Implications of liver disease to the oral health care provider

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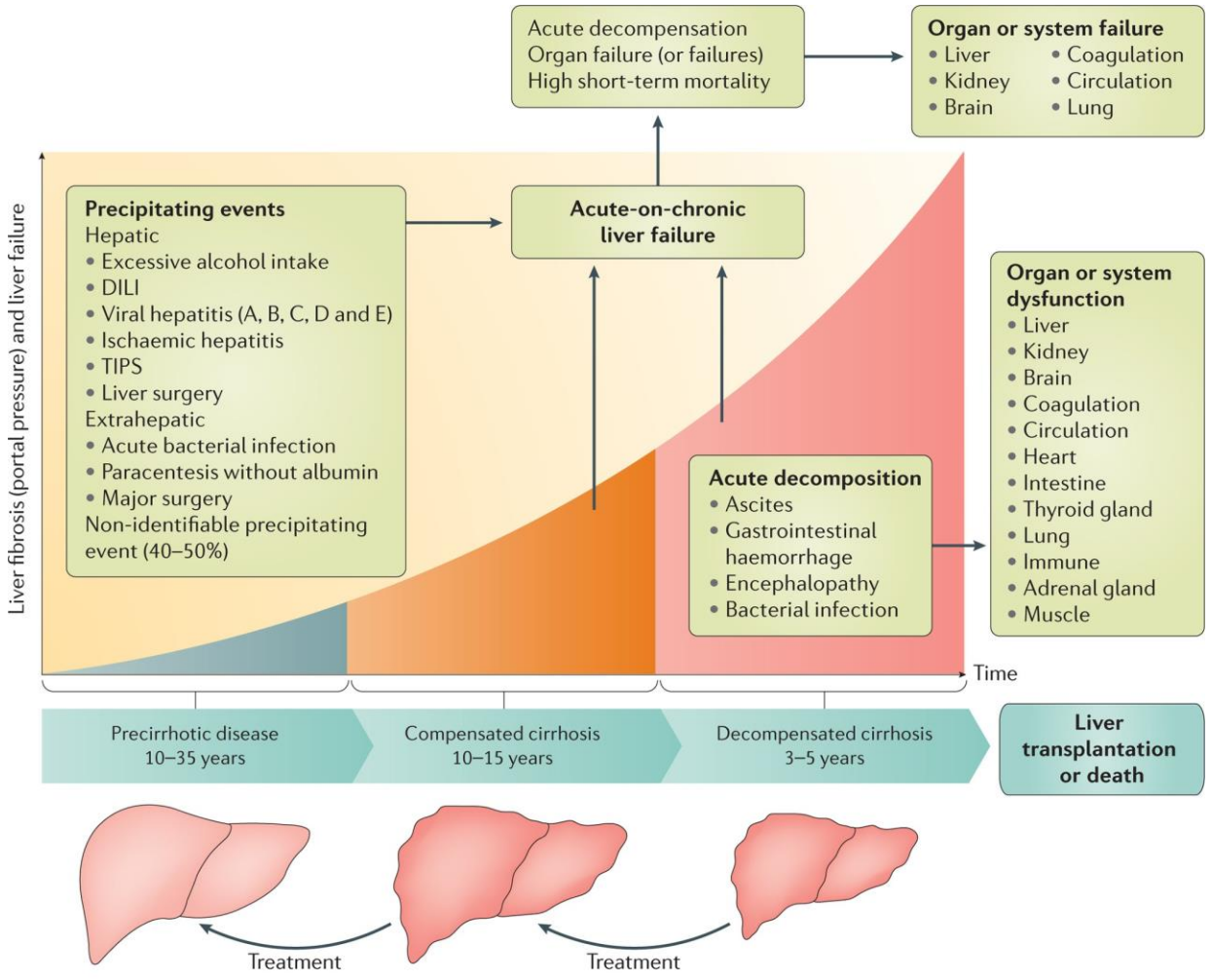
Functions of the liver

- Functions of liver:
  - Storage
    - Vitamins – Vit A, D, B12. Lesser amounts of others – vitamin K, B9
    - Minerals: Iron in the form of ferritin and hemosiderin and copper.
    - Glycogen
  - Synthesis
    - Circulating proteins (except for gamma globulins)
    - Coagulation factors (except for part of factor 8)
    - Components of the complement system
    - Formation of bile
  - Detoxification
    - Nitrogenous waste – ammonia converted to urea
  - Metabolism
    - Hormones
    - Drugs
    - RBCs
    - Glucose, Protein and Lipids
  - Surveillance:
    - Reticuloendothelial system

Natural history of liver disease



Arroyo et al 2016

Chronic hepatitis: defined as *any* hepatitis lasting for 6 months or longer and is classified according to aetiology.

Causes:

- Metabolic: Non-alcoholic fatty liver disease
- Alcohol induced
- Viral:
    - Hepatitis B +/- hepatitis D
    - Hepatitis C
    - Hepatitis E (immunosuppressed)
- Drugs:
    - Ketoconazole, idoniazid, nitrofurantoin
- Autoimmune diseases
- Hereditary: Wilsons Disease, Haemochromatosis
- Unusual causes: infections (syphilis, tuberculosis, various tropical infections), infiltrative diseases (amyloidosis and lymphoma), ingestion of toxins

Liver diseases

- **Alcoholic liver disease**
- Nonalcoholic fatty liver disease (NAFLD)
- Viral Hepatitis
- Autoimmune hepatitis
- Drug induced hepatitis/Drug induced liver injury (DILI)

Alcoholic liver disease (ALD)

3 histological stages of ALD:

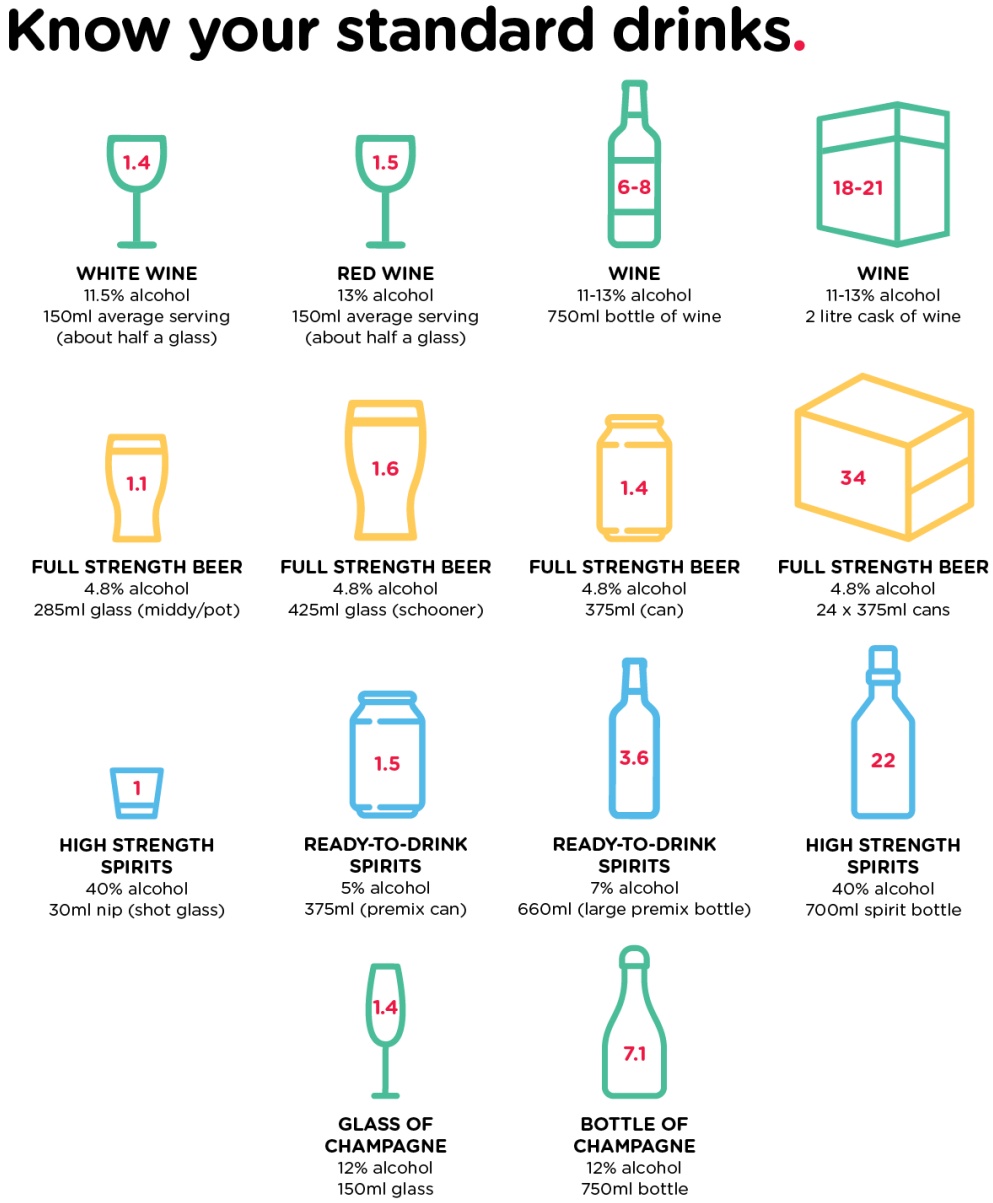
- Alcoholic fatty liver or steatosis – fat accumulation in the liver parenchyma
  - Often asymptomatic
  - If inflammation or necrosis is seen here – termed steatohepatitis (key here is that its asymptomatic)
- Alcoholic hepatitis – inflammation of the liver cells present
- Alcoholic cirrhosis – irreversible liver damage and leads to complications such as cirrhosis

Alcoholic liver disease (ALD)

1 standard drink = 10g of ethanol

NHMRC guidelines:

- No more than 4 std drinks per sitting
- No more than 10 std drinks per week
- < 18 should not drink
- Pregnant or breastfeeding should not drink



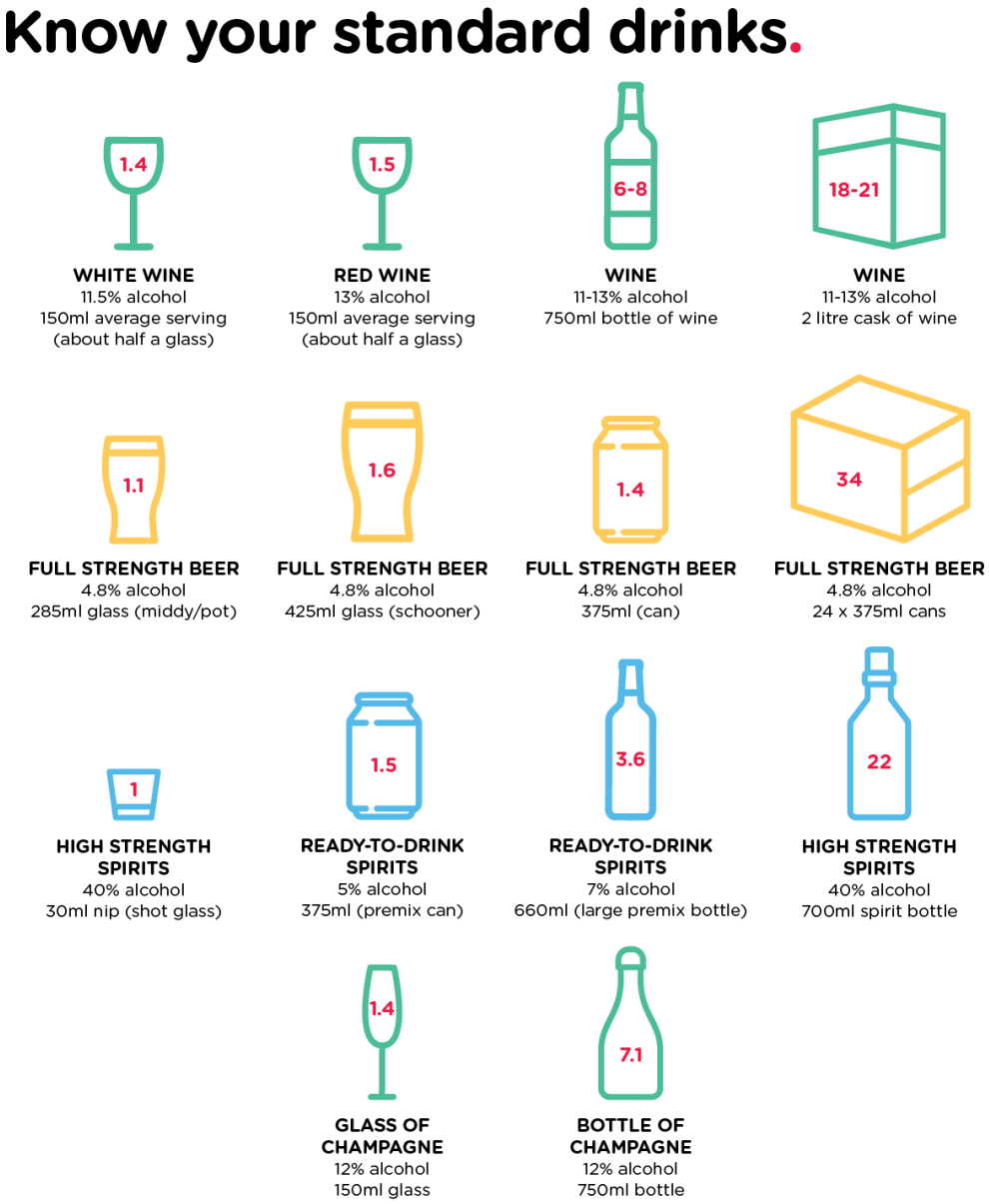
Alcohol (2020) NHMRC

Alcoholic liver disease (ALD)

1 standard drink = 10g of ethanol

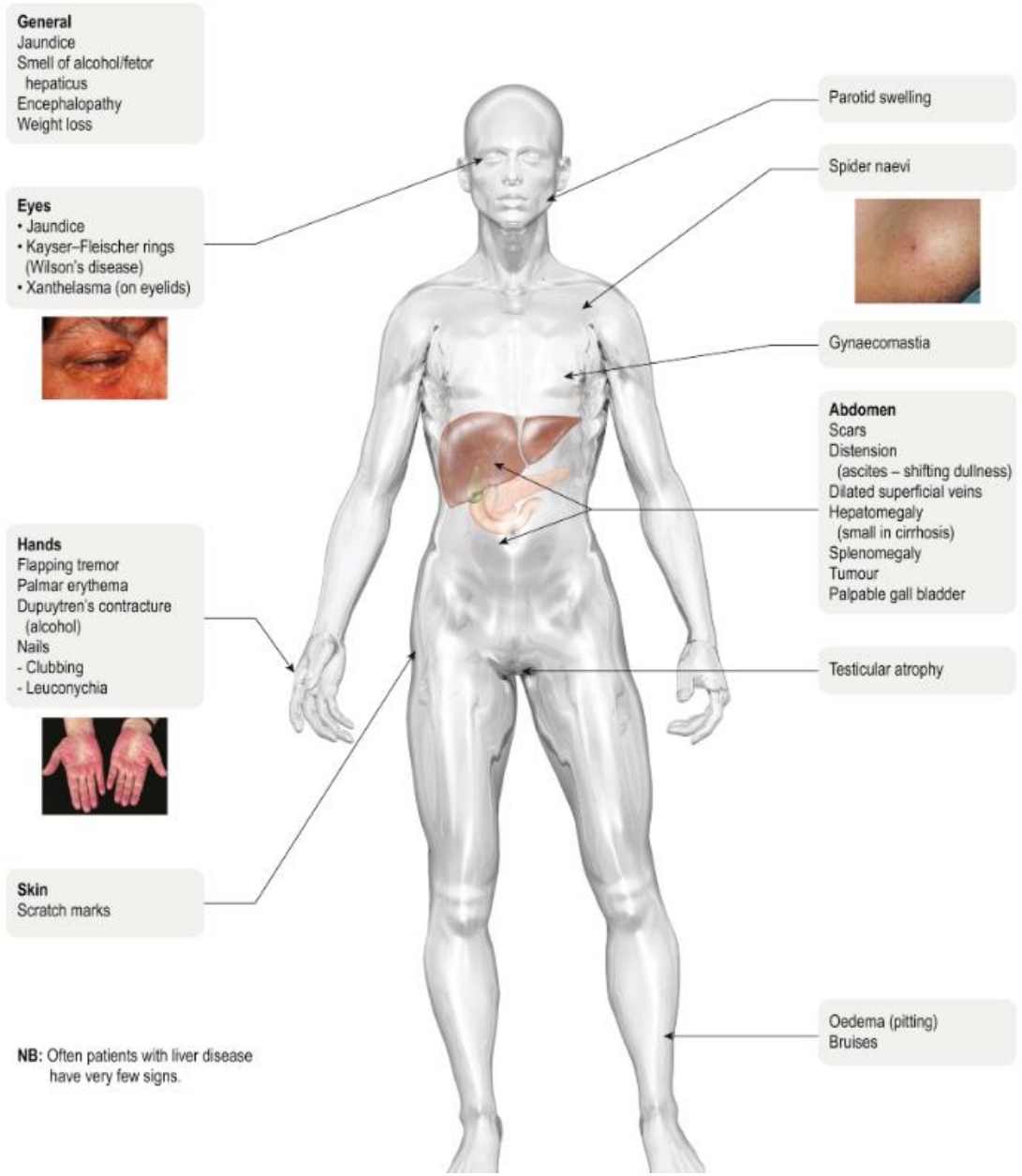
- Daily consumption of 30-50 grams per day over 5 years can cause alcoholic liver disease
- If your patient drinks >60 grams per day, there is a 90% chance they have steatosis
- If your patient drinks >40g per day, 30% chance they have cirrhosis

(Patel et al 2023)



Alcohol (2020) NHMRC

What might you see in the chair?



Randall and Feather 2020

Specific practice implications for patients with alcohol use disorder....

ACE inhibitors and sartans: • e.g. ramipril, perindopril, irbesartan, telmisartan	Alcoholic hepatitis Cirrhosis Especially patients with ascites or renal impairment	Increased risk of interactions with increasing severity of liver disease due to progressive alteration in renal haemodynamics. Commence at a low dose and titrate slowly. The risk of harm in Child-Pugh C cirrhosis may outweigh benefits.
Antibiotics: • metronidazole, nitrofurantoin, sulfamethoxazole	Alcohol use disorder	Interaction with alcohol may lead to disulfiram-like reactions (nausea, vomiting, flushing, headache, palpitations). Patients should avoid consuming alcohol during treatment and for 24 hours after finishing the course. Nitrofurantoin may cause drug-induced liver injury.
Opioids: • e.g. oxycodone, tramadol, morphine, tapentadol	Alcohol use disorder Cirrhosis Especially patients with history of hepatic encephalopathy	Alcohol consumption enhances the sedative effect of opioids including drowsiness, sedation and impaired motor skills. May precipitate hepatic encephalopathy, especially in patients not taking appropriate laxatives. All slow-release formulations (especially patches) should be avoided due to reversal difficulties if hepatic encephalopathy occurs. If an opioid is indicated, immediate-release tramadol or oxycodone appear safe if commenced at a low dose and titrated slowly. Use paracetamol as an opioid-sparing drug. Avoid tapentadol in Child-Pugh C cirrhosis.
Benzodiazepines: • e.g. diazepam, oxazepam, temazepam	Alcohol use disorder Cirrhosis Especially patients with history of hepatic encephalopathy	Alcohol consumption enhances the sedative effect of benzodiazepines including drowsiness, sedation and impaired motor skills. Even short-term use can precipitate hepatic encephalopathy. If a benzodiazepine is indicated, oxazepam or temazepam are preferred due to the comparatively simple hepatic metabolism.
Calcium channel blockers: • e.g. felodipine, lercanidipine, verapamil	Cirrhosis Especially patients with symptomatic hypotension or those co-prescribed non-selective beta blockers	If a calcium channel blocker is indicated, amlodipine, nifedipine and diltiazem appear safe if commenced at a low dose and titrated slowly. Felodipine, lercanidipine and verapamil should be avoided in Child-Pugh C cirrhosis.
Non-steroidal anti-inflammatory drugs: • e.g. ibuprofen, diclofenac, celecoxib	Alcohol use disorder Alcoholic hepatitis Cirrhosis Especially patients with ascites or renal impairment	Alcohol consumption increases the risk of peptic ulcer disease and gastrointestinal bleeding. Increased risk of renal impairment, acute kidney injury and hepatorenal syndrome in acute and chronic hepatic impairment. All non-steroidal anti-inflammatory drugs should be avoided. Paracetamol is a safe alternative (maximum 2–3 g daily in malnourished patients and those with cirrhosis).

Liver diseases

- Alcoholic liver disease
- **Nonalcoholic fatty liver disease (NAFLD)**
- Viral Hepatitis
- Autoimmune hepatitis
- Drug induced hepatitis/Drug induced liver injury (DILI)

Nonalcoholic fatty liver disease (NAFLD)

- Most common cause of chronic liver disease in may developed countries
- NAFLD is a spectrum of liver diseases
  - Nonalcoholic steatosis (fatty liver) → nonalcoholic steatohepatitis
    (no risk of progression) (10-30% may develop cirrhosis or HCC)
    Simple fatty change Fat and inflammation -→ fibrosis and cirrhosis

Cause: thought to be the liver component of metabolic syndrome (obesity, HTN, HLD, T2DM)

Oxidative stress injury (and other factors) leading to lipid peroxidation in the presence of fatty infiltration and inflammation.

Randall and Feather 2020

Nonalcoholic fatty liver disease (NAFLD)

- Management:
  - Lifestyle advice (weight loss, increased physical activity, attention to cardiovascular risk factors).
  - Medical management:
    - Orlistat – enteric lipase inhibitor causing malsobroption of dietary fat
    - Pioglitazone – (antidiabetic), used for biopsy proven NASH when lifestyle inteventoin has failed.
    - Vitamin E
  - Surgical management:
    - Bariatric surgery
    - Liver translation in NASH cirrhosis
  - Monitor for HCC – 2.6% cumulative incidence for patients with NASH,

  Implications: Consider this in patients with metabolic syndrome

Randall and Feather 2020

Liver diseases

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- **Viral Hepatitis**
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Viral Hepatitis

	A	B	C	D	E
Virus	RNA	DNA	RNA	RNA	RNA
	27 nm	42 nm	Approx. 50 nm	36 nm (with HBsAg coat)	27–35 nm
	Picornaviridae	*Hepadnaviridae*	*Flaviviridae*	*Deltaviridae*	*Hepeviridae*
Spread					
Faeco-oral	Yes	No	No	No	Yes
Blood/blood products	Rare	Yes	Yes	Yes	No
Vertical	No	Yes	Rare	Occasional	No
Saliva	Yes	Yes	Yes	? No	?
Sexual	Rare	Yes	Yes (rare)	Rare	No
Incubation	Short (2–3 weeks)	Long (1–5 months)	Long	Intermediate	Short
Age	Young	Any	Any	Any	Any
Carrier state	No	Yes	Yes	?	No
Chronic liver disease	No	Yes	Yes	Yes	No [a]
Liver cancer	No	Yes	Yes	Yes	No
Mortality (acute)	<0.5%	<1%	<1%	<1%	1–2% (pregnant women 10–20%)
Immunization					
Passive	Normal immunoglobulin serum i.m. (0.04–0.06 mL/kg)	Hepatitis B immunoglobulin (HBIg)	No	No	No
Active	Vaccine	Vaccine	No	HBV vaccine to prevent co-infection	Vaccine

Randall and Feather 2020

Implications for the dentist>

Needlestick injury - Risk of transmission for

- Hep B – 6-30%
- Hep C is 1-3%

Chance of resolution:

- Hep B – 80% chance of resolution of acute hepatitis, with <20% progressing to a chronic state.
- Hep C – 20% chance of resolution of acute hepatitis, with 80% chance of progressing to a chronic state.

Hepatitis C – testing

- HCV is an RNA virus
- Hence, PCR for RNA is the only method to distinguish chronic vs cleared infection.
- Any patient with +ive HCV RNA should be treated.

Hepatitis B – testing

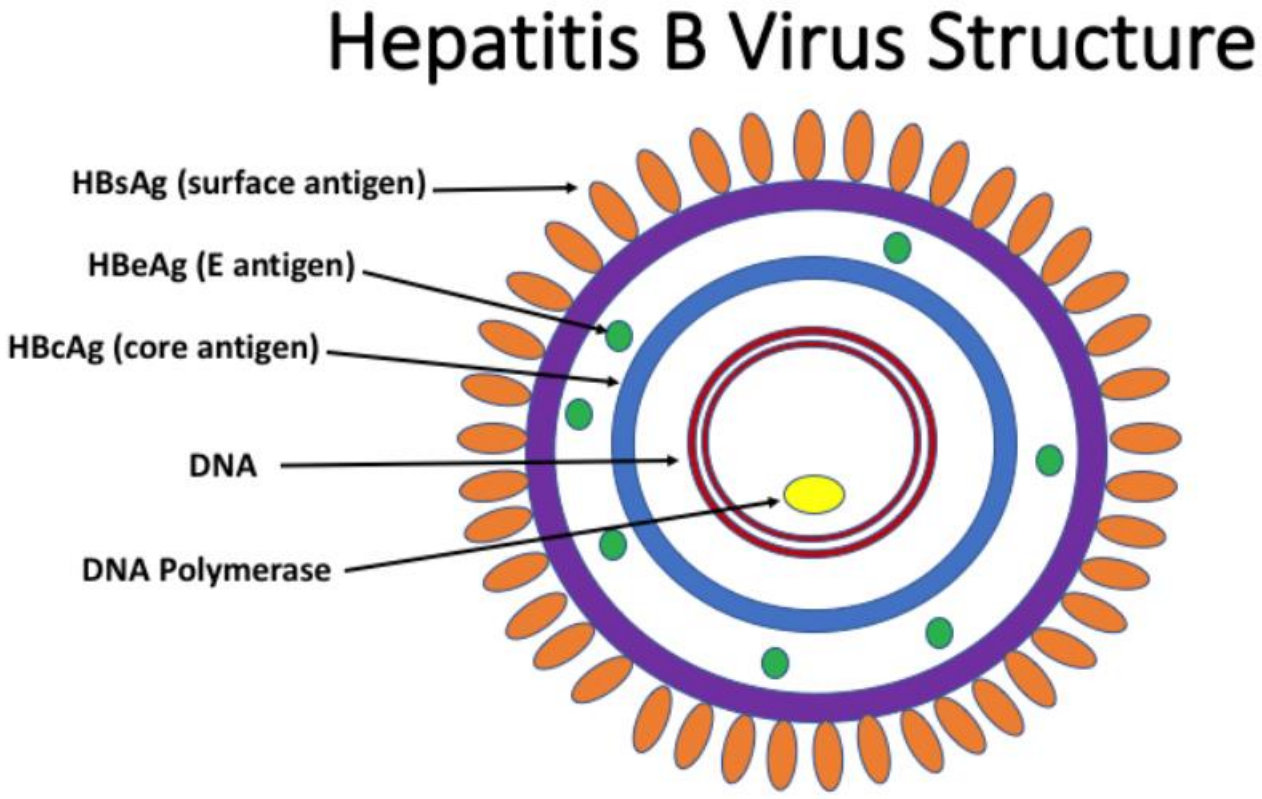
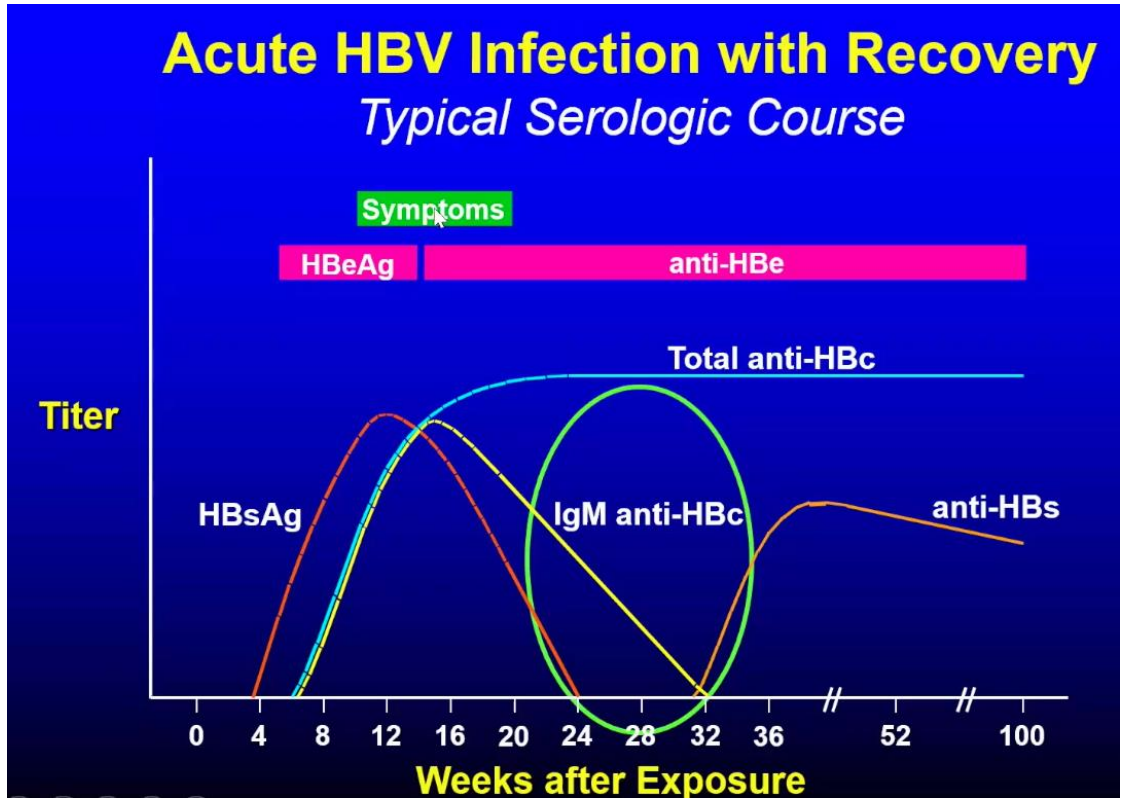
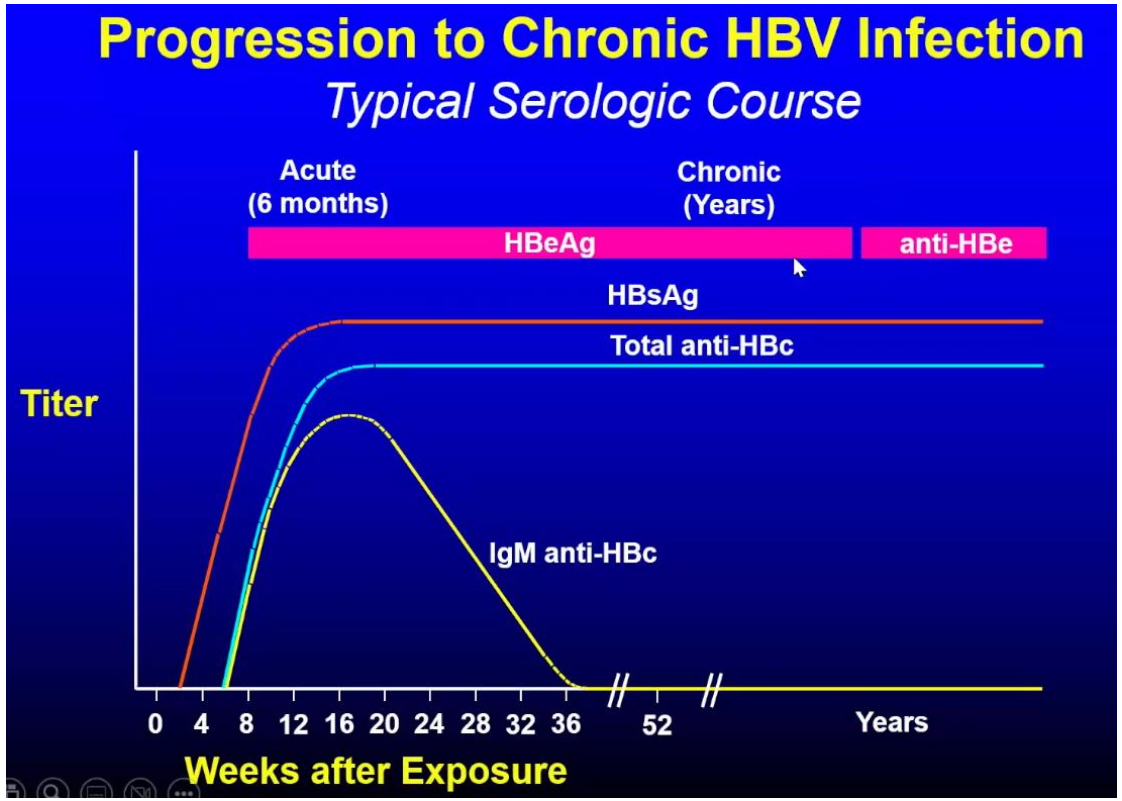
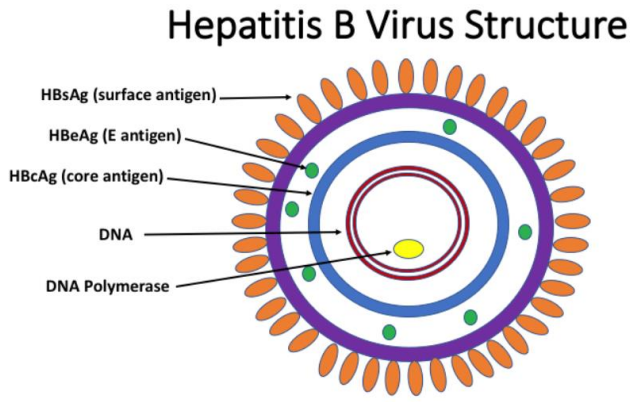


Figure 1. Hepatitis B Virus Structure Simplified to Highlight Serologic Targets.







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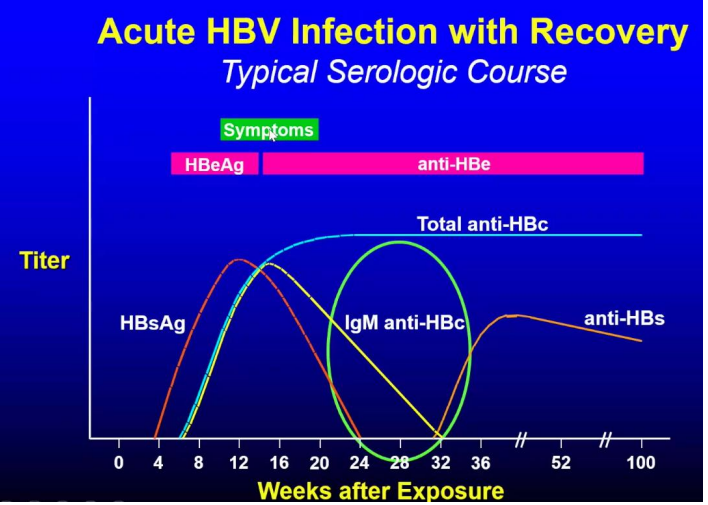
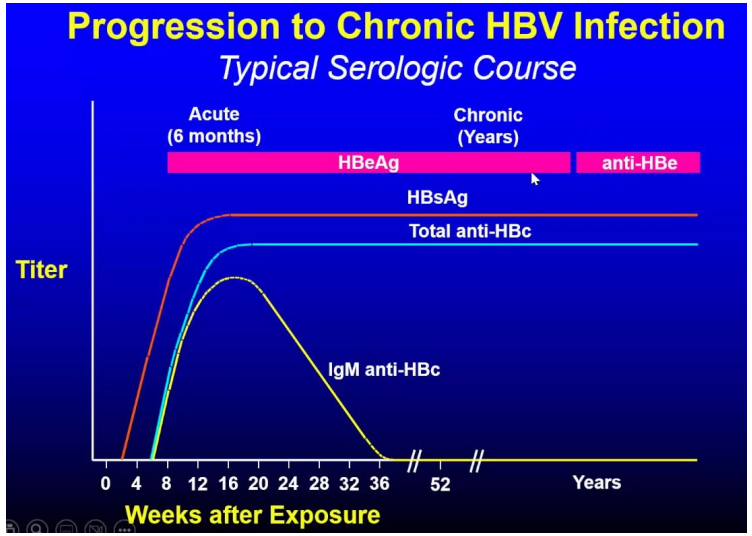
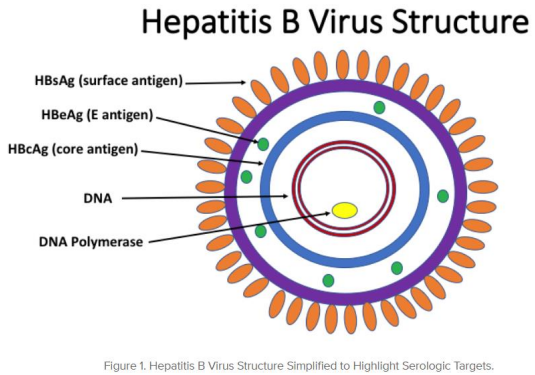
Initial screen and testing for Hep B:

- HBsAg – any active infection or carrier state (which can be re-activated)
- Anti-HBs – immunity
- Anti-HBc – any hx of infection
- IgM Anti-HBc – recency of infection and/or detection in surface antigen seronegative window







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If HBsAg +ve, further tests:

- **HBV DNA (PCR)**
- HBeAg
- Anti-Hbe

HBV DNA is the single test that can distinguish between active replicative state – however it is very expensive!

Liver diseases

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- Viral Hepatitis
- **Autoimmune hepatitis**
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Autoimmune hepatitis

Description: immune mediated inflammatory disease of the liver characterized by circulating Abs, increased concentration of IgG and distinctive histological features.

Epidemiology:

- Gender: 4:1 F predominance
- Age: >18
- Race: higher in Europeans and US (Caucasian background, but can be anyrone)
- Incidence: 1 per 100 000
- Prevalence: 22.8 per 100 00

Etiology: multifactorial – genetic factors, altered immune tolerance, environment (smoking, toxins), individual risk factors, viral infection, DILI

Pathogenesis: antibodies against proteins expressed in liver cells

Diagnosis: bloods (exclude other hepatitis), ultrasound and liver biopsy

Management:

- Prednisolone – bridging therapy – 0.5mg/kg or upto 1.0 mg/kg for acute cases
- Azapthioprine first line
- Mycophenolate mofetil second line

Muratori et al 2023

Liver diseases

- Alcoholic liver disease
- Nonalcoholic fatty liver disease (NAFLD)
- Viral Hepatitis
- Autoimmune hepatitis
- **Drug induced hepatitis/Drug induced liver injury (DILI)**

It must be considered in the cirrhotic patient; hepatic reserve is limited in the event of DILI.

Hence, prescribing any drugs with potential hepatotoxicity should be done with caution, as any drug related hepatic injury may precipitate decompensation.

What is Drug Induced liver injury (DILI)?

- Definition: acute or chronic liver response to a natural or manufactured compound (Francis 2022)
- Can be categorised by:
  - LFTs
  - Histology
  - Acute vs chronic
  - Pathogenesis:
    - **Direct/Intrinsic – predictable and dose dependent**
    - **Indirect/idiosyncratic – unpredictable and non dose dependent**

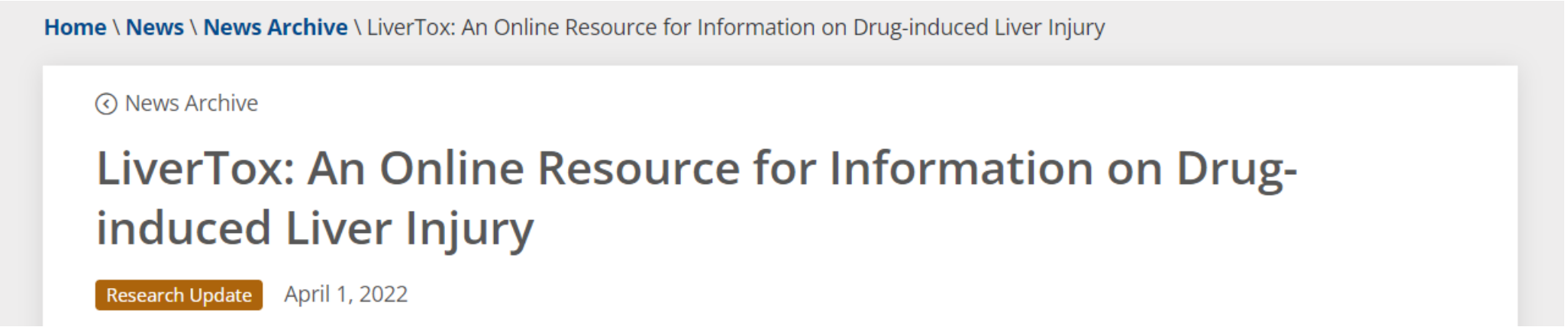
What is Drug Induced liver injury (DILI)?

- Definition: acute or chronic liver response to a natural or manufactured compound (Francis 2022)

- Signs and symptoms: jaundice, weakness, abdominal pain, dark stools or urine, nausea, pruritis
- Treatment
  - withdrawal of offending agent
  - N-acetyl cysteine (NAC) for treatment of paracetamol toxicity (regeneration of glutathione)
  - Steroid for DILI resembling AIH
  - Inpatient assessment if ALF suspected

So which drugs are hepatotoxic?.....

Drug induced liver injury



4 categories of likelihood causing liver injury:

- Category A > 50 published reports
- Category B >12 but <50
- Category C > 4 but <12
- Category D 1-3 case reports
- Category E – no implication

Bjornsson 2016

Drug induced liver injury

Category A > 50 published reports

Drug	Drug Class/Indication
1. Allopurinol	Gout prophylaxis
2. Amiodarone	Arrhythmia
3. Amoxicillin-clavulanate	Antibiotic
4. Anabolic steroids	Body building
5. Atorvastatin	Lipid lowering agent
6. Azathioprine/6-Mercaptopurine	Immunosuppressive agent
7. Busulfan	Malignancy
8. Carbamazepine	Antiepileptic
9. Chlorpromazine	Psychosis
10. Contraceptives	Birth control
11. Dantrolene	Muscle relaxant
12. Diclofenac	NSAID
13. Didanosine	Antimicrobial
14. Disulfiram	Substance abuse agent
15. Efavirenz	Antimicrobial
16. Erythromycin	Antimicrobial
17. Floxuridine	Antineoplastic
18. Flucloxacillin	Antimicrobial
19. Flutamide	Antineoplastic
20. Gold salts	Immunosuppressive agent
21. Halothane	Anaesthetic
22. Hydralazine	Antihypertensive
23. Ibuprofen	NSAID
24. Infliximab	Immunosuppressive agent
25. Interferon alpha/Peginterferon	Antimicrobial
26. Interferon beta	Multiple Sclerosis
27. Isoniazid	Antituberculosis
28. Ketoconazole	Antifungal
29. Methotrexate	Immunosuppressive agei
30. Methyldopa	Antihypertensive
31. Minocycline	Antibiotic
32. Nevirapine	Antimicrobial
33. Nimesulide	NSAID
34. Nitrofurantoin	Antibiotic
35. Phenytoin	Antiepileptic
36. Propylthiouracil	Antithyroid
37. Quinidine	Arrhythmia
38. Pyrazinamide	Antituberculosis
39. Rifampin	Antituberculosis
40. Simvastatin	Lipid lowering agent
41. Sulfamethoxazole/Trimethoprim	Antibiotic
42. Sulfazalazine	Antibiotic
43. Sulfonamides	Antibiotic
44. Sulindac	NSAID
45. Telithromycin	Antibiotic
46. Thioguanine	Antineoplastic
47. Ticlopidine	Platelet inhibitor
48. Valproate	Antiepilepitic

Of note:

- Amoxicillin-clavulanate
- Azathioprine
- Carbamazepine
- Diclofenac
- Erythromycin
- Ibuprofen
- Methotrexate
- Minocycline
- Sulfamethoxazole/Trimethoprim

Bjornsson 2016, Chalasani et al 2015

Jaundice

Bilirubin

Physiology of bilirubin:

- Conversion of heme to bilirubin is a 2-step process:
  - 1st step: heme (from erythrocyte) → biliverdin
    - *Mainly spleen*
  - 2nd step: biliverdin → unconjugated bilirubin (UCB)
    - *Mainly spleen*
- UCB is transported in blood by albumin
- Entry into hepatocytes
- In hepatocytes:
  - Unconjugated bilirubin gets conjugated with glucuronic acid
  - Conjugated biliurubin then gests secreted into bile

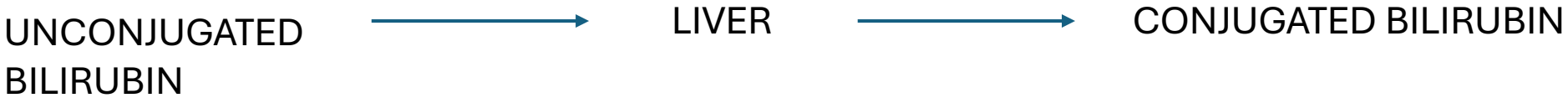
Singh et al 2023

Bilirubin

Physiology of bilirubin:

- Conjugated bilirubin is water soluble and is excreted out of the bile duct into the middle duodenum.
- Conjugated bilirubin is broken down by gut flora to *urobilinogen*. This can be:
- Excreted in stool as *stercobilinogen*
- Reabsorbed via the enterohepatic circulation (portal vein), after which:
    - Liver excretes it back into bile duct with bile salts OR
    - It enters the circulation and is excreted through the kidneys

Singh et al 2023


UNCONJUGATED BILIRUBIN
LIVER
CONJUGATED BILIRUBIN

Excess unconjugated bilirubin

- Increase in bilirubin production:
  - Increased breakdown of heme
    - Due to accelerated or prolonged hemolysis
    - Large hematoma
- Impaired bilirubin uptake
  - Decrease bilirubin delivery to the liver (reduced hepatic flow) e.g. congestive heart failure and portosystemic shunts.
  - Inefficient uptake of bilirubin by hepatocytes - .e.g. drugs or contrast administration
- Impaired bilirubin conjugation
  - Within hepatocytes – from hereditary defect s(Gilbert syndrome and Crigler-Najjar syndrome).

Singh et al 2023

Excess conjugated bilirubin

- Extrahepatic cholestasis:
  - Due to biliary duct obstruction (due to primary sclerosing cholangitis, AIDS cholangiopathy etc)
  - Pressure from the obstructed bile duct allows conjugated bilirubin to overcome resistance of tight junctions in the hepatocytes and reflux into the plasma
- Intrahepatic cholestasis:
  - Aberrations in conjugated bilirubin transport, bile canalicular membrane fluidity and hepatocyte cytoskeletal function – these deviations are caused by a myriad of processes, usually hereditary.
    - Dubin-Johnson syndrome – defect in the MRP2 protein.
- Hepatocellular injury:
  - Release of intracellular proteins into the plasma.
  - Acute hepatitis
  - Chronic hepatitis – cirrhotic

Tripathi et al 2023)

Summary and key points for patients with liver disease

- Be mindful of DILI in patients with cirrhosis (antibiotics, NSAIDs paracetamol dosage) – they have limited hepatic reserve
- Special drug consideration for patients with alcohol use disorder
- Query bleeding in cirrhotic patient – clotting ability and risk of variceal bleeding
- Antibiotic prophylaxis may be considered for patients with ascites to prevent bacterial peritonitis – discuss with medical GP

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