Alcoholism and Hepatitis

History of Presenting Illness
- Anorexia
- Nausea and Vomiting
- Weight loss
- Fever
- Generalized Abdominal Pain
- Malaise
- Diarrhoea
- Ankle swelling
- Abdominal distension
- Yellow eyes
- Itching
- Bruising
- Black tarry stools

ASK ABOUT:
- Tattoos
- Blood transfusions
- Needlestick injury
- Injecting drug use
- Sexual practices
- Recent contacts
- Travel
- Medications (see below)

Differential Diagnoses
Nonalcoholic steatohepatitis (NASH)
Drug-induced liver disease
(valproic acid, tetracycline, antiviral agents such as zidovudine)
Viral hepatitis

Examination
- Tender Hepatomegaly (80-90% of cases)
- Jaundice
- Ascites
- Splenomegaly
- Spider naevi

Epidemiology
Alcoholic Hepatitis seen in 33% of chronic alcoholics

JAUNDICE
- The eyes are first to go.

ASK ABOUT THE COLOUR OF URINE AND STOOL:

JAUNDICE WITHOUT DARK URINE OR PALE STOOL means HAEMOLYSIS (unconjugated bilirubin released into circulation, thus not water soluble and cannot be excreted by kidneys)

JAUNDICE WITH DARK URINE AND PALE STOOLS means OBSTRUCTIVE JAUNDICE

| VIRAL HEPATITIS |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| virus group     | virus type      | mode of infection | incubation period | frequency of infection in UK/USA | severity of hepatitis | persistent carriage of virus | other comments |
| hepatitis A (HAV) | enterovirus 72 | ssRNA | fecal-oral | 2-4 weeks | ++ | ± | common in UK and USA |
| hepatitis B (HBV) | hepadnavirus | dsDNA | from blood or sexual | 1-3 months | ± | ++ | carriage associated with liver cancer |
| hepatitis C (HCV) | togavirus | ssRNA | from blood (also sexual) | 2 months | ± | + | uncommon in UK, USA |
| hepatitis D (HDV) | very small | ssRNA | from blood | 2-12 weeks | ± | + | needs concurrent hepatitis B virus infection |
| hepatitis E* (HEV) | calicivirus | ssRNA | fecal-oral | 6-8 weeks | ± | - | common in Far East |
| yellow fever | togavirus | ssRNA | mosquito | 3-6 days | - | + | no person-to-person spread |
Tests and Investigations

**FBC + blood microscopy:**
- looking for macrocytic anaemia of alcoholism

**alpha-fetoprotein:** very specific marker of hepatocellular carcinoma

**LIVER FUNCTION TESTS:**
- **ALT** = the necrosis enzyme
- **AST** = alcoholic hepatitis enzyme
- **SAP/ALP** = cholestasis enzymes (with GGT)
- **GGT** = induceable alcoholism enzyme

**Billirubin:**
- **Conjugated** = hemolysis or liver dysfunction
- **Unconjugated** = biliary obstruction or liver failure

**SERUM ALBUMIN** → will be low; trying to explain ascites

**PROTHROMBIN Time** → low due to reduced rate of clotting factor synthesis

**Thiamine** = low mainly due to malnutrition

**RBC Folate** (alcohol inhibits the gut transporter of folate)

**HEPATITIS VIRUS SEROLOGY:**
- **HBsAg** - earliest ACUTE marker, may persist chronically
- **HBeAg** - ACTIVE INFECTION, virus is replicating (25% don’t have this)
- **HBV DNA**

**Ascites Fluid Aspiration:** Looking for malignant cells

**Abdominal ultrasound**
- looking for cysts, focal lesions, biliary tree stones etc.

**Abdominal CT scan**
- looking for masses, enlarged lymph nodes, vascular malformations

**Liver Biopsy:** only way to objectively diagnose alcoholic liver disease

**MANAGEMENT:**

**Limit progression to cirrhosis:**

**Stop drinking.**

**Antiviral drugs:**
- nucleoside analogue lamivudine for hepatitis B
- interferon-alpha plus ribavirin for hepatitis C

**Immune suppression may work** for autoimmune disease

**Control lipid vitamin deficiencies: A, D, E, K**

**For ascites:**
- salt restriction,
- aldosterone antagonist (first choice)
- loop diuretic (second choice) diuretics

**control variceal bleeding**
- by means of endoscopic surgery (banding or adrenaline injection)
- by reducing portal pressure pharmacologically
  (eg by somatostatin analogues (octreotide) and b-adrenergic blocking agents)

**Screen for hepatocellular carcinoma**

**LOOK FOR LIVER TRANSPLANT DONOR**
- Survival rates are about 80% in adults and 90% in children
An Occupational Hazard

Problem summary
Seok Kim is a 52-year-old importer. He migrated to Australia with his family from Korea in 1995. Mr Kim has noticed dark urine and yellow eyes for the past three weeks. For about three months he has noticed a poor appetite and decreasing energy. He is known to have a history heavy alcohol intake and hypertension. He has a past history of hepatitis. There is no history of blood transfusion, tattoos or injecting drug use but his mother had liver disease.

Diagnosis & defn
PROLONGED ALCOHOL INTAKE and infection with HEPATITIS B VIRUS resulted in damage to the liver parenchyma, inflammation, fatty infiltration and cirrhosis.

Hepatitis B Virus

DEFINITION
A. Hepadna virus
B. Small double-stranded DNA genome, viral DNA polymerase (DNAP)
C. envelope (SURFACE), protein coat (CORE)

Incubation: 1-5 months (~ 2m)
Transmission: blood**, vertical**, sexual*, saliva
Replication: @ HEPATOCYTE, salivary glands, pancreas, testis

(1) ATTACHMENT: unknown receptor
(2) UNCOATING: core released, DNAP makes DNA circular - CCC DNA (covalently closed circular DNA)
(3) NUCLEUS ENTRY: CCC DNA very stable \(\rightarrow\) PERSISTS for life of cell, may also integrate in host DNA
(4) VIRAL PROTEIN SYNTHESIS:
  - ENVELOPE encodes surface antigen HBsAg
  - CAPSID encodes core antigen HBeAg (not found in blood)
  - encodes circulating peptide HBeAg

Host response: THIS CAUSES THE MOST DAMAGE!!!!
A. Innate immune response INDUCES APOPTOSIS to clear infdx cells.
T-CELL MEDIATED RESPONSE: HBeAg induces cytotoxic Tcell response \(\rightarrow\) FIBROSIS (worse with alcohol)
**if impaired T-cell immunity \(\rightarrow\) less damage to liver but virus never clears & higher cancer risk (high level replication)
B. three antibodies: anti-HBs, anti-HBc, anti-HBe.

Durable & highly infectious
Stable to temperature, dryness, anti-septics
Inactivated by: glutaraldehyde, formulin, urea

INITIAL ACUTE PHASE

HPI ~~ MOSTLY ASYMPTOMATIC
A. TYPICAL ACUTE INFxn
  a. FATIGUE, HEADACHE
  b. FEVER (low grade)
B. GIT
  a. NAUSEA
  b. ANOREXIA
  c. DISTASTE FOR CIS
  d. DIARRHOEA
C. ABDO PAIN (right upper quad)
  \(\rightarrow\) peritoneum stretches over big liver

PHYS EXAM
A. TENDER LIVER
B. CERVICAL LYMPH NODES
C. SPLENOMEG (esp. children)
D. “SERUM SICKNESS” \(\Delta \) (10%)
  circulating Ag-Ab complexes deposited
  a. ARTHRITIS
  b. RASH
  c. FEVER

LATER ACUTE

3-6 WEEKS RESOLUTION
A. GIT RESolves
A. JAUNDICE \(\rightarrow\) SCLERAL
  (advancing) \(\rightarrow\) DARK URINE
  \(\rightarrow\) PALE STOOLS
  \(\rightarrow\) PALPABLE LIVER

CHILDHOOD INFxn \(\rightarrow\) ASYMPTOMATIC \(\rightarrow\) flares in adulthood \(\rightarrow\) SEVERE CHRONIC LIVER DISEASE (high prevalence pattern)
ADULT / OLDER CHILD INFxn \(\rightarrow\) ACUTE HEPATITIS \(\rightarrow\) RECOVERY (low prevalence pattern)
**EPIDEMIOLOGY**

**PREVALENCE:**
- Persistent HBV ~ 300 million worldwide
- ENDEMIC sub-Saharan Africa, China, SE Asia (different viral genotypes)

- Vertical transmission (at birth)
- Chronic liver disease 5-20%
- Acute HB rare, 10-20% adults are carriers
- Most non-carriers are immune

- Low prev: acute hepatitis
- Sexual transmission, IV drugs
- Australia: 1-2% carriers

**HISTORY**

**RISK FACTORS**
- A. IV drug user
- B. HOMOSEXUAL (male)
- C. CLOSE CONTACT with infxd individuals
- 1. mother
- 2. regular sexual partners
- D. HAEMODIALYSIS
- E. HEALTHCARE worker
- F. TRAVEL
- 1. Asia
- 2. Pacific Islands
- 3. Eskimo
- 4. India
- 5. Sub-Saharan Africa
- 6. Haiti
- G. TATTOO'S / ACUPUNCTURE

**DIAGNOSIS**

**A. SEROLOGY - **GOLD STANDARD!!**

**Antigens:**
- HBsAg: earliest ACUTE marker, may persist chronically
- HBeAg: ACTIVE INFECTION, virus is replicating (25% don’t have this)

**HBV DNA**

**DNA polymerase**

**Antibodies:**
- HBsAb: previous Hep B INFECTION + IMMUNITY or VACCINATION + IMMUNITY
- HBeAb: CONVALESCENCE: core window as surface Ag cleared by surface Ab
- HBeAb: earliest Ab, LOW INFECTIVITY: predicts Hep B resolution

**LIVER FUNCTION TESTS**

* ALBUMIN normal
* BILIRUBIN-URIA early — persists to convalescence

**FBC**

* WCC high

**DIFFERENTIAL DIAGNOSES**

A. ALCOHOLIC HEPATITIS
B. MEDICATIONS
C. ISCHAEMIA
D. BILIARY TRACT

**EPIDEMIOLOGY**

**PREVALENCE:**
- Persistent HBV ~ 300 million worldwide
- ENDEMIC sub-Saharan Africa, China, SE Asia (different viral genotypes)
  - Vertical transmission (at birth)
  - Chronic liver disease 5-20%
- Acute HB rare, 10-20% adults are carriers
- Most non-carriers are immune
- Low prev: acute hepatitis
- Sexual transmission, IV drugs
- Australia: 1-2% carriers
ACUTE HEPATITIS

**IMMUNE RESPONSE CAUSES CELL DAMAGE!!** (immuno-suppressed & neonates → asymptomatic infection)

a. immune response against viral Ag’s damages virus-infected hepatocytes
   A. cytotoxic T-cells react to virus Ag’s or virus-modified cell membrane Ag’s → CELL LYSIS
   B. antibody-dependent cytotoxicity → circulating immune complexes containing viral Ag’s and Ab’s can cause POLYARThritis, VASCULITIS, GLOMERULO-Nephritis

b. strength of immune response determines clinical expression
   PROMPT response → cell injury & virus clearance → ACUTE HEPATITIS
   ACCELERATED & EXCESSIVE response → fulminant liver necrosis → total clearance → FULMINANT HEPATITIS
   WEAK response → persistence of antigenic hepatocytes → continued low-level destruxn → CHRONIC HEPATITIS
   FAILED response → virus perpetuates, no liver damage → CARRIER STATE

<table>
<thead>
<tr>
<th>INCUBATION</th>
<th>ACUTE – preicteric</th>
<th>ACUTE – icteric</th>
<th>CONVALESCENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA Viral replication</td>
<td>Immune response causing liver cell destruction</td>
<td>Bile canaliculi obstruction &amp; damage → cholestasis</td>
<td>Viral replication stops, LIVER architecture restores, inflammatory exudate clears</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>usually mild illness</td>
<td>Non-specific symptoms intensify (or cessation = “anicteric”)</td>
<td>Clinical &amp; chemical recovery in 12-16wks</td>
</tr>
<tr>
<td></td>
<td>→ malaise, nausea, anorexia</td>
<td>→ high fever, chills, headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ “serum sickness”</td>
<td>→ abdo pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PHYS EXAM</td>
<td>→ big, tender LIVER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>→ tender LIVER</td>
<td>→ jaundice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ pale stools (cholestasis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ pruritis (bile salt irritation)</td>
<td></td>
</tr>
<tr>
<td>(late stage) HBsAg</td>
<td>↑ ALT, AST</td>
<td>↑ Bilirubin (conjugated)</td>
<td>(1) HBcAb (2) HBeAb</td>
</tr>
<tr>
<td></td>
<td>early acute markers HBsAg, HBeAg</td>
<td>→ serum</td>
<td>(3) HBsAb (gives immunity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ urine DARK</td>
<td>antigens no longer detectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>as acute phase ends, HBcAb rises and e Ag falls</td>
<td></td>
</tr>
</tbody>
</table>

**NORMAL LIVER**

**ACUTE HEP B – LIVER (micro)**

**HISTOLOGY – ACUTE HEPATITIS**

GROSS
A. enlarged
B. pigmented: red, greenish (if cholestasis)

MICRO
A. CELL INJURY – lobular disarray
   BALLOON DEGENERATION: cytoplasm swelling (E.R., MITO)
B. NECROSIS – single cells / sml clusters
   (1) Cytolysis: cells “disappear” from framework
   (2) Apoptosis: condensation & fragmentation → COUNCILMAN BODIES
C. INFLAMMATORY Δ’S
   (1) KUPFFER CELL HYPERTRPHY
   (2) MONONUCLEAR INFLAMMATORY INFILTRATE from portal region
D. BILE DROPLETS
   @ ballooned cells, Kupffer cells, within canaliculi
E. REGENERATION (in recovery phase)
   (1) nuclei enlargement & mitosis
   (2) hepatocyte plates 2 cells thick

**NORMAL LIVER**

**ACUTE HEP B – LIVER (low power)**

A. portal MONONUCLEAR INFLAMM EXUDATE: limited to hepatocyte plate → “PIECEMEAL NECROSIS”

**ACUTE HEP B – LIVER (gross)**

A. NECROSIS, LOBULE COLLAPSE (pale yellow areas)
### Complications

**Fulminant Hepatitis (1-4%)**

- Can supervene any type of hepatitis, often kills the patient
- Acute hepatitis deteriorates within TWO WEEKS of symptom onset
  - A. Liver Failure: coagulopathy
  - B. Encephalopathy
  - (submassive necrosis lasts several months, same outcome)

**Prognosis – 70-90% mortality**
- **If you survive, life is good!**
  - A. lifelong immunity
  - B. no liver damage
  - C. not carriers

**Histo**
- **Gross**
  - Shrunken, red, soft, flabby
- **Micro**
  - A. liver cells almost all gone
  - B. little inflammation

**Carrier State**

- Clinically either asymptomatic or chronic hepatitis
  - **Vertical Transmission** responsible for high carrier rates
  - (transplacental / perinatal). Persistence of virus in infx'd infants
  - Suggests TOLERANCE produced by early exposure.

**Diagnosis**

- All antigen markers + anti-HBc – but NO anti-HBe

**High Risk Group**
- Male
- Very young & elderly
- Immunodeficient

**Management**

- **Hep B Vaccine**: recombinant HBsAg. Effective & affordable
  - WHO policy to provide neo-natal vax
- **Anti-viral Drugs**: limited success, resistant virus common
  - A. Lamivudine: targets viral enzyme (reverse transcriptase)
  - B. Pegylated IFN: mimics innate immune response
- **Liver Transplant**: Reinfusion from extra-hepatic reservoir → prevention with HepB specific Ig + lamivudine

**Acute Support**
- → Bed-REST until signs & symptoms disappeared
- → Drug AVOIDANCE until recovery (incl alcohol, OCP)

---

**Chronic Hepatitis**

- **Lasts longer than 6 months**
- Weak immune response. HB X antigen incorporated into host genome allowing chronic infxn and expresses oncogene inactivating p53.

**Non-Viral Causes**:
- A. Drugs (methotrexate) & Alcohol
- B. Auto-immune
  - → Wilson’s Δ – Cu overload
  - → Haemochromatosis – Fe overload
  - → α-1 Anti-Trypsin defic

**Onset**
- A. follows acute or
- B. develop independently INSIDIOUS ONSET

**Diagnosis**

- All antigen markers + anti-Hbc – but NO anti-HBe

**Liver Failure**: coagulopathy

- **If you survive, life is good!**

**Encephalopathy**

- **Submassive Necrosis lasts several months, same outcome**

**Prognosis**

- **70-90% mortality**

- **A. Lifelong immunity**
- **B. No liver damage**
- **C. Not carriers**

**Histo**
- **Gross**
  - Shrunken, red, soft, flabby
  - **Micro**
  - A. Liver cells almost all gone
  - B. little inflammation

**Carrier State**

- **Chronic Infection, Infectious**
- Clinically either asymptomatic or CHRONIC HEPATITIS
- **Vertical Transmission** responsible for high carrier rates
  - (transplacental / perinatal). Persistence of virus in infx'd infants
  - Suggests TOLERANCE produced by early exposure.

**Diagnosis**

- All antigen markers + anti-Hbc – but NO anti-HBe

**High Risk Group**
- Male
- Very young & elderly
- Immunodeficient

**Prognosis**

- **Acute Hepatitis**
  - Low mortality ~0.5%
  - Higher if
    - → over-60’s
    - → other serious disease
    - → Hep E in pregnancy

**Management**

- **Hep B Vaccine**: recombinant HBsAg. Effective & affordable
  - WHO policy to provide neo-natal vax
- **Anti-viral Drugs** limited success, resistant virus common
  - A. Lamivudine: targets viral enzyme (reverse transcriptase)
  - B. Pegylated IFN: mimics innate immune response
- **Liver Transplant**: Reinfusion from extra-hepatic reservoir → prevention with HepB specific Ig + lamivudine

**Acute Support**
- → Bed-REST until signs & symptoms disappeared
- → Drug AVOIDANCE until recovery (incl alcohol, OCP)
Alcoholic Liver Disease

**AETIOLOGY – who is at risk?**

**ALCOHOL TOXICITY DEPENDS ON HOST RESPONSE** – no dose response, unpredictable

A. **HAZARDOUS DRINKING**
   
Yet only 10% alcoholics develop cirrhosis!!

- >60g / day - male
- >30g / day - female

B. **FEMALE**:
   
- ↓ body weight
- ↑ fat content

C. **NUTRITION**
   
- High sat fats & low carbo diet

D. **OTHER LIVER INSULTS**: co-toxins, drugs, disease

E. **ORIENTAL ETHNICITY**
   
- Inactive ALDEHYDE DEHYDROGENASE

**ACETALDEHYDE ACCUMULATION**

**ALCOHOL METABOLISM @ LIVER**

- **ABSORPTION**
  
  **some metabolized here (first pass metabolism)**

- **BULK OF METABOLISM @ LIVER**
  
  - **fasting increases gastric emptying, decreases first pass metabolism, gets into blood quicker.**

- **PROX INTESTINE**

**2 MAIN METABOLIC PATHWAYS @ LIVER CELL**

(1) **ADH-mediated (MAJOR PATHWAY – STANDARD)**

- Ethanol $\rightarrow$ ADH $\rightarrow$ NAD $\rightarrow$ Acetaldehyde $\rightarrow$ NADH $\rightarrow$ ALDH $\rightarrow$ Acetate

- **EXCESS H+ IONS produced $\rightarrow$ impairs FATTY ACIDS $\rightarrow$ [o] $\rightarrow$ FFA’s accumulate $\rightarrow$ esterified to 3-GLY’s $\rightarrow$ FATTY CHANGE (REVERSIBLE)

- **enhanced by FATTY DIET (↑ flux FFA’s to LIVER), LIVER DISEASE (impaired lipoprotein synth)**

(2) **MEOS & CYP2E1 (INDUCED BY CHRONIC DRINKING)**

- Ethanol $\rightarrow$ CYP2E1 $\rightarrow$ Acetaldehyde $\rightarrow$ NADP $\rightarrow$ NADPH

- **MEOS – microsomal ethanol-oxidising system. Involves cytochrome P450 2E1**
  
  - key enzyme in alcohol toxicity. **INDUCIBLE ENZYME** $\rightarrow$ thus the more you drink, the more you produce, the more damage it causes

  a) **OXIDATION RADICALS produced $\rightarrow$ lipid peroxidation $\rightarrow$ cell membrane damage**
  
  b) **chronic alcohol UPREGULATES P4502E1 $\rightarrow$ other metabolic actions upregulated (with toxic products) $\rightarrow$ thus, toxicity of certain drugs & chemicals is greater**

How does ACETALDEHYDE cause problems?

A. **MITOCHONDRIA DAMAGE** $\rightarrow$ impaired cellular respiration

B. **IMPAIRED MICROTUBULAR CELL TRANSPORT**

C. **protein-acetaldehyde ADDUCTS $\rightarrow$ immunogenic! $\rightarrow$ Incite B-cell & cytotoxic T-cell response**

D. **OXIDATIVE STRESS**: cell membrane damage, fat can’t exit $\rightarrow$ fatty accumulation $\rightarrow$ enhanced free radical activity $\rightarrow$ lipid peroxidation

- **P4502E1** contributes directly to this damage

- **GLUTATHIONE (GSH)** = Major cellular anti-oxidant @ LIVER, decreased with chronic alcohol exposure

E. **↑ CYTOKINE RELEASE** (TNF, TGF-β) from KUPFFER CELLS

**Hepatitis**

A. **ADDUCTS incite immune response**

B. **↑ ENDOTOXIN** = a LPS (lipopolysaccharide) found in wall of gram $\rightarrow$ ve bacteria.

- High levels in ALD (increased gut bacteria?)

- **induces ↑ TNF-α $\rightarrow$ apoptosis / necrosis** of hepatocyte

C. **N-PHIL & MONONUCLEAR INFILTRATE**

**Cirrhosis**

A. **FIBROSIS STARTS AROUND CENTRAL VV** (home of P4502E1 $\rightarrow$ major site of oxidative stress) **STELLATE (ITO) CELLS $\rightarrow$ COLLAGEN deposition**

B. **NODULES**: hepatocyte regeneration confined with FIBROUS BANDS $\rightarrow$ disrupts vasculature and bile channels (twists & squashes) $\rightarrow$ PORTAL HT

**Stellate cells produce collagen & ECM**

**PDGF = Stellate cell growth factor**

**TGF β =** for ECM production

**Cirrhosis – micronodular (gross)**
**DIAGNOSIS**

A. HISTORY
B. MACROCYTOSIS: vit B12 deficiency
C. LFTS: AST > ALT, high GGT

**TREATMENT**

SYMPTOMATIC & SUPPORTIVE

A. STOP ALCOHOL → beat craving with naltrexone
B. NUTRITION: B12, protein control etc.
C. PREDNISALONE (severe hepatitis)
D. BLOCK TNF with PENTOXIFYLLINE

**PROGNOSIS**

A. FATTY LIVER: disappears after 3 months abstinence
B. HEPATITIS: one third die in acute phase (esp if poor liver function), if keep drinking...
C. CIRRHOSIS: (only 10% alcoholics get this)
   → serious complications: ascites, varices
   → if keep drinking: 35% survive 5y
   → if quit: 70% survive beyond 5y
LIVER: ANATOMY

SITUATION: upper abdo (R) cavity, inside thoracic cage but midline covered by abdo mm.

SURFACES:
Diaphragmatic
A. SUPERIOR: peritoneum covering, DIAPHRAGM above, FALCIFORM LIGAMENT divides into R & L lobes.
B. POSTERIOR: R lobe connects to DIAPHRAGM via CORONARY LIGAMENT (folds of peritoneum, in between is the BARE AREA: direct contact with diaphragm). Behind are R ADRENAL, IVC, AORTA, OESOPHAGUS.
C. ANTERIOR: contact with DIAPHRAGM, ANT ABDO WALL.
D. RIGHT Visceral
TH-SHAPED!!! UPRIGHTS: fissures for ligamentum venosum & teres (L), fossae for IVC, GALL BLADD (L). CROSSBAR: porta hepatitis. Contacts OESOPH, STOMACH, DUO, TRANSVERSE COLON, R COLIC FLEX, R KIDNEY, ADRENAL, GALL BLADDER.

BLOOD SUPPLY ~~ DUAL SUPPLY ~~ highly vascularized, easily ruptured (1.5L blood/min)

THE LOBULE: the functional unit
= hexagonal unit, 1mm diameter.

BLOOD FLOW:
At each corner of hexagon = HEPATIC TRIAD
At centre = CENTRAL VEIN
Blood flows from triad → mixed in SINUSOIDS (large, leaky capillaries) → drains thru central vein → hepatic veins → IVC
**Cells near central vein most vulnerable to O2 depletion**
**Cells near portal triad most vulnerable to poisons**

SINUSOIDS:
DISCONTINUOUS (leaky) EPITHELIUM lined with MPHAGES (KUPFFER CELLS): remove debris and old RBC’s
**beneath endothelium = PERISINUSOIDAL SPACE (of Disse)**
—drains interstitial fluid: much of body’s lymph = site of HAEMATOPOIESIS for anaemics, foetus.

BILE FLOW:
Sheets of HEPATOCYTES (1 cell thick) radiate from central vein = PARENCHYMA. Bile made in hepatocytes → secreted into BILE CANALICULI (betw h-cytes) → drain to PORTAL TRIAD DUCTS

BLOOD & BILE TRAVEL OPPOSITE DIRECTIONS!!!
**LIVER FUNCTION**

**A. KUPFFER CELLS (2%)**
- reticular endothelial MACROPHAGE
- endocytosis: Ag-Ab, toxins, microparticles
- killer function: release superoxide
- TNF-a release

**B. ENDOTHELIAL CELLS (3%)**
- barrier
- endocytosis: receptor-mediated (lipids)
- pinocytosis possible
- FENESTRATED = PERMEABLE!!!

**LIVER = MAJOR PRODUCER OF BODY PROTEINS**
- standard fns (eg factor VIII synth)
- C. ITO CELLS (1.5%)
- FAT STORAGE
- vit A storage
- contractile: can adjust blood flow in response to local immune events

**D. PIT CELLS (<1%)**
- NATURAL KILLER CELLS

**E. HEPATOCYTES**
- REGENERATE!!!
  1. METABOLISM: carbo’s, lipids, proteins & AA’s
  2. ACID-BASE balance
  3. HORMONE activation & inactivation
  4. DETOX & EXCRETION
     - endogenous: BILIRUBIN
     - exogenous: DRUGS
  5. PLASMA PROTEIN production
  6. BILE SALTS
  7.BILE
  8. VITAMIN, MINERALS storage
  9. ??ENDOCRINE role

**BIOTRANSFORMATION & DETOX**

**LIVER** alters exogenous & endogenous CHEMICALS, FOREIGN MOLECS, HORMONES to make less toxic / active.
- Metabolism & Excretion.

**2 PHASES:**
- **PHASE I** – addition of REACTIVE GP via REDOX rxns
- **PHASE II** – makes WATER SOLUBLE by adding POLAR GP via CONJUGATION rxns

**Transformations USUALLY PROTECTIVE** but PHASE I CAN INCREASE TOXICITY when end-products become toxic.

eg. Alcohol → acetaldehyde (mito damage) + H+ (fat acclm)

**BILIRUBIN** – Haem breakdown product
- PROTECTIVE as anti-oxidant, also HARMFUL to NEURONES, therefore LIVER must dispose of it.
  - A. UNCONJUGATED Br binds to Albumin in blood (soluble)
  - B. undergoes Phase II → CONJUGATED Br (water soluble)
  - C. DECONJUGATED by gut flora @ terminal ILEUM → urobilinogen → urine
  - Bilirubin = PIGMENT in BILE (brown), URINE (yellow)

**METABOLISM**

**CARBOHYDRATE**

**LIVER KEEPS BLOOD GLUCOSE STABLE:** hormonal triggers
- A. If low (<4.5nmol) GLUCAGON
  - GLUCOSE RELEASE from glycogen stores
- GLYCOGEN → Glucose-6-phosphate → (G-6-P-ase) → GLUCOSE
  - GLUCONEOGENESIS from AA’s & glycerol when glycogen used up
- B. If high (>5nmol) INSULIN
  - GLUCONEOGENESIS: stores as glycogen
  - (all monosaccharides converted to glycogen)
  - GLUCOSE → (hexokinase) → Glucose-6-phosphate → GLYCOGEN
  - LIPOGENESIS: excess glucose stored as fat
- GLUCOSE → glycocysis → ACETYL CoA → diverted to FATTY ACID synth instead of Krebs cycle
- =LONG-CHAIN FATTY ACIDS

**FATS**

LIVER IS MAIN PLAYER IN FAT METABOLISM
- A. when more energy needed,
  - FAT BREAKDOWN = β oxidation @ MITOCHONDRIA:
    - FATTY ACIDS → acetyl CoA → krebs or (if glucose sparing) → KETONE BODIES & CHOLESTEROL
    (ketones diffuse into blood, providing alternative fuel for tissues)
- B. if XS carbo’s AA’s
  - LIPOGENESIS: fat storage
- C. CHOLESTEROL METABOLISM
  - SATURATED FA’s love cholesterol: enhance synthesis, inhibit excretion from body
  - UNSAT FA’s healthy: enhance catabolism and excretion
  - CHOLESTEROL → BILE SALTS → excreted in BILE
  - → STEROIDS
  - D. LIPOPROTEIN SYNTHESIS
    - Contain 3-GLY’S, PHOSPHOLIPIDS, CHOLESTEROL, PROTEIN. Function as transporters: (1) make hydrophobic lipids soluble (2) docking signals for target cells
    - VLDL → ADIPOSE TISSUE (once 3-GLY’S unloaded, VLDL→LDL)
    - LDL→cholersterol to PERIPH TISSUE
    - HDL→XS cholesterol @ PERIPHR TISSUE → LIVER → BILE

**PROTEIN**

MOST VITAL ROLE OF LIVER, all significant proteins made @ LIVER
- A. ESSENTIAL PROTEIN SYNTH
  - A. ***ALBUMIN***
  - B. COAGULATION FACTORS: exc VIII – @ ENDOTHELIUM
  - C. TRANSPORT PROTEINS: dxf can affect nutrient absorption eg. Fe++
  - D. ACUTE PHASE REACTANTS: released at inflammation
  - E. INHIBITORS OF INFLAMM & COAGULATION eg. α-antitrypsin
  - F. APO-LIPOPROTEINS
  - G. AMINO ACID FUEL USE
    1. TRANSMATION
    2. OXIDATIVE DEAMINATION: NH3 removal for → KREBS or → GLUCONEOGENESIS
  - C. RIDS AMMONIA
    - Ammonia toxic to cells: from (1) deamination (2) pyrimidine breakdown
    - AMMONIA (NH3) + CO2 → H2O + UREA → urine

**VITS / MINS STORAGE**
- A. VITS A, (months) D, B12 (years)
- B. IRON as FERRITIN (most stored here)

**MACROPHAGES @ LIVER, SPLEEN**
- RBC destruxn
- → Haem
- → Biliverdin
- → Bilirubin
- → urobilinogen

**PLASMA**
- → + Albumin
- → glucuronide

**HEP-CYTE**
- → unconj. Bilirubin
- → Conjugated Bilirubin

**BILE CHANNELS**
- → excreted in BILE

**SML**
- → urubaribenogen

**INTESTINE**
- → gut flora

**LIVER - FATTY ACIDS**
- → ADAPOSE TISSUE
- → GLYCOGEN
- → GLYCOGENESIS
- → WATER soluble waste prods
- → METABOLISM: carbo’s, lipids, proteins & AA’s
- → ACID-BASE balance
- → HORMONE activation & inactivation
- → DETOX & EXCRETION
- → endogenous: BILIRUBIN
- → exogenous: DRUGS
- → PLASMA PROTEIN production
- → BILE SALTS
- → VITAMIN, MINERALS storage
- → ??ENDOCRINE role

**LIVER: enhance catabolism and excretion**
- CHOLESTEROL
- Water soluble waste prods
- METABOLISM: carbo’s, lipids, proteins & AA’s
- ACID-BASE balance
- HORMONE activation & inactivation
- DETOX & EXCRETION
- endogenous: BILIRUBIN
- exogenous: DRUGS
- PLASMA PROTEIN production
- BILE SALTS
- VITAMIN, MINERALS storage
- ??ENDOCRINE role
LIVER FUNCTION TESTS → COLLECTIVE PATTERN IMPORTANT, individual tests often vary

USE: disease progress (not cause, prognosis, liver function)
SPECIMEN: serum sample

ALT, AST (serum TRANSFERASES / TRANSAMINASES)
Neither specific to LIVER but higher [ALT] there (constant low levels in plasma – 10x normal significant)
@ CYTOPLASM & MITOCHONDRIA → leak out with cell damage.
ALT: [alanine aminotransferase] - MORE SPECIFIC FOR LIVER
AST: [aspartate aminotransferase]

SAP, GGT ("Biliary Enzymes")
@ CELL MEMBRANES – Bile salts damage membranes in bile obstruction (cholestasis)
NB/ increase much less with cell damage
SAP: [Alkaline Phosphatase]: also @ BONE, INTESTINE, PLACENTA
GGT: [Gamma-glutamyl transpeptidase]: everywhere but sensitive to LIVER

SERUM BILIRUBIN
HIGH [GGT], [SAP] → CHOLESTASIS
GGT may be normal EARLY in course of acute hepatocellular damage

ALBUMIN
Specific: made only in LIVER
LOW → chronic disease (long half-life 3-4 wks: no changes with acute disease)
A. ↓ synthesis @ LIVER
B. ↑ excretion @ KIDNEY
C. malnutrition
D. dilution due to ascites

GLOBULINS (= total protein – albumin)
HIGH → dysregulation of protein synth in liver disease
↑ UNCONJUGATED / (no un-Br in urine as binds to Albumin) - haemolysis
- inefxvite erythropoiesis
↑ CONJUGATED → bile duct obstruction

COAGULATION FACTORS
LIVER makes all factors, Prothrombin Time (I, II, V, VII, X) = good indicator of acute liver disease since short half-life of factors
(5-72h), 30% reduction in coags will increase PT.
PT prolonged → SEVERE LIVER DAMAGE
.prevents fat absorption → ↓ VIT K absorption → vit-K dependent factors inactivated (TV)
**give Vit K suppts & repeat to distinguish

OTHER TESTS
↑ FERRITIN
A. haemochromatosis
B. Alcoholic Liver disease
Caeruloplasmin: copper-containing globulin, made @ LIVER

SEROLOGICAL TESTS
Hep A (HAV): acute infection (lasts 1-2wks post onset)
Hep B (HBV): acute infection (lasts years, implies immunity)
Hep B (HBV): - ACUTE
HBsAg (surface Ag): acute infection (days-wks post onset)
anti-HB: (antibody) previous infxn / vaccination (3-6months post infxn)
anti-HBc (antibody to core Ag): acute (early marker, subsides & persists)
HBeAg (e Ag): active replication in LIVER (transient at onset)
anti-HBc: follows HBeAg

HbsAg and anti-HBc (lgG)
AUTOANTIBODIES
IMAGING
BIOPSY
CHRONIC LIVER DISEASE

~~HEPATOCYTE DAMAGE~~

→ usually CHRONIC HEPATITIS

CAUSES:
A. ALCOHOL
B. VIRUSES (hep B, C, D)
C. DRUGS & TOXINS
D. FATTY LIVER (NASH) → assoc with METABOLIC Δ
E. AUTOIMMUNE

- autoimmune chronic hepatitis:
  - genetic, mostly female, associated with other AID, ↑ IgG & AUTO-ANTIBODIES
  - Wilson’s Δ – toxic Cu overload → CONSIDER IF UNKNOWN CAUSE OF LIVER DISEASE IN <40’s (childhood PX)
  - autosomal recessive, abN Cu metabolism. Normal: absorbed @ stomach, smn intestine → LIVER stores & makes caeruloplasmin → into blood → excretion via bile. Failed: caeruloplasmin synth or bile excretion
  
  Affects LIVER (acute/chronic disease starts in childhood), BASAL GANGLIA (dementia late adolescence), EYES (KAYSER-FLEISCHER RINGS), KIDNEYS, SKELETON

  LOW SERUM CAERULOPLASMIN
  PENICILLAMINE = Cu-binding agent – GIVE ASAP, must produce Cu in urine
  
  - Haemachromatosis – toxic Fe overload → LEAD-GREY SKIN → childhood PX
  
  Autosomal recessive, male
  Increased absorption of dietary Iron → portal fibrosis & cirrhosis. Affects LIVER (macronodular cirrhosis), PANCREATIC ISLETS (DIABETES), ENDOCRINE GLANDS, HEART (HEART FAILURE)
  
  ↗ SERUM IRON ↑ FERRITIN ↑ IRON-BINDING CAPACITY, BIOPSY
  WEEKLY VENESECTION!!

  Prognosis: HEPATOCELLULAR carcinoma (one third of ppl ± RX)
  -α-1 anti-trypsin deficiency → CIRRHOSIS IN CHILDREN
  α-1 antitrypsin = a protease inhibitor. LIVER fails to secrete into blood → necrosis, inflammation

  CHOLESTATIC JAUNDICE (neonates) ACUTE HEPATITIS (children) CIRRHOSIS (adults)

  LOW PLASMA α-1 AT

CHRONIC CHOLESTATIC DISEASE

~~BILIARY SYSTEM DAMAGE~~

→ injury to small intrahepatic ducts or larger bile ducts. Causes (1) PROLIFERATION of small ducts (2)HEPATOCYTE damage → CIRRHOSIS

CAUSES:
A. OBSTRUCTION: gallstones, cancer
B. SURGERY
C. DRUG REACTION
  - Anti-psychotics – CHLORPROMAZINE
  - Anti-biotics – FLUCLOXACILLIN, AUGMENTIN
D. AUTOIMMUNE
  - Primary biliary cirrhosis:
  Chronic granulomatous inflammation damages intrahepatic bile ducts. Portal fibrosis spreads. Cirrhosis. middle-aged WOMEN, PRURITIS & BIG LIVER (no abdo pain & fever of large bile duct obstruction)
  
  anti-mitochondrial AUTOANTIBODIES, ↑ IgM, ERCP BIOPSY
  
  Primary sclerosing cholangitis → ASSOC WITH INFLAMM BOWEL DISEASE (70%)

  strictures & dilation throughout LIVER

  ERCP IMAGING of biliary system

HEPATOCELLULAR CANCER

→ SUSPECT WHEN CIRRHOTICS START TO DETERIORATE

→ Most common 1° liver malignancy

CAUSES:
CIRRHOSIS of any cause PREDIPOSES: especially HAEMOCHROMATOSIS and ALCOHOLIC CIRRHOSIS

HISTO:
- well-differentiated tumour cells (look like hepatocytes)
-BILE SECRETION
- spreads to regional lymph nodes. LUNGS, BONES
  MASSIVE α-FETOPROTEIN

  Bleak future – surgery only possible if tumour in one lobe + no cirrhosis, few survive beyond 1 year

  3 Mechanisms:
A. CHRONIC NON-SPECIFIC INJURY + REGENERATION: predisposes to host oncogene [a]
B. VIRAL ACTIVATION OF HOST ONCOGENES: upon integration into host genome
C. VIRUS ONCOGENES: eg. HBX

SECONDARY METASTASES

→ SUDDEN BIG LIVER + FEVER, WEIGHT LOSS, JAUNDICE

  from (→ 4 step ladder)
  BRONCHUS       BREAST       ABDOMEN       PELVIS

IMAGING & BIOPSY (LFT’s may be normal, ↑ SAP, high protein ascites)
Liver failure of CIRRHOSIS...

**Liver inflammation**
- pain
- fever
- Nausea, vomiting, anorexia
- fatigue

**Liver necrosis**
- HORMONE metabolism
  - androgens & oestrogens
  - gynaecomastia
  - loss of body hair
  - menstrual dysfyn
  - spider naevi
  - palmar erythema
  - ADH & aldosterone
  - oedema

- BILIRUBIN FX
  - bilirubin metabolism
  - hyperbilirubinemia
  - jaundice
  - bile in GIT
  - pale stools
  - vit K absorption
  - bleeding
  - urobilinogen
  - dark urine

- BIOCHEMISTRY
  - ASR, ALT
  - SAP
  - bilirubin
  - low albumin
  - PT

- PROTEIN metabolism
  - metabolism of proteins, carbs, fats
  - hypoglycaemia
  - plasma proteins
  - ascites & oedema

**Liver fibrosis & scarring**
- PORTAL HYPERTENSION
  - ascites
  - oedema
  - splenomegaly
  - anaemia
  - thrombocytopenia
  - leukopenia
  - varices

**Liver failure**
- encephalopathy
- coma
- Death

**Liver failure of CIRRHOSIS...**

**ACUTE**
Massive loss of hepatocytes causes:
A. FEVER
B. ACIDOSIS
C. RENAL FAILURE
  - Mechanism unclear but evidence for DECREASED RENAL BLOOD FLOW due to vasoconstriction from:
  1. gut flora endotoxins not cleared
  2. ↑ thromboxane A₂ by platelets
  3. ↑ renin & aldosterone from effective ↓ blood volume
  (ascites)
D. HAEMORRHAGE

**CHRONIC**
- Hepatocyte loss + portal HT
  - Increased pressure on PORTAL VEIN from blockage higher up:
    - (1) VARICES
    - FIBROSIS and REGENERATIVE NODULES squash vasculature.
    - Since flow can’t pass thru liver -- EXITS THE WAY IT CAME IN –
    - Death
      - (caput medusae)
  - (2) SPLEEN → THROMBOCYTOPENIA
  - (3) ASCITES & OEDEMA (also ALBUMIN deficiency)
    - risk SPONTANEOUS BACTERIAL PERITONITIS
B. GYNAECOMASTIA & hypogonadism
  - Impaired OESTROGEN breakdown
C. WASTING & MALNUTRITION
  - Metabolic disturbances: ↑ gluconeogenesis
D. PALMAR ERYTHEMA
E. SPIDER NAEVI (upper body)
  - both from ↑ OESTROGEN
**ASCITES**
- accumulation of free fluid in peritoneal cavity

**CAUSES:**
A. **CIRRHOSIS** (high pressure in mesenteric circulation) >11g/L
B. **MALIGNANCY** < 11
C. **INFECTION**
D. **BILIARY COMMUNICATION**
E. **LYMPHATIC OBSTRUCTION**

CLINICAL:
A. **ABDO DISTENsION & FLANK FULLNESS**
B. **SHIFTING DULLNESS** (only if fluid > 1L)
C. **UMBILICUS EVERSION**
D. **HERNIAE**
E. **STRIAE**

**PATHOGENESIS:**
Arterial vasodilation theory

**PATHYOSGENESIS:**
- Splanchnic & systemic vasodilation
  - ↓ effective blood vol
  - Renin-angiotensin system activation
    (symp NS, ADH)
  - Na & water retention
    - ↑ plasma vol
    - Continuous Na & water retention
- Inadequate for homeostasis

**PHYSIOLOGY OF ASCITES**
- ↑ Hydrostatic P
- ↓ Oncotic P
- Na+ water retention

Liver lymphatics work overtime but can’t fully compensate → fluid escapes liver capsule “jail” into peritoneal cavity

**MANAGEMENT:**
1. low salt diet
2. diuretics
3. drain + IV albumin
4. shunt – peritoneovenous
5. liver transplant

**COMPLICATIONS:**
- 11 OmniOUS
  A. **SPONTANEOUS BACTERIAL PERITONITIS**
    1. Portal HT → gut wall oedema
    2. bacteria translocate from gut lumen → circulation
    3. poor Retic Endo System In → bacteraemia
    4. ascitic fluid poor antimicrobial defences → infxn
      a. ASCITES
      b. FEVER, CHILLS
      c. SUDDEN ABDO PAIN
      d. ENCEPHALOPATHY – worse

**ASYMPTOMATIC (30%)**

**Diagnosis:**
- Asitic WCC > 500/μL
- PMN > 250/μL

(no need to culture but – MOSTLY single organism, -- E.COLI – 70% gram negative bacteria

→ if multiple organisms & HUGE protein level think 2° BACTERIAL PERITONITIS

**Causes:**
- BOWEL PERFORATION
- ABSCESS
- ISCHAEMIA

**Prognosis:** NOT GOOD!!!
- only 25% survival after 5y
- high recurrence but – NORFLOXACIN fxive

B. **HEPATORENAL A – III OMNIOUS!!!**
= progressive renal failure with advanced CIRRHOSIS and ASCITES (no actual renal disease)

**Diagnosis:**
- CREATININE rises & URINE reduces
  → LIVER DISEASE + portal HT
  → low GFR
  → no obvious trigger:
    - shock
    - sepsis
    - nephrotoxic drugs
    - XS fluid losses
  → no other renal A (no proteinuria)
  → no improvement with volume expansion

**Prognosis:**
- 50-95% mortality
PORTAL HYPERTENSION

= INCREASED PRESSURE on PORTAL VEIN leaving liver from any cause:
  - intrahepatic → obstruction
  - pre-hepatic → obstructive thrombosis
  - post-hepatic → Heart failure

since can’t pass thru liver, EXITS THE WAY IT CAME IN causing VARICES @:
  1. OESOPHAGUS
  2. ANT. ABDO WALL (caput medusae)
  3. RECTAL VV (haemorrhoids)
  4. VERTEBRAL VV

FOUR MAJOR CLINICAL CONSEQ:
A. ascites
B. varices
C. splenomegaly
D. hepatic encephalopathy

GI BLEEDS

A. VARICES
B. PEPTIC ULCER
C. CLOTTING DYSFN
  ↓ clotting factors @ LIVER
  ↓ platelets @ SPLEEN

high risk of VARICES??
CLINICAL: cirrhosis, severe disease
BLOOD PRESSURE: HVPG >12mmHg (portal venous P)
  ** higher it gets, less chance of survival
variceal >15

ENDOSCOPY: diameter >5mm
ULTRASOUND: portal flow
OTHER: (1) bacterial infxn
  (2) NSAIDS
  (3) alcohol