Cases in Liver Disease and Cancer

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Speaker Disclosure

- Dr. Alkhouri has disclosed that he has received grant support from Allergan, Cirius, Enyo, Galmed, Genfit, Gilead, Hanmi, HepQuant, Intercept, Inventiva, and Madrigal and he is on the speaker's bureau and advisory board for Alexion, Gilead and Intercept.
Learning Objectives

By the end of this educational activity, the learner should be better able to:

1. Describe the disease burden, natural history and management of nonalcoholic fatty liver disease.
2. Discuss screening strategies and new systemic therapies for liver cancer.
3. Describe end-stage liver disease complications and their management for primary care physicians.
Nonalcoholic Fatty Liver Disease (NAFLD): Screening, Current Management and Treatments on the Horizon
Overview

• Describe the burden, disease spectrum and natural history of NAFLD.
• Discuss management strategies for patients with NAFLD:
  • Noninvasive diagnosis of disease severity
  • Novel therapeutic agents expected to be available soon
Case Presentation

Tony

- 60 y.o. M with DM2, BMI of 39 kg/m² and Metabolic Syndrome
- Presents with persistently elevated LFTs
  - ALT – 66 U/L (10-40 U/L)
  - AST – 76 U/L (10-40 U/L)
  - Albumin – 3.5 g/dL (3.5-4.5 g/dL)
  - Platelet count – 170 k/uL (150-400 k/uL)
Epidemiology and Natural History of NAFLD
NAFLD is the Hepatic Manifestation of Obesity/IR

Metabolic Syndrome
- Insulin Resistance
- Dyslipidemia
- Hypertension
NAFLD Prevalence

**Adults**

- Overall: ~ 25%
- Obese: ~ 50%
- Severely Obese: ~ 85%
- DM2: ~ 65-75%

The NAFLD Spectrum

NAFL → Early NASH → Fibrotic (F2-F3) → NASH Cirrhosis

- **Steatosis (0-3)**
  - 5-33%: 1
  - 34-65%: 2
  - ≥66%: 3

- **Inflammation (0-3)**
  - <2 under 20x: 1
  - 2-4 under 20x: 2
  - >4 under 20x: 3

- **Ballooning (0-2)**
  - Few: 1
  - Many: 2
Fibrosis Stage is the Most Important Prognostic Factor in Predicting Liver-related Outcomes

NASH is the Most Common Indication for Listing and OLT in Women in the U.S.

Noureddin M, Alkhouri N, et al. AJG. 2018
Determining the Presence and Severity of NAFLD
Current Diagnosis of NAFLD: ALT and Ultrasonography

ALT can be normal in patients with NAFLD

ALT/ US cannot diagnose NASH or stage the severity of fibrosis in patients with NAFLD

Lee SS et al. WJG. 2014
Noninvasive Diagnosis of Fibrosis

Simple
- AST/ ALT ratio
- APRI
- FIB-4
- NFS

Complex
- FibroSURE
- ELF
- HA

Imaging
- VCTE
- MRE
- ARFI
NAFLD fibrosis score

Online calculator

Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score
A noninvasive system that identifies liver fibrosis in patients with NAFLD

Fibrosis-4 (FIB-4) Calculator

\[ \text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\sqrt{\text{Platelet Count (10^9/L)} \times \text{ALT (U/L)}}} \]

- Score: 2.00
- Original score: 4.040
- < -1.455: predictor of absence of significant fibrosis (F0-F2 fibrosis)
- -1.455 to \leq 0.675: indeterminate score
- > 0.675: predictor of presence of significant fibrosis (F3-F4 fibrosis)

Score: 3.30

- < 1.4: absence of significant fibrosis
- 1.4-2.66: Indeterminate
- > 2.67: presence of advanced fibrosis
### 6 Serum Markers
- A2-macroglobulin
- Haptoglobin
- Apolipoprotein A1
- Total bilirubin
- GGT
- ALT

### Metavir scale

<table>
<thead>
<tr>
<th>Fibrosis Stage (FibroTest)</th>
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<tbody>
<tr>
<td>F0 - No fibrosis</td>
<td>0.00 - 0.21</td>
</tr>
<tr>
<td>F0 - F1</td>
<td>0.21 - 0.27</td>
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<td>F1 - Portal fibrosis</td>
<td>0.27 - 0.31</td>
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<td>F1 - F2</td>
<td>0.31 - 0.48</td>
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<tr>
<td>F2 - Bridging fibrosis with few septa</td>
<td>0.48 - 0.58</td>
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<tr>
<td>F3 - Bridging fibrosis with many septa</td>
<td>0.58 - 0.72</td>
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<td>F3 - F4</td>
<td>0.72 - 0.74</td>
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<tr>
<td>F4 - Cirrhosis</td>
<td>0.74 - 1.00</td>
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<table>
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<tr>
<th>Activity Grade (ActiTest)</th>
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<td>A0 - No activity</td>
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<tr>
<td>A0 - A1</td>
<td>0.17 - 0.29</td>
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<td>A1 - Minimal activity</td>
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<td>A1 - A2</td>
<td>0.36 - 0.52</td>
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<td>A2 - Moderate activity</td>
<td>0.52 - 0.60</td>
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<td>A2 - A3</td>
<td>0.60 - 0.63</td>
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<tr>
<td>A3 - Severe activity</td>
<td>0.63 - 1.00</td>
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Shear Wave Movement

Controlled Frequency 50 Hz Shear Wave
Staging the Severity of Steatosis and Fibrosis in NAFLD: VCTE + CAP
VCTE + CAP: A Powerful Tool
### Advantages

- Can be performed in clinic with real-time results
- Accurate in obese patients and examines the entire liver
- Can be integrated into a conventional ultrasound

### Disadvantages

- Increased failure rate with obesity
- Expensive device
- Expensive and time consuming
- Limited availability
- Only a few published studies
- Increased failure rate with obesity
- Cutoff values for advanced fibrosis vary significantly
NAFLD Management: Current and Future
How Do I Manage My Patient with NAFLD Today

• Rule out other etiologies of elevated ALT or fatty infiltration of the liver
• Assess for co-morbidities (DM2, HTN, Dyslipidemia, OSA)
• Assess severity (NASH, advanced fibrosis)
• Treatment:
  • Lifestyle
  • Pharmacologic
## Laboratory Assessment for NAFLD

### Chronic Liver Disease Panel
- CBC + AUTO DIFF
- HEPATIC FUNCTION PNL
- GGT BLD
- BASIC METABOLIC PNL
- LIPID PANEL BASIC
- PROTHROMBIN TIME/PT
- HEPT REMOTE PANEL BL
- HEPA AB TOTAL
- ANA BLOOD
- SMOOTH MUSCLE AB PNL SCR
- LKM AB
- ALPHA-1-ANTITRYSNS BL
- IRON + TIBC
- FERRITIN BLD
- CRUOPLASMIN BLD
- CELIAC SCREEN WITH REFLEX
- CK CREATINE KINASE
- Lab, Routine, BLOOD

### NASH Panel
- CBC + AUTO DIFF
- HEPATIC FUNCTION PNL
- GGT BLD
- BASIC METABOLIC PNL
- LIPID PANEL BASIC
- TSH BLD
- HGB A1C
- INSULIN ASSAY BLOOD
- GLUCOSE FASTING BLD
- C-REACTIVE ULTRA SEN
- LIPOPROTEIN (A)
- ALBUMIN RANDOM URINE
- VITAMIN D 25 HYDROXY
- Lab, Routine, BLOOD

### Lab, Routine, BLOOD
Assessment of the Severity of NAFLD

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score
A noninvasive system that identifies liver fibrosis in patients with NAFLD

Age (years) [ ]
BMI (kg/m²) [ ]
IGF/diabetes [ ]
AST [ ]
ALT [ ]
Platelets (x10⁹/l) [ ]
Albumin (g/l) [ ]

[calculate score]
Patient with DM2 or Met S

Screen for NAFLD with ALT and US

Determine Severity with NFS and FIB4

1. NFS < -1.455 and FIB4 < 1.4
   - No advanced disease
   - Consider repeating every 2-3 years
   - Lifestyle modifications

2. Indeterminate zone or discordant
   - FibroTest
     - Low
     - High

3. NFS > 0.676 and FIB4 > 2.67
   - Advanced fibrosis
   - Refer to GI/Hepatology
Treatment: % Weight Loss Associated with Histological Improvement

- Steatosis (35% - 100%)<sup>a</sup>
  - Weight Loss ≥ 3%<sup>5,7,12-13</sup>

- Ballooning/Inflammation (41% - 100%)<sup>a</sup>
  - Weight Loss ≥ 5%<sup>5,7,12</sup>

- NASH Resolution (64% - 90%)<sup>a</sup>
  - Weight Loss ≥ 7%<sup>12</sup>

- Fibrosis (45%)
  - Weight Loss ≥ 10%<sup>12</sup>

247 patients with NASH and w/o DM
- Pioglitazone: 30 mg/d
- Vitamin E: 800 IU/d
- Placebo

Primary outcome: Improvement in histologic features of NASH

Resolution of NASH with Vitamin E and Pioglitazone Compared to Experimental Drugs

- Vitamin E: Increased overall mortality/ stroke/prostate cancer
- Pioglitazone: Increased risk of bladder cancer, osteoporosis/? HF

Sanyal A et al. *NEJM* 2010
The Race to Cure NASH: Six Medications in Phase III Controlled Trials

- Elafibranor
- Aramchol
- MGL-3196
- **Obeticholic acid (OCA):** FXR agonist (REGENERATE)
- **Cenicriviroc (CVC):** CCR2/CCR5 inhibitor (AURORA)
- **Selonsertib:** Apoptosis signal-regulating kinase (ASK1) inhibitor (STELLAR-3)

Alkhouri et al. *Clinical Liver Disease*. 2018
NAFLD is the New Type 2 Diabetes!

TE with CAP is the New HbA1C
The NAFLD Spectrum

NAFL -> Early NASH -> Fibrotic (F2-F3) -> Cirrhosis

HbA1C 5.7-6.4: Pre-Diabetes
HbA1C 6.5-8.5: Controlled DM2
HbA1C > 8.5: Uncontrolled DM2

Diabetes Complications: CKD, Retinopathy, CAD

TE < 6 kPa: CAP > 250 db/m
TE 7-8 kPa: CAP > 250 db/m
TE 9-14 kPa: CAP > 250 db/m
TE >15 kPa: TE > 25 kPa

Lifestyle Modifications
Elafibranor: ACC inhibitor
OCA, CVC, ASK1

Combination HCC/EV Screening
How Do We Manage NAFLD?

Case 1

• 50 y.o. F with BMI of 42 kg/m² and Metabolic Syndrome presents with elevated LFTs. ALT 66, AST 56, albumin 4.5, platelet count of 270

• CAP = 356, TE = 4.8 → Consistent with NAFL (= pre-diabetes)

• **Lifestyle modifications:** Weight loss of 7-10% + **exercise**

• Follow-up Fibroscan every 1-2 years
How Do We Manage NAFLD?
Case 2

• 60 y.o. M with DM2, BMI of 39 kg/m² and Metabolic Syndrome presents with elevated LFTs. ALT 66, AST 76, albumin 3.5, platelet count of 170.
• TE = 12.8 → Consistent with advanced fibrosis (F3-F4)
• Refer to stage 3 fibrosis clinical trials: STELLAR3 (ASK1 inhibitor), REGENERATE (OCA), or AURORA (CVC)
• Consider HCC screening with US every 6 months
NAFLD is very common and a serious liver disease even among young adults

Screening for NAFLD should be considered in patients with DM2 and Metabolic Syndrome

The severity of NAFLD-associated fibrosis can be determined with non-invasive methods

NASH-specific therapies are coming soon and should change the attitude toward screening and treatment
Screening, Diagnosis, and Management of Hepatocellular Carcinoma – A Texas Epidemic

Naim Alkhouri, MD
Texas Liver Institute and UT San Antonio
Outline

• Why Focus on Hepatocellular Carcinoma (HCC)?
• How to Screen and Diagnose HCC
• How to Manage HCC
• New Systemic HCC Therapies
Hepatocellular Carcinoma (HCC)

- Primary tumor of the liver that usually develops in the setting of chronic liver disease
- Cirrhosis (all etiologies), chronic hepatitis B without cirrhosis, and even NASH without cirrhosis (up to 13% in the VA)
Hepatocellular Carcinoma (HCC) is a Global Problem

- **Worldwide**
  - 5th most common cancer in men
  - 9th most common cancer in women
- **Yet, 2nd most common cause of cancer-related deaths worldwide**
  - ~746,000 deaths in 2012
- 76% of HCC worldwide is in Asia

http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp
HCC is a United States Problem

- U.S. HCC incidence has tripled since 1980
- 5th highest cause of cancer-related death in U.S. (behind lung, colon, pancreas, and breast)
- U.S. HCC 5 year-survival is still low at <12%
- HCC will continue to increase until 2030 with highest increase in Hispanics > Blacks > Caucasians

AASLD Guidelines for Treatment of Hepatocellular Carcinoma 2018
American Cancer Society 2019
In the U.S., Hispanics > Asians have Highest Rate of HCC (2011-2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>Hispanic</th>
<th>White</th>
<th>Black</th>
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To Note, California with Highest # of Hispanics

<table>
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<th>Top Latino states in 2014, by population and share</th>
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<tbody>
<tr>
<td><strong>Millions</strong></td>
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<tr>
<td>California</td>
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<tr>
<td>Texas</td>
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<td>Florida</td>
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<td>Colorado</td>
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<td>New Mexico</td>
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<td>Georgia</td>
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<table>
<thead>
<tr>
<th><strong>% of population that is Latino</strong></th>
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<tbody>
<tr>
<td>California</td>
</tr>
<tr>
<td>Texas</td>
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<td>Arizona</td>
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<td>Nevada</td>
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<td>Colorado</td>
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<td>New Jersey</td>
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<tr>
<td>New York</td>
</tr>
<tr>
<td>Illinois</td>
</tr>
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</table>

Note: Charts show the top 10 states for the number of Latinos and the share of the population that is Latino.

Source: Pew Research Center tabulations of the 2014 American Community Survey (IPUMS) “U.S. Latino Population Growth and Dispersion Has Slowed Since Onset of the Great Recession”

PEW RESEARCH CENTER
And Hawaii with Highest # of Asians

YET, Texas is #1 in HCC Rates in the USA

- By 2012, Texas has the highest rates of HCC in the nation
  - **Texas 9.71** [95% CI, 9.33–10.33] per 100,000
  - **Hawaii 9.68** [95% CI, 8.22–11.33] per 100,000

Hawaii is 55.9% Asian as per the U.S. Census in 2017. Recall Asians previously with highest HCC rate...

For Every Ethnic Group, Texas has Highest HCC Rate in 2012

Supplementary Figure 3. Age-adjusted rates for HCC by race/ethnicity in the 5 most populous US states in 2012.

Why Does Texas Have Highest HCC Rate in Every Ethnic Group?

• Decreased access to screening, diagnosis, and treatment (especially HCV treatment)?
  • TX did not adopt Medicaid expansion as part of the ACA
• Tacos:Person ratio?
• Too hot to exercise here?
• More alcohol use because we are indoor more because it is too hot to exercise here?
Outline

• Why focus on Hepatocellular Carcinoma (HCC)?
• How to Screen and Diagnose HCC
• How to Manage HCC
• New Oral HCC Therapies
Clinic Patient

**HPI:** 63 yo Hispanic woman with PMH of obesity (BMI 36), Type 2 DM (HbA1C 6.8%), HTN, hyperlipidemia, and compensated NASH cirrhosis who is here for her q6 month follow up. **To discuss with her today a newly found liver lesion seen on screening ultrasound.**
AASLD 2018 Recommendations for HCC Screening

- **Cirrhosis (all etiologies)**
  - HCC incidence rate is 2-8%/year
- **Chronic hepatitis B carriers who are Asian man (>40 yo), Asian woman (>50 yo), or African blacks**
  - HCC incidence rate is 0.4%-unknown
- **Chronic hepatitis B with family history of HCC**
  - HCC incidence rates are > than those without family history

**AASLD recommends HCC screening every 6 months with ultrasound +/- AFP**

AASLD Guidelines for Treatment of Hepatocellular Carcinoma 2018
Hepatocellular Carcinoma (HCC)

- Recommendations to perform imaging every 6 months as doubling time of HCC is 3-6 months
- Goal to **diagnose** when HCC is **early** (i.e., ≤2 cm) as more treatment options can be made available
- However, HCC is often diagnosed too late
  - Lack of symptoms of HCC until it is already advanced
  - HCC screening may not be done routinely
AFP is not PERFECT as a Screening Test for HCC

- **AFP**
  - Sensitivity of 66%
  - Specificity of 82%

- Assuming a *5% HCC prevalence rate* in liver clinic, the positive predictive value of an **AFP of 20 ng/mL** is **41.5%**
Back to the Patient

- **U.S.:** Liver with irregular border and nodular contour. Increased echogenicity consistent with hepatic steatosis or hepatic fibrosis. **1.8 cm hyperechoic lesion in segment VIII.** Splenomegaly.
- **AFP:** 4 (normal)
Diagnosis of HCC

• Generally made by pursuing triphasic CT of liver or MRI with GAD.

• Diagnosis can be made on imaging characteristics of the lesion based on dual blood supply to the liver.
Diagnosis of HCC

- Generally made by pursuing **triphasic CT of liver or MRI with GAD.**  
  (Diagnosis can be made on imaging characteristics of the lesion based on dual blood supply to the liver.)

  **Normal liver parenchyma** is supplied for **80% by the portal vein** and only for **20% by the hepatic artery.** Normal liver will enhance in the portal venous phase.

  **All liver tumors** get **100% of their blood supply from the hepatic artery**, so when they enhance it will be in the arterial phase.

- **There can be atypical features seen on imaging.** If there is high suspicion for HCC (i.e., elevated AFP, growth in size, etc.) or an indeterminate concerning lesion, then can pursue biopsy.
Further Investigation

- CT Triphasic Liver with Contrast

Nodular appearance of liver consistent with cirrhosis. 2.0 cm lesion seen in segment VIII with arterial enhancement and portal venous washout consistent with **hepatocellular carcinoma**.

Diagnosis of HCC

Cross-sectional imaging can be enough to diagnose HCC and biopsy often not needed.
Outline

- Why Focus on Hepatocellular Carcinoma (HCC)?
- How to Screen and Diagnose HCC
- How to Manage HCC
- New Oral HCC Therapies
SUMMARY: 63 yo Hispanic lady with PMH of metabolic syndrome and compensated NASH cirrhosis who is found to have a 2 cm hepatocellular carcinoma as confirmed by triphasic CT of liver.

- CT CHEST non-con done and negative for metastasis
- She overall is feeling well and able to perform ADLs

What is next for treatment of her newly diagnosed hepatocellular carcinoma?
HCC Treatment

- It’s actually really complicated
- Treatment of a liver cancer depends on number of factors:
  - Liver function
  - Performance status/age
  - Size of tumor
  - Location of tumor
  - Transplant candidacy
  - Funding
  - Your center’s expertise
2018 Modified BCLC Staging System/Treatment Strategy

HCC in cirrhotic liver

Prognostic stage

Very early stage (O)
Single <2 cm
Preserved liver function* PS 0

Early stage (A)
Solitary or 2–3 nodules <3 cm
Preserved liver function* PS 0

Intermediate stage (B)
Multinodular, unresectable
Preserved liver function* PS 0

Advanced stage (C)
Portal invasion/extrahepatic spread
Preserved liver function* PS1−2

Terminal stage (D)
Not transferable HCC
End-stage liver function PS 3–4

Treatment
Ablation Resection Transplant Ablation Chemoembolization Systemic therapy BSC

Survival
>5 years >2.5 years ≥10 months 3 months

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019
Treatment of HCC Requires Input from Many Specialties

- Patient with HCC
  - Interventional radiology
  - Hepatology
  - Hepatobiliary and Transplant Surgery
  - Diagnostic Radiology
  - Pathology
  - Primary care Provider
  - Radiation Oncology
  - Medical Oncology
  - Palliative Care
Therapeutic Delays Associated with Worse Survival

Median time to treat 1.7 months, with 31% having delays > 3 mo

N=267
HR 2.0 (95% CI 1.19 - 3.33)

Outline

• Why Focus on Hepatocellular Carcinoma (HCC)?
• How to Screen and Diagnose HCC
• How to Manage HCC
• New Oral HCC Therapies
## Landscape of Systemic Treatment 2019

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Line of Treatment</th>
<th>Status</th>
<th>Result</th>
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<td>SOC</td>
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<td>Regorafenib</td>
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<td>FDA Approved 2017</td>
<td>Median OS 10.6 mos</td>
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<tr>
<td>Cabozantinib</td>
<td>Anti-MET</td>
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<td>FDA Approved 2019</td>
<td>Median OS 10.2 mos</td>
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<tr>
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<td>FDA Approved 2018</td>
<td>New data 2/2019 – No improvement OS</td>
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<td>Anti-VEGFR2</td>
<td>Second line</td>
<td>Phase III</td>
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Conclusion

- South Texas has the highest incidence of HCC in the USA
- Please screen for HCC every 6 months in patients with cirrhosis
- HCC treatment is complicated and HCC prognosis is poor, overall. Please refer early.
Management of Cirrhosis
Case Presentation

- 59-year-old male who presents with newly diagnosed HCV infection detected during routine screening (baby boomer)
- He c/o fatigue but otherwise asymptomatic
- Labs: ALT 25, AST 22, albumin 3.5, bilirubin 0.9, INR 1, platelet count 152
- Liver US: Nodular liver c/w cirrhosis
- What are the next steps?
Standard of Care for Compensated Cirrhosis

1. Treat the underlying etiology:
   • HCV: DAAs, HBV: NUCs, ETOH: Abstinence, NASH: Weight loss
2. Screening for HCC: Imaging +/- AFP every 6 months
3. Screening for EV/GV
   • EGD in all cirrhotics OR
   • Obtain VCTE + Platelet count:
     • LSM $\leq 20$ kPa + platelets $\geq 150$ k $\rightarrow$ Repeat yearly
     • LSM $> 20$ kPa OR platelets $< 150$ $\rightarrow$ EGD
4. Calculate MELD score/CTP score: MELD $\geq 15$ or CTP $\geq 7$ $\rightarrow$ OLT referral
5. Abstinence from alcohol
6. Nutrition counseling: Midnight snack
Fibroscan in Cirrhotic Patients with HCV
MELD and CTP Calculators

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Numerical score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>1-3</td>
</tr>
<tr>
<td>(prolonged in seconds)</td>
<td></td>
</tr>
</tbody>
</table>

Child’s Pugh Class A = 5-6 points; Child’s Pugh Class B = 7-9 points; Child’s Pugh Class C = 10-15 points.
Frailty is an Important Prognostic Factor

Hand-grip: the 5th Vital Sign in Cirrhosis

Nutritional status
(Forget 'pre-albumin')

Risk Prediction
\[\downarrow \text{Grip} = \uparrow \text{Mortality}\]

Cognitive Status
(Asterixis=can't hold grip)
Multi-stage Model for the Clinical Course of Cirrhosis

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction

<table>
<thead>
<tr>
<th>Compensated</th>
<th>Decompensated</th>
</tr>
</thead>
</table>
| **Stage 0**: no varices, mild PH  
LSM >15 and <20 or HVPG >5 and <10 mmHg | **Stage 3**: Bleeding     |
| **Stage 1**: no varices, CSPH  
LSM ≥20 or HVPG ≥10 mmHg | **Stage 4**:  
First non-bleeding decompensation |
| **Stage 2**: varices (=CSPH) | **Stage 5**:  
Second decompensating event |

**Stage 6**: late decompensation:  
Refractory ascites, persistent PSE or jaundice, infections, renal and other organ dysfunction

ACLF  
Death

EASL CPG decompensated cirrhosis. J Hepatol. 2018;doi: 10.1016/j.jhep.2018.03.024
Multi-stage Model for the Clinical Course of Cirrhosis

- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/system dysfunction

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Pathophysiology of DC

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Management Strategies for DC

• Management of DC aims to improve outcomes of complications

    Uncomplicated
    Refractory
    Ascites
    Hepatic hydrothorax
    Renal impairment
    AKI
    CKD
    Hyponatremia
    Complications of DC
    GI bleeding
    Cardiopulmonary
    CCM
    HPS
    PPHT
    Bacterial infections

Increased understanding of DC pathophysiology permits the development of more comprehensive therapeutic and prophylactic approaches to prevent or delay disease progression

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018; doi: 10.1016/j.jhep.2018.03.024
Key Recommendations
Topics

1. Overall management of DC
   • Suppression of aetiological factor(s)
   • Treatment of key pathogenic factors

2. Management of specific complications of DC
   • Ascites
   • Refractory ascites
   • Hepatic hydrothorax
   • Hyponatremia
   • Gastrointestinal bleeding
   • Bacterial infections
   • Renal impairment
   • Acute-on-chronic liver failure
   • Relative adrenal insufficiency
   • Cardiopulmonary complications

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018; doi: 10.1016/j.jhep.2018.03.024
Overall Management of DC

- Management should aim to prevent progression, not treat complications
- No treatment exists that can act on cirrhosis progression directly
- Two alternative approaches can be taken:
  - Suppress aetiological factor(s) that cause liver inflammation and cirrhosis development
  - Target key factors in the pathogenesis of cirrhosis decompensation and progression

EASL CPG decompensated cirrhosis. J Hepatol. 2018;doi: 10.1016/j.jhep.2018.03.024
Treatment of Key Pathogenic Factors

- Several strategies have been evaluated to prevent disease progression in patients with DC
  - Targeting microbiome abnormalities and bacterial translocation to improve the gut–liver axis (i.e., rifaximin)
  - Improving the disturbed circulatory function (i.e., long-term albumin)
  - Treating the inflammatory state (i.e., statins)
  - Targeting portal hypertension (i.e., β-blockers)

Further clinical research is needed to confirm the safety and potential benefits of these therapeutic approaches to prevent cirrhosis progression in patients with DC

EASL CPG decompensated cirrhosis. J Hepatol. 2018;doi: 10.1016/j.jhep.2018.03.024
Ascites

• Common complication of decompensation in cirrhosis
  • Develops in 5–10% of patients with compensated cirrhosis per year
• Significant impact on patients
  • Impairs patient working and social life
  • Frequently leads to hospitalization
  • Requires chronic treatment
  • Direct cause of further complications
  • Poor prognosis (5-year survival, ~30%)

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Evaluation and Diagnosis

- Cirrhosis is responsible for 80% of cases of ascites
- Initial patient evaluation:
  - History
  - Physical examination
  - Abdominal ultrasound
  - Laboratory assessment
    - Liver and renal function, serum and urine electrolytes, analysis of ascitic fluid
- Ascites is graded based on amount of fluid in the abdominal cavity

<table>
<thead>
<tr>
<th>Grading of Ascites*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild ascites: only detectable by ultrasound examination</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate ascites: manifest by moderate symmetrical distension of abdomen</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Large or gross ascites: provokes marked abdominal distension</td>
</tr>
</tbody>
</table>

*Ascites recurring on ≥3 occasions within a 12-month period despite dietary sodium restriction and adequate diuretic dosage are considered recurrent EASL CPG decompensated cirrhosis. J Hepatol. 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Evaluation and Diagnosis

- Diagnostic paracentesis is indicated in:
  - All patients with new-onset grade 2 or 3 ascites
  - Patients hospitalized for worsening ascites or any complication of cirrhosis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
</table>
| Neutrophil count and culture of ascitic fluid culture† should be performed to exclude bacterial peritonitis  
  • Neutrophil count >250 cells/µl denotes SBP | II-2              | 1                       |
| Ascitic total protein concentration should be performed to identify patients at higher risk of developing SBP‡ | II-2              | 1                       |
| The SAAG should be calculated when the cause of ascites is not immediately evident, and/or when conditions other than cirrhosis are suspected§ | II-2              | 1                       |
| Cytology should be performed to differentiate malignancy-related from non-malignant ascites | II-2              | 1                       |

*Grade of evidence II-2, grade of recommendation 1; †Bedside inoculation blood culture bottles with 10 ml fluid each;  
‡A total protein concentration <1.5 g/dl is generally considered a risk factor for SBP;  
§SAAG ≥1.1 g/dl indicates that portal hypertension is involved in ascites formation with an accuracy of about 97%

EASL CPG decompensated cirrhosis. J Hepatol. 2018; doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Prognosis

- Development of ascites in patients with cirrhosis is associated with a poor prognosis
  - 1-year mortality: 40%
  - 2-year mortality: 50%
- Patients with ascites should be considered for referral for LT

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Since the development of grade 2 or 3 ascites in patients with cirrhosis is associated with reduced survival, LT should be considered as a potential treatment option</td>
<td>II-2</td>
<td>1</td>
</tr>
</tbody>
</table>

- Patients may not receive adequate priority in transplant lists
  - Most commonly used prognostic scores can underestimate mortality risk
- Improved methods to assess prognosis in these patients are needed

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Management

- **Grade 1** or mild ascites
  - No data on evolution and not known if treatment modifies natural history
- **Grade 2** or moderate ascites
  - Hospitalization not required
  - Correct sodium imbalance:
    - Dietary restriction and increased renal excretion with diuretics

<table>
<thead>
<tr>
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<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate restriction of sodium intake (80–120 mmol/day, corresponding to 4.6–6.9 g of salt) is recommended</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Generally equivalent to a no added salt diet with avoidance of pre-prepared meals. Adequate nutritional education of patients on how to manage dietary sodium is also recommended</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>Very low sodium diets (&lt;40 mmol/day) should be avoided</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged bed rest cannot be recommended</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Sodium Tracker App

Today's Sodium
870 mg
1,430 mg
Left for today

Milligrams (mg) of sodium consumed:

1
2
3
4
5
6
7
8
9

French Fries 750 mg
Pasta 550 mg
Salad 23 mg
Sandwich 120 mg

Dec 27, 2013  870 mg
Dec 26, 2013  1265 mg
Dec 25, 2013  2142 mg
Dec 24, 2013  685 mg
Dec 23, 2013  1065 mg
Dec 22, 2013  1550 mg
Dec 21, 2013  1945 mg

Today's goal is 2,300 mg
Uncomplicated Ascites: Recommended Diuretics

- Mainstay of medical treatment are anti-mineralocorticoid drugs*
- Loop diuretics may be added in patients with long-standing ascites

<table>
<thead>
<tr>
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<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First episode of grade 2 ascites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anti-mineralocorticoid drug alone (from 100 mg/day with 100 mg stepwise increased every 72 hours to a maximum of 400 mg/day if no response to lower doses)</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td><strong>In patients who do not respond to anti-mineralocorticoids† or who develop hyperkalaemia, furosemide should be added (from 40 mg/day with 40 mg stepwise increases to a maximum of 160 mg/day)</strong></td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td><strong>Long-standing or recurrent ascites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Combination of an anti-mineralocorticoid drug and furosemide (dose increased sequentially according to response)</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Torasemide can be given in patients exhibiting a weak response to furosemide</td>
<td>I</td>
<td>2</td>
</tr>
</tbody>
</table>

*Spironolactone, canrenone or K-canrenoate; †Body weight reduction <2 kg/week
EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Considerations Prior to Initiating Diuretics

• Patients with cirrhosis and ascites are highly susceptible to rapid reductions in extracellular fluid volume
• Can lead to renal failure and hepatic encephalopathy

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</tr>
</thead>
<tbody>
<tr>
<td>GI haemorrhage, renal impairment, hepatic encephalopathy, hyponatraemia, or alterations in serum potassium concentration, should be corrected before starting diuretic therapy</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>• In these patients, cautious initiation of diuretic therapy and frequent clinical and biochemical assessments should be performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic therapy is generally not recommended in patients with persistent overt hepatic encephalopathy</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Monitoring of Patients Receiving Diuretics

- Loop diuretics can lead to potassium and magnesium depletion and hyponatraemia
- Muscle cramps can impair quality of life in patients receiving diuretics

<table>
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<tr>
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<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent clinical and biochemical monitoring during the first weeks of treatment (particularly on first presentation)</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Recommended maximum weight loss: 0.5 kg/day in patients without oedema, 1 kg/day in patients with oedema</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>Once ascites have largely resolved, the dose of diuretics should be reduced to the lowest effective dose</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>Discontinue diuretics in case of severe hyponatraemia, * AKI, worsening hepatic encephalopathy, or incapacitating muscle cramps</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>Discontinue furosemide for severe hypokalaemia (&lt;3 mmol/L ) Discontinue anti-mineralocorticoids for hyperkalaemia (&gt;6 mmol/L)</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>Albumin infusion or baclofen administration† are recommended in patients with muscle cramps</td>
<td>I</td>
<td>1</td>
</tr>
</tbody>
</table>

*Serum sodium <125 mmol/L; †10 mg/day, with a weekly increase of 10 mg/day up to 30 mg/day
EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Management of Grade 3 Ascites

- **Grade 3** or large ascites
  - LVP, under strict sterile conditions, is the treatment of choice
    - Ascites should be completely removed in a single session*
  - Contraindications to LVP include:
    - Uncooperative patient, abdominal skin infection at puncture sites, pregnancy, severe coagulopathy, severe bowel distention

<table>
<thead>
<tr>
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<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVP should be <strong>followed with plasma volume expansion</strong></td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td><strong>Plasma volume expansion</strong> should be performed by albumin infusion** (8 g/L ascites)</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>• For &gt;5 L of ascites: more effective than other plasma expanders</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>• For &lt;5 L of ascites (low risk of PPCD): treat with albumin due to concerns about use of alternative plasma expanders</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td><strong>After LVP, patients should receive the minimum dose of diuretics necessary to prevent re-accumulation of ascites</strong></td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>When needed, LVP should be performed in patients with AKI or SBP</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

*Grade of evidence I, grade of recommendation 1
EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Uncomplicated Ascites: Contraindicated Drugs

- Patients with DC and ascites are at increased risk of renal impairment from several types of drug

<table>
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<tr>
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<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs should not be used</strong> (high risk of developing further sodium retention, hyponatraemia, and AKI)</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors, angiotensin II antagonists, or α1-adrenergic receptor blockers should not generally be used</strong> (increased risk of renal impairment)</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Aminoglycosides are discouraged</strong> (increased risk of AKI)</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>• Reserved for patients with severe bacterial infections that cannot be treated with other antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contrast media</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In patients with preserved renal function: does not appear to be associated with increased risk of renal impairment</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>• In patients with renal failure: insufficient data, cautious use and preventative measures recommended</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

EASL CPG decompensated cirrhosis. *J Hepatol.* 2018;doi: 10.1016/j.jhep.2018.03.024
Refractory Ascites: Definition

- **International Ascites Club:**
  - “Ascites that cannot be mobilized or the early recurrence of which (after LVP) cannot be satisfactorily prevented by medical therapy”

---

**Refractory ascites**

- **Diuretic resistant**
  - Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment

- **Diuretic intractable**
  - Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage

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EASL CPG decompensated cirrhosis. *J Hepatol*. 2018;doi: 10.1016/j.jhep.2018.03.024
Refractory Ascites: Indications for TIPS

- **TIPS decompresses the portal system** *
  - **Short-term**: Accentuates peripheral arterial vasodilation
  - **Within 4–6 weeks**: Improves effective vollaemia and renal function to increase renal sodium excretion

### Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients should be evaluated for TIPS insertion when:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• There is refractory or recurrent ascites</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>• Paracentesis is ineffective</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>TIPS insertion is recommended in patients:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• With recurrent ascites as it improves survival</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>• With refractory ascites as it improves the control of ascites</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>The use of small-diameter PTFE-covered stents is recommended to reduce the risk of TIPS dysfunction and hepatic encephalopathy</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>After TIPS insertion, continue the following until ascites resolution:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diuretics and salt restriction</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>• Close clinical follow-up</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

*By shunting an intrahepatic portal branch into a hepatic vein
EASL CPG decompensated cirrhosis. *J Hepatol*. 2018;doi: 10.1016/j.jhep.2018.03.024