Mumps

- Infection of Parotid gland (salivary) → Swelling
- Acute, systemic, Viral → Endemic worldwide.
- Very effective vaccine.
- Affects mainly → Children
  - ↳ may affects vaccinated young adults
- Why do outbreakes of Mumps occur?
  - * Easy spreading of Respiratory viruses (crowding)
  - * waning of vaccine immunity with time.
  - * lack of wild-type viruses to ↑ immune response
  - * Repeated global epidemics: (↓ vaccination)

⇒ Paramyxo family, ~~contains~~ size/shape: pleomorphic particles.

⇒ RNP core surrounded by an envelope (lipids) from host.

⇒ The Replicative core has? + viral protein (Binding)

⊖ss RNA, Nucleoprotein, phosphoprotein, Polymerase

⇝ Examples on Viral Protein in the envelope →

Hemagglutinin-neuraminidase + Fusion protein

↳ have antibodies ↓

Notes :-

* Affects humans only by Saliva spreading
* Incubated 1-3 weeks in upper R.S mucosa, then → lymph nodes
* Shed in 2 weeks around the symptoms onset
  - ↳ Termination of shedding by IgA, IgM

* After replication (URT mucosa) → Lymph → Viremia
  → Heart / CNS / Kidneys / Glands
  → specific antibodies in serum.
  → Viremia / Shedding may occurs without Parotid involv.

* Clinical Features →
  → 1/2 of infections → asymptomatic / non-specific
  → Symptoms include: Mild fever, Parotid swelling
    Aseptic meningitis, Epididymo-orchitis (post-puberty)
    malaise, anorexia, headache.
  → Submandibular / Sublingual < Parotid involvement
  → Testicular atrophy (50% cases). Sterility (rare)
  → Oophritis, mastitis → 5% women-cases. Sterility (rare)
  → 50% cases → CNS invasion, while 10% only: aseptic meningitis
    more in males
    Drowsiness, stiff neck, headache
  → Pancreatic involvement (mild — severe + hemorrhage)

* Diagnosis → if Parotitis presents → straight forward.
  → Detect viral antigens (rtPCR) in Saliva, CSF, urine, semen. Rarely in Blood.

* Treatment → Supportive + Analgesics.
  ∴ it's a benign, self-resolving illness

Viral Gastroenteritis ..

- Viral diarrheal diseases are very common in Children + infants worldwide.
  + severe in elderlies with bad health conditions.
- By certain viruses:
  [Rota-, Adeno-, Calici-, Norwalk, Corona-, Toro-..]
- Acute onset of vomiting / Diarrhea, fever, anorexia
- By [CMV, HSV, VZV, HIV] in immunocompromised.

III Rotavirus ..

- Reoviridae family, stable, non-enveloped
- Feco orally transmitted, children, neonates (mild)
- 7 major groups (A-G), human infections by A mainly.
- Infections mainly in winter.
- Groups (A B C): humans + animals. The rest → only animals
  - B: Epidemics within adults in Asia.
- Icosahedral in shape (3 layers), segmented dsRNA
  - (within same group) Reassortment
- Antibodies against VP7 and VP4 layer and proteins

* Pathogenesis :

- Tropism to mature enterocytes in small intestine.
- Protease activation → Cleaving outer VP4 proteins →
  Loss of villi, ↑ secretory crypt cells → Enterotoxin Secretory Diarrhea. M

(↓ microvilli)

- ↓ Brush Border enzymes → ↑ unmetabolized disaccharides → Osmotic Diarrhea.
- ↑ Enteric NS → ↑ Fluid secretions.
- Dehydration + Death.

* has (NSP4) Protein : enterotoxin → Alters epithelial Permeability → Secretory diarrhea

* Clinical Features :
  - Short incubation Period (1-3 days)
  - Most severe : 1st infection at age : 3 months.
  - Abrupt Onset, Vomiting, diarrhea, watery stool, fever.
  - Complications → severe diarrhea, dehydration, acidosis.
  - Re-infections are less severe.
  - Protracted diarrhea + Systemic dissemination (rare) in immunodeficient patients.
* Specific, short-lived IgA antibodies in intestines protects temporarily against the disease.
* Diagnosis → ELISA, RNA detection, difficult clinically.
* Prevention → Early vaccines, New vaccines not orally.
* Treatment → Rehydration
  - IV fluids in severe cases + Vomiting.
  - Avoid antibiotics + anti-motility agents.

[2] Calicivirus ..

- small, non-enveloped, ↑ contagious, feco-orally ↔
- Affects all age groups, short term, specific immunity.
- Prototype strain: Norwalk, ↑ infections in winter.
- Sapovirus type: specially in Children

→ causes traveler's Diarrhea.

→ Most common in adults + ↑ children

→ 2nd most common (after Rota-) in young children.

- Icosahedral in shape. dimers of (90 VP1) protein
- Single, linear +ve RNA genome
- Cup-like hollows on surface
- Quick lytic replication. Trigger apoptosis
- has VP2 minor structural protein + VPg (non-structural protein) binds the genome covalently and packaged into released virions

* Pathogenesis

- VP1 interacts with (HBGA) carbs on gastroduodenal cells
  - Blood group O: ↑ susceptibility.
- Reversible lesions in jejunum, Broad villi, shortening of microvilli, vacuoles in lining epithelium, Crypt hyperplasia, infiltration of lamina Propria by WBCs

→ Malabsorption, ↓ brush border enzymes, ↓ motor functio

nausea + vomiting. No histopathologic changes.

→ Clinical Features

- Short incubation period
- IF symptomatic, symptoms include: fever, Adults. headache, Nausea, Vomiting in children, Cramps, watery diarrhea
- Complications → Dehydration + rarely death.

* During acute illness: ↑ shedding, ↑ infectivity.

→ Diagnosis

ELISA, RNA detection (in outbreaks)

* EIA kits → limited sensitivity.

* Provisional diagnosis during outbreaks if:-

Kaplan criteria:

1- No detection for bacteria / Parasite.
2- Vomiting in 50% of cases
3- (12-60) hour; mean duration of illness.
4- Incubation period: 24-48 hours.

→ No vaccine

→ Hygeine Hygeine Hygeine.

→ Treatment: Rehydration (orally)
: IV fluids in severe cases + Vomiting.

[3] Astrovirus ..

- Feco-oral ↔ , similar to Rota infections clinically
- Requires proteolytic cleavage by (trypsin) to be infective
- infections ↑ in winter. Outbreaks anytime.
- Mild, self-limiting usually. May be severe.
- Food / water borne. [shellfish]
- Pediatric Pathogen mainly.

* Icosahedral in shape, with spikes.
* Star-Shape after cleavage by trypsin.

[4] Adenovirus ..

types 40, 41 → Diarrhea in Children

types 1, 2, 5, 6 → Mesenteric Adenitis (Intussusception)

type 12 → Celiac Disease.

↳ has E1b-55k protein that induces cross reacting antibodies to A-gliadin.

* structural homology.

Viral Hepatitis – Introduction

- The liver has a huge regeneration power.
- If patients tolerate the metabolic insult of liver failure after massive necrosis, Restoration may occur.
- All types of viral hepatitis produce clinically similar illnesses.
- Readily spread. contagious before/without symptoms.

[1] Hepatitis A

- Self-limited in children, more severe in Adults
- feco-oral ⇐ . No chronic hepatitis, No carrier state.
- Resistant to ↑ Temp. ↓ PH, drugs
- Inactivated by boiling for 1m, with formaldehyde, Cl_2, UV
- immunologically indistinguishable strains, one serotype.

* Picorna family, non-enveloped, +ve ssRNA
Produces 1 polyprotein that forms 4 capsid proteins.
VP1, 3 → antigenic.

* Pathogenesis → (the virus itself isn't toxic to hepatocytes)
- Has TIM-1 receptors (everywhere, not specific to liver)
But the virus has tropism mainly to the liver.
- TIM receptors → for T-cells regulation + differentiation.
- Replicate in liver, viremia, Shedding in bile/stool
↳ slowly, without cytopathic effect.
- The damage results from T-cell responses + apoptosis.

Clinical Features :-

- Age dependent, from (mild → Fulminant (rare))
- Incubation period: 4-6 weeks, asymptomatic.
- ↓ viremia, ↓ shedding when jaundice appears

→ The virus is found in (stool, Blood, bile), but replicates only in liver.

* Death (rare) in Patients with chronic HBV, HCV + elderly
* Damaged tissue is restored in 8-12 weeks

A) Prodrome (Pre-icteric) phase : quick transition, Fever, anorexia, malaise, vomiting, Fatigue, Diarrhea, Hepatomegaly → upper quadrant Pain

B) Icteric phase : Bilirubinuria (gold/Brown urine), yellowish mucous membranes (sclera) + skin.

- Reduction in liver size → Bad sign. (necrosis)

* Complications :- - Fulminant Hepatitis
- Relapsing Hepatitis → [recurrent symptoms ↑ amino transferase, Jaundice, Fecal excretion of HAV]
- Cholestatic Hepatitis → [protracted cholestatic jaundice + pruritis]

Diagnosis

* Biochemical liver Panel
  - AST/ALT
  - PT ⇝ important in acute hepatitis.
    if high PT → severe defect + necrosis.
  - Billirubin ⇝ usually high in hemolytic anemia patients (like G-6PDH deficiency, sickle cell).

* Serology → HAV-IgM ⇝ Acute
  → HAV-IgG ⇝ Past infection

* Viral Antigens: rtPCR → not routinely done.

* Prevention → Hygiene, Immune Globin.
  → Vaccines
  - Formalin-inactivated Vaccines
  - older than 1 year
  - Provide protection within 4 weeks

* If before imminent travel to endemic area: Vaccine + IG.
* If Vaccines to measles, mumps, rubilla, varicella are given, HAV IG is delayed to prevent interference.
  ↳ won't interfere with Polio / Yellow fever vaccine
* ↑ Risk in: children, injection drug users, travelers, Patients with clotting disorders, Men who have sex with men
* Treatment → Supportative. [IV feeding], If Pruritis presents: give: bile-salt-sequestering resin Cholestyramine.
  - Glucocorticoids → No value * Avoid Cholestasis + drugs metabolized in liver.

[2] Hepatitis B..

- Parenteral, Sexual, Perinatal transmission.
- Causes Chronic hepatitis + Carrier state.
- ↑ Chronicity in childhood. ↑ Symptomatic inf. in adults.
- May cause → Hepatocellular Carcinoma.
- No direct viral cytopathic effect. (like HAV)
- Host immune responses produce Hepatic + extrahepatic lesions.

* In endemic areas, HBV inf. is acquired at birth
  → Immunologic tolerance → ↓ acute, ↑ chronic
* Hepadnaviridae family, enveloped with HBsAg (S, M, L), indistinguishable in serum.
  - they adsorb to antibodies to facilitate spreading + maintenance in host cells.
  - (S) → most abundant antigenic determinant.
  - (L) → a primary ligand for the receptor.

* Has HBc Ag : naked core particles, not in serum, detected by IHC (in hepatocytes).
* HBe Ag : secreted nucleocapsid protein, detectable in serum, marker of replication + infectivity.

* Partially circular ds DNA, replicat by reverse transcription.

* Pathogenesis

- Hepatocytes are the main targets
- Viral target Ag (HBcAg, HBeAg) + host antigens induce the response of Cytolytic T cells → clearance + injury.
- Different outcomes are due to differences in the robustness + broad polyclonality of CD8+ T cells + cytokines. * outcomes are age, immune dependent.
- HBe Ag (small, traverse placenta) → induces tolerance + Chronicity, without immunologic clearance.
- HB x Ag → transactivate the transcription of viral + cellular genes
- Regeneration also → ↳ Hepatocellular Carcinoma (HCC).

* Clinical Syndromes

- Asymptomatic Acute infection : serologic evidence only
- Acute Hepatitis : anicteric / icteric
- Fulminant Hepatitis : necrosis + Acute liver failure
- Chronic Hepatitis : may / may not develop cirrhosis
- Chronic carrier state : asymptomatic (no apparent disease)

More Details

* Asymptomatic Acute infection
  - ↳ Subclinical, Mild ↑ AST / ALT
  - ↳ Incidental diagnosis, 100% recovery.

* Acute Hepatitis → 99% recovery, 1% → Fulminant

4 phases → 1. Incubation (↑ infectivity)

2. Symptomatic Pre-icteric (↑ infectivity)

Headache, nausea, ↓appetite ↔ non specific symptoms

3. Symptomatic Icteric.

↓ NS symptoms, mainly Conjugated Hyperbilirubinemia, then become unconjugated (liver damage)

4. Convalescence.

* 10% of cases develop a serum sickness (rash, arthralgias)
* liver enlargement + upper quadrant pain may occur.
* Hyperbilirubinemia → Dark urine, light stool, Pruritis.
* Icteric phase is usual in Adults with HAV, not HCV.

* Fulminant Hepatitis → 99% recovery, 1% Fulminant
  - massive necrosis, A/B/D/E
  - DDx, drug/toxin Hepatitis.

* Chronic Hepatitis → Recovery, Cirrhosis, HCC → death
  - > 6 months symptomatic, inflammation + necrosis
  - ↑ AST/ALT, ↑ PT, Varied S&S
  - Other causes than HV, like: Autoimmunity, Wilson' disease AAT deficiency, drugs + toxins.
  - In females / ↑ IgG / No viral serology → May develop: Glomerulonephritis (nephrotic syndrome) + Polyarteritis Nodosa

* Chronic Carrier state
  - Asymptomatic person, has the virus + can transmit it.
  - Most early infections (during birth) : carrier state.
  - Liver damage occurs
  - In immunocompromised mainly.

* Clinical features ..
  - long incubation period (4-26) weeks
  - HBsAg → Firstly detected, remains the icteric phase
  - HBeAg → if in serum → highly infectious.
    → After HBsAg disappears, HBs Antibodies are detectable
  - HBcAg → intracellular, not detectable,
    But Anti-ABc → detectable in serum
    → Appears in the gap between HBsAg disapperance and Anti-HBs apperance, showing an evidence of current or recent HBV infection

* HBsAg → marker of infection
* Anti-HBs → marker of recovery + immunity
* Anti-HBc IgM → marker of acute infection (→ or acute exacerbation of chronic.)
  Anti-HBc IgG → marker of past / Chronic infection.

* Anti-HBe → no longer replication, even if HBsAg presents.
* HBV-DNA → active replication, ↑ accurate than HBeAg. →

* After recovery, Anti-HBs + Anti-HBc persist.
* An immune clearance of infected hepatocytes →
↑ aminotransferases (like acute cases). Anti-HBe appear.

⇒ 2 special Variants ⇝

1 — severe chronic HBV, with HBV DNA But with anti-HBe instead of HBeAg
↳ due to mutation in the core region

2 — No activity of anti-HBs due to mutation in HBsAg escape mutation

* Humoral immunologic pressure [due to active, passive immunization]
↳ may favor evolutionary change "escape"

* Diagnosis:
- By HBsAg levels in serum. (serology)
↳ if low, look for IgM anti-HBc.
- Biochemically [AST/ALT, PT, Billirubin]

* Vaccination: HBsAg vaccines, then we'll find Anti-HBs.
- Pre vs post exposure (with HBIG)

* Treatment ⇝ Most acute infections don't need Anti-virals, they (99%) resolve.
- Chronic inf. → IFN (no longer used), PEG-INF
or Inhibit RT By → Nucleoside Analogue (Lamivudine)
or nucleotide Analogue → Adefovir Dipivoxil → (less relapse)
→ Good treatment: No HBsAg, No HBV-DNA, ↑ Anti-HBe.

Hepatitis C ∞ (Non A, non B)

- Parenteral transmission (Blood), IV drug use.
- Sexual + Perinatal ↔ : not efficient.
- Antibodies are produced, but short lived.
  No lasting imm.
- ↑ genetic variability + ↑ rate of mutations.
- Prevalence in Egypt. (contaminated equipment)
  type 4
- 6 genotypes, type 1 → the most common
  ↳ long therapy, ↓ response.

* Flaviviridae family, enveloped
* Linear, +ve ssRNA → gives 1 protein
  ↓ cleaved to 10 Protein
* conserved 5'UTR, core gene
* Has a hypervariable region responsible for envelope proteins + immune evasion.
* Does not replicate via a DNA intermediate
  ↳ does not integrate into host genome. Unlike HBV
* E1-E2 dimers on surface.

→ 85% of acute hepatitis C develop into chronic cases.

15% → resolution, rarely → Fulminant hepatitis

* Pathogenesis

- Hepatocyte tropism :-
  - nonliver-specific CD81 receptors
  - liver-specific tight junctions: claudin-1
- Evade immunity by being similar to LDLs

* liver tropism, why?

- ↑ levels of certain Protein on the surface of hepatocytes, like LDL-receptor, [SR-BI].
- Liver-specific miR-122 → for replication
- Similar to liver's Lipoproteins assembly pathways.

- spread by: blood (viremia) / cell to cell.
- It affects lymphoid cells to ↓ immune responses, But still, the damage of hepatocytes occurs due to T-cells reaction. Cytolytic T cells also contribute to the damage (less)

* when HLA-I molecules (important for immunity) ↓ : Natural killer cells ↑ → limiting the infection.

- Cross reactivity between viral antigens and the host' cytochrome P450 → Autoimmune hepatitis + Antibodies to liver-kidney microsomes

→

→ Extra-hepatic manifestation ..

1- Cryoglobulinemia (EMC) → [Arthritis, Vasculitis-purpura-, glomerulonephritis]

- Cause chronic liver disease, ↑ HCV, ↓ HBV

↑ immune complex glomerulonephritis.

2- Prophyria Cutanea tarde (PCT) →

[Disorders of skin + nails (onycholysis), scarring]

- associated with liver disease + alcohol + estrogen use + hereditary hemochromatosis, HFE gene mutation

→ Clinical Features ..

- Long incubation period (2-26) weeks.
- Commonly asymptomatic.
- Symptoms: Fatigue (common), ↑ aminotrans., rarely Jaundice
- Less severe Jaundice than HBV or HAV. It's ≈ anicteric
- HCV infection becomes complicated by: hepatic steatosis, hypercholesterolemia, type II DM, Insulin resistance ⇝ Hepatic fibrosis
- Cirrhosis appears in 20% - 50% of chronic cases.
- Increased risk when there's HIV-co infection
- HCC risk ↑↑ after cirrhosis + 3 decades of disease.
- Other complications: Immune cross reactivity + Metabolic disorder + Extra-hepatic immune manifestation.

* Diagnosis →
- Biochemically: [PT, Billirubin, AST/ALT (less useful)]
- Serology: Detect Anti-HCV in serum in chronic cases or initial phase of acute cases (↑ aminotransferase)
- RNA detection (gold standard) →
Appears before Anti-HCV and initial phases

* Prevention: Precutaneous precautions.
: No vaccine, No effective IG

* Treatment:
1- INF-α → ↓ rate of Chronicity.
2- INF + nucleoside analogue → for acute cases
3- PEG-INF + " " (ribavirin) → for chronic cases
* higher dose for genotype 1
→ Adding Protease inhibitor (boceprevir): ↑ efficiency.

Goal of therapy: Sustained viriologic response (SVR)
↳ Undetectable HCV RNA after 24 w after treatment ends.

* Acute cases are more responsive to INF treatment than chron

Hepatitis D ..

- Not true virus, it's a natural satellite of HBV
- Parenteral co-infection (with HBV simultaneously) or super-infection (after presented HBV infection).
- ↑Commonly develop to Fulminant Hepatitis
- Chronicity is associated with more cirrhosis than HBV, HCV
- Endemic in HBV patients of Mediterranean countries.
- Depends on HBV duration, never outlasts it.

* Deltavirus genus, no family. Enveloped, membrane proteins from HBV
* Circular, -ve ssRNA with internal complementarity areas that fold (pair) → stable, rodlike structure that contains: stable, ~~def~~ self-cleaving, self-ligating ribozymes.
* HDV protein: HDAg ⇒ in hepatocyte nuclei, occasionally in serum
  ↳ found in 2 forms:
  - small → For replication
  - Large → for packaging, suppress replication.

* Pathogenesis ..
  - If it has HBV-S ⇝ Assembly
  - " HBV-S + HBV-L ⇝ Assembly + infectivity
  - Once the virus enters, it replicates. we should restrict the entry
  - HDV assembly uses a secretory pathway like sub-viral particles.
  - Hepatocyte tropism only in HBV infected cells
  - Directly cytotoxic + cytopathic to cells + immune-mediated damage.
    ↳ Most severe liver injury.

- Distinguishable (LKM antibodies) from those with HCV or autoimmune hepatitis
- Induce more HBV- fulminant hepatitis.

* Clinical Features ..
- Same incubation period as HBV or shorter.
- Co-infection with HBV produces similar symptoms to HBV infection alone or more severe → usually acute self-limited.
- Super-infection (old chronic HBV) → severe acute hepatitis + Fulminant course. (overt illness + Jaundice.)
or exacerbation of Preexisting HBV. or misdiagnosed as HBV.

→ Check HBsAg status to know about the virulence of HDV.
- IgG (chronic) + IgM (chronic / acute.) against HDAg.
↳ Non-neutralizing because HDAg is in the interior.
- Anti-HBs → protection from HBV and HDV for they have the same protein (HBsAg)

→ In some cases, they may become indolent (after years).

* Diagnosis → Biochemical, serology, RNA detection HDAg or Anti-HDV seroconversion ↔ hard to be detected
→ LP we found HBsAg + Anti-HDV: look for Anti-HBc
Past inf ← IgM do not present / recent inf ← IgM present
super infection ← IgG ↑

* Prevention: HBV vaccine. No Prophylaxis for HBsAg carriers. (Product)

* Glucocorticoids, Nucleoside Analogue → not effective.
↑ dose of INF-α for (12m) may help. in chronic cases.

Hepatitis E

- enterically transmitted, non A, non B, India + Asia + Africa /epidemic
- 5 genotypes, 1 serotype
  - 4 of them in humans
    - types 1, 2 → most virulent, humans + Primates
    - types 3, 4 → attenuated, // + // + swines + rabbits. (Zoonotic)
- rare secondary person-to-person spreading.
- Fatality is higher than HAV infections but still rare.
- Fatality ↑ in infections during Pregnancy (20%)
- Doesn't cause chronic disease except in immunocompromized
- More heat labile than HAV, acid stable, mild-alkaline stable
  survive in GIT.
- Inactivated by adding Cl^- in water + other agents (like HAV)

* Hepeviridae family, non-enveloped, linear +ve ssRNA
  encodes 3 proteins (structural, replication, unknown)

* Pathogenesis
  - Feco-oral transmission
  - Primary replication in GIT (stool, bile, (liver))
  - excreted in stool during the late incubation Period
  - Not cytopathic, the damage is immune-mediated
  - Cholestatic hepatitis is often presents.

Clinical Features ∞

- Incubation Period (2-8) weeks.
- Early immune response with IgG and IgM Anti-HEV then fall rapidly ↓
- self-limiting, uncommonly cause Fulminant cases except in pregnant ladies. ↓

+ Patients with other chronic liver disease → 30% death

* Diagnosis

Biochemical, Serology, RNA Detection

Look for IgM, IgG ↓ * Reactive RT-PCR ↑ acute inf. Blood ↓ feces

Peaks between (1-4) or (2-4) weeks after onset, then ↓.

* Prevention → Hygiene, Cooking meat thoroughly
→ Vaccines (in endemic areas)

Treatment : Symptomatic / Supportive.

* No specific treatment for acute cases.
* INF-α + Ribavirin → chronic cases

Diagnostic Algorithm for Acute Hepatitis

→ 4 main Serologic tests :

[HBsAg , IgM anti-HAV , IgM anti-HBc , Anti-HCV]

* HBsAg + IgM anti-HBc → Acute HBV inf.
  HBsAg - IgM anti-HBc → Chronic HBV inf.
  IgM anti-HBc alone → Acute HBV inf. also.

* IgM anti-HAV + HBsAg → simultaneous HAV + HBV
  IgM anti-HAV + IgM anti-HBc (± HBsAg) → // + //

* Anti-HCV → Acute HCV inf.
* IF all markers are absent → non A, non B, non C hepatitis

→ For chronic Patients, initial testing : HBsAg + anti-HCV.
→ To evaluate infectivity in HBV chronic inf. →
HBeAg + anti-HBe testing.
→ To evaluate the replication : HBV-DNA test.
* In chronic HBV patients, without HBeAg, and normal aminotransferases → Serial testing to distinguish between inactive carriers and HBeAg-ve chronic HBV patients.
* with any HBV inf (acute/chronic) or severe liver disease
  → test for anti-HDV.