

# Basic patterns of liver damage: What information can a liver biopsy provide?

**RCPATH, March 2019**

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 @robdgol

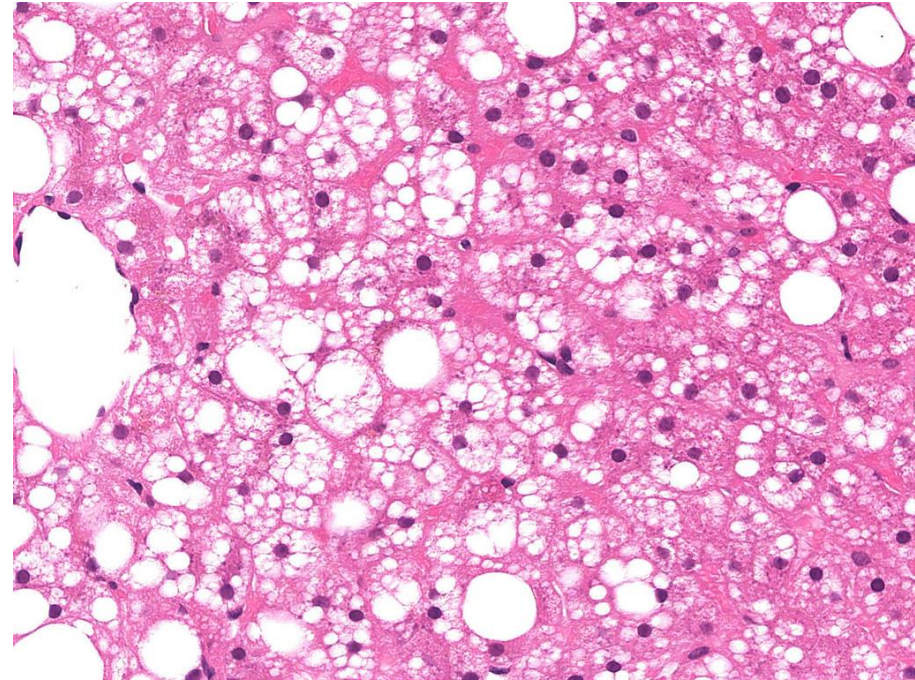
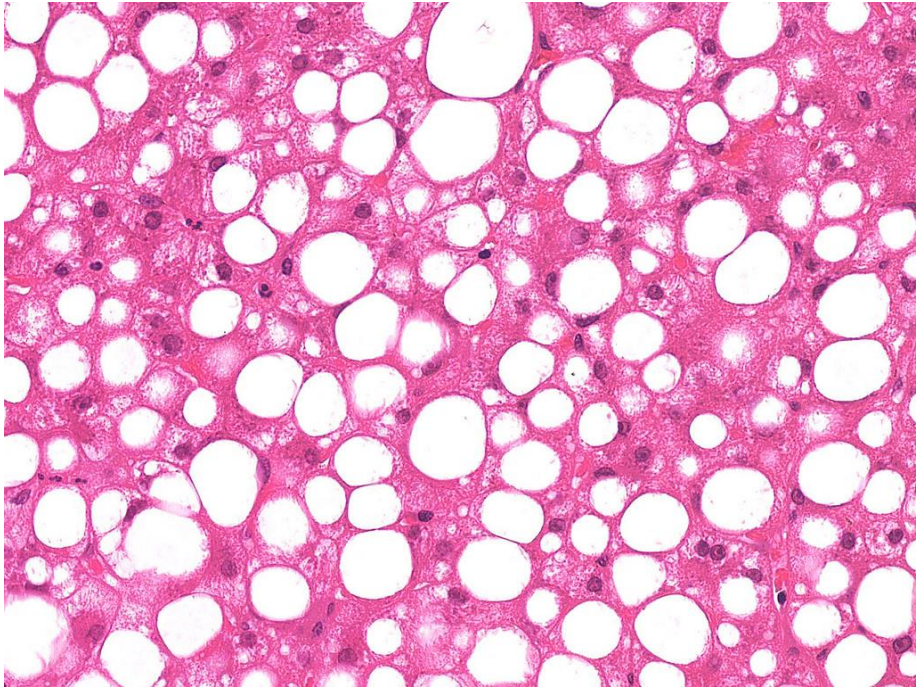
# Fatty liver disease: Core features

- Fat
- Ballooning
- Inflammation
- Fibrosis

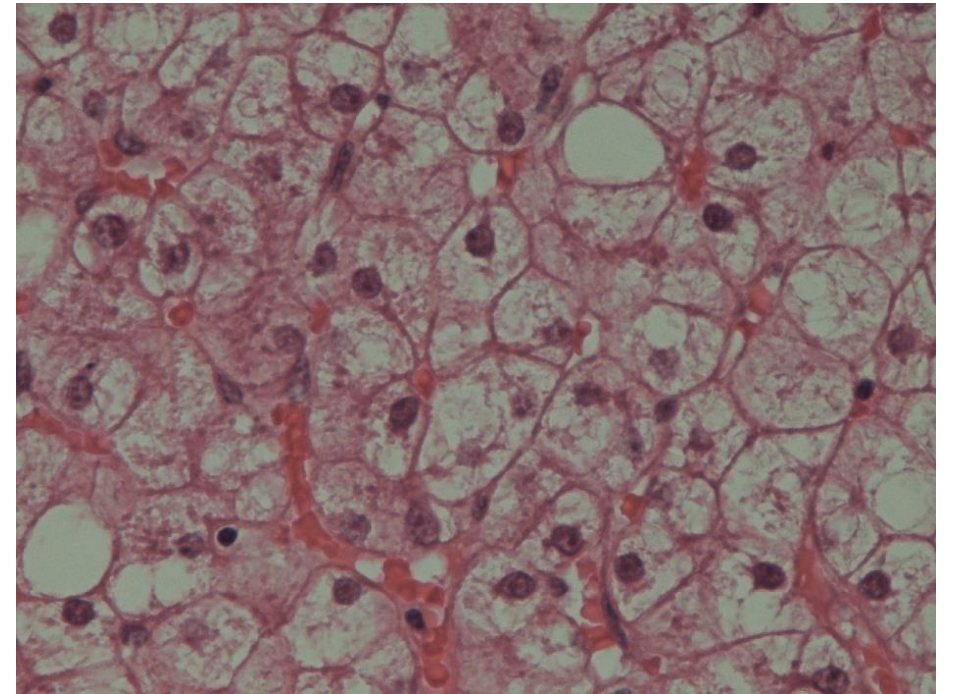
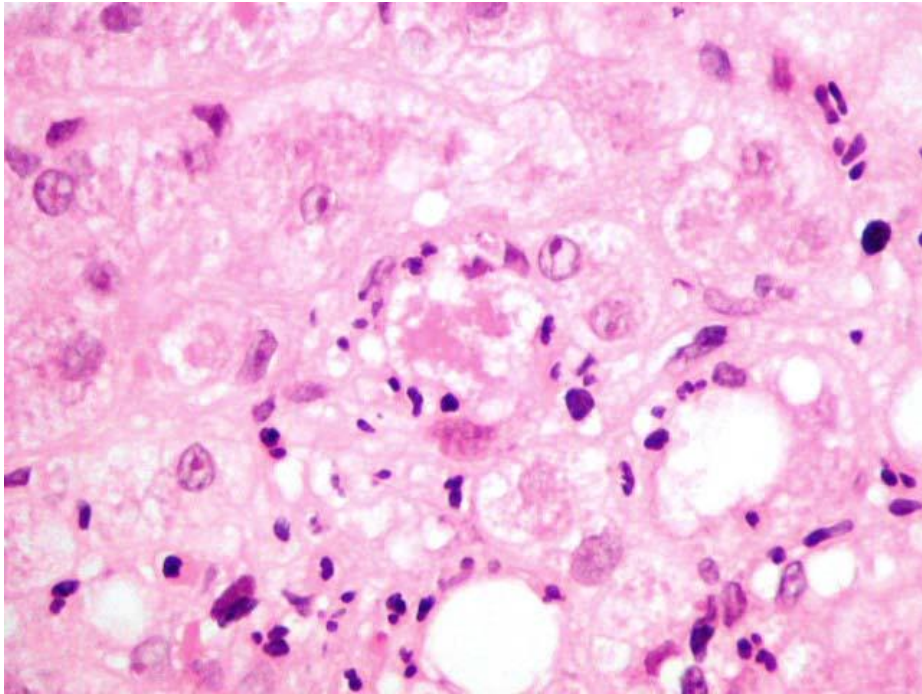
Bedossa P. Diagnosis of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Why liver biopsy is essential. *Liver International*. 2018 Feb;38:64-6.

Roth NC, Qin J. Histopathology of Alcohol-Related Liver Diseases. *Clinics in liver disease*. 2019 Feb 1;23(1):11-23.

# Large droplet fatty change

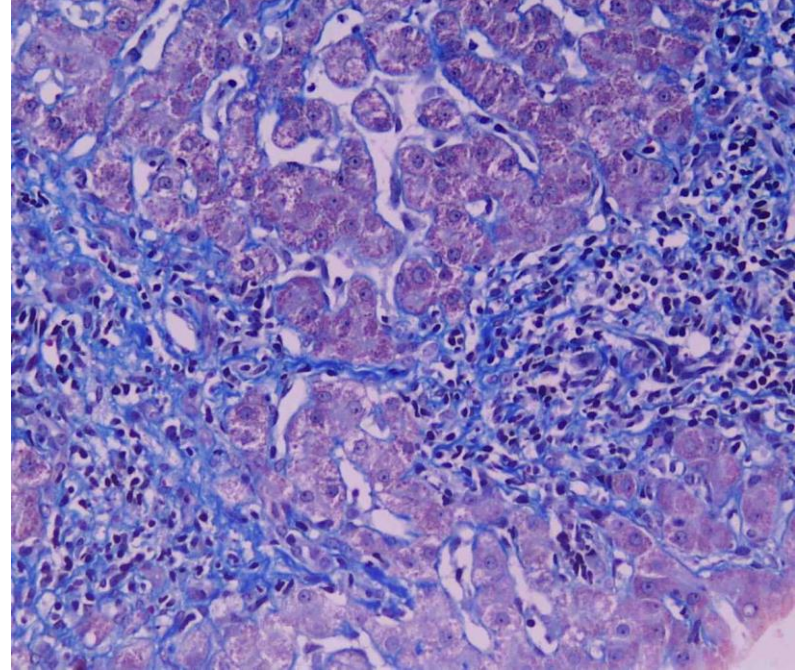
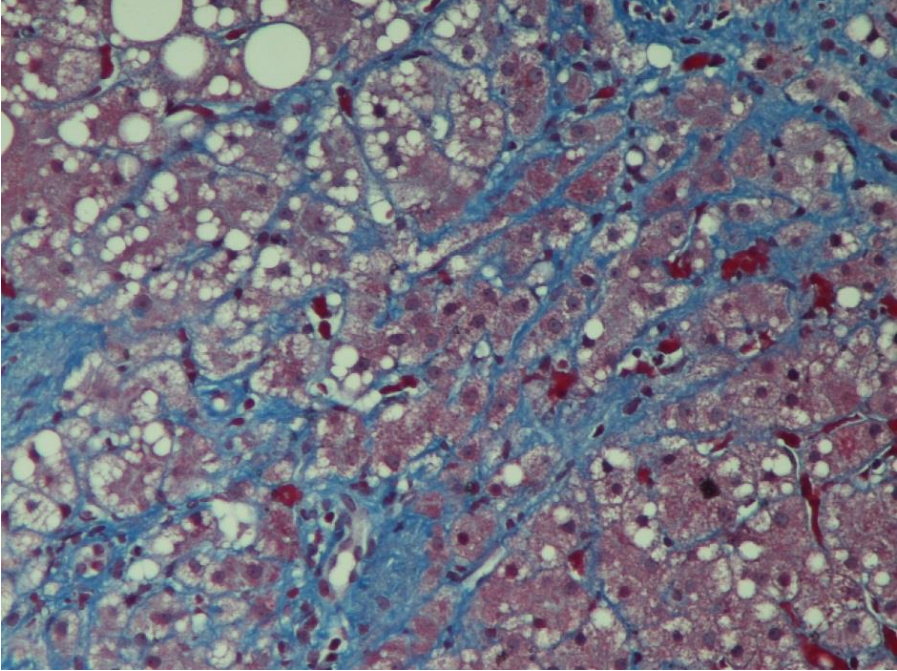


# Ballooning



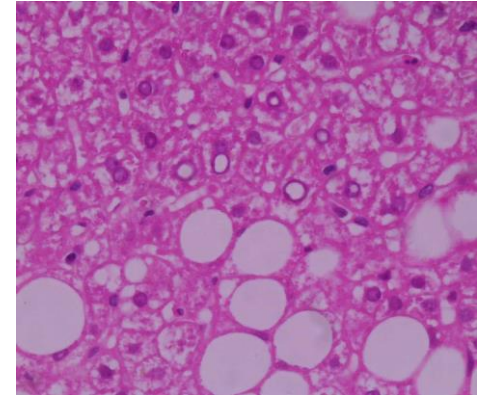
Bedossa, Pierre, et al. "Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients." *Hepatology* 56.5 (2012): 1751-1759.

# Fibrosis



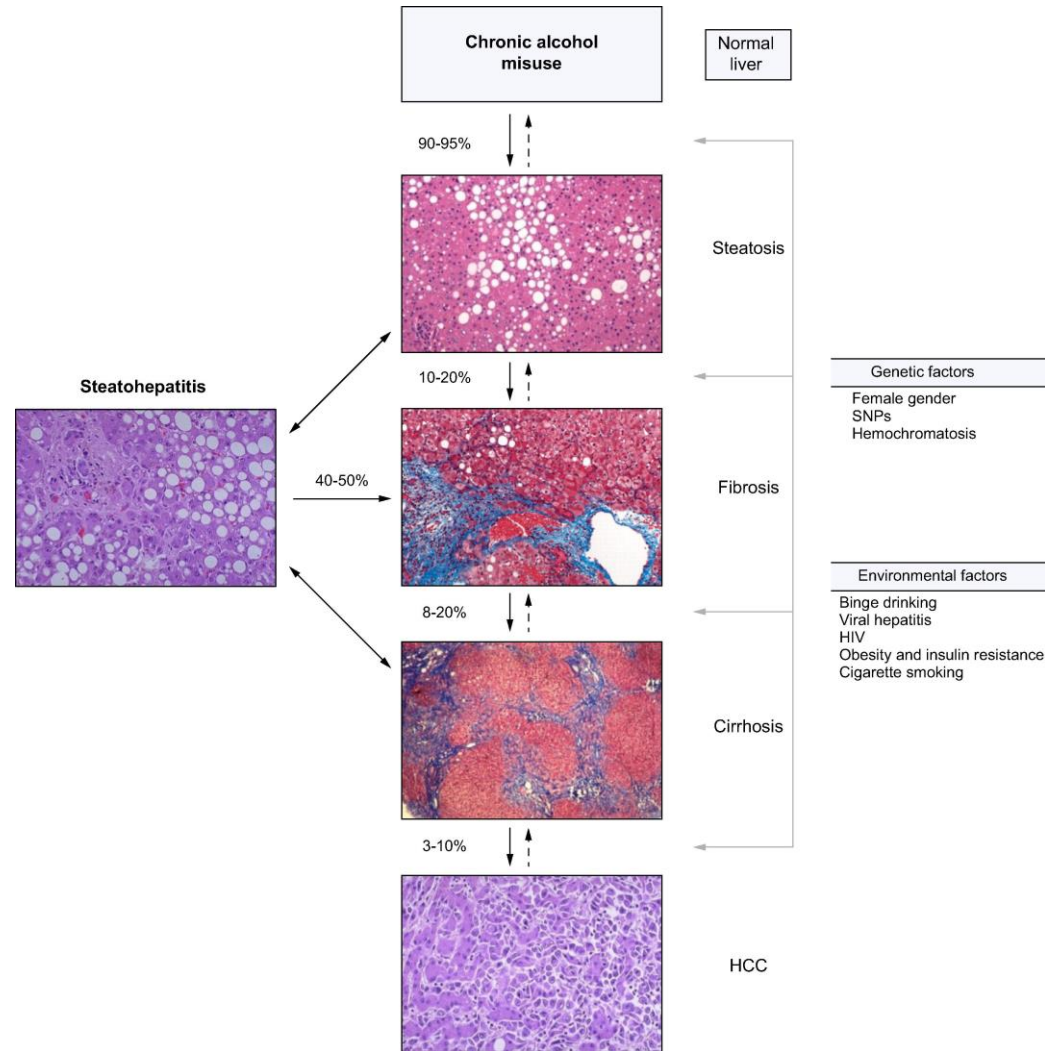
# Differentiating ALD from NAFLD

- Hepatocellular injury and fibrosis are often more severe in ALD
- Some lesions of ALD are very rare or have not been described in patients with pure NAFLD:
  1. nuclear vacuolation
  2. cholestasis
  3. microvesicular steatosis
  4. fibro-obliterative changes in hepatic veins (sclerosing hyaline necrosis)



# EASL Guidelines: ALD Guidelines

Thursz M, et al. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *Journal of Hepatology*. 2018 Jul 1;69(1):154-81.



European Association For  
The Study Of The Liver.  
EASL clinical practical  
guidelines: management of  
alcoholic liver disease.  
Journal of Hepatology. 2012  
Aug 1;57(2):399-420.

# ALD: Indications for liver biopsy

- Establish the definite diagnosis of ALD
- Assess the exact stage and prognosis of liver disease
- Predict response to treatment
- Exclude alternative or additional causes of liver injury
- Trials

# Predicting Response to Treatment in Alcoholic Hepatitis

	Points
Stage of fibrosis	
No fibrosis or portal fibrosis	0
Expansive fibrosis	0
Bridging fibrosis or cirrhosis	+3
Bilirubinostasis	
No	0
Hepatocellular only	0
Canalicular or ductular	+1
Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
No/Mild	+2
Severe	0
Megamitochondria	
No megamitochondria	+2
Megamitochondria	0

## The AHHS categories:

mild, 0–3;  
intermediate, 4–5;  
severe, 6–9.

Altamirano J et al.

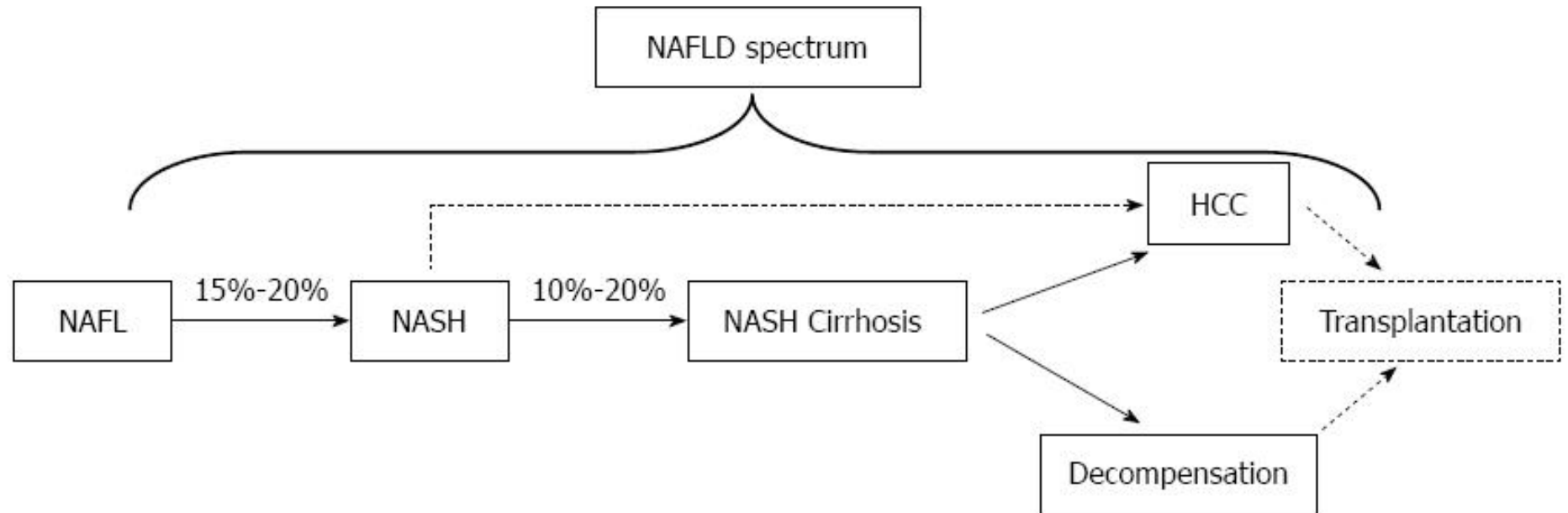
A histologic scoring system for prognosis of patients with alcoholic hepatitis.

Gastroenterology. 2014 May 1;146(5):1231-9.

# EASL Guidelines: NAFLD Guidelines

European Association For The Study Of The Liver, European Association for the Study of Diabetes (EASD). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Obesity Facts. 2016;9(2):65-90.

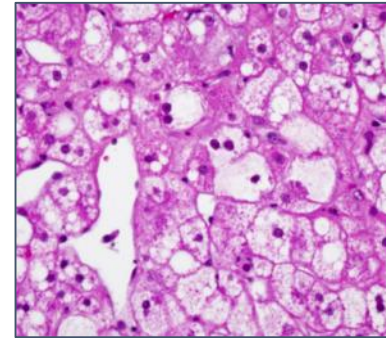
# Natural History of Non-alcoholic Fatty Liver Disease



Preiss D, Sattar N. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. *Clinical Science*. 2008 Sep 1;115(5):141-50.

# Liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NASH requires
  - Steatosis **AND**
  - Lobular or portal inflammation **AND X**
  - Ballooning
- NAS scoring indicates disease severity\*



Recommendations	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing <b>steatosis, hepatocyte ballooning and lobular inflammation</b>	A	1

\*Should not be used for initial diagnosis **X**

Obesity Facts. 2016;9(2):65-90.

# Nash Activity Score

“In conclusion, we present a strong scoring system and NAS for NAFLD and NASH with reasonable inter-rater reproducibility that should be useful for studies of both adults and children with any degree of NAFLD. *NAS of  $\geq 5$  correlated with a diagnosis of NASH, and biopsies with scores of less than 3 were diagnosed as “not NASH.”*”

Kleiner DE, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005 Jun;41(6):1313-21.

# Indications for Liver Biopsy in NAFLD

- If based on non-invasive tests (e.g. Fibro-Test and Elf Test) the patient is placed in a high risk group; “consider liver biopsy”
- “In selected patients at high risk of liver disease progression, monitoring should include a repeat biopsy after  $\geq 5$ -year follow-up”
- Trials

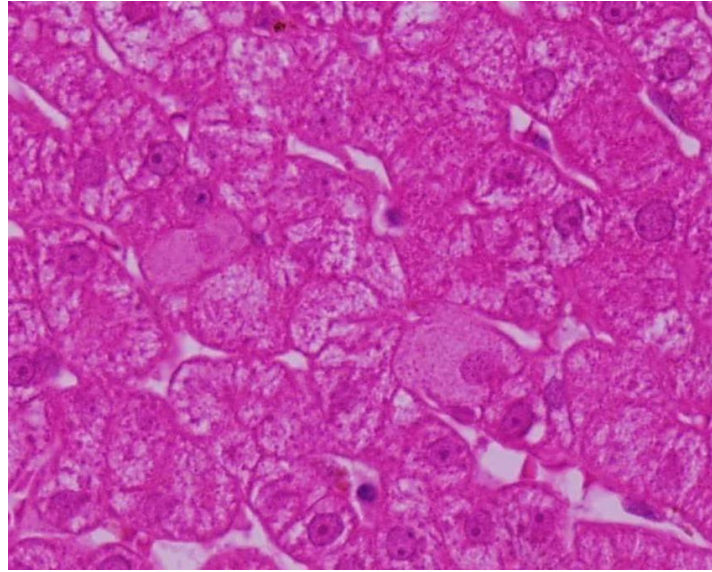
# Factor(s) determining the prognosis of NAFLD

“Patients with fibrosis, regardless of steatohepatitis or NAFLD activity score, had shorter survival times than patients without fibrosis.”

Angulo P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015 Aug 1;149(2):389-97.

# Chronic hepatitis

# EASL Guidelines: HBV



European Association For The Study Of The Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology. 2017 Aug 1;67(2):370-98.

# Indications for treatment

- Primarily based on the combination of 3 criteria
  - HBV DNA, serum ALT and severity of liver disease

Recommendations	Grade of evidence	Grade of recommendation
<p><b>Should be treated</b></p> <ul style="list-style-type: none"> <li>• Patients with HBeAg-positive or -negative chronic hepatitis B*</li> <li>• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level</li> <li>• Patients with HBV DNA &gt;20,000 IU/mL and ALT &gt;2x ULN, <b>regardless of severity of histological lesions</b></li> </ul>	<p>I I II-2</p>	<p>1 1 1</p>
<p><b>May be treated</b></p> <ul style="list-style-type: none"> <li>• Patients with HBeAg-positive chronic HBV infection<sup>†</sup> &gt;30 years old, <b>regardless of severity of liver histological lesions</b></li> </ul>	<p>III</p>	<p>2</p>
<p><b>Can be treated</b></p> <ul style="list-style-type: none"> <li>• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations<sup>‡</sup></li> </ul>	<p>III</p>	<p>2</p>

\*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis;

<sup>†</sup>Defined by persistently normal ALT and high HBV DNA levels;

<sup>‡</sup> Even if typical treatment indications are not fulfilled

# Liver Biopsy in HBV

Patients with HBV may have significant liver pathology despite normal liver function tests.

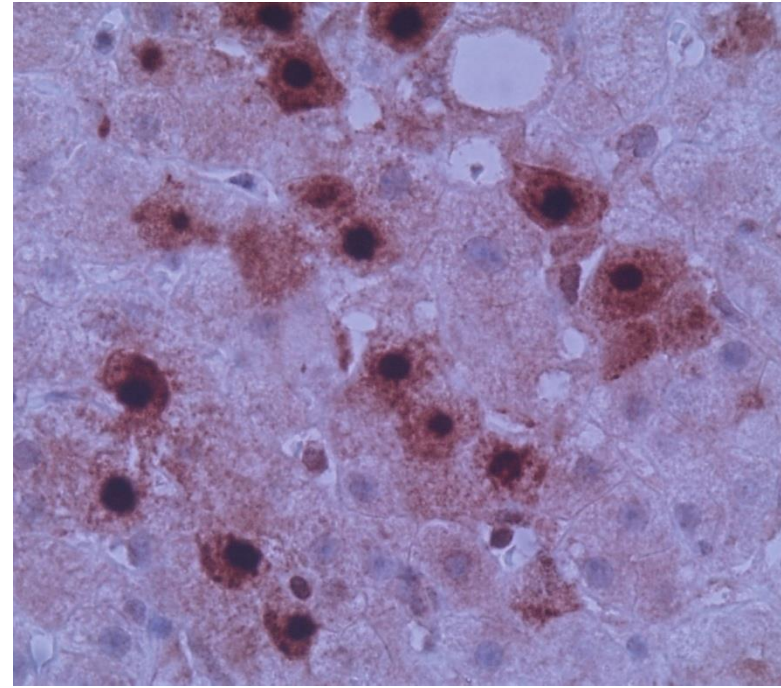
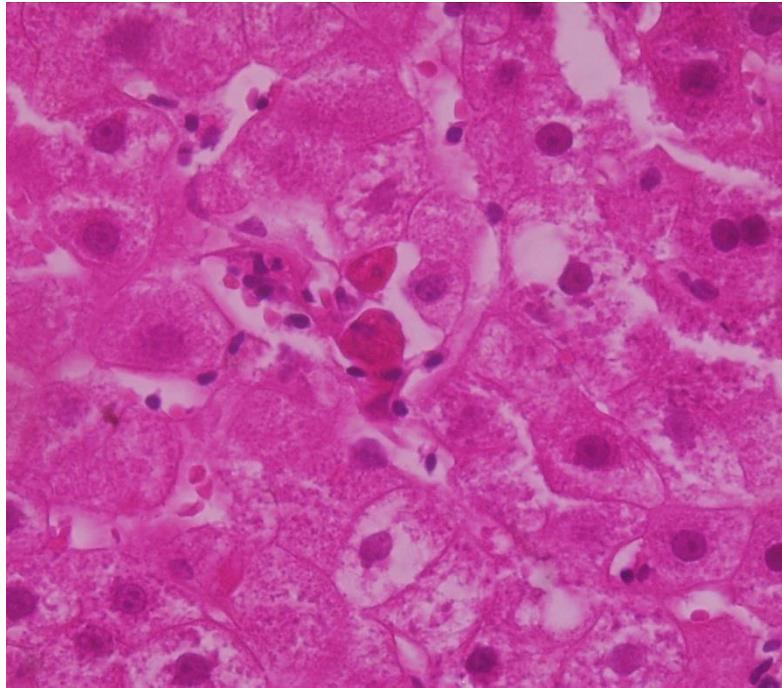
“Our results showed that histological changes in liver tissues were observed in a significant proportion of patients with persistently normal alanine aminotransferase level.

According to the data evaluation results, liver biopsy is advisable for HBeAg-positive chronic hepatitis B infected patients aged older than 40 and high HBV-DNA viral load in China.”

Xing Y, et al. (2018) Clinical and histopathological features of chronic hepatitis B virus infected patients with high HBV-DNA viral load and normal alanine aminotransferase level: A multicentre-based study in China. PLOS ONE 13(9): e0203220.

Dolman GE, Koffas A, Mason WS, Kennedy PT. Why, who and when to start treatment for chronic hepatitis B infection. Current opinion in virology. 2018 Jun 30;30:39-47.

But don't forget HDV

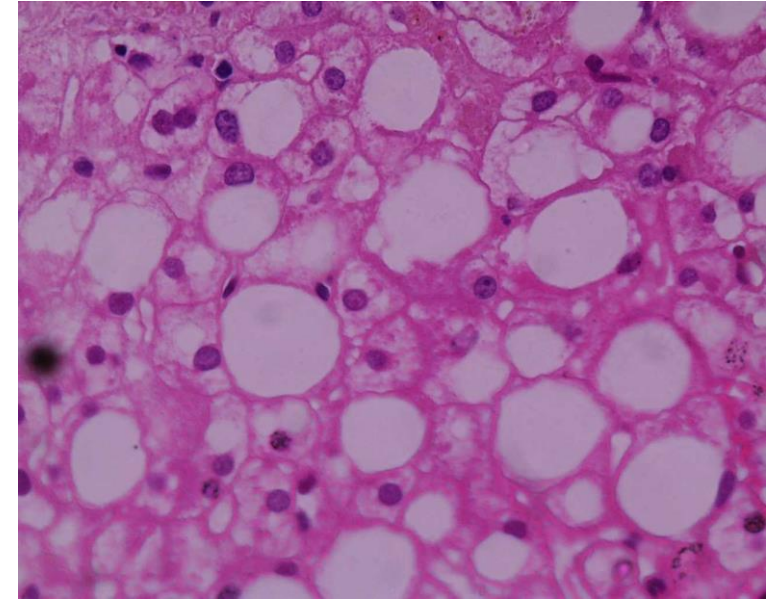
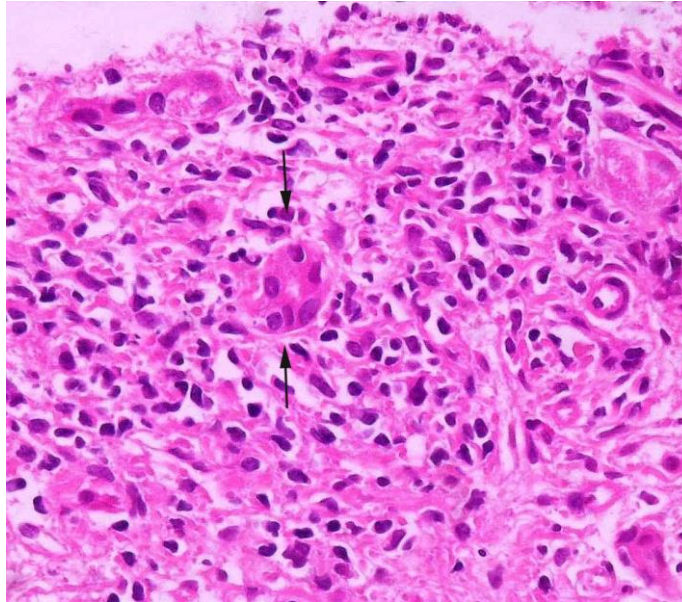
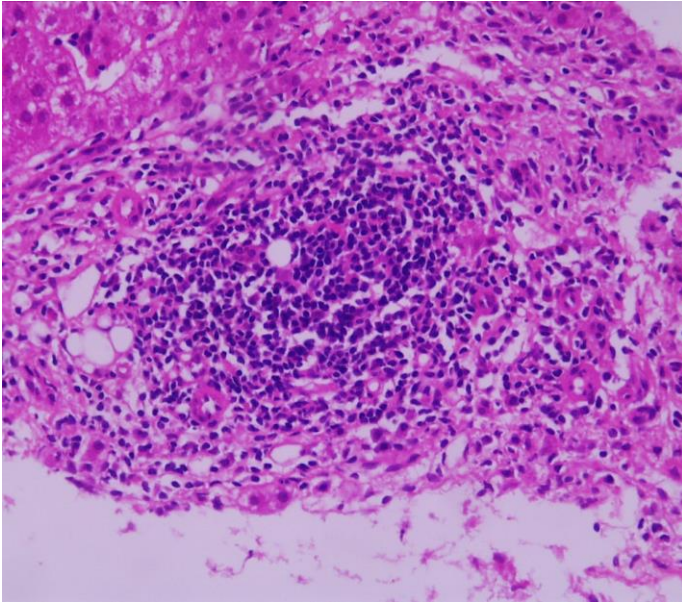


# HDV

- A systematic review found that 11% of HBsAg carriers (without histories of either intravenous drug use or high-risk sexual behaviour) were co-infected with Hepatitis D virus, which is twice previous estimates.
- A significantly higher HDV prevalence was noted intravenous drug users (38%) and high-risk sexual behaviour (17%).

Chen H, Shen D, Ji D, et al Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis Gut 2019;68:512-521.

# EASL Guidelines: HCV



Craxi A, European Association for Study of Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. *Journal of Hepatology*. 2014;60:392-420.

# Liver Biopsy in HCV

- The introduction of direct-acting antiviral agents and interferon free regimens has reduced the need for liver biopsy in hepatitis C, as the high rate of sustained viral response makes the decision to treat less reliant on the the underlying pathology

# Indications for Liver Biopsy in HCV

- “Liver biopsy *may* be required in cases of known or suspected mixed aetiologies (e.g. metabolic syndrome, alcoholism or autoimmunity). “

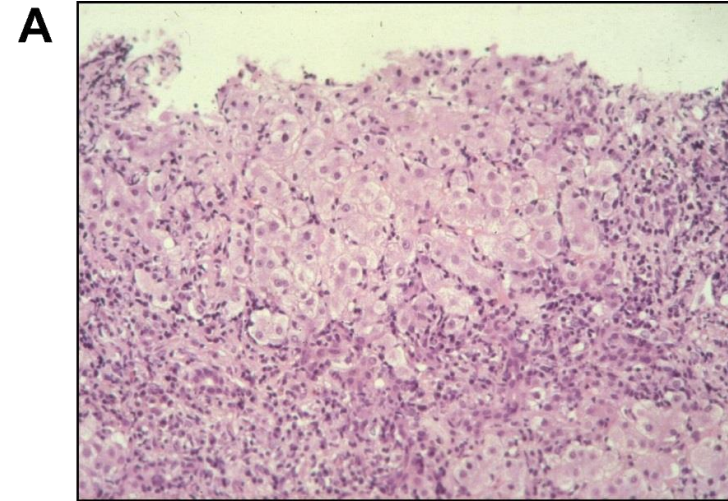
Journal of Hepatology. 2014;60:392-420.

# EASL Guidelines: Autoimmune Hepatitis

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *Journal of Hepatology*. 2015 Oct;63(4):971.

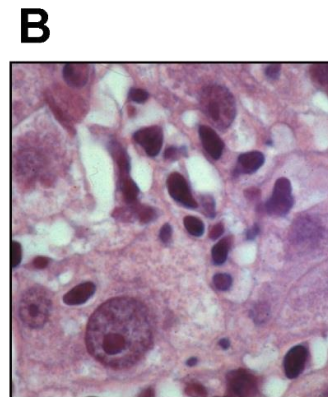
# Typical histopathology of AIH

A. Typical histopathology of AIH with portal/periportal predominance of necro-inflammatory lesions and broad interface hepatitis.  
*Prominent plasma cells are characteristic*



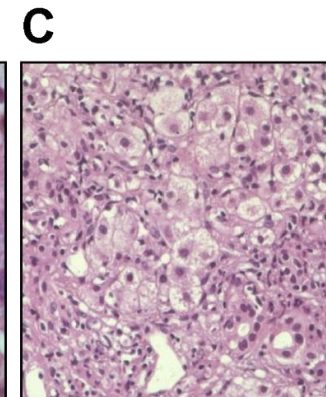
HE 100x

B. Emperipolesis with a lymphocyte in the cytoplasm of a damaged hepatocyte



HE 240x

C. Typical rosetting of hepatocytes in the area of interface hepatitis



HE 160x

“Rosettes and emperipolesis are difficult to interpret, and lack sensitivity and sensitivity for autoimmune hepatitis diagnosis.”

Balitzer D, et al. Autoimmune hepatitis: review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. *Modern Pathology*. 2017 May;30(5):773.

# Indications for Liver Biopsy in AIH

- Liver biopsy examination at presentation is recommended:  
to establish the diagnosis and  
to guide the treatment decision.  
(In acute presentation unavailability of liver biopsy should not  
prevent from start of therapy)
- Assessment of the response to treatment

# “to establish the diagnosis”

Liver histology (evidence of hepatitis is a necessary condition)

Compatible with autoimmune hepatitis  
Typical for autoimmune hepatitis

1  
2

**Table 4** Proposed criteria for the histologic scoring of autoimmune hepatitis

*Histology score 0*

Features not observed in autoimmune hepatitis: florid duct lesion (primary biliary cholangitis), bile duct loss, or copper/CK7 positivity (latter applicable only in cases without any bridging fibrosis)

*Histologic score 1<sup>a</sup>*

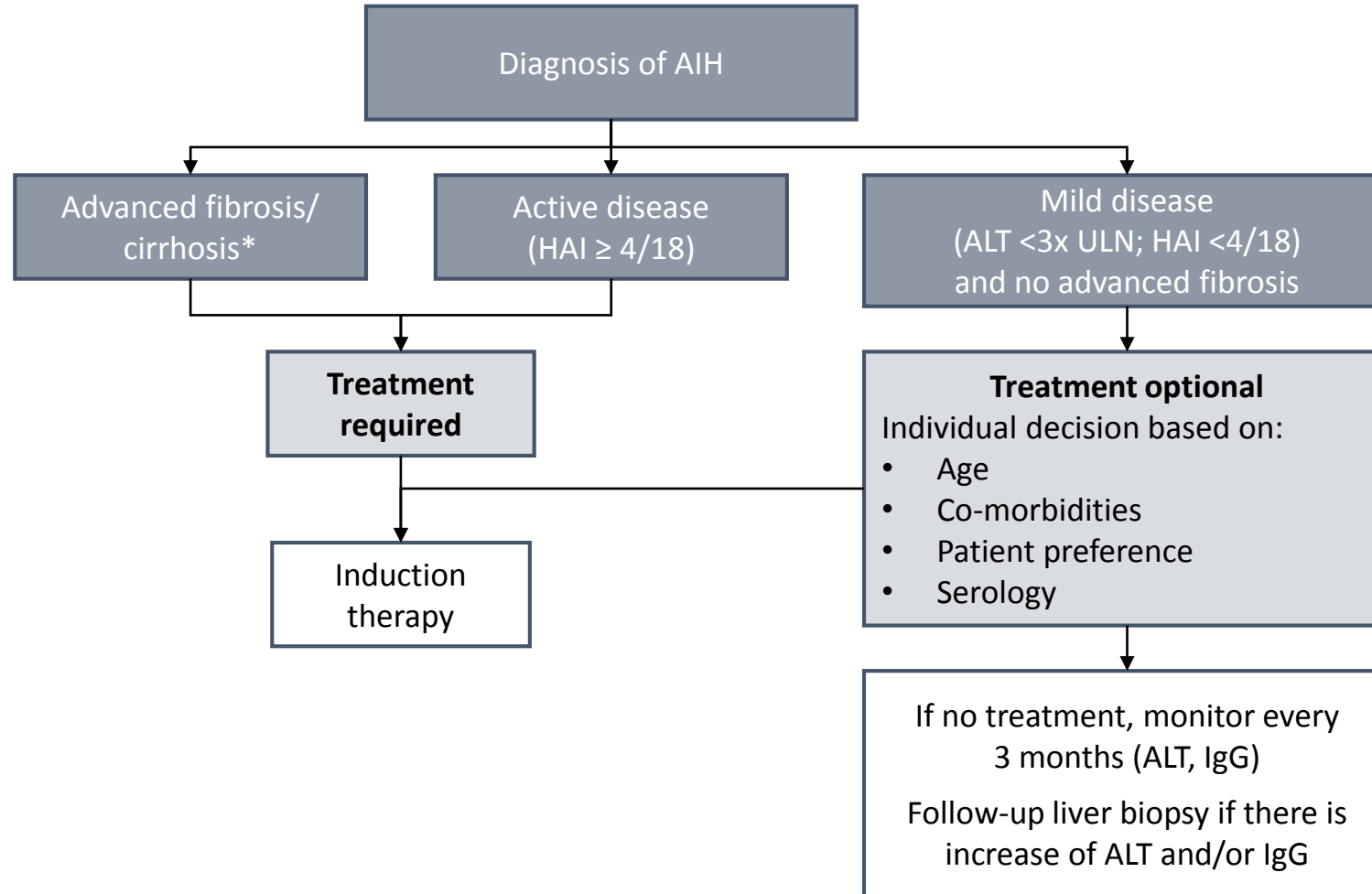
- (1) Hepatitis with mild or moderate necroinflammatory activity with any of the following:
- (a) Ishak A2 (mild/moderate interface activity)
  - (b) Ishak B1 (focal confluent necrosis)
  - (c) Ishak C2 (2–4 foci of lobular activity per × 10)
- (2) CK7 and copper stains negative (applicable only for cases with Ishak fibrosis score < 3, this feature is not applicable to acute cases)

*Histologic score 2*

- Hepatic picture with any of the following:
- (1) Plasma cells: numerous or in clusters
  - (2) High necroinflammatory activity featuring at least one of the following:
    - (a) Ishak score A3 or higher (at least moderate interface activity)
    - (b) Ishak B2 or higher (confluent necrosis in zone 3 or beyond)
    - (c) Ishak C3 or higher (5 or more foci of lobular activity per × 10)

<sup>a</sup>Both (1) and (2) are necessary for histologic score of 1 except in cases with acute presentation when biliary disease is not a consideration and these stains are not relevant.

# “To guide the treatment decision”



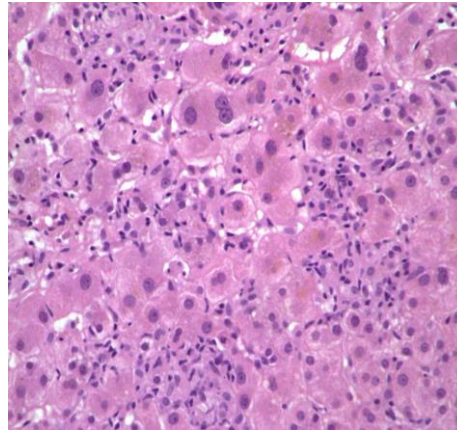
# “Assessment of the response to treatment”

In patients who have been in biochemical remission for >2 years, liver biopsy should be considered prior to treatment withdrawal:

In those patients with continued histological disease activity (HAI >3), treatment should not be discontinued

# Drug-induced AIH

- Develops of AIH after drugs, supplements or herbals
- Acute onset
- Biochemical improvement after stopping the cause
- Relapse after immunosuppressive treatment withdrawal less common
- **Lobular inflammation**



# Drug Induced Liver Injury

“Any type of liver disease can be caused  
by a drug”

Kleiner DE. The histopathological evaluation of drug-induced liver injury.  
Histopathology. 2017 Jan 1;70(1):81-93.  
<http://livertox.nih.gov/>

# What is the role of the liver biopsy in DILI?

**Liver biopsy can provide useful information about:**

- nature and severity of liver injury
- expected clinical outcome.
- guide therapy
- **exclude other causes of liver injury**

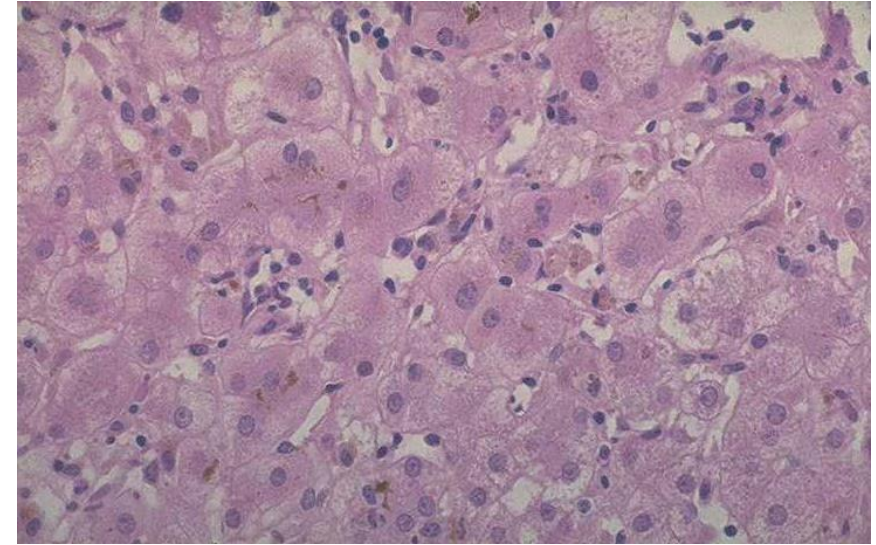
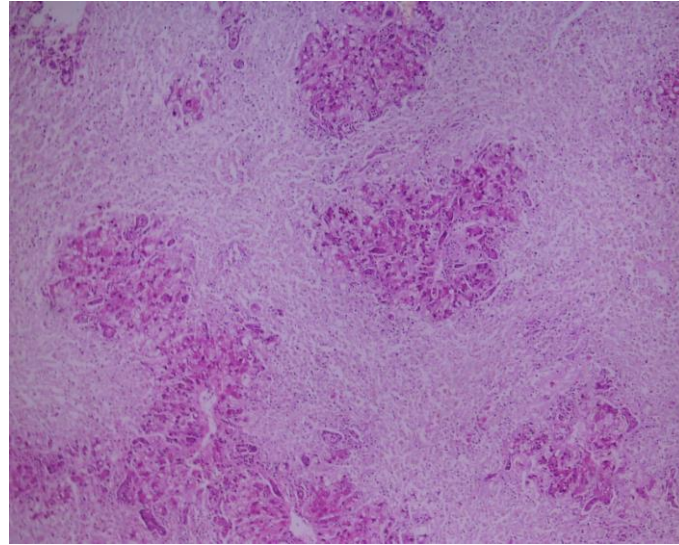
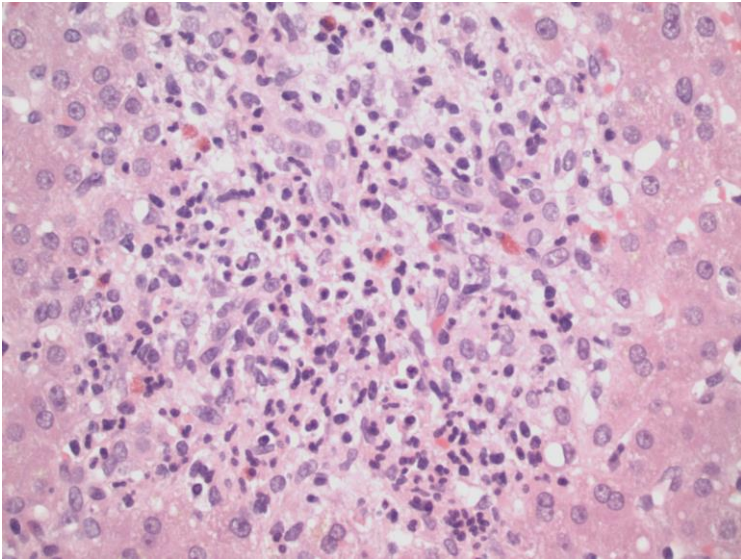
Fisher K, Vuppalanchi R, Saxena R. Drug-induced liver injury. Archives of Pathology and Laboratory Medicine. 2015 Jul;139(7):876-87.

# Histological features suggesting a drug reaction:

- eosinophils,
- plasma cells,
- granulomas,
- sharply demarcated necrosis,
- cholestatic hepatitis

Chalasani N,et al . Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*. 2008 Dec 1;135(6):1924-34.

# Histological Features Suggesting a Drug Reaction



# Histological predictors of severity in drug-induced liver disease.

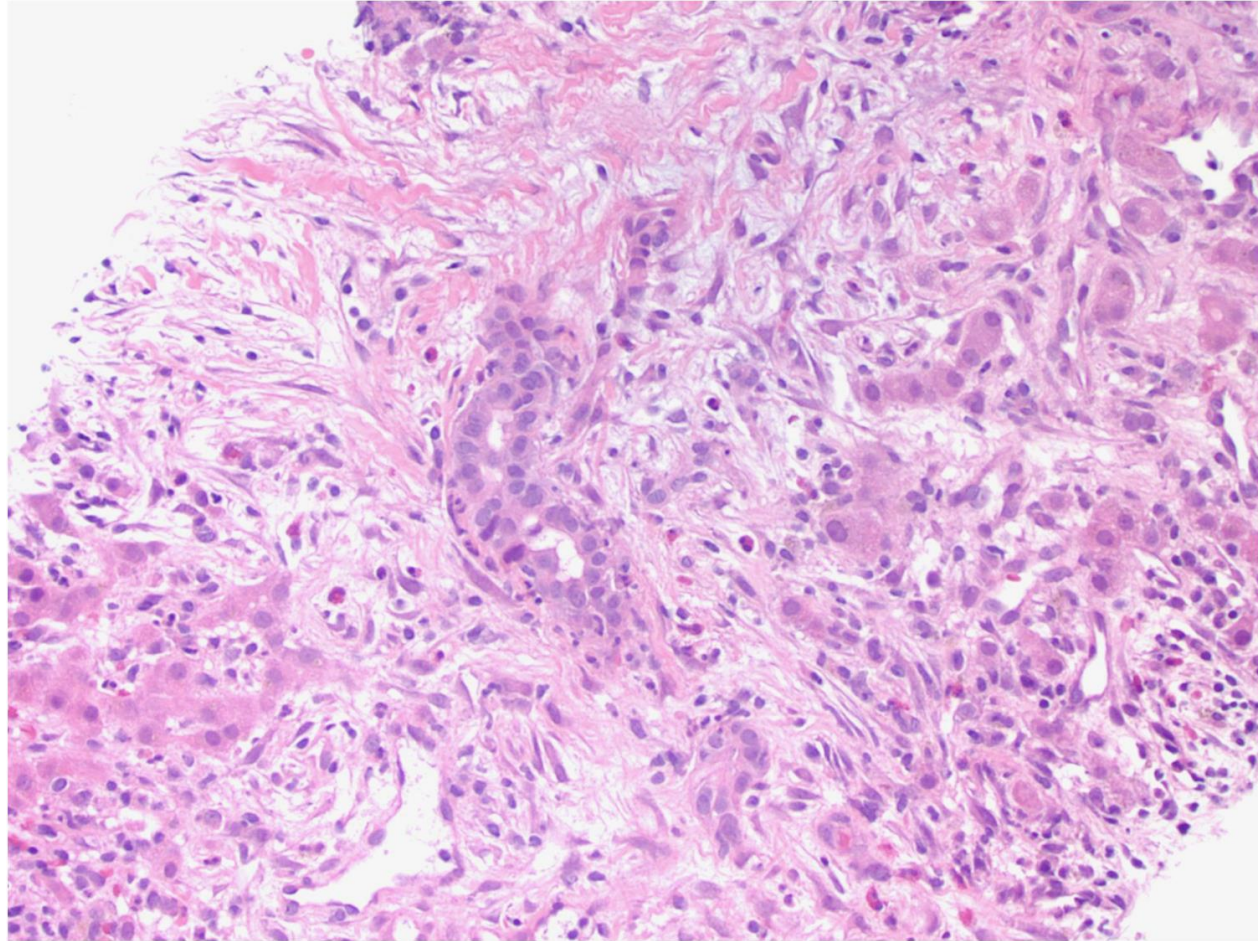
- **Milder disease associated with:**

1. granulomas
2. eosinophils

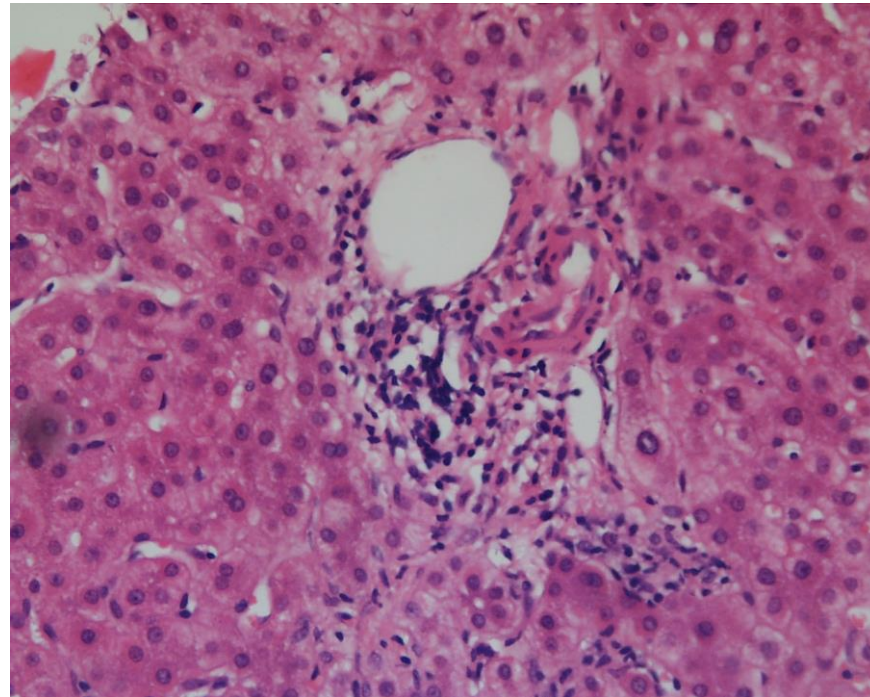
- **More severe disease associated with:**

1. necrosis
2. fibrosis stage
3. microvesicular steatosis
4. cholangiolar cholestasis
5. bile duct damage

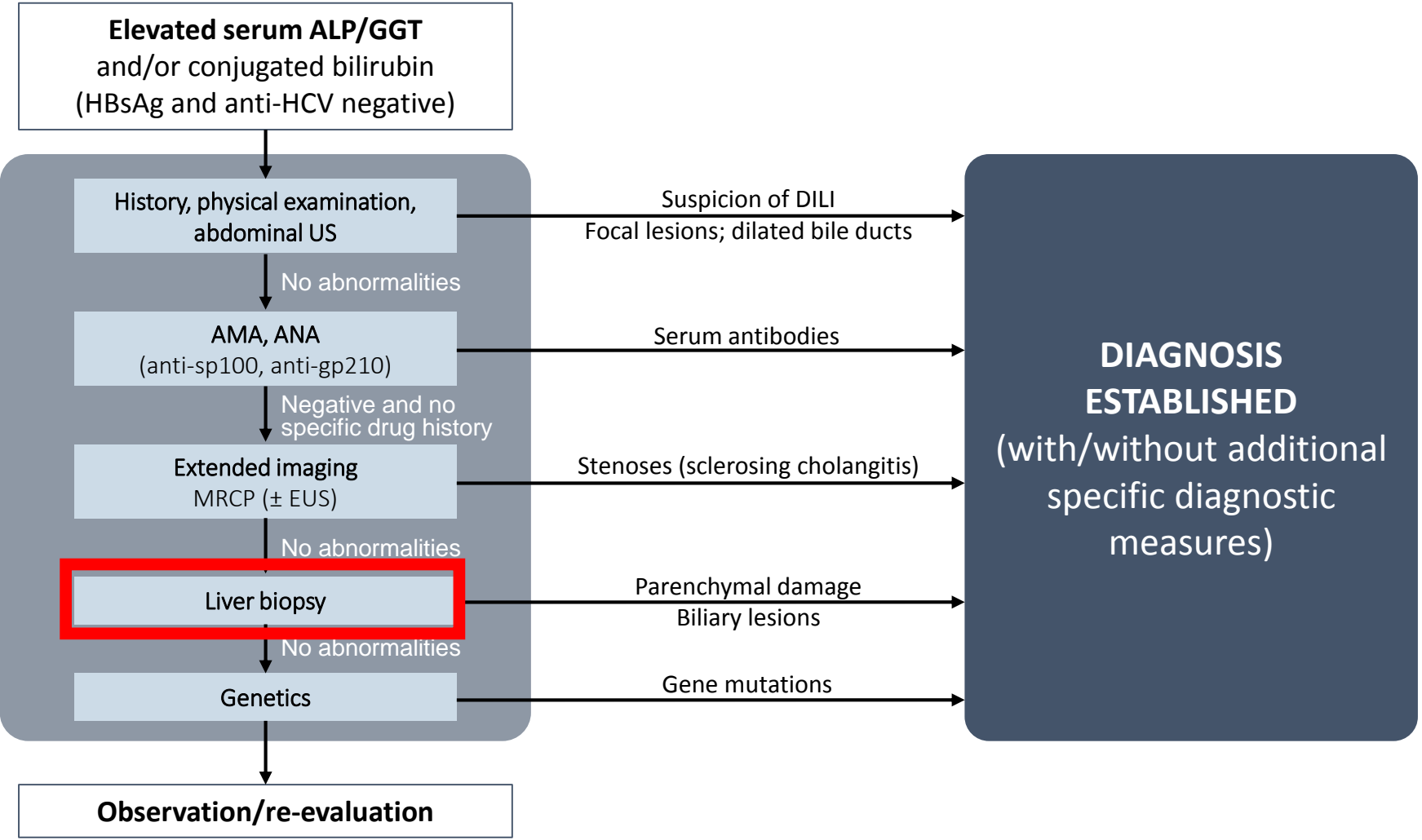
# Histological predictors of severity in drug-induced liver disease.



# Biliary tract disease

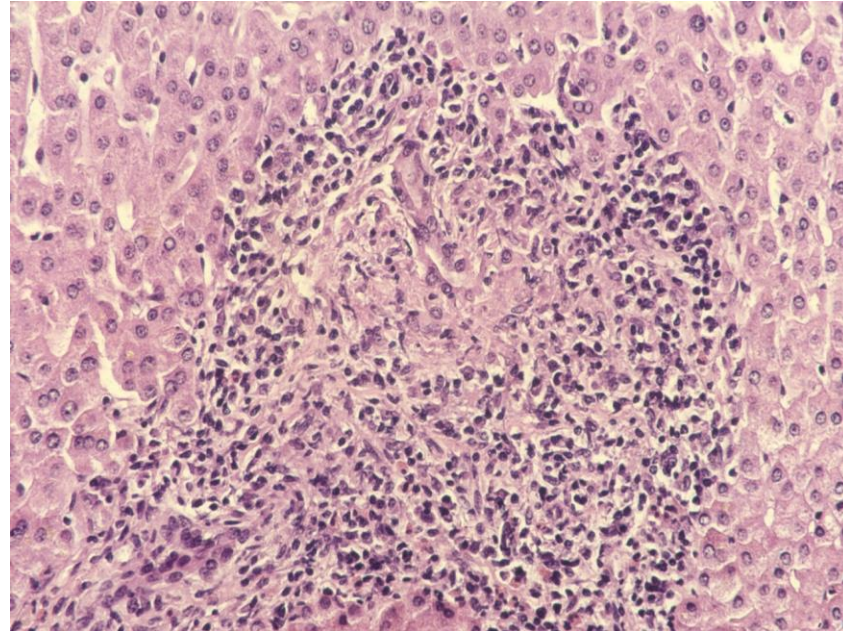


# Structured algorithm to diagnose chronic\* cholestasis



\*Lasting for >6 months

# BSG Guidelines: Primary Biliary Cholangitis



Hirschfield GM, et al, The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut*. 2018 Sep 1;67(9):1568-94.

# Histological Assessment of PBC

## Stage:

- Fibrosis
- Bile duct damage
- Accumulation of copper associated protein

## Grade :

- Bile duct inflammation
- Hepatocyte inflammation

# Indications for liver biopsy in PBC

We recommend liver biopsy is **not usually required in the diagnosis of PBC or for monitoring of disease progression** unless its use is within the context of clinical trials.

We recommend that, in the presence of cholestatic serum liver tests but an **absence of diagnostic autoantibodies**, the confirmation of PBC requires a liver biopsy.

We recommend that liver biopsy can be considered if there is a clinical suspicion of **co-existing disease** (eg, additional injury from non-alcoholic fatty liver disease (NAFLD), viral hepatitis or alcohol use) or the presence of **overlapping autoimmune hepatitis**, either at diagnosis or during follow-up.

Gut. 2018 Sep 1;67(9):1568-94.

# PBC - AIH Overlap

Patients must meet 2 of 3 criteria for both entities to qualify as overlap:

## **PBC**

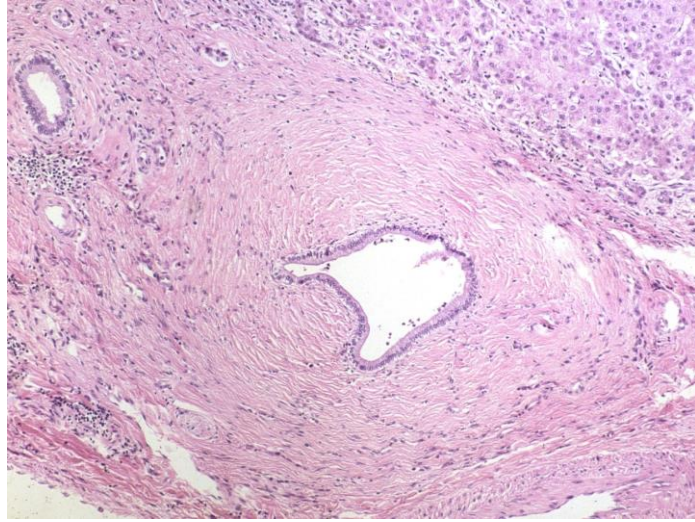
1. Florid duct lesions
2. AMA
3. Alkaline phosphatase  $>2x$  or GGT  $>5x$

## **AIH**

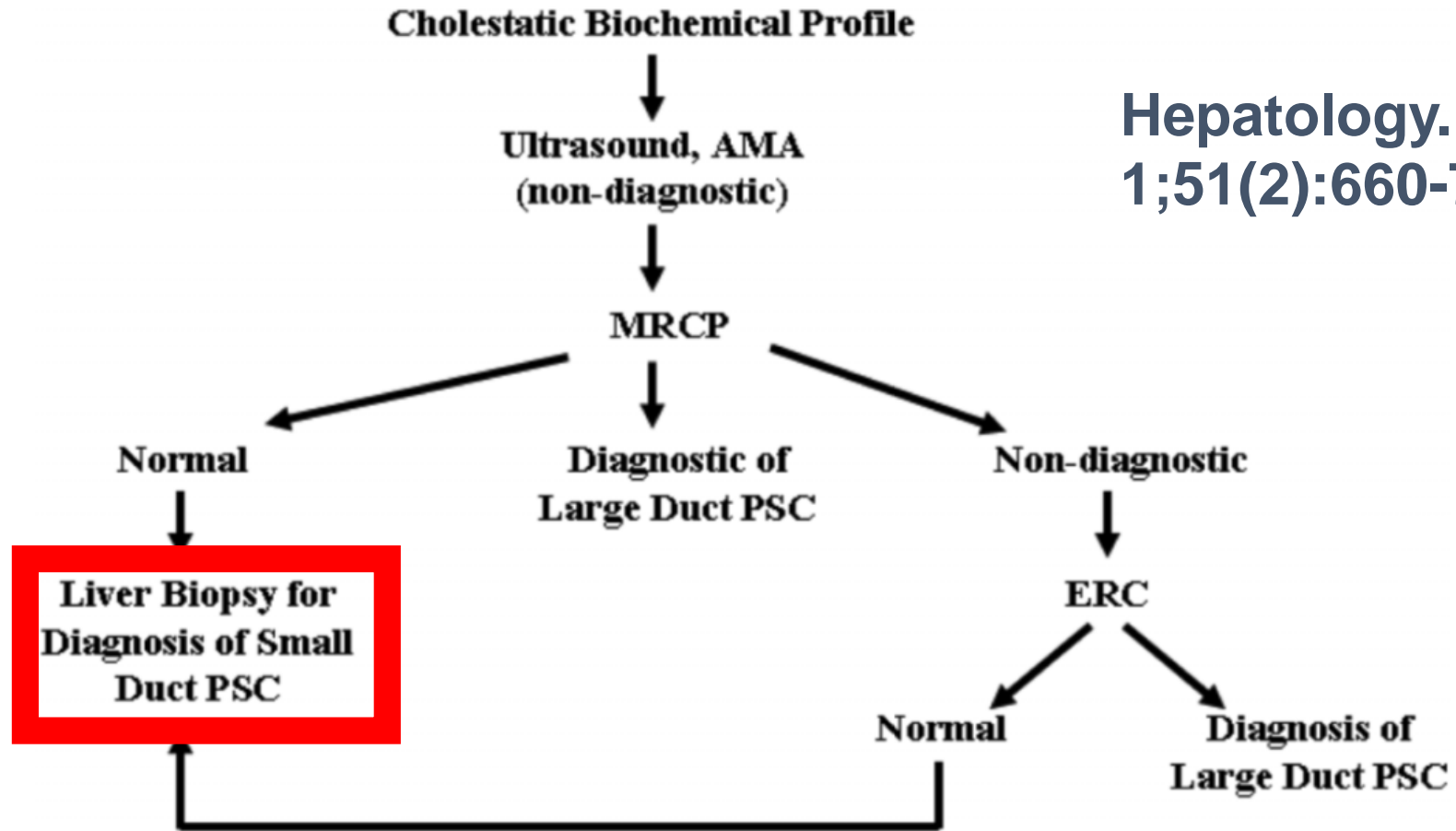
1. Moderate to severe interface hepatitis
2. IgG  $>2x$  or SMA positive
3. ALT  $>5x$

Boberg KM, et al. Overlap syndromes: the International Autoimmune Hepatitis Group position statement on a controversial issue. *Journal of Hepatology*. 2011 Feb 1;54(2):374-85.

# Primary Sclerosing Cholangitis



Chapman R, et al, Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010 Feb 1;51(2):660-78.



**Hepatology. 2010 Feb  
1;51(2):660-78.**

Fig. 1. Algorithm for the diagnosis of PSC.

What clinical information  
does the pathologist need?

**The question!**

# Buddha: How do you answer a question?

- **There are questions that should be answered categorically:**

e.g. This is a fatty liver hepatitis.

- **There are questions that should be answered with an analytical answer.**

e.g. This a chronic biliary tract disease with features favouring PBC.

- **There are questions that should be answered with a counter-question.**

e.g. This isn't an autoimmune hepatitis, it's a fatty liver hepatitis.

Does the patient have risk factors for this?

- **There are questions that should be put aside.**

e.g. The biopsy is too small to assess

# General references

- Mullish BH, Kumar N, Goldin RD, Manousou P. Liver biopsy. Evidence-based Gastroenterology and Hepatology. 2019 Feb 13:395.
- Boyd A, Cain O, Chauhan A, Webb GJ. Medical liver biopsy: background, indications, procedure and histopathology. Frontline Gastroenterology. 2019 Mar 2:flgastro-2018.