Liver disease: GEMS

1. Liver: GEMS

Please follow the link for a PDF version of the GEMS for download/printing:
Liver disease: GEMS

Liver GEMS: abnormal liver function tests

NICE 2016, NG50, NICE 2013, CG165, JAMA 2022;327:580, Gut 2017 doi:10.1136/gutjnl-2017-314924, Lancet 2021;397:2212, BMJ 2018;362:k2734, Lancet 2014;384:1953, BMJ 2009;339:b3305, JAMA 2021;326:165, Lancet 2020;396:1915

Red Whale GEMS
Guidelines & Evidence Made Simple

Do not use this GEMS if any red flags of liver disease, e.g. suspected cancer, ascites, jaundice, encephalopathy, sepsis, abnormal clotting, haematemesis, low albumin/platelets, rapid deterioration or ALT or ALP ≥5 x upper limit of normal: **if any ONE of these present, consider admission/urgent referral**

Raised ALT

Consider investigation even if mildly raised

The degree of abnormality of the blood test doesn't necessarily correlate with the degree of liver pathology

Any clues in the history as to the cause?

- Alcohol history
- Metabolic syndrome, BMI, type 2 diabetes
- Drug history: any hepatotoxic drugs, e.g. tetracyclines, amiodarone, tamoxifen, oestrogens, valproate, carbamazepine, macrolides, nitrofurantoin, statins, terbinafine, methyldopa and methotrexate
- Risk factors for viral hepatitis
- Personal history, comorbidities, family history, e.g. haemochromatosis or Wilson's disease

Raised ALP

ALP is a marker of cholestasis: check GGT

ALP also raised by bone pathology, vitamin D deficiency, metastatic cancer and pregnancy. Consider other causes, especially if GGT is normal. ALP isoenzymes may help. If non-liver cause suspected, see our article on alkaline phosphatase

Any clues in the history as to the cause?

- Symptoms often non-specific, e.g. fatigue, nausea, anorexia
- Associated with other autoimmune conditions
- Primary sclerosing cholangitis is associated with inflammatory bowel disease, cholangiocarcinoma and colorectal cancer

Initial tests

- Liver function: bilirubin, albumin, ALT, AST, ALP, GGT, FBC, ferritin and transferrin saturation
- Liver autoimmune screen: antimitochondrial antibody, anti-smooth muscle antibody, ANA, serum immunoglobulins
- Abdominal ultrasound scan

If raised ALT or AST, also do:

- Hepatitis serology: B+C
- HbA1c

AST:ALT ratio:

- AST:ALT ratio >1 indicates advanced fibrosis/cirrhosis
- In alcohol-related hepatitis, ratio is often >1.5
- Ratio rises in cirrhosis as reduced hepatocyte production of ALT and impaired clearance of AST

ALT can also be raised by non-hepatic causes, e.g. thyroid disease, coeliac disease and muscle diseases

Interpreting liver autoimmune screen results

Autoimmune hepatitis:

- AST, ALT and/or IgG raised
- ANA and smooth muscle antibody positive

Primary biliary cholangitis:

- ALP, GGT and IgM raised
- Antimitochondrial antibody or ANA usually positive

Primary sclerosing cholangitis:

- Raised ALP and GGT
- ANA or smooth muscle antibody may be positive

Based on the history and results, what is the most likely underlying cause?

- **Alcohol-related liver disease: see alcohol excess GEMS**
- **Suspected MASLD: see MASLD GEMS**
- **Hepatitis B or C: refer**
- **Autoimmune liver disease: refer**
- **If liver screen normal but ALT or ALP remains raised: refer**

Liver GEMS: raised bilirubin

Gut 2017 doi:10.1136/gutjnl-2017-314924, BMJ 2011;342:d2293, DTB 2019;57(2):27, BMJ 2018;362:k2734, Am Fam Physician 2004;69:299, Am Fam Physician 2017;95:164

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Raised bilirubin

Repeat LFTs with split bilirubin

Measure conjugated/unconjugated bilirubin

Bilirubin is a product of the breakdown of haem in haemoglobin. This creates unconjugated bilirubin, which is transported to the liver in the plasma for conjugation and excretion

Unconjugated bilirubin elevated

Unconjugated isolated hyperbilirubinaemia may be due to haemolysis or Gilbert's syndrome

Rule out haemolysis

Haemolysis can cause an isolated raised bilirubin

Consider Gilbert's syndrome

In Gilbert's syndrome, there is:

- Unconjugated hyperbilirubinaemia (due to a defect in a liver enzyme which conjugates bilirubin in the liver)
- Conjugated (direct) bilirubin is <20% of the total bilirubin
- Blood film, Hb and reticulocyte count should all be NORMAL. Clotting should be normal
- Urine dipstick: no bilirubin because unconjugated bilirubin is not water soluble

If bloods indicate Gilbert's syndrome:

- Ultrasound abdomen not required
- Make diagnosis, code and inform patient

Manage in primary care

See separate article: *Gilbert's syndrome*

Conjugated bilirubin elevated

Conjugated hyperbilirubinaemia will usually be intra- or post-hepatic in origin

Causes
(assess and manage as appropriate)

- Drugs, e.g. paracetamol (consider need for acute admission), corticosteroids, oestrogens, chlorpromazine
- Infection: viral hepatitis, CMV, cryptosporidium, pancreatitis
- Blockage of the biliary tract: gallstones, strictures, malignancy (see below)
- Hepatocellular disease:
  - Alcohol-related liver disease
  - MASH/MASLD
  - Autoimmune liver disease (primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis)
- Malignancy: liver cancer, cholangiocarcinoma, pancreatic cancer, lymphoma, biliary tract tumours
- Sarcoidosis
- Dubin-Johnson syndrome, Rotor syndrome
- Metabolic: ischaemic hepatitis, Wilson's disease, haemochromatosis

These are unlikely to cause an **isolated** raised bilirubin

If there is raised ALT, ALP or GGT, or concern about MASLD, alcohol-related liver disease or autoimmune liver disease, please see separate GEMS.

Liver GEMS: alcohol-related liver disease

NICE 2016, NG50, Gut 2017 doi:10.1136/gutjnl-2017-314924, BMJ 2018;362:k2734, Low risk drinking guidelines DOH 2016, AUDIT-C and AUDIT, Gov.uk, accessed July 2023

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Alcohol excess

Remember: normal LFTs do not rule out advanced liver fibrosis/cirrhosis

>50 units/w and male OR
>35 units/w and female AND sustained for several months
OR
known alcohol-related liver disease

Yes → **Offer fibroscan (transient elastography) to diagnose cirrhosis** (NICE 2016, NG50)

Fibroscan results

NICE does not comment on what to do with the results. The British Society of Gastroenterology says:

- Refer if fibroscan ≥16Kpa
- Consider referral if fibroscan 8–16KPa and continued harmful drinking
- If <8KPa, repeat pathway in 3–5y if risk factors remain

NICE says if alcohol-related liver disease, repeat fibroscan every 2y

No

NICE does not comment on what to do if people do not meet the above criteria but you are still concerned. The British Society of Gastroenterology suggests the following

AUDIT-C questionnaire (+ full AUDIT if indicated)

Full AUDIT >19 → **HIGHEST RISK**
ELF test or fibroscan
(refer as above if abnormal)
Consider referral to alcohol services

Full AUDIT 8–19 → **MEDIUM RISK**
Brief alcohol intervention
Check GGT (if >100U/L, consider investigating as per 'highest-risk' group above)
Review 3 months
Consider referral to alcohol service if ongoing drinking

AUDIT-C <5 or Full AUDIT 7 → **Lower risk**

Units of alcohol

The UK CMO issued guidance on low-risk drinking in 2016, concluding that there is no safe level of drinking. To keep health risks from drinking to a low level, it is safest not to regularly drink **>14 units/w** (1/4 of the UK population exceeds this).

How many units are in an alcoholic drink?

- 1 shot (25ml) of spirit = 1 unit
- Half a pint of 4% beer/lager = 1 unit
- Small glass of wine (175ml) = 2.3 units; large glass of wine (250ml) = 3.2 units

AUDIT-C and Full AUDIT

AUDIT (the alcohol use disorders identification test) was developed by the World Health Organisation
AUDIT-C is a shorter initial questionnaire which concentrates on alcohol consumption; if the score is ≥5, proceed to Full AUDIT

Liver GEMS: investigation of suspected MASLD

NICE 2016, NG49 and NG50, Gut 2017 doi:10.1136/gutjnl-2017-314924, BMJ 2018;362:k2734, Lancet 2014;383:1953, Lancet 2021;397:2212, NICE CKS NAFLD, http://gihep.com/calculators/hepatology/fibrosis-4-score/

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Suspected MASLD (metabolic dysfunction-associated steatotic liver disease) (previously NAFLD) in adults

When should we suspect MASLD? And when should we investigate?

MASLD is more likely in those with T2DM or metabolic syndrome, but many of these patients will be asymptomatic and have normal bloods. Should we go looking for it in this case? No! We should start looking for it in those with:

- **Abnormal ALT or AST** (because the cost-effectiveness of case-finding has not yet been demonstrated) (British Society of Gastroenterology)
- **Scan suggesting fatty liver** (investigate for MASLD and assess for other causes)

ALT raised:
See GEMS on abnormal liver function tests for initial investigations of a raised ALT
Come back to this page if you think MASLD is the most likely cause of the raised ALT after initial tests

Or

Ultrasound shows steatosis:
Any metabolic risk factors, e.g. obesity, type 2 diabetes, dyslipidaemia, hypertension?
Rule out other causes: investigate as for a raised ALT (abnormal LFTs GEMS) if not already done

If MASLD is still the most likely diagnosis and no other cause has been found, proceed to further tests below. Different guidelines suggest different pathways; you may also have local guidance.
The tests below aim to identify those at risk of advanced fibrosis

NICE guidance

LIFESTYLE! LIFESTYLE!

Offer testing for advanced liver fibrosis to people with MASLD. Consider using the ELF (enhanced liver fibrosis) score

- ELF <10.51 → **Advanced liver fibrosis unlikely** → Reassess every 3y Advise lifestyle modification
- ELF ≥10.51 → **Advanced liver fibrosis: refer** → Should have fibroscan; if no cirrhosis, repeat scan every 2y

Alternative: British Society of Gastroenterology guidance

LIFESTYLE! LIFESTYLE! LIFESTYLE!

Calculate FIB-4 *or* NAFLD fibrosis score
(both scores less accurate if patient <35y)

FIB-4		NAFLD fibrosis score
>2.67*	**High risk of advanced fibrosis: REFER**	>0.675
1.30–2.67 (if >65y: 2.0–2.67)	ELF >9.5 or Fibroscan >7.8kPa or invalid **Do ELF test or Fibroscan** ELF ≤9.5 or Fibroscan ≤7.8kPa	-1.455–0.675 (if >65y: 0.12–0.675)
<1.30 (if >65y: <2.0)	**Low risk of advanced fibrosis: MANAGE IN PRIMARY CARE**	<-1.455 (If >65y: <0.12)

- Advise about alcohol
- Calculate QRISK, consider statin
- Assess for and manage obesity, hypertension, diabetes
- Reassess every 2–5y depending on clinical risk

*The British Society of Gastroenterology uses a cut-off of >3.25 based on primary care data *(correspondence with author)*, but other sources, including NICE CKS, MDCalc and a BMJ review, quote the lower cut-off of >2.67. Seek advice if referral cut-offs have not been agreed locally.

Liver disease: GEMS

- Keywords: liver, alcohol, function, ALT, ALP, bilirubin, Gilbert's, NAFLD, non-alcoholic fatty liver, FIB-4, fibroscan, hepatitis, autoimmune liver disease, AUDIT, unit, ultrasound, hepatology, hepatic

Useful resources:

Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- NAFLD score
- FIB-4

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