EPIDEMIOLOGY:

- Approx. one third of the global population has been exposed to HBV
  - 350-400 million individuals harbor chronic HBV
  - 1 million people die every year due to the consequences of CHB
    - Cirrhosis, HCC (hepatocellular carcinoma)

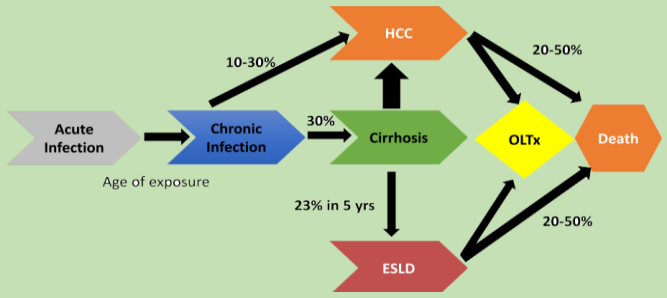
MODE OF TRANSMISSION: contact with blood or bodily fluids

- Perinatal (as high as 90% in HBeAg+ mothers)
- Sexual transmission
- Percutaneous inoculation
  - Needlestick or sharing needles (IVDU)
  - Contaminated tattoo or piercing equipment
- Transfusions
- Close person-to-person contact (RARE)
  - Bites, cuts, toothbrush or razor sharing
  - Breast feeding

MODE OF TRANSMISSION OF HBV & CHRONICITY:

- **HORIZONTAL** (person → person) = LOW RISK OF CHRONICITY
  - Adults and children > 5 years = 2% CHB
  - 1-5 years old = 30% CHB
- **VERTICAL** (mother → newborn) = HIGH RISK OF CHRONICITY
  - > 90% of infected infants progress to CHB

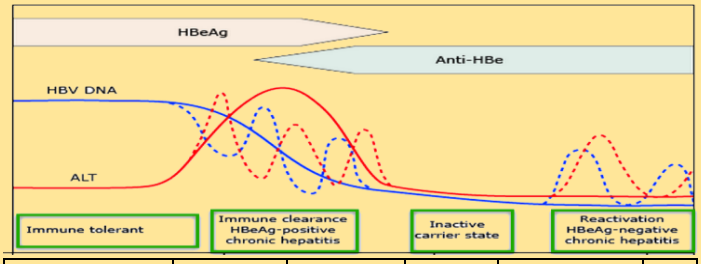
HBV NATURAL HISTORY & COMPLICATIONS:



HEPATITIS B VIRAL PROTEINS:

HBsAG	Hepatitis B surface antigen • Envelope protein • Marker of HBV infection • Antibodies against HBsAg signify recovery • Persistence of HBsAg for > 6 months represents CHB
HBcAG	Hepatitis B core antigen • Structural nucleocapsid core protein • Anti-HBc + signals past exposure
HBeAG	Hepatitis B e antigen • Soluble nucleocapsid protein • Serum marker of active viral replication • Accompanied by high serum HBV DNA (>100,000 – 1 million IU/mL)

CLINICAL PHASES OF CHB:



Phase	HbeAg	HBV DNA	ALT	Liver Histology	Txt
Immune tolerant	Positive	Very high >20,000	Normal	Normal or mild inflammation & scant fibrosis	No
Immune active	Positive or negative	> 2000 (often > 20,000)	Elevated	Degree of inflammation and fibrosis varies	Yes
Inactive chronic carrier	Negative	< 2000	Normal	Normal or mild inflammation	No

INTERPRETATION OF HBV SEROLOGIC PANEL:

TESTS	RESULTS	INTERPRETATION
HbsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HbsAg	Negative	Immune due to natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HbsAg	Negative	Immune due to hepatitis B vaccination
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HbsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	

CURE AS A GOAL OF THERAPY:

- **ACTUAL CURE =** very difficult (if not impossible)
  - True cure = all traces of HBV gone from liver (like HCV)
- **FUNCTIONAL CURE** = attainable!
  - Prevent progression to cirrhosis and ESLD
  - Prevent HCC development

SURROGATE MARKERS FOR RESPONSE:

SEROLOGIC	• HBeAg loss or seroconversion • HBsAg loss or seroconversion (rare) ○ Closest marker to clinical cure
VIROLOGIC	• HBV DNA suppression
BIOCHEMICAL	• Normalization of ALT
HISTOLOGIC	• Improvement in the necroinflammatory grade and stage of fibrosis

AASLD GUIDELINES: WHEN TO START HBV THERAPY

HBeAg positive			HBeAG negative		
HBV DNA (IU/mL)	ALT	Liver disease	HBV DNA (IU/mL)	ALT	Liver disease
> 20,000	≥ 2 x ULN	N/A	≥ 2000	≥ 2 x ULN	N/A
N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis

TREATMENT ALTERNATIVES:

	Dosage	Adjust CrCl	Comments	Preferred
PEGINTERFERON ALFA-2A	180 mcg SC weekly	None	Select populations	X
ENTECAVIR (ETV)	0.5 mg PO daily 1 mg if lamivudine resistance or decompansated cirrhsosis	< 50	High potency, high genetic barrier to resistance	√
TENOFOVIR ALAFENAMIDE (TAF)	25 mg PO daily	< 50		√
TENOFOVIR DISOPROXIL FUMARATE (TDF)	300 mg PO daily	< 15		√
LAMIVUDINE (3TC, LAM)	100 mg PO daily 300 mg PO daily for HIV	< 50	Low genetic barrier to resistance	X

TREATMENT DURATION:

	HbeAg-positive	HbeAG-negative
Peginterferon	48 weeks	Not recommended
Nucleotide analogues	Treat until ALL: • HBV DNA undetectable • HBeAg seroconversion • 6-12 months of consolidation therapy Sustained response in 50-90%	Life-long therapy recommended Relapse frequent even if HBV DNA undetectable

PEG-INTERFERON ALPHA:

- **MOA:** dual immunomodulatory and antiviral activity against HBV
- ↓ cirrhosis, HCC and liver-related death in long-term responders
- Consider in young women contemplating pregnancy, HBeAG +, genotype A and B, ↑ ALT
  - **ADVANTAGES:**
    - Fixed duration of treatment (typically 48 hrs)
    - Superior durable serologic response off treatment
      - 80-90% after 4-8 years
      - Greater rates of HBeAg seroconversion
      - ↑ HBsAG seroconversion
  - **DISADVANTAGES**:
    - +++ side effects
    - Moderate antiviral effect
    - Risk of decompensation in cirrhotics
    - SC injection

LAMIVUDINE:

- The first oral agent approved for hepatitis B
- High rate of drug resistance with longer duration of use
  - 65-70% after 4-5 years of therapy
- +++ landmark trials on clinical outcomes:
  - Slower disease progression and ↓ HCC
  - Benefit in patients with decompensated cirrhosis
  - Safe & effective in ↓vertical transmission (+ HBIG & vaccine)

ENTECAVIR:

- A potent guanosine analogue that inhibits HBV DNA replication at 3 different steps
  - >100-fold more potent than either adefovir or lamivudine
- High genetic barrier for resistance in treatment-naïve
  - 1.2% risk of cumulate resistance in 5 years
  - Resistance ↑ to 51% in 5 years in LAM refractory pts
- Less effective in lamivudine resistance
  - Increase dose to 1.0 mg once daily?

TENOFOVIR DISOPROXIL FUMARATE (TDF):

- An acyclic nucleotide analogue of adenosine
  - Structurally similar to Adefovir
- Potent *in vivo* and *in vitro* activity against both HIV and HBV
- No cross-resistance with lamivudine but there is with adefovir
- Viral breakthrough due to resistance is rare
- Durable HBV DNA suppression (up to 96-130 wks of therapy)
- **ADRs:** renal impairment (AKI, Fanconi's syndrome), decreased BMD

TENOFOVIR ALAFENAMIDE (TAF):

- Improved pharmacokinetics (vs. TDF) = reduces systemic exposure to tenofovir and potentially improves renal and bone safety
  - 92% decrease in systemic exposure to tenofovir with TAF 25 mg vs. TDF 300 mg
- Phase 3 registration trials revealed:
  - TAF non-inferior to TDF in both HBeAg +ve and -ve patients
  - Less reduction in eGFR and BMD
- No dosage adjustments needed in pts with CrCl > 15 mL/min

HEPATITIS B REACTIVATION:

OVERVIEW:

- Clinical syndrome characterized by an abrupt, marked increase in HBV replication usually with elevations in ALT/AST and sometimes with jaundice
  - Loss of immune control over viral replication
- Occurs in pts with active (HBsAg+) and resolved (HBsAg-, anti-HBc+) HBV
- Can occur during treatment with many immunosuppressive agents
  - May occur up to 12 months after IMS treatment
- Preventable by antiviral prophylaxis

DEFINITION OF HBV REACTIVATION:

VIROLOGIC	• 100-fold (2 $\log_{10}$ IU/mL) increase in HBV DNA • De novo detection of HBV DNA or HBeAg • Reverse HBsAg seroconversion
BIOCHEMICAL	• 3-5 fold increase of ALT above baseline (HBV flare)

RISK OF REACTIVATION:

Risk	HBV serology	IMS
Very high (>20%)	HBsAg+	• Anti-CD20 txt • Undergoing HSCT
High (10-20%)	HBsAg+	• High dose steroids * • Anti-CD52 therapy
Moderate (1-10%)	HBsAg+	• Chemotherapy **w/o** glucocorticoids • Anti-TNF therapy • Anti-rejection therapy for SOT
	HBsAg- Anti-HBc+	• Anti-CD20 therapy • Undergoing HSCT
Low risk (<1%)	HBsAg+	• Methotrexate • Azathioprine
	HBsAg- Anti-HBc+	• High dose steroids • Anti-CD52 therapy
Very low risk	HBsAg- Anti-HBc+	• Chemotherapy **w/o** glucocorticoids • Anti-TNF therapy • Anti-rejection therapy for SOT • Methotrexate • Azathioprine

* ≥ 20 mg/day for at least 4 weeks

TREATMENT TO PREVENT HBV REACTIVATION IN HIGH RISK PATIENTS:

- Antiviral therapy be initiated concurrently or prior to immunosuppressive therapy
  - Most experience with preventive therapy has been with lamivudine
  - Tenofovir and entecavir preferred?
- Treatment duration:
  - At least 6 months after withdrawal of IMS (except anti-CD20 therapy)
  - At least 12 months after stopping anti-CD20
    - Lag in recovery of B cell function among these patients
  - Might consider long-term antiviral therapy for patients who have undergone HSCT or SOT since they often remain on chronic IMS

HEPATITIS A:

- RNA virus, 4 human subtypes
- Spread via fecal-oral route
  - More prevalent in low socioeconomic arreas
  - Can occur sporadically or in an epidemic form
- Incubation period average 28-30 days
  - Maximum infectivity in latter half of incubation period to few days after onset of jaundice (= communicability)

CLINICAL PRESENTATION:

- Injury to liver is secondary to host's immune response
- Prodromal symptoms: fatigue, N/V, anorexia, RUQ pain
- Most common findings : jaundice and hepatomegaly (70-80% of cases)
- Marked elevation of ALT (higher than AST) usually > 1000
  - Pecedes bilirubin elevation

DIAGNOSIS:

- Positive HAV IgM antibodies
- HAV IgG antibodies are evidence of previous exposure or vaccination

TREATMENT AND PREVENTION:

- Treatment is supportive and prognosis is good
- Recovery by 3 months (up to 6 months)
- Fatalities are rare (0.1% infants, 0.4% young adults, 1.1% > 40 yrs old)
- Prevention by hand washing, avoidance of water and foods from endemic areas, vaccination
  - Prevention is key = vaccination

HEPATITIS A AND B VACCINE:

- 2 single-antigen inactivated hepatitis A vaccines HAVRIX & VAQTA
  - Two doses q6-12 months
  - Comparable immunogenicity, fewer side effects
- Combo inactivated vaccine, TWINRIX contains both hepatitis A (HAVRIX) and hepatitis-B (Engerix-B)
  - 3 doses (0, 1 and 6 months)
  - Well-tolerated and highly immunogenic)