ACG VIRTUAL GRAND ROUNDS

Gastroenterology & Hepatology Fellowship Match Application: Tips & Tricks For Prospective Fellowship Applicants

WEDNESDAY, MAY 11, 8-9:30 PM EDT

Moderators
Anne Tuskey, MD, FACP
Mohammad Bilal, MD

Faculty & Panelists
Carl Crawford, MD
Kathryn Hutchins, MD
Lin Chang, MD, FACP
Mariam Naveed, MD
Rashmi Advani, MD
Lauren Feld, MD
Judy Trieu, MD, MPH
Chiazotam Ekekezie, MD

Register: gi.org/ACGVGR #GIhomeschooling

ACG Institute
YOUNG PHYSICIAN LEADERSHIP SCHOLARS PROGRAM

Application Deadline: Friday, June 3, 2022
Apply Online: gi.org/ylsp
Virtual Grand Rounds

ACG 2022
CHARLOTTE NORTH CAROLINA
OCTOBER 21 - 26, 2022

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Present Your Abstract at ACG 2022
The Deadline for Submission is Monday, June 20, 2022 at 11:59 pm ET

Abstract Categories:
- Biliary/Pancreas
- Colon
- Colorectal Cancer Prevention
- Endoscopy Video Forum
- Esophagus
- Functional Bowel Disease
- General Endoscopy
- GI Bleeding
- IBD
- Interventional Endoscopy
- Liver
- Obesity
- Pediatrics
- Practice Management
- Small Intestine
- Stomach
- Clinical Vignettes/Case Reports

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.
How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
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Empowering Patients Through the Transition of Care in IBD
Sneha Dave, Leah Clark, and Isabela Hernandez from the Crohn’s and Colitis Young Adults Network
May 5, 2022 at Noon Eastern and 8pm Eastern!

Week 19
An Updated Approach to Idiopathic Acute Pancreatitis in 2022
Gregory Coté, MD, MS, Oregon Health and Science University
Dhiraj Yadav, MD, MPH, UPMC Presbyterian Shadyside
May 5, 2022 at Noon Eastern and 8pm Eastern!

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Liver Biopsy Interpretation for Gastroenterologists

Paul Y Kwo, MD
Professor of Medicine
Director of Hepatology
Stanford University School of Medicine
pkwo@stanford.edu
Objectives

- Understand liver microanatomy
- Understand basic stains used in interpretation of liver biopsies
- Recognize when biopsy size may not be sufficient for fibrosis determination
- Be able to recognize and correlate patterns of hepatocellular injury

The normal liver architecture: hepatic lobules
Normal Liver Histology: Portal tract has 5 structures, 3 are typically seen microscopically

- Portal vein
- Lymphatic vessel
- Hepatic arteriole
- Bile duct
- Portal vein
The Hepatic Sinusoids

1. Hepatic lymph flow toward portal triads majority in Space of Disse
2. Hepatic lymph flows toward portal triads
3. Hepatic lymphatic channel in portal triad
4. Ultimately drains to thoracic duct

Utility of Liver Biopsy

- Assess fibrosis severity
- Assess type of hepatocellular injury/diagnostic dilemma
- Assess severity of necroinflammation
- Evaluate possible concomitant disease processes
- Role of Liver Biopsy
- Disease monitoring
- Assess therapeutic intervention
Seven morphologic patterns of liver injury

Pattern 1: Portal cellular infiltrates (the blue portal tract)

Pattern 2: Ductular reaction (the bloomed portal tract)

Pattern 3: Lobular injury (the drugged lobule)

Pattern 4: Steatosis (the bubbly liver)

Pattern 5: Near-normal appearance (calm but not quiet)

Pattern 6: Fibrosis (the scowled liver)

Pattern 7: Mass lesion (a jumpy kind of guy)

Fibrosis Stages in any chronic hepatitis

Ishak
METAVIR
Knodell

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American College of Gastroenterology
Early cirrhosis: Can be missed on Liver Bx

Biopsy width in HCV: A narrow biopsy may understage fibrosis: Ideally 3 cm with 16 gauge needle with > 10 portal tacts

<table>
<thead>
<tr>
<th></th>
<th>≥ 3 cm</th>
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<th>1.5 cm</th>
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<tr>
<td></td>
<td>1.4 mm</td>
<td>1 mm</td>
<td>1.4 mm</td>
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<tr>
<td>Portal tacts</td>
<td>22.4± 4.9</td>
<td>11.2± 2.4</td>
<td>10.3± 2.2</td>
<td>5.4± 1.3</td>
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<tr>
<td>Ishak fibrosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mild (1,2)</td>
<td>59%</td>
<td>79%</td>
<td>68%</td>
<td>87%</td>
</tr>
<tr>
<td>Mod (3,4)</td>
<td>30%</td>
<td>18%</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Sev (5,6)</td>
<td>11%</td>
<td>3%</td>
<td>7%</td>
<td>1%</td>
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(Bedossa J Hep 2003; 39: 239)
Typical Stains for liver biopsy

- Hematoxylin and eosin (H&E) routinely done
- Masson’s trichrome
- Reticulin Stain
- Periodic acid-Schiff (PAS): alpha-1 antitrypsin deficiency with Z allele, glycogen storage disease)
- Perl’s iron stain (Prussian blue reaction): Hemosiderin and ferritin
- Rhodanine stain is used to detect copper-binding protein (copper): Wilson’s disease, cholestatic diseases
- Congo Red:Amyloid
- Immunohistochemical Stains: HBV, CMV, HSV, alpha-1-antitrypsin

Hepatocyte Death

Apoptosis

Necrosis
Trichrome for fibrosis stains for Type 1 collagen

Cirrhosis: Masson trichrome stain
Reticulin stain for fibrosis stains for type 3 collagen
Useful in acute hepatitis presentation, confused on imaging as cirrhosis

Normal

Collapse

Genetic Hemochromatosis: Presence of iron in hepatocytes
H&E stain
hemosiderin (brown granules)
Prussian stain
hemosiderin (Blue)
**Prussian Blue Stain**

Hemosiderin in Kupffer cells  
ferritin in cytoplasm  
Iron staining in NASH (DIOS)

![Image of Prussian Blue stain](image)

DOI: 10.1007/s12072-011-9304-9

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**Rhodanine stain**  
for Copper in Wilsons Disease

![Image of Rhodanine stain](image)
PAS diastase stain removes glycogen allows identification of alpha-1 antitrypsin globules in those with homozygous and heterozygous Z allele

Patterns of injury: Hepatitis
Ballooning or Swollen Hepatocytes

Scattered inflammatory cells, acidophil bodies (apoptosis)
Drug induced liver injury has diverse range of histologic findings

Ciprofloaxicin  |  INH  |  Immune Checkpoint Inhibitor


### Injury Patterns of Selected Drugs in Common Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pattern of Injury</th>
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<tr>
<td>Acetaminophen</td>
<td>Zone 3 necrosis (with little additional inflammation)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Steatohepatitis-like, with numerous Mallory-Denk bodies and fibrosis</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>Cholestatic hepatitis (with prominent duct injury)</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Acute cholestasis to cholestatic hepatitis with little duct injury</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Variable: Hepatitis with or without cholestasis</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Zone 3 necrosis with lymphocytic inflammation</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Acute or chronic hepatitis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Steatosis and fibrosis, sometimes steatohepatitis-like</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Acute or chronic hepatitis</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Acute or chronic hepatitis</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Hepatoportal sclerosis, sinusoidal dilation, nodular regenerative hyperplasia</td>
</tr>
</tbody>
</table>
Coagulative Necrosis: Common in ischemia, DILI, severe viral hepatitis

Histologic variants of acute hepatic failure
Macrovesicular Steatosis: single, large vacuole of fat fills up the hepatocyte and displaces the nucleus to the periphery

Microvesicular steatosis: acute mitochondrial dysfunction that leads to an impairment of beta-oxidation of fatty acids (AFLP)
Dilated sinusoids with atrophic plates
HV outflow obstruction, congestive hepatopathy

Giant Cell hepatitis seen in autoimmune hepatitis
Cholestatic Patterns of Injury

Chronic Cholestasis: Impairment in bile flow– Ductular Reaction (proliferation)
Acute Cholangitis

Sequelae of Chronic Cholestasis: Cholate stasis
Due to retention of bile acids
Canilicular Cholestasis

Inflammation of the liver: Causes and patterns of injury
Alcoholic Hepatitis with Mallory Hyaline

Mallory Body: Intermediate cytokeratin 8/18 filament proteins that have been ubiquinated, or bound by other proteins such as heat shock proteins, or p62.

recognized feature of Wilson’s disease (25%), primary biliary cirrhosis (24%), non-alcoholic cirrhosis (24%), hepatocellular carcinoma (23%) and morbid obesity (8%), among other conditions

Megamitochondria in alcoholic hepatitis
NASH requires Steatosis AND Lobular or portal inflammation AND Ballooning: Fibrosis staged separately

**Steatosis (≥5%)**
- Macro-Micro
- Accentuated in zone 3
- Periportal areas usually spared in early disease

**Lobular Inflammation**
- Any degree (mixed, mild)
- Scattered polymorphonuclear leukocytes as well as mononuclear cells

**Hepatocellular Ballooning**
- Most apparent near steatotic liver cells
- Typically zone 3

**NAS Activity Score Components (total is 0-8 points)**
- Steatosis (0, <5%; 1, 5-33%; 2, 34-66%; 3, >66%), lobular inflammation (0, none; 1, <2 foci/20x field; 2, 2-4 foci/20x field; 3, >4 foci/20x field) and ballooning degeneration (0, none; 1, few; 2, many)

**Non-alcoholic steatohepatitis with fibrosis stages on trichrome stain**

Autoimmune hepatitis with Interface hepatitis with piecemeal necrosis

Autoimmune : Histology Zone 1 or Zone
Brisk inflammation
Liver Inflammation due to HCV with piecemeal necrosis

F1 (portal or periportal Fibrosis)

F3 (bridging Fibrosis)
Fibrous band From portal tract to central vein

F2 (septal fibrosis)

F4 (cirrhosis)
Chronic Hepatitis B

Ground Glass Hepatocytes Chronic HBV infection
distinct cytoplasmic appearance of these cells results from a marked increase of smooth endoplasmic reticulum which contains filamentous and spherical HBsAg particles
HBV Immunostain: Core Antigen in nuclei

Herpes Simplex hepatitis with intra-nuclear inclusions
CMV Hepatitis

CMV inclusion body. Hepatocyte with a large intranuclear inclusion body. Surrounded by a clear halo

Neutrophilic microabscess in acute CMV hepatitis

Alpha 1-antitrypsin deficiency (ZZ)

- PAS positive globules represent polymerized mutant protein retained in the rough endoplasmic reticulum in those with Z allele
- Homozygous ZZ, Znull and heterozygotes may have PAS positive globules (1/30 heterozygote prevalence)
PBC: Florid Bile Duct Lesion

PSC: Onion Skin Lesion
Sinusoidal Obstruction Syndrome Pathology

Summary

- Review description to ensure biopsy is adequate to draw conclusions
- Focus on the patterns and severity of injury (hepatitis, cholestatic, mixed, or other)
- In difficult cases, it is helpful to discuss with pathologist clinical context for the liver biopsy
- If fibrosis present to correlate with elastography or other non-invasive test of fibrosis to follow longitudinally
Acknowledgements

- Oscar Cummings MD
- Romil Saxena MD
- John Higgins MD
- Neeraja Khambam MD

Thank you!
Questions?

Speaker: Dr. Paul Kwo, MD, FACP

Moderator: Dr. Ashwani K. Singal, MD, MS, FACP

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