Evolving Role of Liver biopsy in an Era of Expanding Non-invasive Assessments

Dr Susan E Davies,
Cambridge University Hospitals NHS Foundation trust

Leeds Pathology 2019

BDIAP & Pathological Society

Evolving role of liver biopsy

- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management – presence of SH, interface activity
  - Not responding to therapy
- Diagnostic uncertainty/ unknown disease
  - Problems of dual pathology
  - Atypical presentation
- Questions to address in main disease categories
- Summary

Introduction

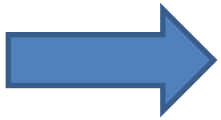
- Jaundice mentioned in 3000BC
- Hippocrates – first use of term icteric
- Middle ages detail histories of epidemics
- 1923 First percutaneous liver biopsy (Germany)
- 1940s & 50s realisation of 2 types of transmissible hepatitis
- 1950s Menghini aspiration needle

Intro – rapid hepatology advances

- 1963 Australia antigen discovered, leading to Hepatitis B virus identification in 1967 & a vaccine 1969
- 1964 First liver transplant in UK
- 1978 Trans-jugular approach for liver biopsy
- 1970s HAV, 1977 HDV, 1989 HCV, 1990 HEV, (2000 acquired in UK) , 1995 HGV
- 1980 description of Non Alcoholic Steatohepatitis, prominence in mid 1990s, term NAFLD in 2002.

Reasons for biopsy - Historical

- Biopsy initially taken for **diagnosis** in jaundice or deranged LFTs
- **Patterns** of injury indicated portal/ biliary or parenchymal; acute or chronic
- With recognition of chronic viral hepatitides, biopsy for **grading and staging** of disease
- Always a role for masses



Diagnosis made but little treatment options

Evolving role of liver biopsy

- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management – presence of SH, interface activity
  - Not responding to therapy
- Diagnostic uncertainty/ unknown disease
  - Problems of dual pathology
  - Atypical presentation
- Questions to address in main disease categories
- Summary

But now no need for biopsy…

- Most viruses diagnosable on serology and/ or PCR
- Most viruses amenable to treatment or prevention – vaccination, high sustained viral response with modern direct-acting anti-viral agents
- Fatty liver disease striking increase, obvious risk factors
- Serological parameters for assessing stage and grade of chronic liver disease
- Liver stiffness for assessing fibrosis
- Genetic testing for metabolic diseases, quantitative studies and imaging
- Biliary disease diagnosable on Ab serology and radiology; increase in 2^{nd} order antibodies (line blot testing) important in all autoimmune conditions

NOT DIAGNOSTIC

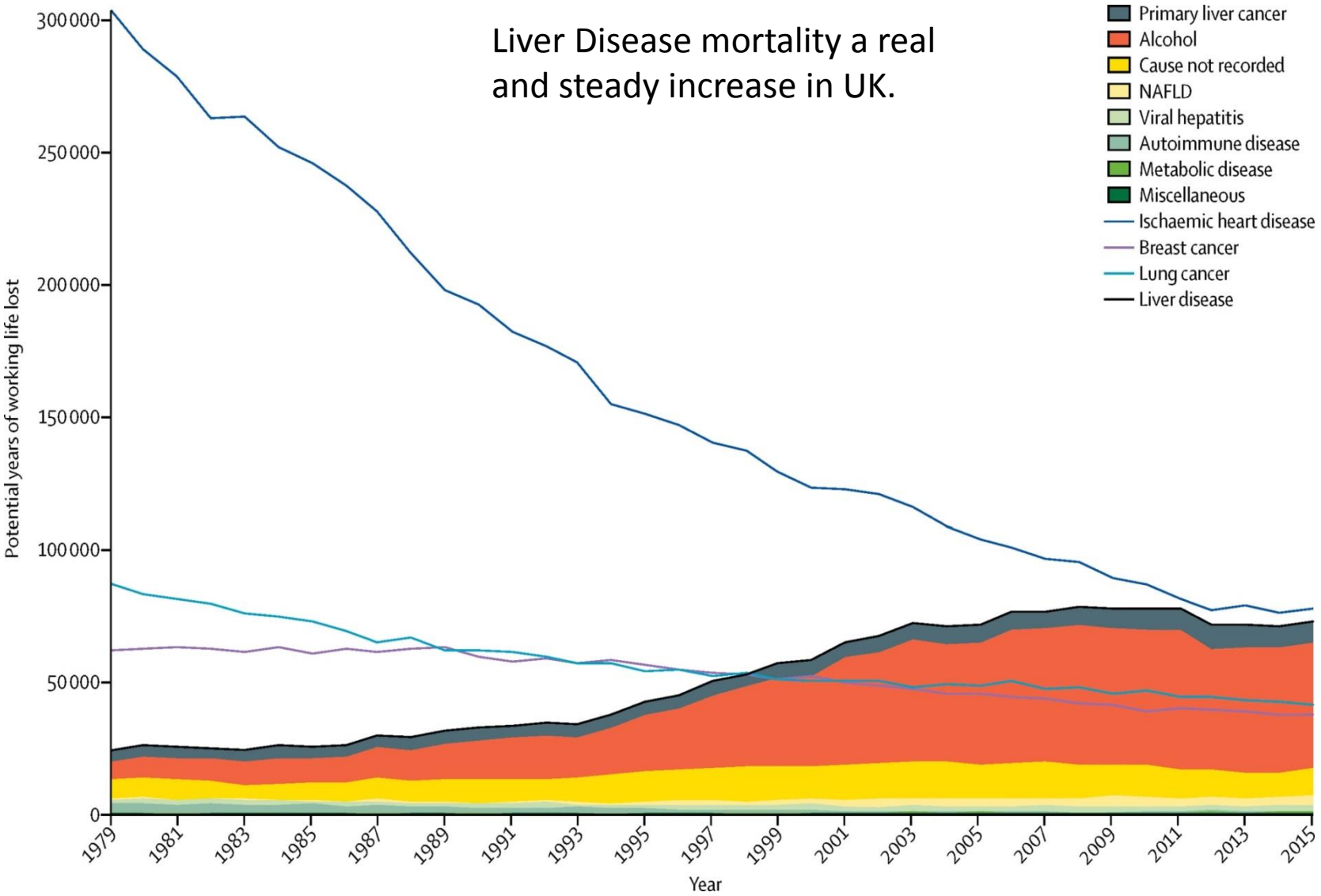
Report on liver biopsy should not simply state *consistent with* the diagnosis given in clinical information

So…Why else not to biopsy?

- Liver biopsy has always been regarded as the **Gold Standard** (everything! fibrosis, inflammation, steatosis, disease presence or absence)
  BUT tarnished, gilt plated at best**,** limitations of sampling error (disease process and specimen adequacy) and intra- and inter-observer variability.
- Safe but as an invasive procedure not without risk
  - (Pain 30%, bleeding 2-3%, death 0.01%-0.33% - greater in focal lesions, cancer, abnormal clotting and historical cohorts)
- WHO launched No Hep – aiming to eliminate viral hepatitis as a public health threat by 2030

What about the UK?

Liver Disease mortality a real and steady increase in UK.



Liver Disease 3rd most common cause of premature death; most deaths 50-59yrs (life expectancy of 84yr)

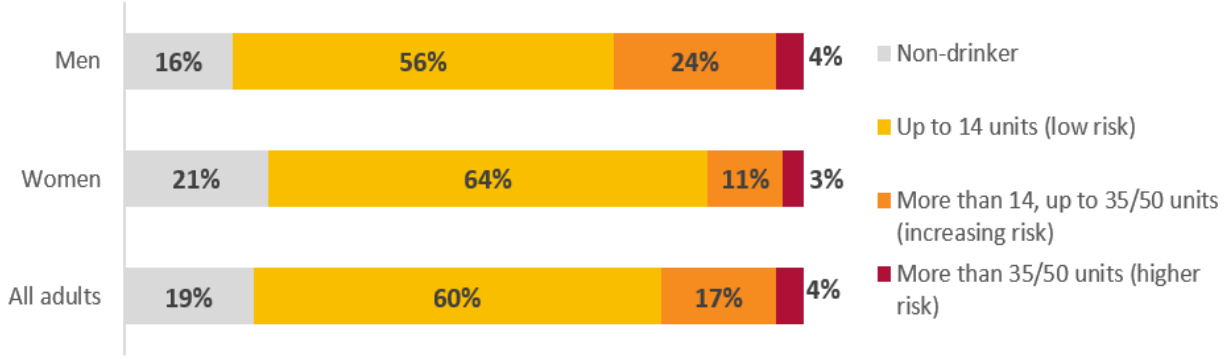
ELSEVIER

Alcohol related Liver Disease

Think before you Drink…

- Nearly 10 million adults in England have drinking habits potentially harmful
- Difficult to separate from NAFLD, risk factors.
- May be denied, so harder to establish clinically

Figure 1: Summary of weekly alcohol consumption, 2017
Source: NHS Digital (2018) *Health Survey for England 2017*. Table 13.
Note: Aged 16 and over.



NAFLD - WHO figures, based on BMI

between 1975 and 2016.

Why not to biopsy -Non-invasive markers of Fibrosis

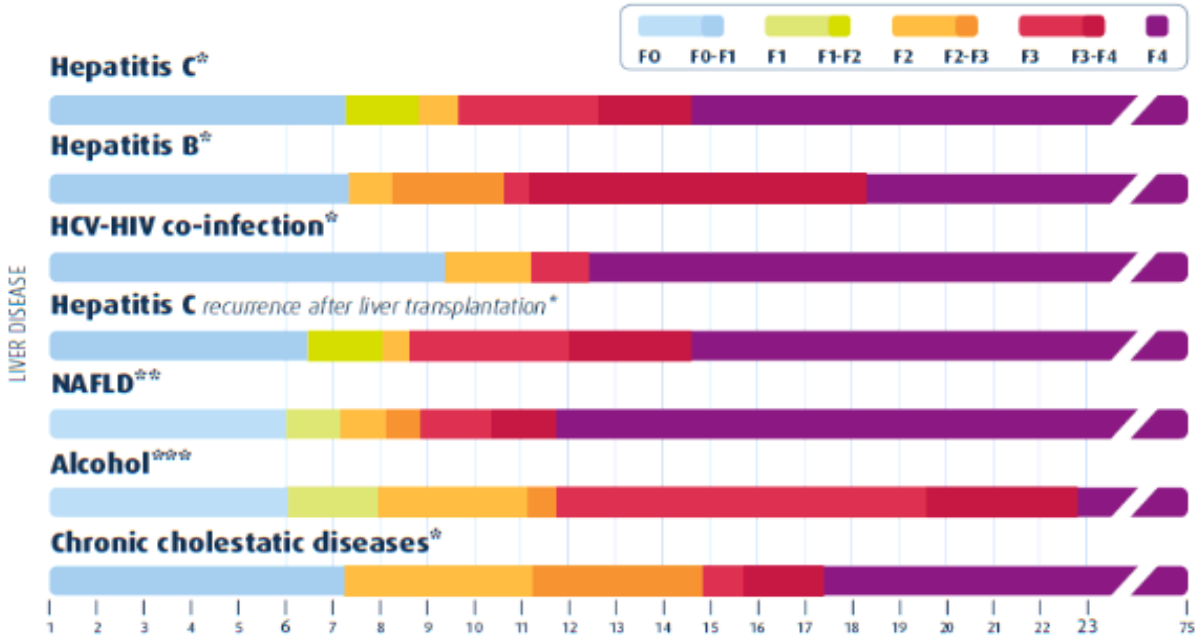
- Degree of fibrosis predicts morbidity and mortality; portal hypertension, cirrhosis & liver failure, HCC.
- Various methods of assessing liver stiffness by **elastography** - Fibroscan, ARFI, MRE - validated in common diseases; good or ruling out fibrosis or ruling in advanced fibrosis but limited ability in the middle.
- Serum biomarkers – ELF, Fibrotest, FIB4, APRI, Fibroindex (common markers, age, tissue breakdown and inflammation and complex formulae) - limited ability in the middle

But helps stratify/ triage those requiring biopsy

Fibroscan

Scale of measurements for known diseases

- Reading is converted into 5 stage fibrosis score F0-4



Evolving role of liver biopsy

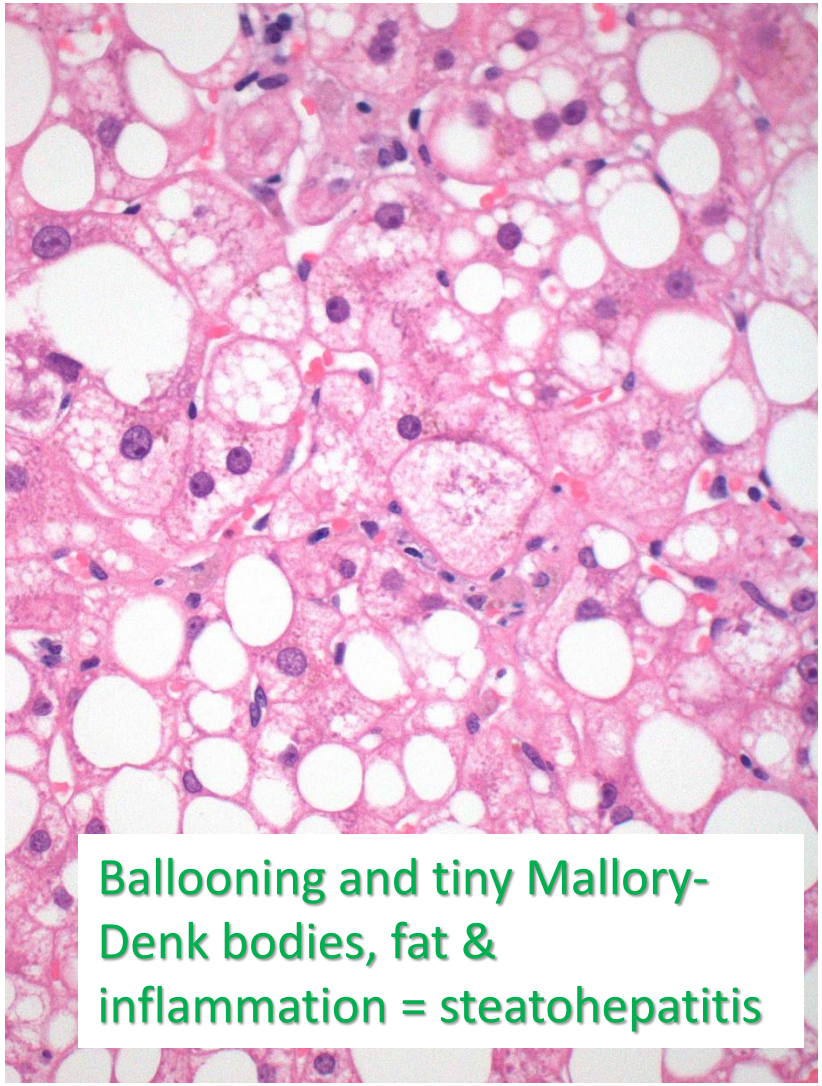
- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management
  - Not responding to therapy
- Diagnostic uncertainty/ unknown disease
  - Problems of dual pathology
  - Atypical presentation
  - No obvious aetiology
- Questions to address in main disease categories
- Summary

53 yr ♀; deranged LFTs - ↑ALT 3yrs, now in 90s

PMH PsA on secukinumab, psoriasis, Klinfelter syndrome, asthma, dyslipidaemia, OA, BMI 35.49

USS - fatty liver, normal PV, spleen. No ascites

Fibroscan Elastography score: 12.9 kPa = F4

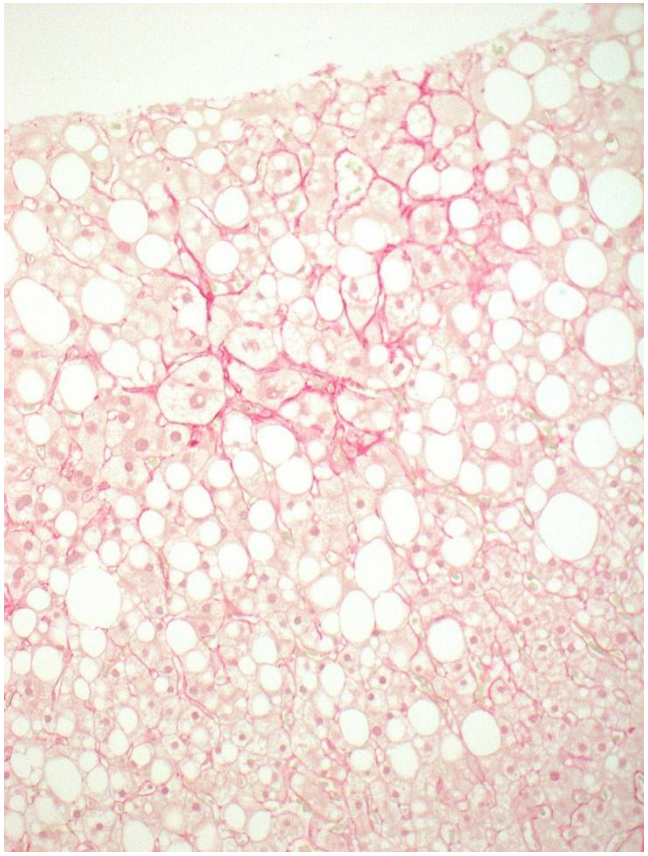


Ballooning and tiny Mallory-Denk bodies, fat & inflammation = steatohepatitis

Mismatch of clinical and non-invasive assessment – decision to biopsy

Presence of steatohepatitis currently not assessable by other means Important for progression.

Pericellular fibrosis, zone 3

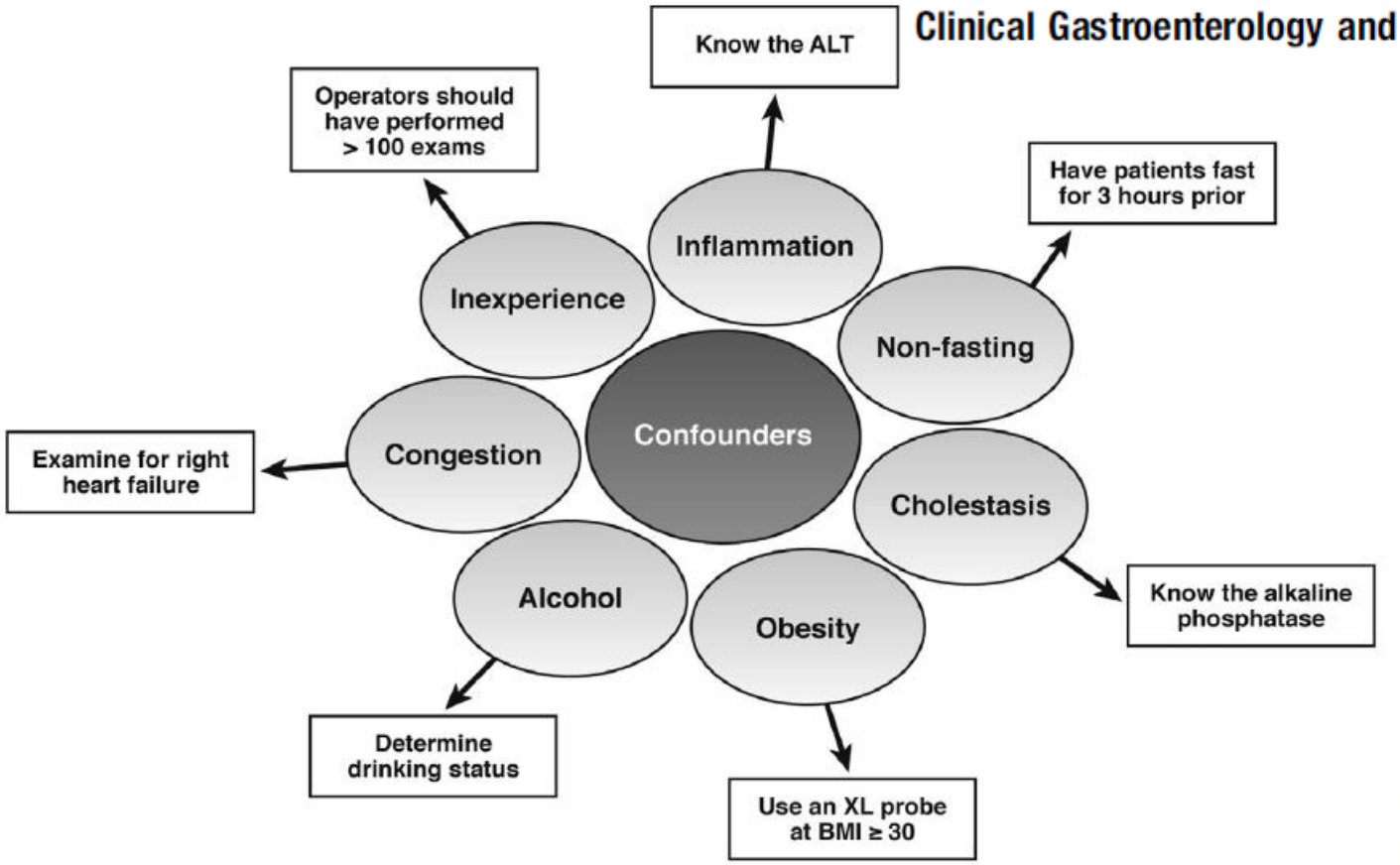


No bridging, minimal portal

Staging by description or scores – NAS (Kleiner) or SAF (Bedossa); with trails of treatment, possibly more biopsies and more numbers

Fibroscan - Possible Confounders

- Factors altering depth of liver in relation to probe eg BMI
- Factors altering viscoelastotic properties eg inflammation, steatohepatitis (bx remains gold standard)



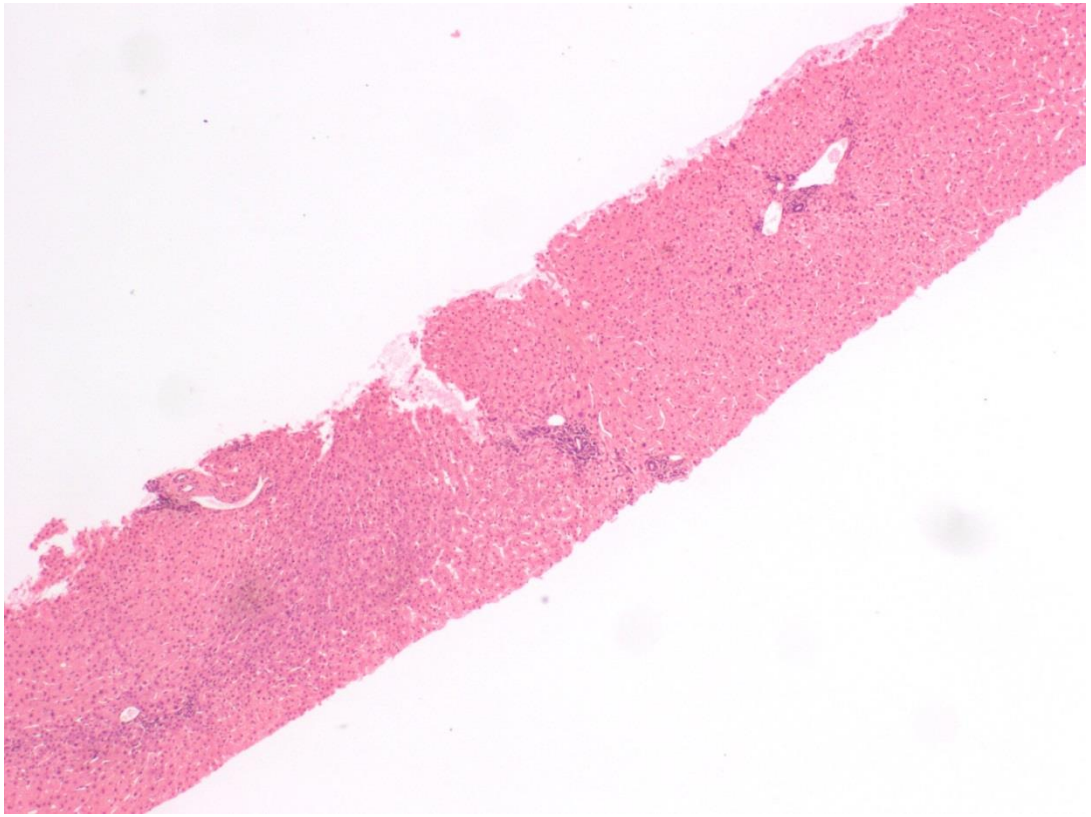
Clinical Gastroenterology and Hepatology Vol. 13, No. 1

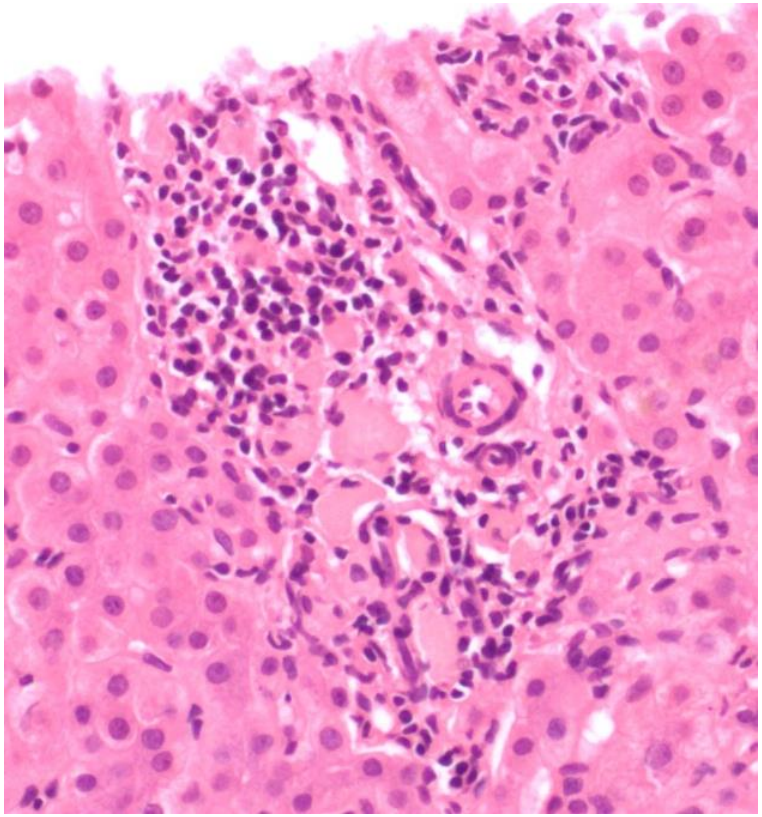
Figure 1. Confounders of VCTE. Strategies to anticipate and account for known confounders of VCTE are detailed.

Evolving role of liver biopsy

- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management – presence of SH, interface activity
  - Not responding to therapy
- Diagnostic uncertainty/ unknown disease
  - Problems of dual pathology
  - Atypical presentation
  - No obvious aetiology
- Questions to address in main disease categories
- Summary

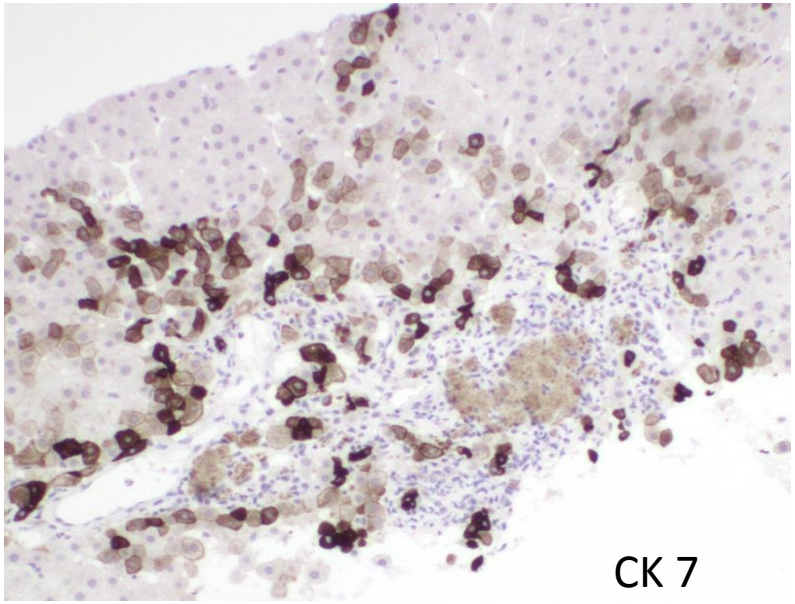
55♀ ALT 276, ALP 317, bilirubin normal, AMA positive. Limited response to ursodeoxycholic acid. ?overlap.

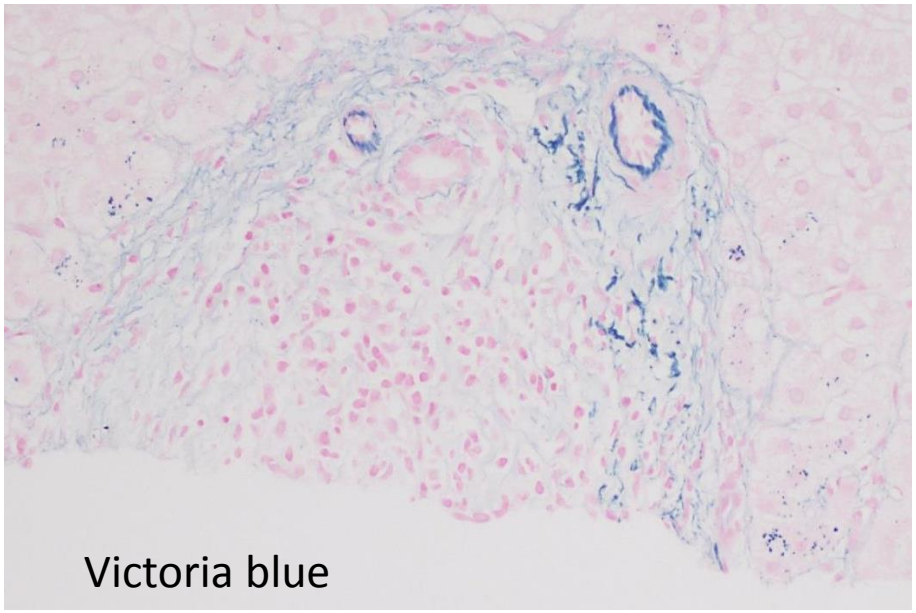




Little portal, lobular or interface inflammation; duct loss

Not responding to therapy


CK 7


Victoria blue

Prominent ductopenia, CAP +++, little fibrosis or ductular reaction.
Ductopenic variant of PBC

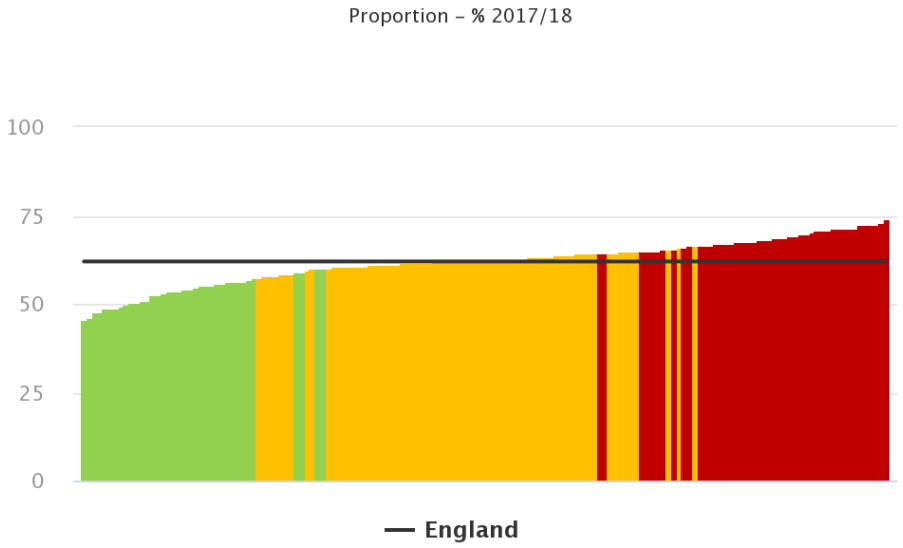
Japanese staging gives good prognosis, including urso response,
Nakamura Hepatology Res 2015

Evolving role of liver biopsy

- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management – presence of SH, interface activity
  - Not responding to therapy
- Diagnostic uncertainty
  - Problems of dual pathology
  - Atypical presentation
- Questions to address in main disease categories
- Summary

Dual Pathology

- In 2017, 1.11 billion **prescription** items were dispensed in the community. *(NHS Digital England)*
- With attendant co-morbiditites
- In 2017-8, **62%** of adults **overweight or obese** in England. *(Public Health England)*
- alcohol



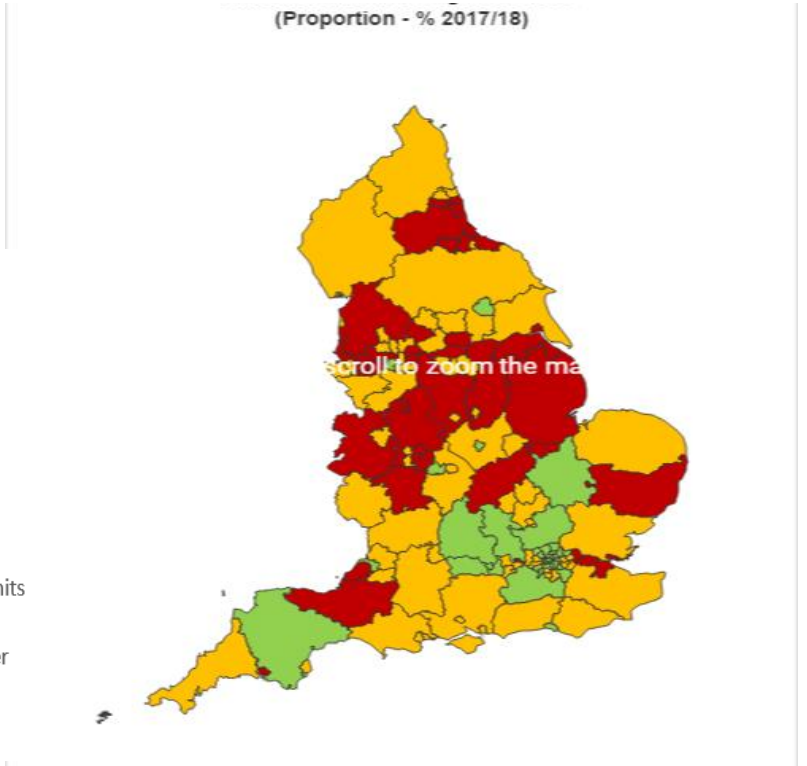
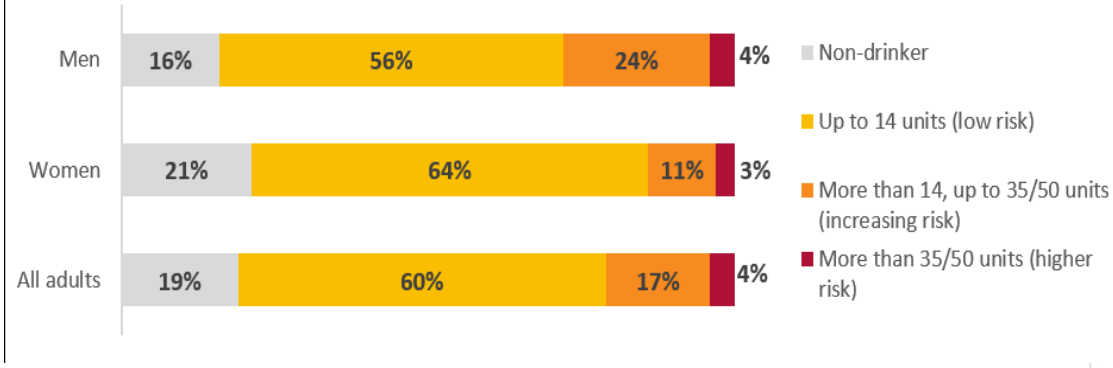


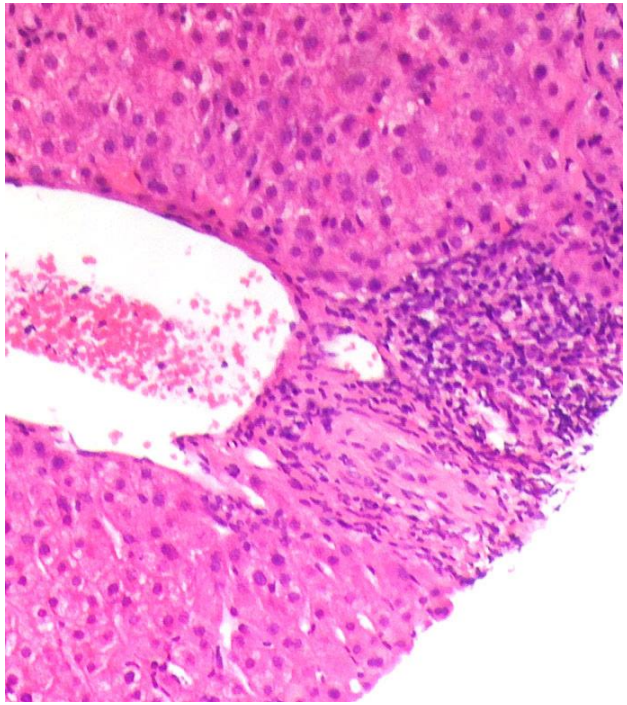
Figure 1: Summary of weekly alcohol consumption, 2017
Source: NHS Digital (2018) *Health Survey for England 2017*. Table 13.
Note: Aged 16 and over.

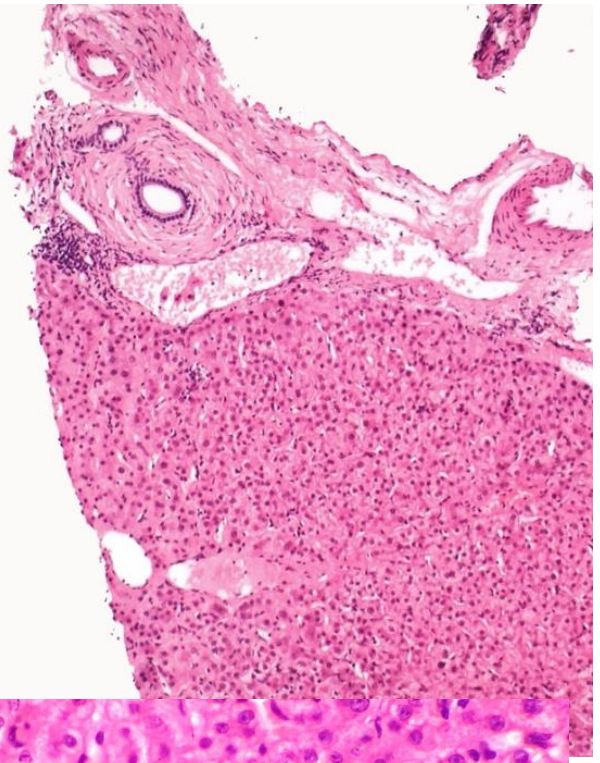


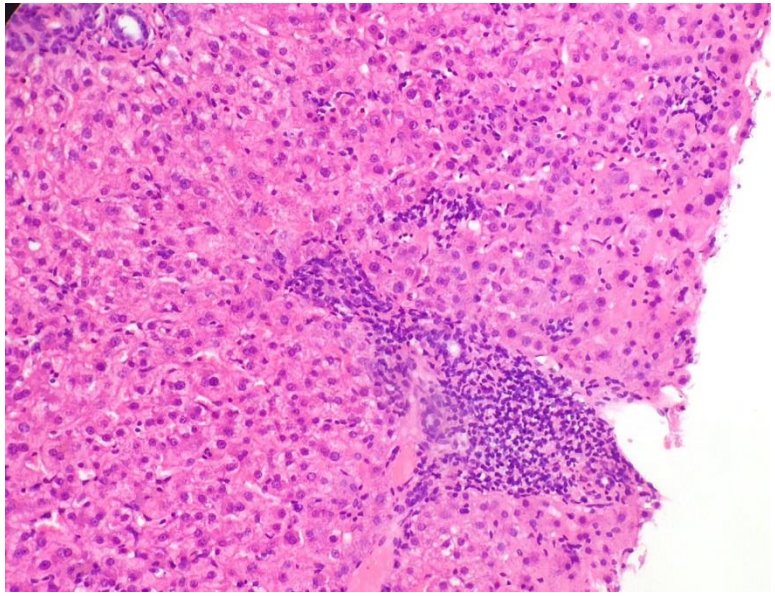
When could there be a 2nd pathology?

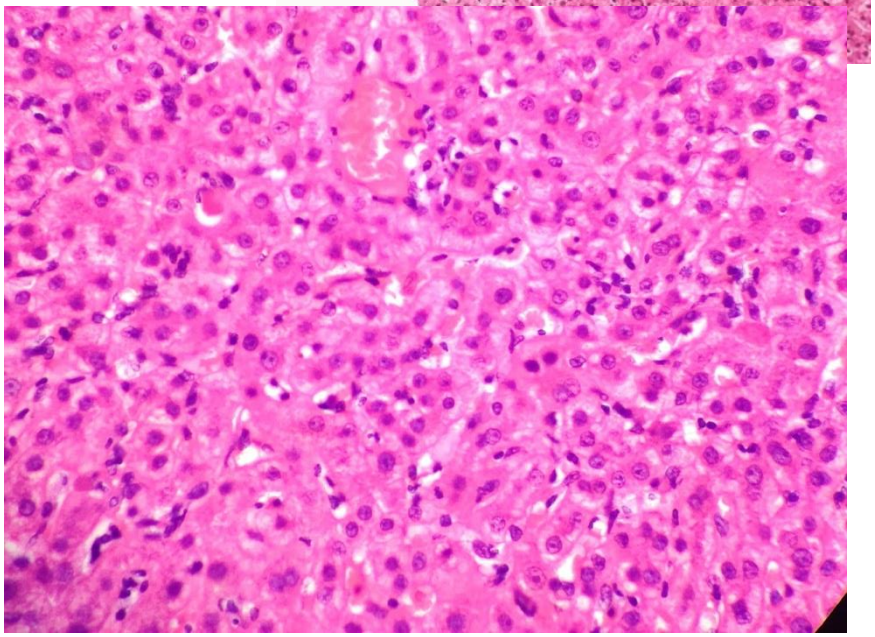
- Natural history or complication of the disease
- Same risk factors for other diseases
- Related to the treatment of that disease
- Genetic abnormalities common within the population
- Potential injurious agents common in the population
- Totally incidentally

29yr , 13yr h.o IBD, 3yr ago MRCP - PSC; now raised ALT and AP.

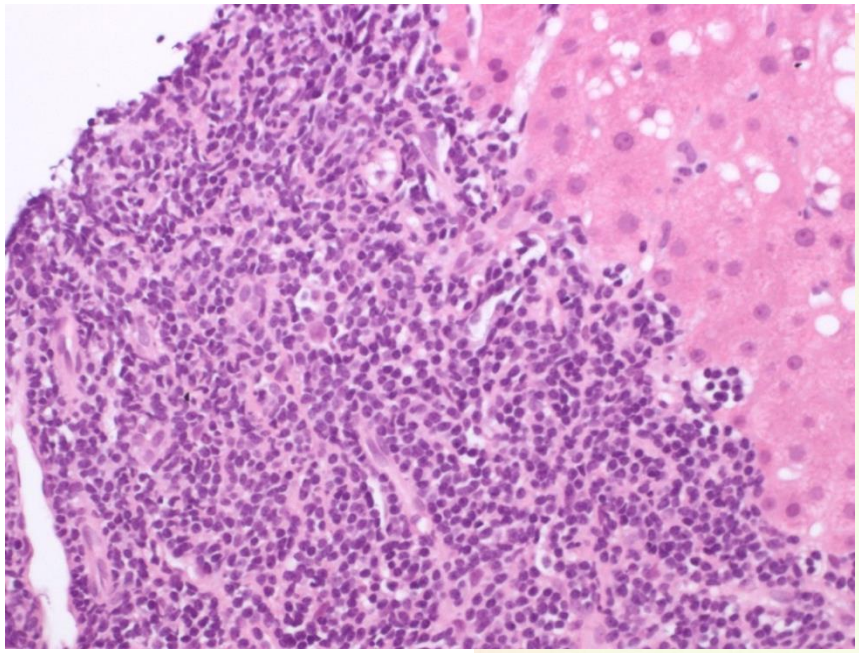


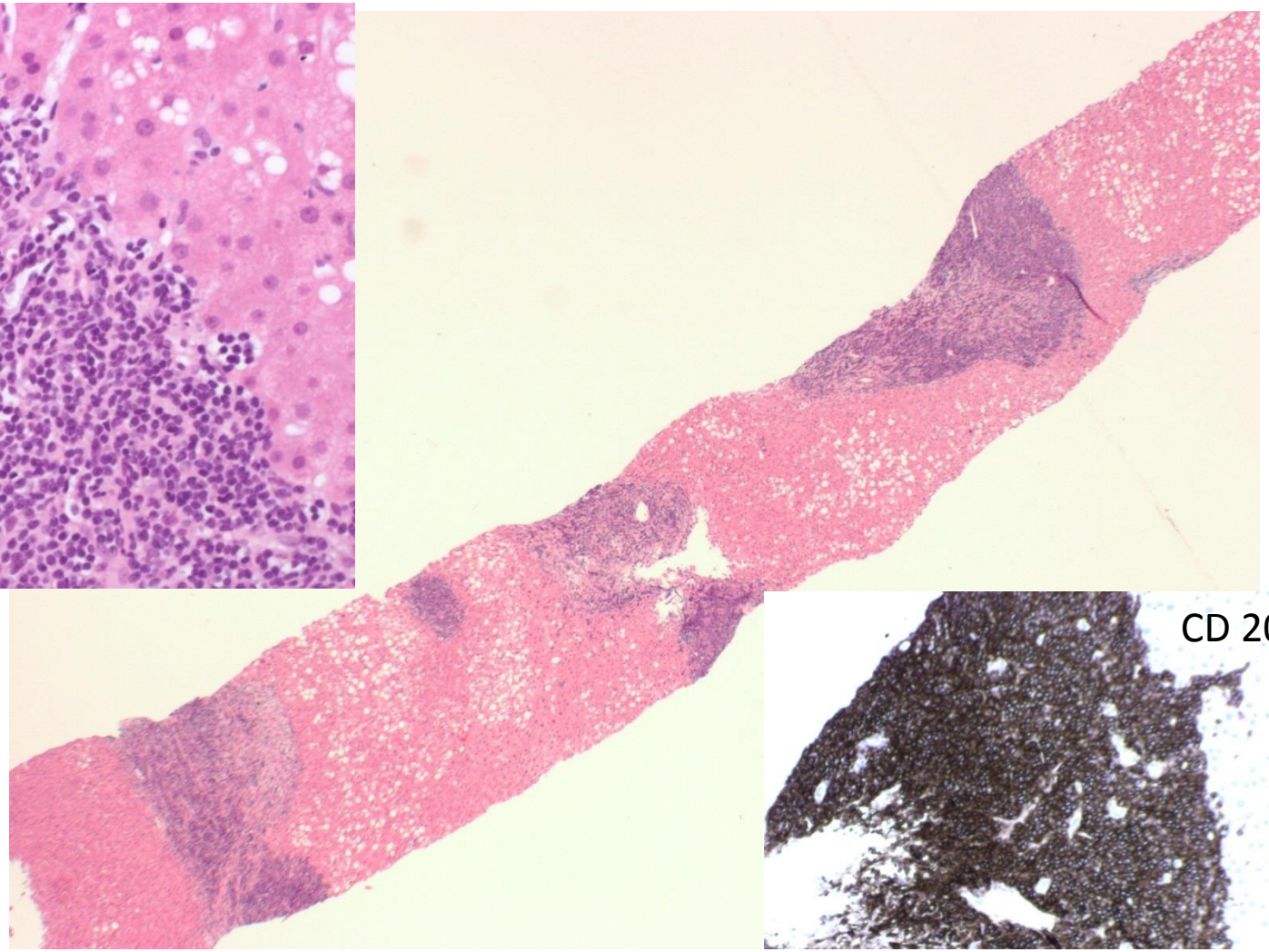






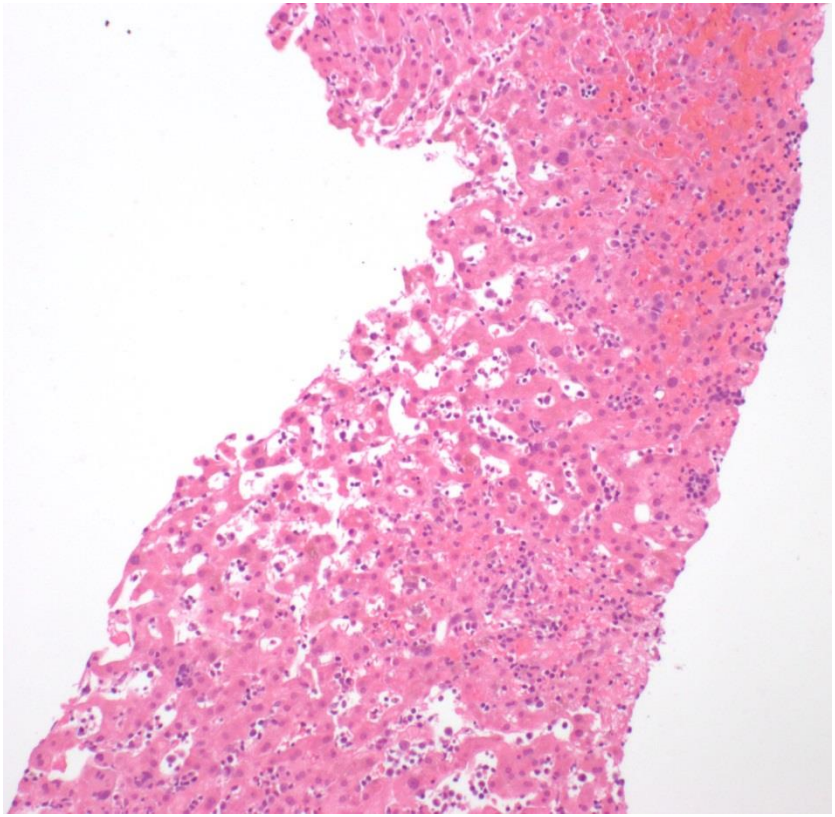
65♂ HCV+ve, also chronic lymphocytic leukaemia. Hepatosplenomegaly. ?secondary to CLL or hep C.

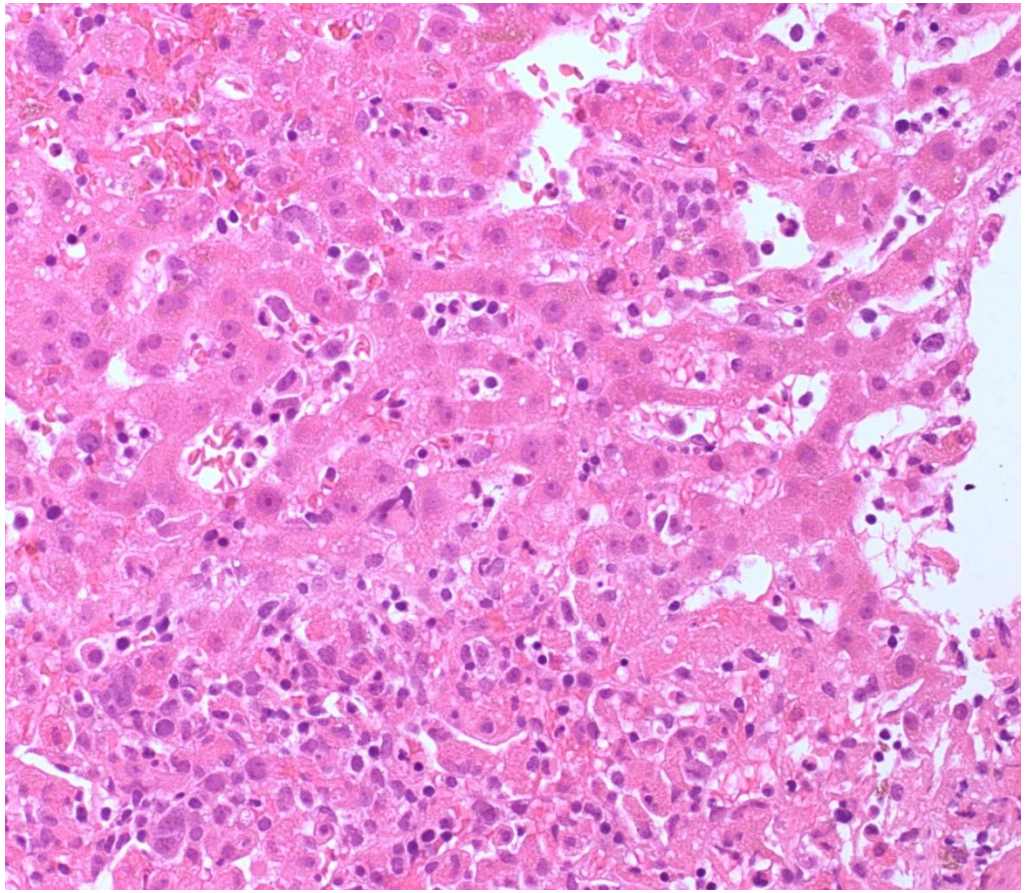




Multiple possible causal factors

46♂ metastatic melanoma receiving immunotherapy.
Deranged LFTs. ?immune related vs malignant infiltration





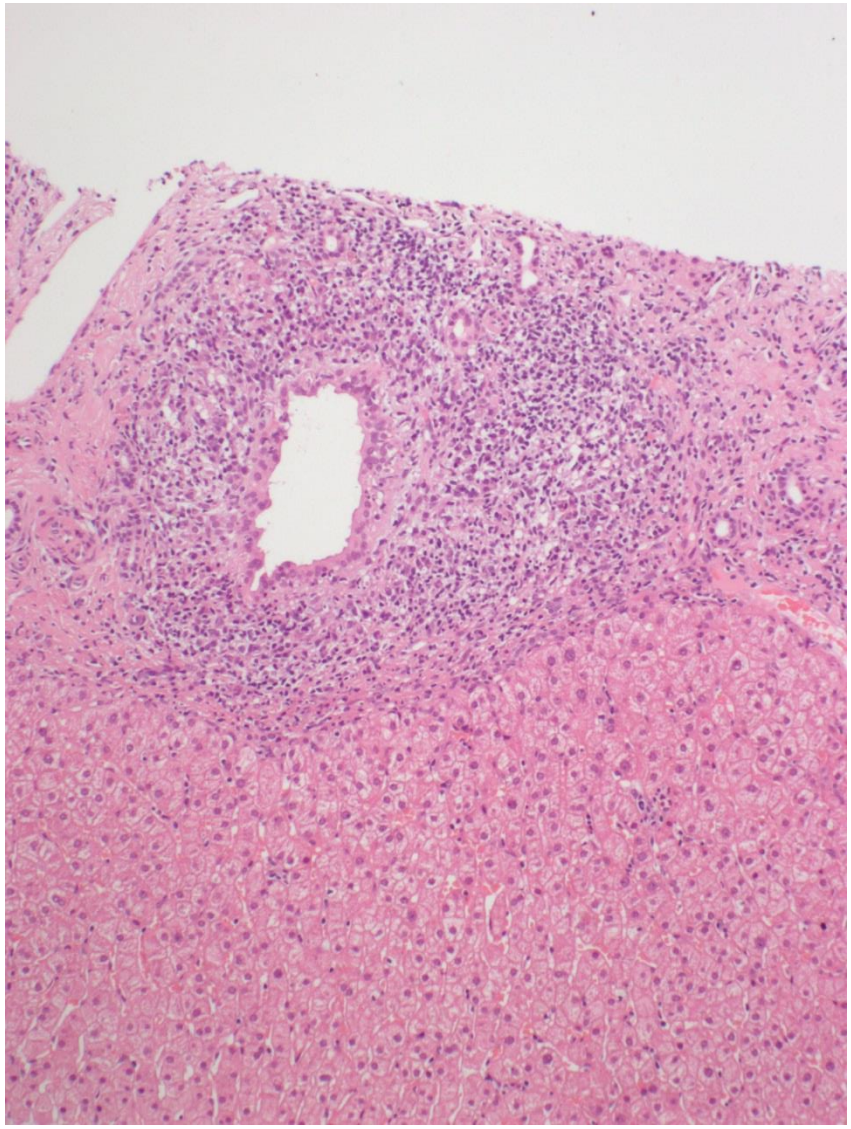
Consequences of more than one diagnosis

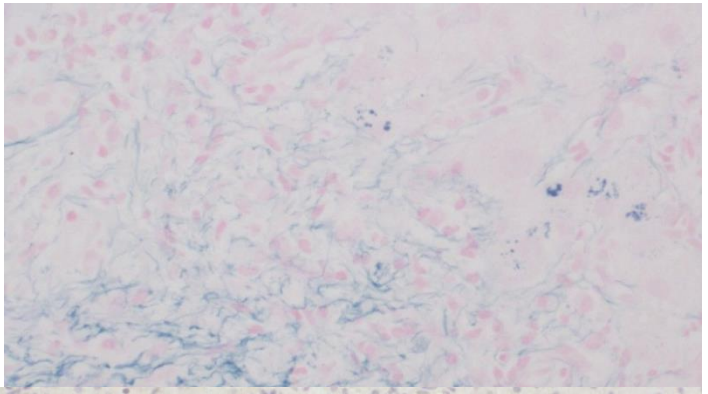
- Different treatment strategies – overlap, venesection iron
- Different follow-up strategies – clear HCV or HBV but still with N/AFLD; family members
- Symbiotic effect of more than one ‘hit’ to accelerating CLD, decompensation and HCC

Evolving role of liver biopsy

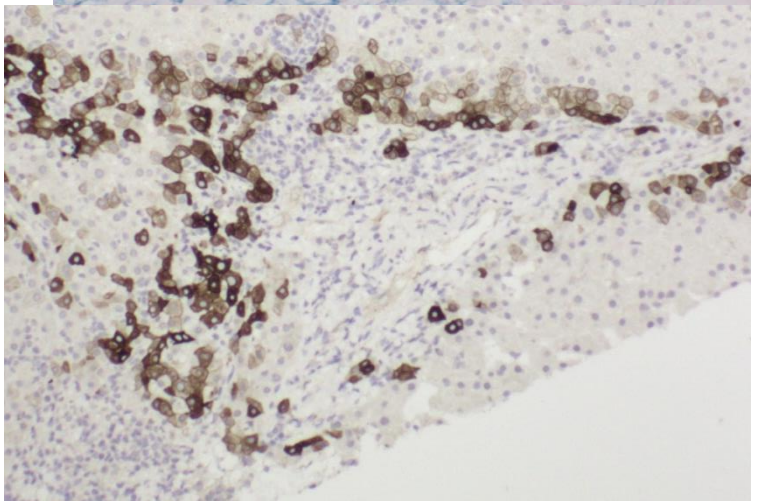
- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management – presence of SH, interface activity
  - Not responding to therapy
- Diagnostic uncertainty/ unknown disease
  - Problems of dual pathology
  - Atypical presentation
- Questions to address in main disease categories
- Summary

63♀ AST 59, ALP 262, ASMA +ve, AMA –ve (including extended panel).





Victoria blue



CK 7

Duct inflammation, ductopenia & cholate stasis

AMA negative primary biliary cholangitis

Liver biopsy reporting

- Adequacy, adequacy, adequacy
- Ample evidence under-stage and under-scoring if specimen too short and/ or narrow, esp. for portal based disease, (viral hepatitis and NAFLD
- Need > 20mm (30mm for AASLD guidelines) and of 16 gauge needle ~1mm

Evolving role of liver biopsy

- Introduction
- Reasons to NOT biopsy
- Reasons FOR a biopsy in known disease:
  - Staging of disease
  - Guide management – presence of SH, interface activity
  - Not responding to therapy
- Diagnostic uncertainty/ unknown disease
  - Problems of dual pathology
  - Atypical presentation
- Summary
- Questions to address in main disease categories

Summary

- Indications for liver biopsy are changing; more complicated clinical scenarios and less common diseases.
- Don’t state – ‘consistent with’ proffered diagnosis - address the clinical question.

Are all the features explicable by the known diagnosis.

Clinico-pathological communication essential for helpful report.

Role of liver biopsy in Biliary disease

- Limited; radiology paramount for large duct disease
- To diagnose small duct PSC
- To diagnose variants of PBC – accelerated ductopenia, early PHT, AMA negative
- To assess if a component of autoimmune hepatitis exists and how much.
- To stage the disease, especially if other risk factors for CLD (NAFLD) .

Role of Liver biopsy in ArLD

- Acute setting of jaundice - ? Alcholic hepatitis, ? Decompensation ? Other (esp. sepsis), drugs
- If Alc Hep, prognostic information
- To confirm abstinence???

Role of liver biopsy in NAFLD

- To clarify stage of fibrosis when not clear/ discrepant from non-invasive markers.
- To establish if steatohepatitis is present; stratify for trails and treatment.
- Risk factors v. common, so may be masking another aetiology.
- When dual pathology present to identify dominant pattern of injury.
- Follow up in trail setting.

Role of liver biopsy in DILI

- Are changes compatible with such a diagnosis
- Is this a known pattern
- Prognostication – severity of hepatitis, regeneration, degree of duct damage or ductopenia
- Is there DILI in addition to underlying chronic liver disease

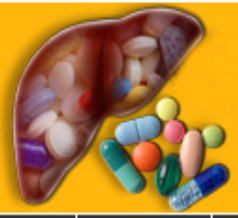
Search Livertox Database

https://livertox.nih.gov

Apps Hans Popper Hepato

United States National Library of Medicine

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases



LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

Home | NIDDK | NLM | SIS Home | About Us | Contact Us | Search Enter a drug name

- Home
- Introduction
- Clinical Course
- Phenotypes
- Immune Features
- Clinical Outcomes
- Causality
- Severity Grading
- Likelihood Scale
- Classes of Drugs
- Submit a Case Report
- Meetings/Alerts/News
- Information Resources
- Glossary
- Abbreviations

SEARCH THE LIVERTOX DATABASE

Search for a specific medication, herbal or supplement:

Search

Browse by first letter of medication, herbal or supplement:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

LIVERTOX® provides up-to-date, accurate, and easily accessed information on the diagnosis, cause, frequency, patterns, and management of liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements. LIVERTOX also includes a case registry that will enable scientific analysis and better characterization of the clinical patterns of liver injury. The LIVERTOX website provides a comprehensive resource for

Role of liver biopsy in Autoimmune hepatitis

- Are the features compatible on initial presentation, how active
- Is there underlying chronicity, how much fibrosis
- Are there other, biliary features
- Is there histological remission prior to stopping treatment
- Is any change in biochemistry due to flare of disease, or is there 2nd pathology eg NAFLD, DILI or virus.

Get an expert opinion –
have Prof Stefan Hubscher on fast-dial