Cases of abnormal liver tests

GLMS GP symposium

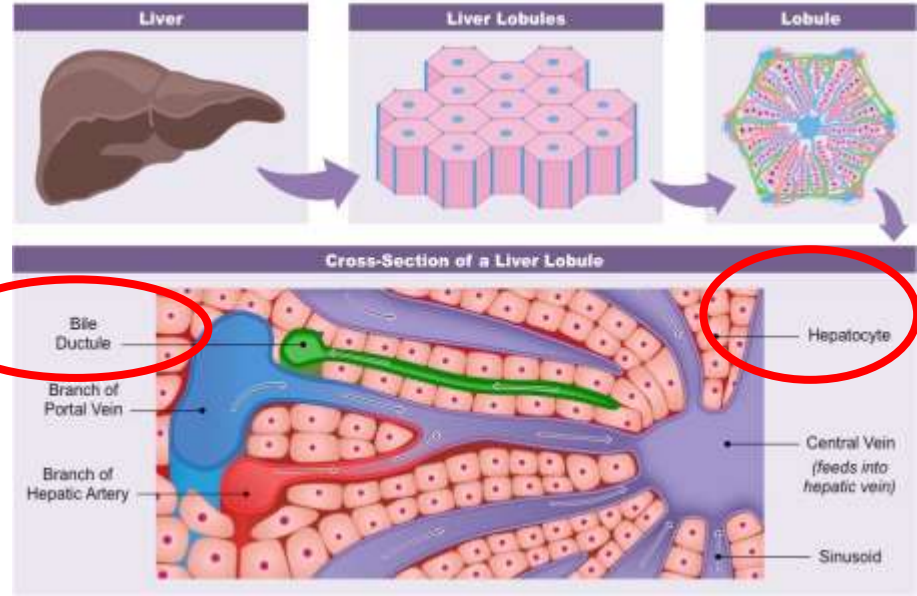
Saturday 17th February 2024

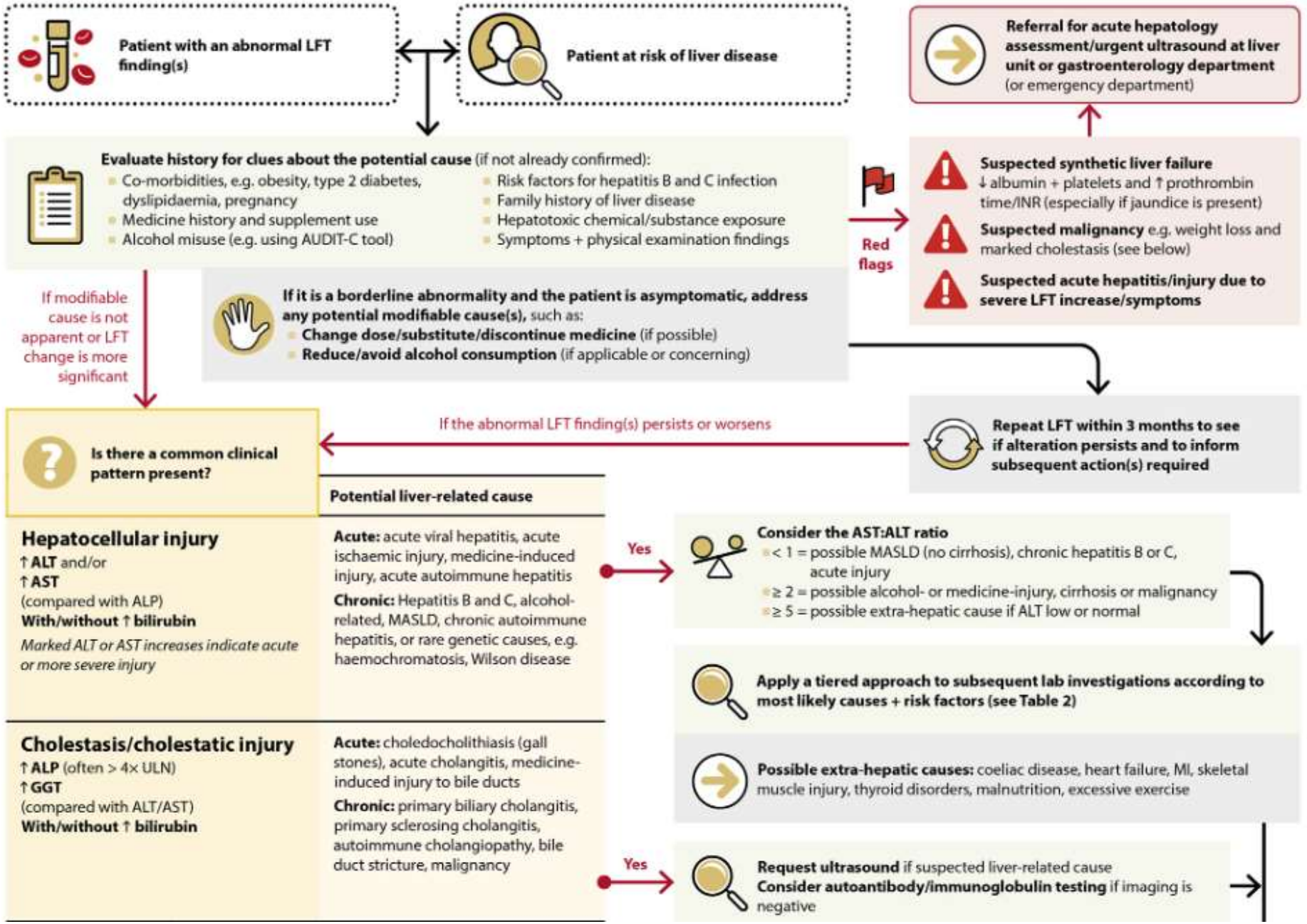
Gastroenterology session

Dr. Henry Wei

Biochemical tests for the liver

- Markers of liver **injury**
  - **Aminotransferase - ALT, AST**
    - Hepatocyte/hepatocellular parenchymal injury/necrosis; aka transaminitis, hepatitis
    - ALT is more specific/sensitive
    - AST is also found in cardiac muscle, skeletal muscle, kidney, brain (consider in isolated AST rise)
    - Males have higher ULN then Female
  - **ALP, GGT**
    - Cholestatic injury; aka obstructive, biliary
    - ALP also found in bone and produced by placenta. Higher in adolescents (bone development)
    - GGT also found in kidney, pancreas, spleen, heart, brain – NOT bone
  - **Bilirubin**
    - Direct (conjugated) – biliary obstruction and hepatic disease
    - Indirect (unconjugated) – haemolysis
- Markers of liver synthetic **function**
  - **Albumin**
  - **Bilirubin**
  - **Prothrombin time** (and/or INR)





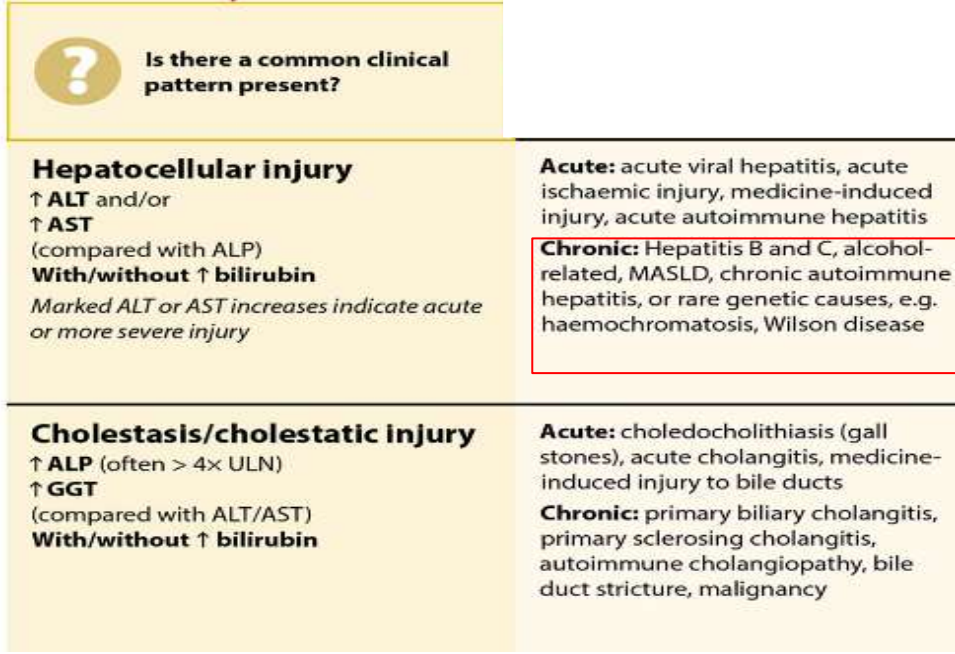
Liver function tests in primary care –bpac nz

Case 1: Mr. F

- 45yo Tongan man
- Went to GP to pick up allopurinol script
- **Background:** T2DM, BMI 37 kg/m^2, Gout
- **Blood tests**
  - **AST 70, ALT 80, GGT 100**, Bilirubin 5 – similar for the last **10 years**
  - **Hba1c 66**, LDL 3.4. **Ferritin 850,** Tsat 0.3
  - Normal FBC, Plt 200, INR, Albumin 35

Q: What is the <u>least likely</u> cause for his deranged liver tests?

1) Alcohol
2) MASLD
3) **Hereditary Haemochromatosis**
4) Combinations of 1,2 and 5
5) Chronic Hepatitis B



Is there a common clinical pattern present?	
Hepatocellular injury ↑ **ALT** and/or ↑ **AST** (compared with ALP) **With/without ↑ bilirubin** *Marked ALT or AST increases indicate acute or more severe injury*	**Acute:** acute viral hepatitis, acute ischaemic injury, medicine-induced injury, acute autoimmune hepatitis **Chronic:** Hepatitis B and C, alcohol-related, MASLD, chronic autoimmune hepatitis, or rare genetic causes, e.g. haemochromatosis, Wilson disease
Cholestasis/cholestatic injury ↑ **ALP** (often > 4× ULN) ↑ **GGT** (compared with ALT/AST) **With/without ↑ bilirubin**	**Acute:** choledocholithiasis (gall stones), acute cholangitis, medicine-induced injury to bile ducts **Chronic:** primary biliary cholangitis, primary sclerosing cholangitis, autoimmune cholangiopathy, bile duct stricture, malignancy

Elevated ferritin: 90% from non-iron overload conditions, where **venesection is NOT indicated.**

Hereditary Haemochromatosis (HH)

1 in 200 people of Caucasian race are homozygous for the C282Y
Compound heterozygous H63D/C282Y and H63D homozygous have much lower penetrance (even if ferritin elevated, unlikely overload)

Transferrin saturation is a better marker of iron overload than ferritin

>0.5 male
>0.45 females

Case 1: Mr. F

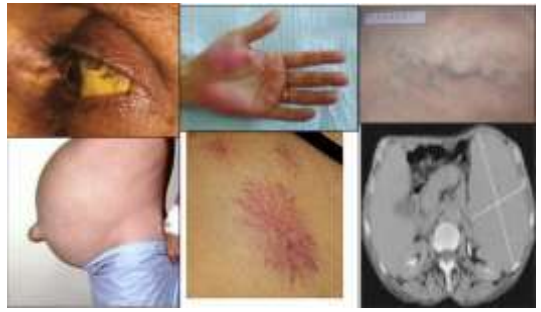
- Reports alcohol 3u beer a week
- **Liver screen** unremarkable
  - ***Viral*** *Hepatitis (HBV, HBV, HCV (consider delta), HEV (acute), EBV and CMV)* ***Auto-immune*** *screen (ANA, AMA, LKM, SLA, Tissue Autoantibodies, Coeliac Ab, Globulins)* ***Rare causes*** *(Ceruloplasmin, Alpha-1 antitrypsin),* ***Iron studies***
- **USS:** diffusely hyperechoic 'fatty' liver. No gallstones

  No features of portal hypertension or cirrhosis

Q: What is <u>best</u> non-invasive test to assess fibrosis

1) Ultrasound
2) NFS (age, BMI, diabetes, AST, ALT, platelet, albumin)
3) FIB-4 (Age, AST, ALT, platelet)
4) APRI (AST, platelet)
5) **Fibroscan**

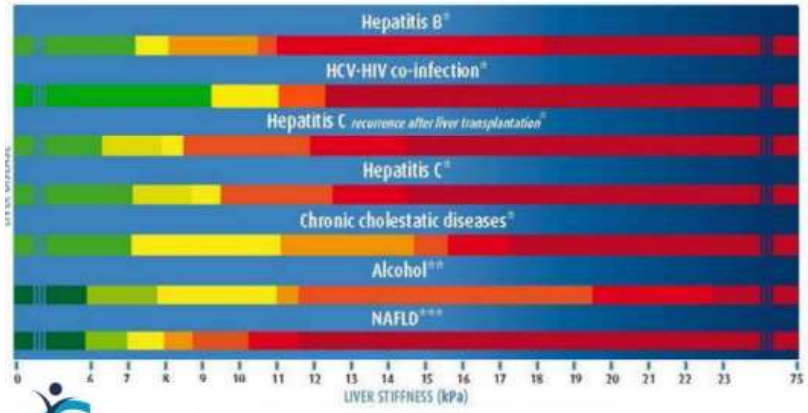
Diagnosing and staging fibrosis without a biopsy



- Ultrasound is not sensitive for detecting early fibrosis
  - Overt cirrhosis on USS usually advanced stage
  - Helpful for structural information of the liver
- **Image based tests of fibrosis** e.g. Fibroscan or SWE has **better performance than serological based tests** e.g. APRI, FIB4, NFS

Fibroscan

CAP (dB/m)		E (kPa)	
IQR	MEDIAN	MEDIAN	IQR
7	400	7.9	0.8
			IQR/med. 10%



CAP Score	Steatosis Grade	Amount of Liver showing Fatty Change
150 – 248 dB/m	S0	0 – 10%
248 – 260 dB/m	S1	11% - 33%
260 – 280 dB/m	S2	34% - 66%

Availability and referral criteria vary throughout the country. Clinicians are advised to contact their local gastroenterology service to determine if FibroScan is available in their region, which patients should be referred for assessment and how this is done. In some areas, direct general practitioner referral is available for patients with Hepatitis C infection.

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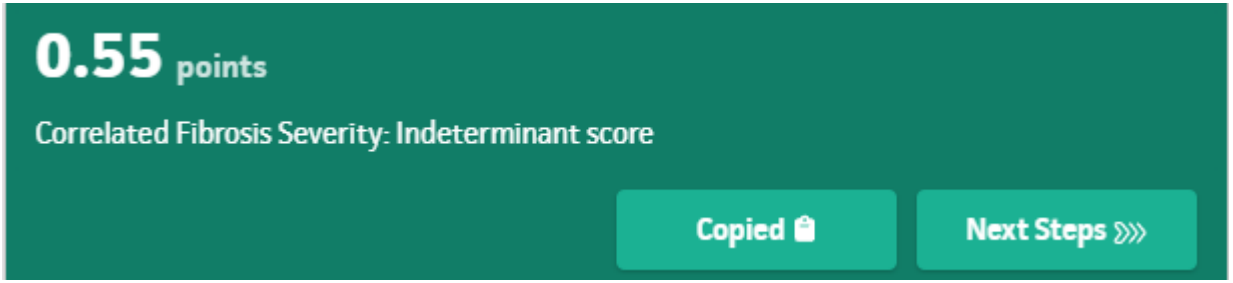
Fibroscan is covered by most insurance companies

Case 1: Mr. F MASLD

- NAFLD Fibrosis score indeterminant
- Fibroscan
  - 8.1 kPa (F2) CAP 270 dB/m (S2 steatosis)
- Referred to gastroenterology clinic
- **Rx:** lifestyle interventions for weight loss
- He asks *"What about Ozempic?"*

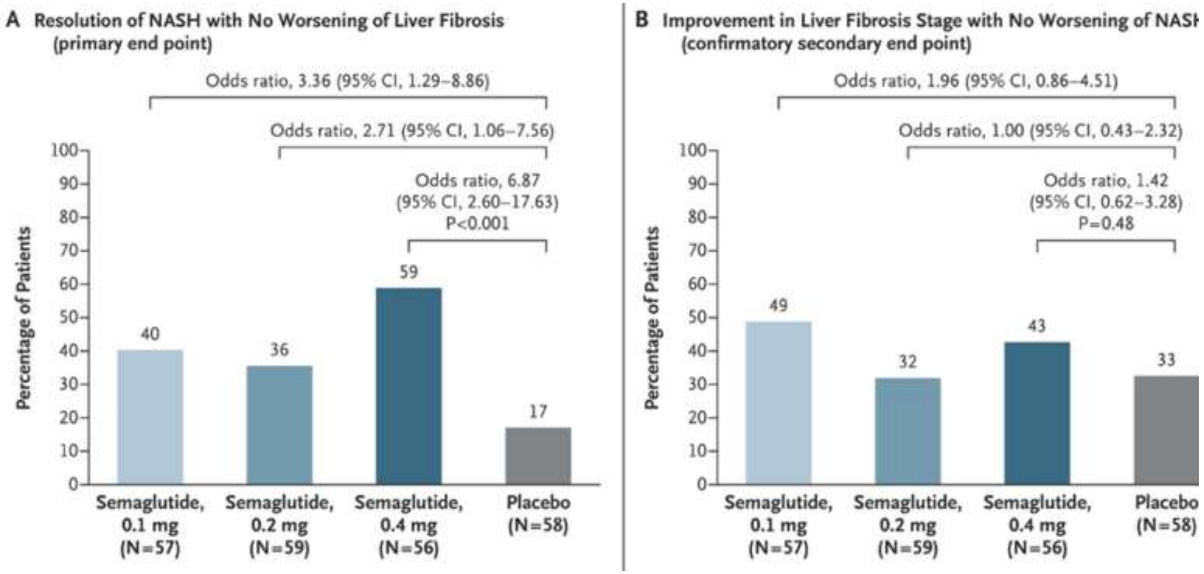


Q: Which statement are true regarding the use of GLP-1 agonists in MASLD

1) Regression of fibrosis will occur over time
2) **Atherosclerotic Cardiovascular disease outcomes should improve in high risk individuals**
3) GLP-1 agonists are FDA approved for MASH
4) GLP-1 agonists should not be used in Cirrhosis

GLP-1 treatment benefit the liver compartment?

- Weight loss >10% associated with regression of fibrosis
- GLP-1 agonists helps weight loss…



….but no fibrosis regression over 72 weeks

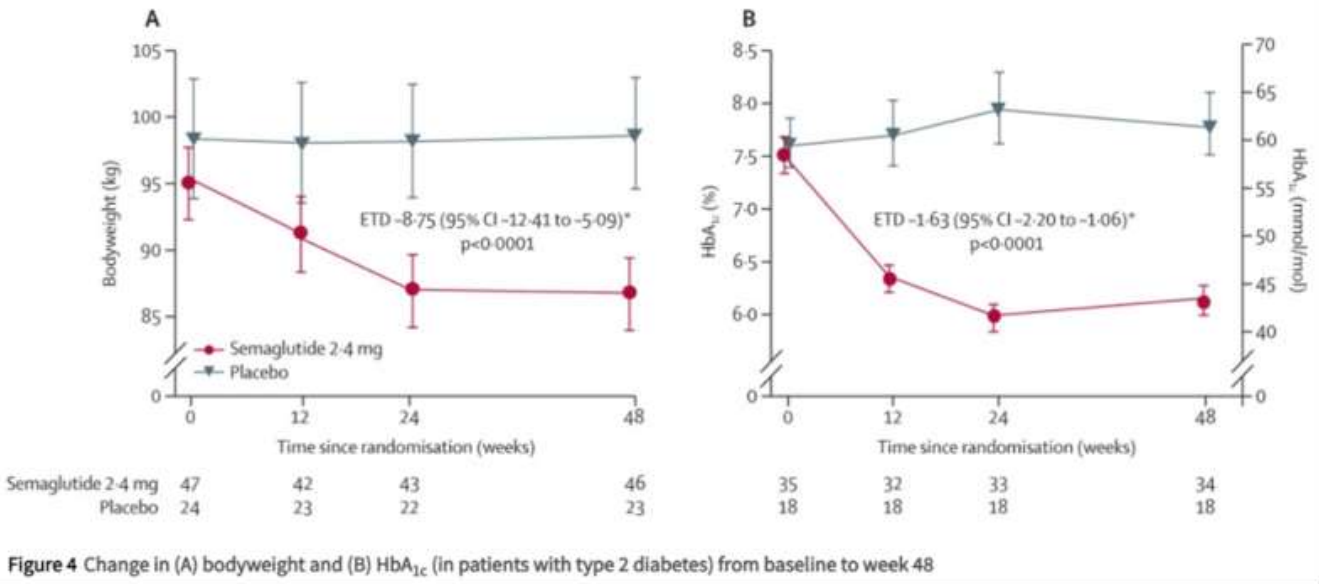


Figure 4 Change in (A) bodyweight and (B) HbA_{1c} (in patients with type 2 diabetes) from baseline to week 48

…no improvement in liver fibrosis in compensated cirrhosis, although appears to be safe with no increased hepatic decompensation

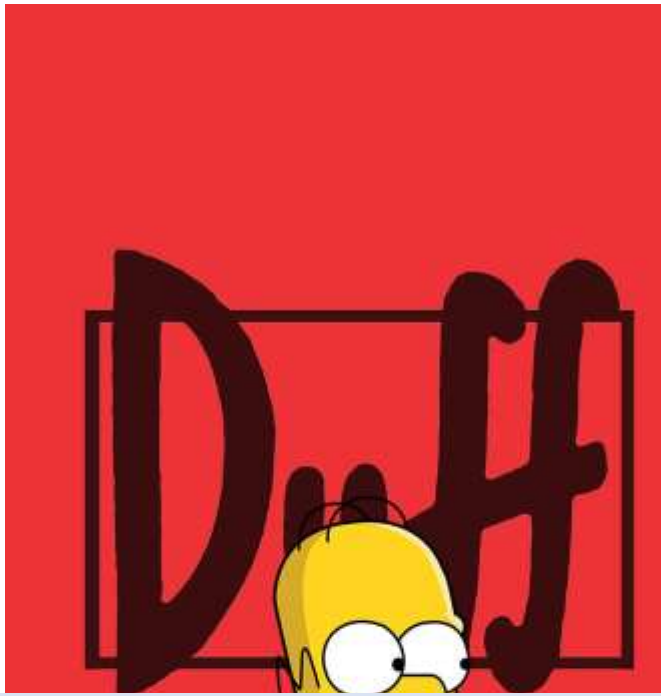
GLP-1 agonists are not currently FDA approved for MASLD

Case 2: Mr. S

- 33 year old European
- Returned from a holiday in Thailand 2 days a ago
- Feeling unwell with nausea and loss of appetite
  - Friend commented “looked like Homer Simpson”
- Binge drinker. No other significant medical history
- **Blood tests:**
  - **AST 4300, ALT 5180 U/L**, GGT 302, ALP 156, **Bilirubin 55**, **INR 1.4**
  - 3 months ago liver tests were normal

Q: What is the <u>least likely</u> cause for his deranged liver tests?

1) Alcohol
2) Ischaemic hepatitis
3) Acute hepatitis B
4) Paracetamol overdose



Few causes of ALT AST >1000: paracetamol, ischaemic injury, acute HBV.

Alcohol alone is NOT a cause of marked transaminitis

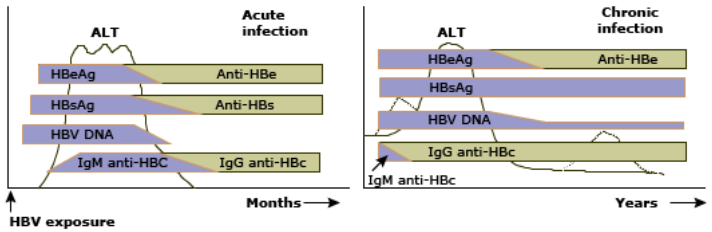
Generally the cause of transaminitis will determine treatment & disposition

Case 2: Mr. S

Emergency department assessment

- No recent paracetamol
- Normal renal function and lactate
- **HBsAg positive**
- **HBV core Ab positive** (**Core IgM Positive** Core IgG Negative)

- **Supportive management** – Discharge criteria: Maintain nutrition, hydration & symptoms
  - Avoid further insults in the meantime (alcohol, liver toxic drugs)
  - Counselling (safe sex, sharing needles/razors)
  - Testing and vaccination for contacts
  - Notifiable disease
  - **Weekly liver tests until improving**
  - **At 6 months HBsAg negative confirms clearance**



Acute HBV confirmed with **HBsAg positive and Core IgM Ab positive**

Most adults who contract HBV infection via sexual or blood contact will have acute infection

70% have symptoms (icteric, fever, nausea, vomiting, abdominal pain)

Supportive management (<1% develop fulminant hepatitis ***exception with underlying liver disease = high risk)**

Most acute HBV in adults will not progress to chronic infection.

*Acute HBV is a notifiable disease whereas Chronic HBV is not

Case 3: Mrs. P

- 38 year old European woman
- Rejected as a blood donor as **AST 150**
- History of quiescent Ulcerative Colitis on mesalazine.
- No risk factors for alcohol, viral or drug induced liver injury
- **ALT 100, ALP 200, GGT 123,** ANA negative. HBsAg negative, HCV RNA negative, HIV negative, HAV negative

Q: What diagnosis have we most confidently excluded

1) Autoimmune hepatitis
2) Primary Sclerosing Cholangitis
3) MASH/MASLD
4) Wilson disease
5) **Chronic HCV**

Autoimmune Hepatitis

Young to middle aged woman
AST/ALT can fluctuate without treatment. Responds to steroids. Other autoimmune disorders. Occasionally drugs can trigger AIH
ANA, Anti-SM, Anti LKM, Anti-SLA, Immunoglobulins
Liver biopsy

Primary Biliary Cholangitis PBC

Female, Cholestatic liver tests, ALP.
Anti-mitochondrial antibody, IgM, ANA

Primary Sclerosing Cholangitis PSC

Male, Cholestatic liver tests GGT/ALP/Bilirubin
Association with Ulcerative colitis.
MRCP diagnosis of large duct PSC
ANCA positive, other Ab positive (can also overlap with AIH)

Haemochromatosis

Family history, more in Europeans, "bronzed diabetes", heart failure, liver disease
Fe saturation >45%, Ferritin, **hereditary haemochromatosis screen**

Alpha 1 Anti-trypsin deficiency

Co-existing lung disease
Serum AAT & genotype

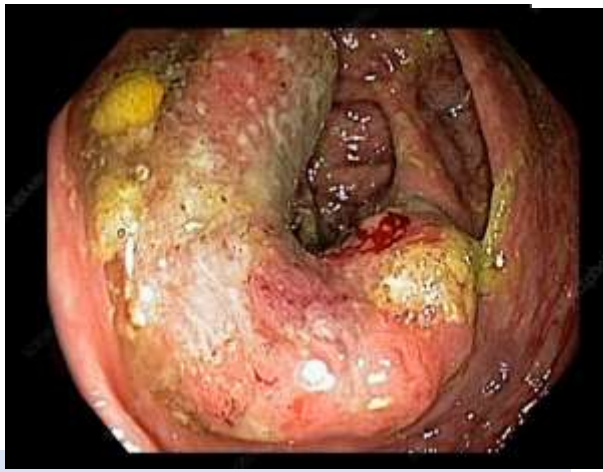
Wilson disease

Young patients with deranged LFTs, liver failure, haemolysis and neurological manifestations
Serum Ceruloplasmin, urinary copper, genetic screen

Structural causes

Mostly cholestatic e.g. stones, strictures, masses – diagnosed via **imaging**

Case 3: Mrs. P



- **MRCP:** Multi-focal intra and extra hepatic strictures consistent with **PSC.**
- 1 year later – screening **colonoscopy** colon cancer
  - Underwent right hemicolectomy and adjuvant chemo

PSC, IBD and malignancy

PSC is strongly associated with IBD (usually UC)

Up to 90% of PSC have UC (c.f. 5% of IBD have PSC)

Independent of disease activity All PSC should have colonoscopy*

10X ↑ risk for **colon cancer** with overlap (>10% lifetime)

Year surveillance colonoscopy from diagnosis*

5 yearly surveillance if no IBD*

↑ risk for **Gall bladder CA** and **HCC** (2-5% lifetime)

MRI at the same time with yearly MRCP for CCA surveillance*

cholecystectomy if GB polyp independent of size*

6 monthly USS if cirrhosis (HCC)*

20% lifetime risk of **Cholangiocarcinoma** but screening strategy not defined

CA 19-9 (>130 U/ml) ≈ 70% sensitivity, 98% specificity in "suspected CCA"

Imaging

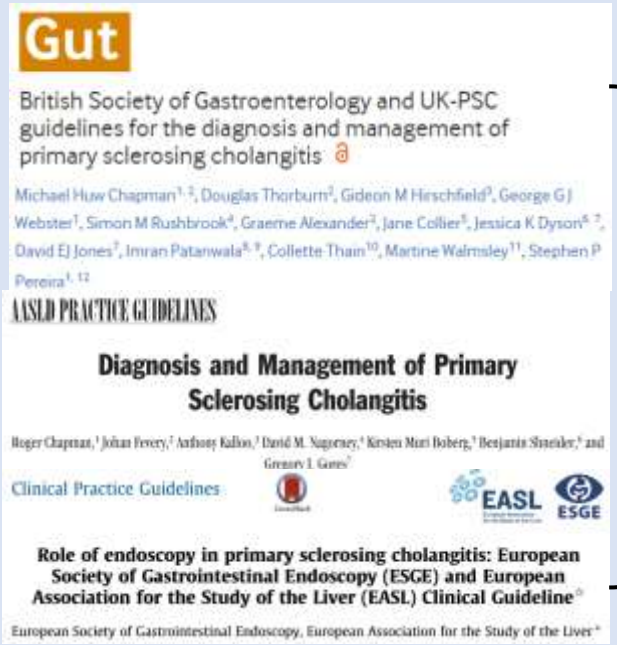
Mass lesion rare in early CCA

Cholangiography by ERCP / MRCP predictive value for CCA ~20%

Cholangioscopy and intraductal USS promising?

Annual surveillance MRCP/MRI +/- CA 19-9*

Low threshold to suspect CCA in PSC e.g. dominant strictures, progressive biliary dilatation*


Gut

British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis

Michael Huw Chapman, Douglas Thorburn, Gideon M Hirschfield, George G J Webster, Simon M Rushbrook, Graeme Alexander, Jane Collier, Jessica K Dyson, David E J Jones, Imran Patanwala, Collette Thain, Martine Walmsley, Stephen P Pereira

AASLD PRACTICE GUIDELINES

Diagnosis and Management of Primary Sclerosing Cholangitis

Roger Chapman, Johan Fevery, Anthony Kalloo, David M. Nagorney, Kirsten Muri Boberg, Benjamin Shneider, and Gregory J. Gores

Clinical Practice Guidelines

EASL ESGE

Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline

European Society of Gastrointestinal Endoscopy, European Association for the Study of the Liver

Strong recommendations *

Discrepancy of recommendations *

Weak recommendations *

Case 4: Mr C

- 72 year old man
- Upper abdominal and thoracic level back pain 9 months
- **10kg weight loss over 2 months**
- **Blood tests**
  - **Lipase 1661**
  - **ALP 159, GGT 222**
  - **Bilirubin 40** and ALT normal.
- **CT** 2.4cm lesion in the uncinate portion of the pancreas with upstream pancreatic duct dilatation 5mm. Minimal interstitial and peri-pancreatic inflammation.

Pancreatic ductal adenomcarcinoma

Lowest survival rate of all cancers

5 year medial survival **5-7%**

Resectable stage at diagnosis **20%**

Unmodifiable risk factors

- Age (average 70yo)
- Men>Woman
- Family history (BRCA, Familial pancreatitis, Lynch syndrome, PJS)

Common **modifiable** risk factors

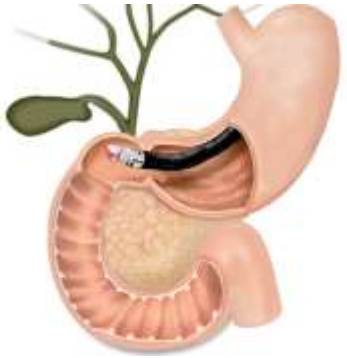
- Smoking (25% attributable to tobacco)
- Obesity
- Diabetes
- Chronic pancreatitis

Q: Which one of these is <u>false</u> regarding Pancreatic Ductal Adenocarcinoma PDAC?

1) PDAC has the lowest survival of cancers
2) Survival has improved for most cancers over the last 40 years, but not for PDAC
3) Most are diagnosed at a late stage, not curable with surgery
4) **Ultrasound is very sensitive for early PDAC**
5) Smoking, obesity and pancreatitis are risk factors

Pancreatic cancer

- **Early diagnosis is key,** survival at 5 years improved x10 fold if resectable
- **No effective screening programme**
  - **Pancreas imaging**
    - Transabdominal USS 75-89% sensitive for large cancers
    - **EUS best for small tumours as small as 2mm**
    - CT and **MR**I also very sensitive but risks of radiation, contrast and costly
  - **CA 19.9**
    - Use of **tumour markers for pancreatic cancer screening is NOT recommended**
    - Poor sensitivity (41-86%) and specificity (33%-100%)
    - 5-10% of population do not express Lewis antigens and so CA 19.9 is not present.
    - Population based study on CA 19.9 (n=71,000)
      - 1065 subjects had elevated CA 19.9 (1.5%) but only 4 (0.4%) had pancreatic cancer
  - **Clinical risk prediction models**
    - Not validated
    - Future – non-invasive blood biomarkers e.g. circulating tumour cells



Who should be screened?

Expert consensus but **low quality evidence**

Population screening is not recommended

No consensus on when to end surveillance

Guidelines

Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium

Who?	When to start?	How?	What
Peutz-Jeghers syndrome and **germline CDKN2A** mutation	Age 40 or 10 years younger than youngest affected relative	<u>Baseline:</u> MRI/MRCP + **EUS** Fasting glucose or HbA1c <u>Follow up:</u> Alternate MRI/MRCP + **EUS*** 6-12 monthly <u>If concerns:</u> CA 19-9, EUS FNA	Surgery if positive FNA and/or high suspicion of cancer on malignancy Goal: Detect and resect stage 1 cancer confined to the pancreas with negative margins.
BRCA, Lynch syndrome, PALB2, ATM mutation **with at least one first degree relative affected**	Age 45 or 10 years younger than youngest affected relative		
No germline mutation but at least **1x affected FDR who in turn has another FDR (Familial Pancreatic Cancer)**	Age 50 or 55* or 10 years younger than youngest affected relative		

Consider: comorbidities, life expectancy and compliance with surveillance

* No consensus reached

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AOTEAROA

Genetic service referral

- Germline mutation in blood relative
- Several close relatives on same side of family with pancreatic cancer
- Young age at diagnosis of affected individual
- Individual with clusters of associated cancers (e.g. BRCA, breast ovarian, Lynch, colorectal and Uterine)
- Jewish ancestry

Diagnostic Yield From Screening Asymptomatic Individuals at High Risk for Pancreatic Cancer: A Meta-analysis of Cohort Studies

What You Need to Know

Background

The CAPS Consortium recommends periodic abdominal imaging (with EUS or MRI) in high-risk individuals to screen for pancreatic cancer.

Findings

We estimate that screening 135 high-risk individuals can identify one case with adenocarcinoma or high-grade dysplasia. EUS and MRI identified similar number of high-risk pancreatic lesions. Diagnostic yield depends largely on patients' genetic background.

Implications for patient care

Pancreatic cancer surveillance in high-risk individuals is comparable with other preventive services. Questions regarding harms of screening and surgery, and cost-effectiveness need to be answered before scale-up implementation.

- **Risk of unnecessary surgery for benign lesions identified during screening**
  - Study of 1551 high risk subjects
  - 135 had surgery for pancreatic lesions
  - Only 30 were PDAC related
  - 105 were "resected unnecessary" (no PDAC or high risk pre-malignant lesions)

Paiella et al, Pancreatology

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Summary:

- **Elevated ferritin:** 90% from non-iron overload conditions, where **venesection is NOT indicated.**
- **Alcohol, MASLD** and **Chronic HBV** are common causes of asymptomatic deranged liver tests and can co-exist
- None of the non-invasive tests of liver fibrosis are perfect, but **imaging based modalities such as Fibroscan has better performance versus serological tests** (?combine)
- **GLP-1 agonists** used in diabetes and weight loss improves cardiovascular outcomes in high risk patients, but long term data on effects on liver fibrosis is required. Hence they are **not currently approved for MASLD.**
- **Few causes of severe transaminitis:** paracetamol, ischaemic injury, acute HBV. **Alcohol alone is NOT a cause of marked transaminitis**
- **Acute HBV** is confirmed with **HBsAg positive and Core IgM Ab positive**, usually managed conservatively. Acute HBV is a **notifiable disease.**
- **PSC** is associated with increased risk of not just cholangiocarcinoma, but also **colorectal, gall bladder and HCC.** Surveillance is required.
- **We need better tools for detecting early pancreatic cancer**. Currently a combination of Endoscopic ultrasound and MRI are the best tools we have (**EUS better for small lesions**)
- There are **potential risks with current screening strategies for Pancreatic cancer** should be discussed (repeat/invasive procedures, subsequent surgery for non-malignant lesions).

Questions? Henry@glms.co.nz