<td>45/68 (66%)</td>
<td>36/65 (55%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; DP, delayed paracentesis; EP, early paracentesis.

Bold values represent outcomes with two-sided P value <0.05.

SBP: Treatment

- Cefotaxime (or similar 3rd generation cephalosporin)
  - 95% of isolates from *Escherichia coli*, *Klebsiella pneumoniae*, and *Strep pneumoniae*
  - 2 grams Q8H
  - 5 days equivalent efficacy as 10 days
  - 25% Albumin 1.5 g/kg day 1 and 1 g/kg day 3
Gastrointestinal Bleeding
Antibiotic prophylaxis in GI bleeding

Antibiotic Prophylaxis for the Prevention of Bacterial Infections in Cirrhotic Patients With Gastrointestinal Bleeding: A Meta-Analysis

Brigitte Bernard,1 Jean-Didier Grangé,2 Eric Nguyen Khac,1 Xavier Amiot,2 Pierre Opolon,1 and Thierry Poynard1

Results of meta analysis

5 trials with 534 patients (264 treated with abx)

- 32% mean improvement in patients free of infection (95% CI: 22-42, P <0.001)
- 19% mean improvement in pts free of SBP/bacteremia (95% CI: 22-26, P<0.001)
- 9.1% increase in mean survival rate (95% CI: 2.9-15.3 P=0.004)

Antibiotic prophylaxis in GI bleeding

Antibiotic Prophylaxis After Endoscopic Therapy Prevents Rebleeding in Acute Variceal Hemorrhage: A Randomized Trial

Ming-Chih Hou, Han-Chieh Lin, Tsu-Te Liu, Benjamin Ing-Tieu Kuo, Fa-Yauh Lee, Full-Young Chang, and Shou-Dong Lee

Antibiotic prophylaxis prevents rebleeding

Summary of antibiotic use in GI bleeding

• Immediate initiation of antibiotic therapy in cirrhotics with GI bleeding and continuing 7 days of therapy
  • Ceftriaxone in patients who have recent history of quinolone exposure
  • Quinolone in others
Infections

• Careful and thorough screening
• Adherence to bundles of care (ventilator and line placement)
• Early removal of all invasive lines and catheters
• Repeat screening and surveillance for *Clostridium difficile* infection
• Hand washing
When should I refer?
Cirrhosis

ACLF

Natural History

Insult

Prevention

Deranged inflammatory response

Multi-organ dysfunction/failure

Liver support?

Early Transplantation?

Death

Recovery

Transplant

Death
When to refer:

• **All** cirrhotics deserve consultation with a transplant specialist-Transplant is the only cure

• **Timing:**
  - Early better
  - At first decompensating event
  - MELD-Na >15
  - Don’t make assumptions about transplant candidacy
Take home messages

• Overall healthcare burden of cirrhosis is increasing
• Acetaminophen is safe and preferred
• Avoid NSAIDS, ARB’s, ACEi, and
• Avoid sedatives when possible
• Always aggressively assess for infection in cirrhosis
• Don’t forget C. diff
• INR does not predict bleeding risk in cirrhosis
• Always replace albumin after LVP
• Refer early
• Having a relationship with a transplant center is important
THANK YOU!

jolson2@kumc.edu