Liver Pathology and the Clinician in 2015:
At the Crossroads

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DISCLOSURES

Consultant for:

- Salix
- Merck
- Gilead
- BMS
- Synageva

Research funding:

- Mass Biologics
- Merck
- Itherx
- Gilead
- Biotest
- Galectin
Overview

• Introduction
• Advances in Hepatitis C (HCV)
• Non-alcoholic fatty liver disease
• Developments in hepatic fibrosis assessment
• Hepatocellular carcinoma (HCC)
Introduction

• Dramatic developments over last 3-5 years in diagnosis and treatment of chronic liver disease:
  • Antivirals
  • Better experience/agents with immunosuppression
  • Novel imaging modalities

• Although liver pathology critical to development of hepatology, overall less need for liver biopsy
  • Staging of fibrosis
  • Post-liver transplant (LT)
  • As part of clinical trials

• Unclear ramifications for pathologists-in-training
  • Biopsies now more likely to be diagnostic dilemmas with several concurrent disease processes
Hepatitis C (1989-2012)

- 2% of US population underestimated
- Most frequent need for LT and re-LT world-wide
- Major role in the epidemic of HCC in the West
- Liver biopsies performed to assess suitability for treatment, and for monitoring patient over time
- Treatments long, modestly effective with major side effects using interferon and ribavirin
- Special populations challenging and difficult to treat; often excluded from clinical trials
Hepatitis C (2012-present)

• Era of DAA, starting with boceprevir and telaprevir in combination with interferon/ribavirin
  • Side effects/Adverse events and drug:drug interactions

• Quickly followed by rapid FDA approvals of:
  • Sofosbuvir (Sovaldi) and Simeprevir (Olysio)
  • Sofosbuvir/ledipasvir (Harvoni)
  • Ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekira-Pak)

• 90-95 % cure (SVR) rates, pan-genotypic, negligible side effects, minimal resistance

• Treatment courses have decreased to 8-24 weeks.
SVR (Cure) Associated with Decreased All-Cause Mortality

530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-1.4) years.

Van der Meer et al. JAMA 2012; 308:2584
Hepatitis C in 2015

• Philosophy has morphed from “Do we treat” to “When do we treat”

• Cirrhotics and post-LT patients 75% cure rate → timing of treatment is now the issue

• Special populations: HIV, ESRD, geriatrics and hematological disorders → high cure rates

• More meds in pipeline; pharma redirecting focus to HBV and NASH

• Liver biopsy rarely needed except for diagnosis of concurrent disease (ie, HCV/AIH overlap, post-LT)
Ramifications of the New Meds

- Number of liver transplants for HCV will remain static in the short term.
- HCC may become the greater indication for LT
  ➔ SCREEN all patients who are cured
- Can we stabilize or reverse disease severity (HBV paradigm)?
Post-SVR Era

• Story of HCV represents one of the great successes in medicine
• Importance of concurrent NASH, alcohol use
• How long will it take for fibrosis to regress in order to decrease risk of HCC?
• What do we tell outpatients about lifestyle changes and duration of HCC screening?
• Research to develop biomarkers is needed
Non-Alcoholic Fatty Liver Disease

- 25-30% of patients in liver practices
- Now 2\textsuperscript{nd} leading cause for LT
- Can be present with normal liver tests
- Association with metabolic syndrome:
  - DM, increased lipids
  - Overweight
  - Gout
- 40% have elevated ferritins, and 30% have low titer ANA and other autoimmune markers
- Decreased long-term survival post-LT
  - Bariatric surgery performed concurrently
Non-Alcoholic Fatty Liver Disease

• Diagnosis readily made via chemistries, hx and imaging

• No guidelines for when to biopsy→? presence of hepatomegaly
  • Does biopsy change management?
  • Imaging can’t distinguish between NAFL and NASH

• No approved treatment: weight loss, control of DM, lipids.

• 8-10 compounds in clinical trials, many requiring serial biopsies
  • FXR agonist obeticholic acid with compelling results and improvement in histology* (also used in PBC & PSC)

• Unclear long-term benefits of bariatric surgery
  • Biopsies should be done intra-operatively
  • Undiagnosed cirrhosis

*Neuschwander-Tetri B et al. Lancet 2014
Hepatic Fibrosis

- More cases of HCC increased being non-cirrhotics
  - HBV
  - NASH
  - Metabolic liver disease
- Good correlation between clinical decompensation and Laennec scoring system and collagen proportionate area
- Perceived sampling error with biopsy and issues with specimen adequacy – interest in biomarkers!!
- Is all fibrosis the same and is it always reversible?
Hepatic Fibrosis Assessment

- FibroScan – 2013 FDA approval
- Sheer wave velocity, converted into measure of liver stiffness
- Transducer utilizing 50 MHz waves reflected back from liver
- Takes 5-7 minutes
- Physician extenders can perform
- ICD-9 codes now available
- Spleen stiffness may correlate with degree of portal hypertension

Manning and Afdahl, Gastroenterology 2008
Hepatic Fibrosis Assessment
Other Modalities

- MR elastography (MRE) can also assess degrees of steatosis and siderosis
  - Cost and time of procedure remain problematic
  - Can also screen for HCC
- Serum studies:
  - Hepascore/Fibrosure
  - FIB-4 index
- All are excellent at detecting extremes of fibrosis
- What do we do for patients with stage 2-3?
- Unclear that any of these modalities can reliably assess fibrosis regression
- Anti-fibrotics currently in early clinical trials
Hepatocellular Carcinoma

• Accounts for 50% of LT
  • Many dropouts on the waiting list

• Medical therapy ineffective

• Locoregional therapy infrequently curative
  • Radiofrequency ablation
  • Chemoembolization
  • Radioembolization
  • Single beam RT

• Resection possible in 10% of patients at presentation

• Underlying liver disease and portal HTN limit intervention

• CPT-C cirrhosis with HCC - 6 month survival
Hepatocellular Carcinoma

• Annual risk is 2-4 % in cirrhotics
• Imaging and AFP imperfect
• Cost effectiveness—U/S vs other imaging modalities
• Size of HCC, multi-focality, degrees of differentiation and vascular invasion all prognostic features for recurrence
• Milan criteria:
  – One HCC ≤ 5 cm or ≤ 3 none > 3cm.
  – HCC < 1cm not taken into account
Hepatocellular Carcinoma

• Ongoing research pursuits:
  – Morphological subtyping and gene signatures to help predict natural history and response to treatment

• Current AASLD and EASL guidelines: No biopsy required.
  – This has constrained personalized medicine approaches and morphological subtyping
  – Mixed HCC-cholangiocarcinoma increasingly recognized

• Does the failure of clinical trials in HCC reflect the heterogeneity of tumors in patients enrolled into trials?

• More interest now in biopsying HCC prior to treatment for prognosis, not diagnosis!
Summary

• Remarkable advances in treatment of HCV, rapidly developing therapeutics in NASH and HBV, and new diagnostic modalities

• Dramatic decrease in the # of liver biopsies being performed as part of standard of care

• There will be an increased need for biomarkers to assess prognosis and risk of HCC, and fibrosis regression.

• Will liver biopsies become important again as part of new proteomic and molecular biologic advances to help guide our therapies?

• Liver biopsies have become more complicated, making ever-important the close working relationship between clinician and pathologist.