Cirrhotics are People Too: 
Primary Care for the Cirrhotic Patient

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Prevalence of Cirrhosis

• ~5.5 million people in the United States have cirrhosis
• Many with cirrhosis remain undiagnosed
  • 40% of cases of cirrhosis “latent”
• Twelfth leading cause of death in US

US Hospital Discharges Due to Cirrhosis Are Increasing

![Graph showing the increase in hospital discharges due to cirrhosis from 2004 to 2011.](image)

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.


To the extent possible, health care goal is to keep cirrhotics out of the hospital

- **General Management**
- **Disease Specific Management**
General Management of the Cirrhotic Patient

• Slowing or reversing disease progression
• Preventing superimposed liver injury
• Ensure safe use of medications
• Follow cancer screening recommendations
• Evaluate bone disease
• Nutrition

Slowing or Preventing Disease Progression

• Alcohol avoidance
• Weight management
• Disease specific treatment to reverse cirrhosis
  • Hepatitis C  DAA’s
  • Hepatitis B  DAA’s
  • Primary biliary cholangitis  URSO
  • Hemochromatosis  Phlebotomy
  • NAFLD?  Weight loss?
Preventing Superimposed Liver Injury

- Vaccinations
  - Hepatitis B
  - Hepatitis A
  - Pneumococcal
  - Yearly influenza

- Medication adjustments
  - Work with pharmacists
  - Safe drugs
    - Acetaminophen
    - Statins

- Avoidance of Hepatotoxins
  - Prescription Medications
    - Diclofenac
    - Nitrofurantoin
  - OTC products
    - NSAID's
    - Herbal and dietary supplements
      - Kava kava
      - Mistletoe
      - Chinese herbs
        - Ma-Huang (ephedra)
      - Chapparral
      - Germander

Cancer Screening in the Cirrhotic Patient

- Follow standard screening guidelines for the general population
  - Colon cancer
  - Breast cancer
  - Prostate cancer
  - Gynecologic cancers
  - ENT – smokers and previous alcoholics
  - Skin cancer

- Hepatocellular carcinoma
  - Will discuss later
General Health Recommendations for the Cirrhotic Patient

- Bone densitometry
  - Follow standard of care recommendations
- Nutrition
  - No specific dietary management
  - Well balanced diet
  - Healthy diet according to healthy eating guidelines
  - Beware of miracle cures

Disease-Specific Management of the Cirrhotic Patient

- Symptom Management
- Variceal Screening
- Hepatic encephalopathy
- Ascites
- Screening for hepatocellular carcinoma
- Portal vein thrombosis
- Determining timing for transplantation referral
Symptom Management in Cirrhosis

• **Fatigue**  
  • Rest, exercise

• **Muscle Cramps**  
  • Check electrolytes  
  • Consider quinine sulfate  
    • Hard to obtain in US  
    • May cause tinnitus  
  • Consider branched chain amino acids (4 g granules 3 times a day)  
    • Hardly palatable  
  • Consider taurine 3 gm once a day  
    • Readily available  
  • Consider vitamin E 200 mg 3 times a day

General Care of the Cirrhotic: Dental Health

• Oral infection potential source of sepsis  
• Severe dental disease in 32% of cirrhotic patients  
• Etiology of liver disease did not affect dental health  
• Edentulous patients less likely to have seen a dentist in the recent past  
• Refer to dentist!!

Guggenheimer et al. Liver Transplant 2007; 13:280-86
Specific Issues in Cirrhotic Patients

• Umbilical hernia
  • Conservative management
  • Repair if symptomatic
  • High complication rate
    • Especially in Childs B and C

• Hyponatremia
  • Common in cirrhosis
  • No treatment in the majority of patients

• Thrombocytopenia
  • No treatment
  • These platelets function
    • 50,000 /μL sufficient for most interventions

• Elevated INR
  • No treatment
  • FFP prior to elective intervention
    • Dental
    • Surgical
    • Radiologic
    • rFactor V11a

Esophageal Varices
Screening for Esophageal Varices

• All patients with cirrhosis should have EGD screening for varices
• Varices uncommon with platelet count >150,000 and transient elastography <20 kPa
• Banding may be considered for primary prevention of bleeding
• Sclerotherapy not indicated

<table>
<thead>
<tr>
<th>Endoscopic Finding</th>
<th>Recommendation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>No varices</td>
<td>Repeat EGD every 3 years</td>
<td></td>
</tr>
<tr>
<td>Small varices</td>
<td>Repeat EGD every 1 year</td>
<td></td>
</tr>
<tr>
<td>Small varices with red signs or Childs B or C</td>
<td>Start non-selective beta blocker*</td>
<td></td>
</tr>
<tr>
<td>Medium varices</td>
<td>Start non-selective beta blocker*</td>
<td>Band ligation</td>
</tr>
<tr>
<td>Large varices</td>
<td></td>
<td>Band ligation</td>
</tr>
</tbody>
</table>

* Recommend Nadolol 40 mg a day

Bandaging Protocol

• Every 2 weeks until eradicated
• Follow up EGD 1-3 months post-eradication
• EGD every 6-12 months to assess for variceal recurrence

Hepatic Encephalopathy
Characterization of HE Stages

Categorization is often arbitrary and varies between raters

Worsening cognitive dysfunction

“Overt” HE Stages

Normal “Covert” HE I II III IV coma

Clinical Diagnosis

Diagnosis of Hepatic Encephalopathy

• Covert
  • Number connection test
  • Encephalapp Stroop test
    • iPhone app
    • Takes 5 minutes
    • Word/color matching
      • BLUE
      • YELLOW

• Overt
  • Clinical
  • ? Ammonia level

Bajaj et al. Hepatology 2013
Role of Ammonia Testing in HE

• “Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”


Management and Treatment of Hepatic Encephalopathy

• **Covert**
  • Initiate treatment
    • Rifaximin
    • Lactulose
  • Key Issues:
    • Driving

• **Overt**
  • Evaluate for precipitating cause and treat
  • Start:
    • Rifaximin
    • Lactulose
  • Treatment is lifelong or until transplant

FDA Approved Treatment Options for Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Potential Adverse Effects</th>
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</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>• Decreases blood ammonia concentration - Promotes elimination of NH₃ - Fermentation by bacteria acidify colon and prevent absorption - Reduces urease-producing bacteria</td>
<td>Diarrhea, cramping Overuse can lead to aspiration, dehydration, hypernatremia, and severe perianal skin irritation;</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>• Decreases blood ammonia concentration - Broad spectrum antibiotic; results in a change in bowel flora - May cause downregulation of intestinal glutaminase activity</td>
<td>Diarrhea (due to overgrowth of <em>C. diff</em>) peripheral edema, nausea, dizziness, fatigue, and ascites³</td>
</tr>
<tr>
<td>Neomycin</td>
<td>• Decreases blood ammonia concentration - Inhibits intestinal glutaminase. Use limited. • Should not be used in clinical practice</td>
<td>Risk of ototoxicity and nephrotoxicity with long-term treatment due to some systemic absorption⁴</td>
</tr>
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Recommended Treatment for Hepatic Encephalopathy is Combination of lactulose/rifaximin

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Ascites

Management of Ascites: First Line

- Diagnostic paracentesis
  - Send fluid for:
    - Albumin to determine SAAG
    - Cell count
    - Culture

- Sodium restriction
  - Effective in 20% of cases
  - Predictors of response
    - Mild or moderate ascites
    - Urine Na excretion >50 mEq/day
    - 2 g (or 5.2 g of dietary salt) a day

- Fluid restriction
  - Not necessary unless there is hyponatremia (<125 mmol/L)
Management of Ascites: Diuretics

- Start with spironolactone 50 mg a day and furosemide 20 mg a day
- Progressive advancement of combination of spironolactone and furosemide
  - Spironolactone 100-400 mg a day
  - Furosemide 40-160 mg/d
- Can increase every 3-5 days
  - Follow Cr, K, Na
- Side effects
  - Renal dysfunction
  - Hyponatremia
  - Hyperkalemia
  - Gynecomastia

Hepatocellular Carcinoma
Screening for Hepatocellular Carcinoma (HCC)

• All patients with cirrhosis, regardless of etiology should be screened
• Interval is every 6 months

Diabetes Is Associated with a Two-fold Increase in Risk of HCC

El-Serag HB, et al, Gastroenterology 2004
Coffee and Hepatocellular Carcinoma

- Epidemiologic studies: coffee consumption is inversely related to
  - Serum liver enzyme activity
  - Liver cirrhosis
  - HCC
- For each additional 1 cup of coffee:
  - Case-control studies
    - (0.77, 0.72-0.83)
  - Cohort studies
    - (0.75, 0.65-0.85)

HCC Surveillance Recommendations

- US and AFP are the recommended screening tests for HCC in patients at the highest risk
  - US is central
  - Not AFP alone
- Triple phase contrast CT
- Triple phase contract MRI
- Diagnostic findings on CT/MRI
  - Arterial phase hyperdense lesion
  - Venous phase hypodense (wash-out)

Bruix et al. HCC AASLD Guidelines Hepatology 2010
HCC Surveillance Recommendations

- Premature to recommend dropping AFP
  - RCTs used AFP + US
  - Only population based cohort used AFP
  - Approximately 20% of HCC cases are detected based only on an increase in AFP (with normal results from US analysis)
  - Most of the current community-based surveillance is either nothing or AFP

Barcelona-Clinic Liver Cancer Staging Classification and treatment Schedule for Hepatocellular Carcinoma: Why we screen

- Very early stage
  - 1 HCC <2 cm
  - Carcinoma in situ

- Early stage
  - 1 HCC or 3 nodules <3 cm, PS 0

- Intermediate stage
  - No portal vein thrombosis
  - Multinodular, PS 0

- Advanced stage
  - Portal invasion
  - Metastases, PS 0-2

- Terminal stage
  - 1 HCC 3 nodules <3 cm
  - Portal pressure / bilirubin

Potential curetive treatments
- Resection
- OLT
- PEI / RFA

Palliative treatments
- Chemo-embolization
- Sorafenib

Symptomatic Therapy
- Normal
Hepatitis B: Association Between Viral Load and Incidence of HCC

Baseline HBV DNA Level (copies/ml)

<table>
<thead>
<tr>
<th>DNA Level (copies/ml)</th>
<th>Year of follow-up</th>
<th>Cumulative Incidence (%)</th>
</tr>
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<tbody>
<tr>
<td>≥10^6</td>
<td></td>
<td>13.50%</td>
</tr>
<tr>
<td>10^5–&lt;10^6</td>
<td></td>
<td>7.96%</td>
</tr>
<tr>
<td>10^4–&lt;10^5</td>
<td></td>
<td>3.15%</td>
</tr>
<tr>
<td>300–&lt;10^4</td>
<td></td>
<td>0.89%</td>
</tr>
<tr>
<td>&lt;300</td>
<td></td>
<td>0.74%</td>
</tr>
</tbody>
</table>

HBeAg negative, normal ALT, no liver cirrhosis at entry (n=2,925)

Chen CJ et al. JAMA. 2006;295:65–73

SVR Reduced HCC and Liver-Related Complications in Patients With Bridging Fibrosis or Cirrhosis

SVR Reduced HCC and Liver-Related Complications in Patients With Bridging Fibrosis or Cirrhosis

*Ascites, variceal bleeding.
307 HCV patients with bridging fibrosis (n=127) or cirrhosis (n=180) were evaluated by Cox regression analysis. Non-SVR in 67% of patients treated with pegylated interferon plus ribavirin. Median follow-up: 3.5 years.

Post – SVR follow up in HCV treated cirrhotics

- DAA induced SVR did not reduce risk of occurrence of HCC
- Patients with previously treated HCC have high short term risk of recurrence after SVR
- Must continue to screen HCV cirrhotics s/p SVR
- Continue screening even if cirrhosis regresses

Conti et al. J Hep 2016; 65:727-33
Reig et al. J Hep 2016; 65: 719-26

Portal Vein Thrombosis
Portal Vein Thrombosis

- Complete or partial obstruction of portal venous flow
- May be intra or extra – hepatic
- May be benign or malignant
- May be acute or chronic
- Prevalence of benign PVT
  - General population 1%
  - Cirrhotic population 0.6 – 26%
- PVT not associated with increased mortality\(^2\)


Portal Vein Thrombosis: Acute

- Recent formation of thrombus within the portal vein and/or left or right branches
- Diagnosed by imaging, usually at HCC screening
  - Doppler
  - CT
  - MRI
- Screen for underlying genetic thrombophilic condition
- Start anti-coagulation after evaluating risks of GU bleeding
  - Initiate GI bleeding prophylaxis
    - PPI'S
    - Band ligation
- Treatment duration at least 6 months after resolution

Portal Vein Thrombosis: Chronic

- Obstructed portion of portal vein is replaced by a network of hepatopetal collaterals bypassing the thrombosed portion of the vein
- Documented portal vein thrombosis of >6 months
- Diagnosed by imaging, usually at HCC screening
  - Doppler
  - CT
  - MRI
- Screen for underlying genetic thrombophilic condition
- Consider anti-coagulation after evaluating risks of GI bleeding
- Treatment until transplantation

Sarin et al. Gastroenterology 2016;151:574-7
Who and When to refer for liver transplantation?
Who and When to refer for liver transplantation?

- Develop relationship with transplant center
  - Get to know what they want
  - Follow the patient until transplant

Who and When to refer for liver transplantation?

- MELD score >16
  - INR, Total bilirubin, INR

Who and When to refer for liver transplantation?

- **MELD exceptions**
  - Familial Amyloidosis
  - Hepatopulmonary syndrome
    - Screen with O₂ saturation
    - Diagnose with bubble echocardiogram
    - Refer before resting PaO₂ <50 mm Hg
  - Portopulmonary HTN
    - Screen with echocardiogram
    - Confirm with right heart cath
    - Refer before pulmonary pressure >45-50 mm Hg

Ioannou Et al. Gastroenterology 2008; 134:1342-51, Rodriguez-Rosin R et al. NEJM 2008;2378-87,
Kawut SM Clin Liv Dis 2006;20:653-63

MELD exceptions for for HCC: Milan Criteria

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

+ Absence of macroscopic vascular invasion, absence of extrahepatic spread

Criteria not considered for transplantation

- Ascites
- Encephalopathy
- Variceal bleeding

Primary Care for the Cirrhotic: Summary

- General medical care
  - Slowing or reversing disease progression
  - Preventing superimposed liver injury
  - Ensure safe use of medications
  - Follow cancer screening recommendations
  - Evaluate bone disease
  - Nutrition

- Disease specific care
  - Symptom Management
  - Variceal Screening
  - Hepatic encephalopathy
  - Ascites
  - Screening for hepatocellular carcinoma
  - Portal vein thrombosis
  - Transplantation referral
Who and When to refer for liver transplantation?

**Contraindications**
- Active alcohol and/or substance abuse
- Recent extra-hepatic malignancy
  - <5 years except non-melanoma skin cancer
- Cigarette smoking
- Morbid obesity
- Psychiatric or social issues
- Significant co-morbidities
  - CAD
  - DM
  - CVA

Ehtisham et al. Liver Transplant 2010;16:550-7

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