The Changing Landscape of Liver Care

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The Evolution of the OSU Liver Program…

From Then…

To Now… Hepatology MDs

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Collaborative Clinical Efforts

- Multi-disciplinary and sub-specialized clinics
  - Liver tumor clinic
  - HCV treatment
  - NASH and metabolic liver disease
  - Post-transplant care

New Tools and Treatment Options

- Hepatocellular Carcinoma (HCC):
  - TACE
  - RFA
  - Y-90
  - SBRT
- Portal hypertensive bleeding:
  - Cyanoacrylate injection of gastric varices
  - Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)
- EUS-guided liver biopsies

Transient Liver Elastography (Fibroscan)

- The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography
- A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making.

Evolution of Care

HEPATOLOGY
Liver Biology/Pathobiology
Hepatic gene expression during treatment with peginterferon and ribavirin: Identifying molecular pathways for treatment response
Jordian J. Field, Santosh Nandia, Ying Huang, Peiying Chen, Maggie Cam, Susan N. Pusek, Lisa M. Scheinberger, Dickson Theodore, Steven L. Zacks, T. Jake Liang O'T, Michael W. Rand
First published: 19 October 2007 - Full publication history
DOI: 10.1002/hep.21853
Cited by (Crossref): 181 articles

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Current Population: Hepatitis C

- Baby Boomers (Born in 1945–1965) account for 76.5% of HCV in the US
- Almost 35% of undiagnosed baby boomers with HCV are estimated to currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)

Future Population: Non-alcoholic Fatty Liver Disease (NAFLD)

Dallas Heart Study (2,200 adults)
- Assessed NAFLD with liver imaging
- General prevalence of fatty liver 31% (range 24% - 45%)
- Most individuals (79%) with fatty liver do not exhibit aminotransferase elevations

NHANES III (15, 700 adults)
- Assessed NAFLD with aminotransferases
- General prevalence of NAFLD 5.5%

NAFLD prevalence 3-10 x more prevalent than Hepatitis C
NAFLD: Risk Factors

- Normal AST, ALT
- 5.5% Unexplained Hepatitis
- BMI
- Waist circumference
- Triglycerides
- Insulin
- HDL cholesterol
- Metabolic Syndrome

NAFLD Natural History

Liver-related morbidity and mortality

NAFL NASH Cirrhosis

NAFLD in High-Risk Populations: Morbidly Obese Gastric Bypass Patients

Liver disease often unsuspected pre-operatively
Intraoperative liver biopsy typically shows NAFLD
- Steatosis: 30-80%
- Steatohepatitis: 33-42%
- Fibrosis:
  - Idiopathic portal fibrosis: 33%
  - Advanced fibrosis: 12%
  - Cirrhosis: 1-2%
- Advanced fibrosis 13-14%

NAFLD in High-Risk Populations: Type 2 Diabetes Mellitus

Prevalence of NAFLD is high
- Ultrasound detects fatty liver in 50%
- NASH unusually common
  - NAFL: 12%
  - NASH: 87%
- Fibrosis or cirrhosis documented in 20%
- Standardized mortality rate for death from liver disease > than that for coronary disease

Clark, Brasacchi, Delhi. Am J Gastro 2003; 98:968
Prognostic Implications of NASH + Fibrosis

More consistent and rapid progression to cirrhosis than NAFL

- NAFL: > 10 years, Cirrhosis 3%
- NASH + fibrosis: 5-10 years, Cirrhosis 30%

Matteoni et al. Gastroenterology 1999; 116:1413

Prognostic Implications of NASH + Fibrosis

- More consistent and rapid progression to cirrhosis than NAFL
- Rate of liver related mortality about 10% within 10 years
- Liver disease is a major cause of mortality

Cardiovascular disease > cancer = cirrhosis

# 1
# 2

Matteoni et al. Gastroenterology 1999; 116:1413

Major Changes in Liver Transplant

- NASH Epidemic: Multiple medical co-morbidities; obesity, HTN, T2DM, hyperlipidemia
- Share 35 ACLF is increasingly common
- Aging Population: Median age at transplant is rising by ~1 year every 2 years
- New HCC Policies: "Healthy" HCC patients now available

Patients with advanced liver disease are getting sicker and sicker
Acute on Chronic Liver Failure (ACLF)

- Acute decompensation (defined as worsening coagulopathy and jaundice) in a patient with chronic liver disease
- Often precipitated by infection
- Multi-organ system dysfunction
- Associated with poor prognosis

Severity and Prognosis of ACLF

1. Acute on Chronic Liver Failure (ACLF)
2. Definition:
   - Acute decompensation (defined as worsening coagulopathy and jaundice) in a patient with chronic liver disease
   - Often precipitated by infection
   - Multi-organ system dysfunction
   - Associated with poor prognosis

Co-morbidities Matter in Cirrhosis

- Diabetes increases risk of death in patients with ESLD
- Older age is associated with increased waitlist mortality
- Older age is associated with increased risk of post-transplant mortality
- CHF, COPD, and DM are predictive of mortality after liver transplant

For the Increasingly Complex Patient, We Need...

- Frameworks: For dynamic, personalized decision-making for patients with multi-organ dysfunction
- Tools: To provide us with information that incorporates all systems to help us prognosticate and engage in shared decision-making

Severity and Prognosis of ACLF Diagram:
- Severity of liver disease/Portal hypertension
- HTN, CHF, CAD
- Small vessel dz., beta-amyloid plaques, ETOH nephropathy
- COPD, OSA, obesity hypovent
- HTN/DM/lgA nephropathy
- Severity of liver disease/Portal hypertension (MELD, Child Pugh)
- Circulatory failure
- Cerebral failure
- Renal failure
- Pulmonary failure
- Death
“Frailty”

- From the geriatrician’s toolbox
- “A distinct biologic syndrome of decreasing physiologic reserve and increasing vulnerability to health stressors”
- “Aggregate expression of risk resulting from age- and disease-related subthreshold decrements of multiple physiologic systems”


Karnofsky Performance Status

<table>
<thead>
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<tbody>
<tr>
<td><strong>Assessed by the clinical provider or patient</strong></td>
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<tr>
<td><strong>High</strong></td>
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<tr>
<td><strong>Intermediate</strong></td>
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<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>• Predicts 3-month mortality after hospitalization (better than MELD + age alone)</td>
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<tr>
<td>• Predicts 30-day mortality after liver transplantation</td>
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Frailty Assessment

The Liver Frailty Index
liverfrailtyindex.ucsf.edu

LFI Predicts Mortality Better Than MELD-Na Alone

![Graph showing survival probability vs. time since assessment for robust and frail MELD-Na categories.]

*S Robust / Frail defined as the 20% / 40%ile Liver Frailty Index values

Sarcopenia

Sarcopenia by Skeletal Muscle Index

![Images of CT scans showing BMI 28 non-sarcopenic, BMI 47 non-sarcopenic, and BMI 47 sarcopenic cirrhotic patients.]

BMI 28 cirrhotic Non-sarcopenic
BMI 47 cirrhotic Non-sarcopenic
BMI 47 cirrhotic Sarcopenic

SMI cut-offs to define sarcopenia that predict mortality: 47 cm²/m² for men; 42 cm²/m² for women

Final Thoughts

- A framework for medical decision-making that accounts for frailty can facilitate more individualized decisions
- Tools for medical decision-making need to move beyond organ-specific assessments and incorporate the aggregate effects of multi-morbidity and aging
- "Frailty" tools such as the KPS, ADL, Liver Frailty Index, and skeletal muscle index should be incorporated into routine assessments
Acknowledgements

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- Nicole O’Bleness Gray, CNP, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University

Update on Hepatitis C

Anthony Michaels, MD
Associate Professor of Clinical Medicine
Medical Director of Liver Transplantation
The Ohio State University Wexner Medical Center

Objectives

1. Review methods of diagnosis.
2. Describe modalities of staging fibrosis.
3. Review current therapeutic options.
4. Discuss how to choose appropriate candidates for therapy.

Disclosures Last 12 Months

- Speaker Contract: Gilead, Abbvie, DOVA
- Advisory Board: Gilead, Abbvie
**Background**

- RNA virus with different subtypes  
  - (i.e., genotypes 1-6 (G1 most common in the US))  
- Blood exposure (IVD in the US)  
- Can cause an acute and/or chronic infection  
- Can cause extrahepatic manifestations  
  - Hematologic: Mixed cryoglobulinemia  
  - Renal: Glomerulonephritis  
  - Dermatologic:  
    - Porphyria cutanea tarda  
    - Leukocytoclastic vasculitis  
    - Lichen planus

**Natural History**

**Acute HCV**
- ~60-80%

**Chronic HCV**
- ~50%
- ~25%
- ~25%

Minimal Progression  
Cirrhosis in ~50 years  
Cirrhosis in ~25 years  
~3-5% per year

- Jaundice  
- Hepatic Enceph  
- Variceal Bleed  
- Ascites  
- HCC

**Worldwide Seroprevalence of Hepatitis C:**
- ~200 million

**Updated Prevalence of Hepatitis C in the U.S. Results from a Simulation Model Including the Non-NIHANES Population**

- In 2017, 1.8 million virologic people were unaware of their HCV status.  
- By 2030, 1.1 million people would still remain unaware of their HCV.

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The Road to Elimination of HCV: Projections for USA Treatment and New Infections from 2016 – 2030

USA not projected to eliminate HCV by 2030 due to projected increase in new HCV infections and projected decrease in treatment rates.

In 2016, WHO called for a 90% reduction in new HCV infection by 2030.

Far higher rates of treatment are required worldwide for elimination of HCV.

Need to Improve Our Screening and Linkage to Care

- Only approximately 50% of chronic HCV pts in the US have been diagnosed.
- Approximately 9% of these patients have been successfully treated.

Need to Improve Our Screening and Linkage to Care

- Baby Boomers (Born in 1945–1965) Account for 76.5% of HCV in the US.
- Almost 35% of undiagnosed baby boomers with HCV are estimated to currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis).

How to Screen and Diagnose?

- Hepatitis C Antibody
  - If positive, then can check for Hepatitis C RNA levels to actually DIAGNOSE.
- Hep C RNA
  - If POSITIVE, this indicates a current infection. Won’t know chronicity until have a repeat RNA level in 6 months.
    - Can obtain a genotype to help further differentiate
  - If NEGATIVE, then the patient doesn’t have an active infection (previous exposure with subsequent clearance vs a false positive).

Pretreatment Assessment

- The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography.
- A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making.

FDA HBV Reactivation Cases

HBV Reactivation Associated with HCV DAA Therapy

Query of the FDA Adverse Event Reporting System (FAERS) for cases of HBV-R associated with HCV DAA therapy from 11/22/2013–10/15/2016

<table>
<thead>
<tr>
<th>Descriptive Characteristics</th>
<th>Data</th>
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<tbody>
<tr>
<td># of cases/geography</td>
<td>29 cases (5 in US, 19 Japan, 5 in other)</td>
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<tr>
<td>Timing</td>
<td>Temporally related to HCV therapy and occurred within 4-8 weeks (mean time to HBV-R was 53 days)</td>
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<tr>
<td>Baseline HBV viral parameters</td>
<td>HBsAg+ (n=15) (n=12 not reported); HBsAb+ (n=6) (n=23 not reported); HBV DNA undetectable/detectable (n=16/9)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Death (n=2) (due to decompensated liver failure); transplant (n=1); hospitalization (n=6); other (n=20)</td>
</tr>
<tr>
<td>Specific DAAs used</td>
<td>SOF-based (n=16); DCV+ASV (n=11); PI-based (n=2)</td>
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<tr>
<td>HBV treatment</td>
<td>In 16 patients who received HBV treatment, treatment was delayed in at least 7 of the cases (44%); one of these 7 patients died; possible delay in at least 7 other cases (one had a liver transplant)</td>
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- “Our data show that HBV-R is a safety concern in pts previously infected with HBV who take DAA”
- “The benefit of high HCV cure rate with DAA continues to outweigh the risks, even in those patients who may be at risk of HBV-R”
- “Patients with a history of HBV require careful clinical monitoring while on DAA therapy”
- “HBV-R is defined as the abrupt increase in HBV replication in a patient with inactive or resolved HBV (HBsAg positive or negative, respectively), and hepatitis B core antibody (HBcAb) positive”

Targeting the Viral Life Cycle: Direct Acting Antivirals (DAAs)

Current Treatment Options Simplified

- Treatment Naïve and IFN Experienced Patients
  - Gileferivir+Pibrentasvir 8-16 wks
  - Sofosbuvir+Velpatasvir 12 wks
  - Sofosbuvir+Ledispavir for 8-24 wks +/- RBV (insurance driven)
  - Elbasvir+Grazoprevir 12-16 wks +/- RBV (insurance driven)
- DAA Experienced Patients
  - Sofosbuvir+Velpatasvir+Voxilaprevir 12 wks
  - (96% overall SVR12 in Polaris-1 (99% in noncirrhotics and 93% in cirrhotics))
  - Gileferivir+Pibrentasvir
  - (i.e, Sofosbuvir+Ledispavir relapers would get 16 wks)
- All HCV patients prior to starting therapy need HBV screening
Sustained Virologic Response

- Co-Infected
- Decompensated Cirrhosis
- ESRD
- G3 Post-Transplant
- HCC
- Fibrosing Cholestatic C
- Active Drug Users
- Morbidly Obese

>90%

Hepatitis C Treatment

- More Common Side Effects of the Current DAAs
  - Headache
  - Fatigue
  - Nausea
  - Insomnia
- Overall very well tolerated
- Discontinuation rates <1%

SVR Associated With a Reduction in HCC, Liver-Related Mortality, Transplantation, and All-Cause Mortality


Veterans Affairs HCV Clinical Case Registry

Impact of SVR with DAAs on Mortality and HCC

All-cause mortality rates and incident HCC rates in Veterans ± advanced chronic liver disease (ACLD) in the HCV registry treated with DAAs through Sept 2016

- SVR was associated with 80% reduction in mortality and 84% reduced incidence in HCC
- SVR was associated with 59% reduction in mortality

ACLD vs. no ACLD at DAAs start

SVR was associated with 59% reduction in mortality

ACLD: Fib-4>3.25 at DAAs start
Reduction in Liver Transplant Waitlist in the Era of HCV DAAs


Annual Standardized Incidence Rates (ASIR) of LT Wait-Listing per 100,000 US Population

The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH.

UNOS Database

Short-Term Survival in HCV Patients Following Liver Transplantation in the Era of DAAs

Impact of the DAA era on short-term post-LT outcomes among HCV patients compared to non-HCV etiologies (pre-DAA era (n=3,872); DAA era (n=3,855))

DAA era was associated with a 34% reduction in one-year post-LT patient mortality (*adjusted HR 0.66, P <.001) among HCV LT recipients.

DAA era was associated with a 34% reduction in one-year post-LT patient mortality (*adjusted HR 0.66, P <.001) among HCV LT recipients.

Patient and graft survival rates have improved during the DAA era and they are no longer different from non-HCV transplant patients.

Current Treatment Options

• Issues still with treatment
  • Not everyone can be treated
    • Insurance/Cost
    • Fibrosis stage
  • Should we be treating active drug users or alcoholics?
  • Pediatrics/Adolescents
  • Should we be treating everyone?
    • Significant comorbidities
    • Older patients with early stage disease
  • What to do with DAA relapers? Any options left?
  • Need more treaters