HEPATITIS B

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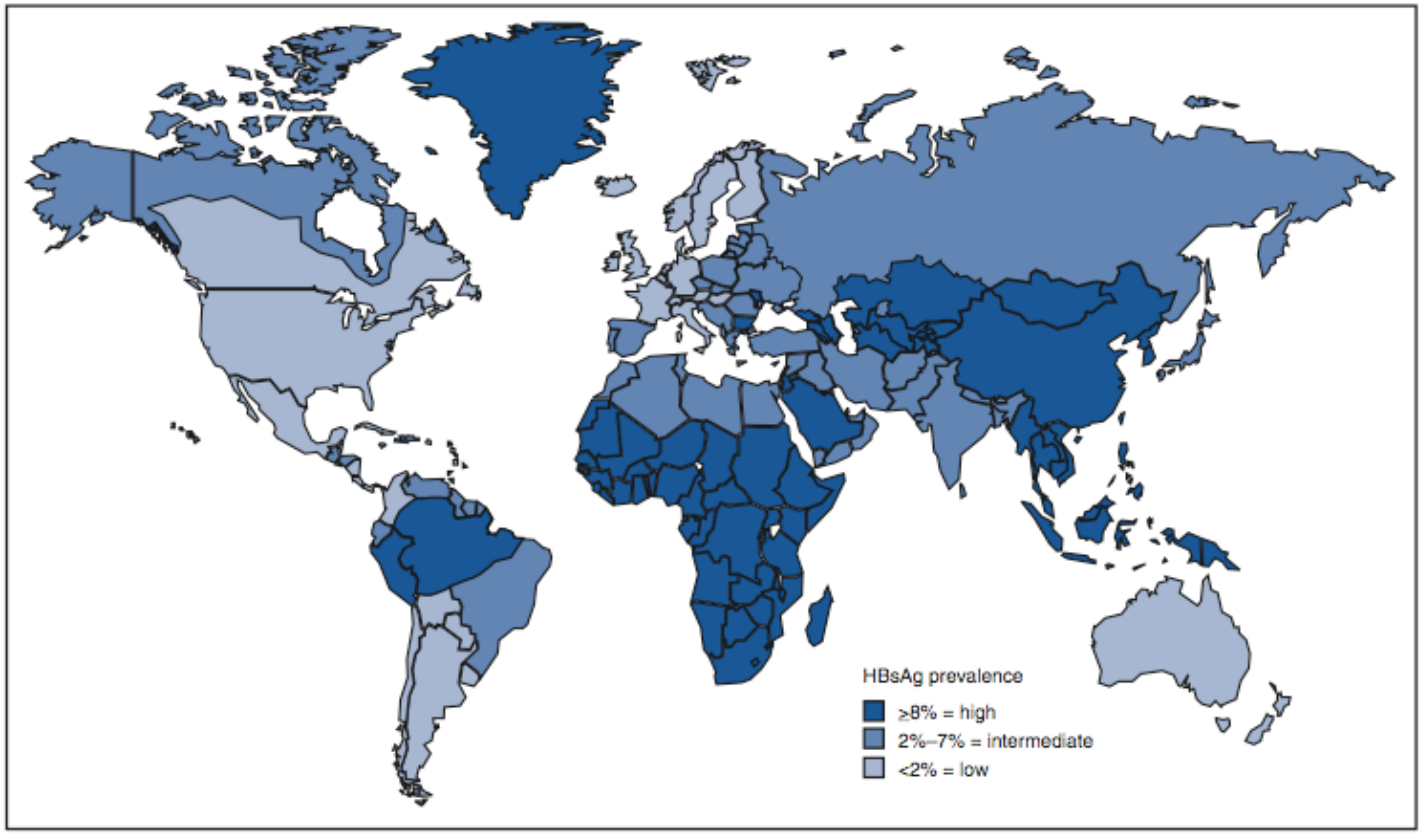
OVERVIEW

- Epidemiology
- Understanding the Markers
- Natural History
- Pregnancy
- Vaccination
- Treatment
- Extrahepatic Manifestations
- Reactivation

AUSTRALIA ANTIGEN

GLOBAL DISEASE

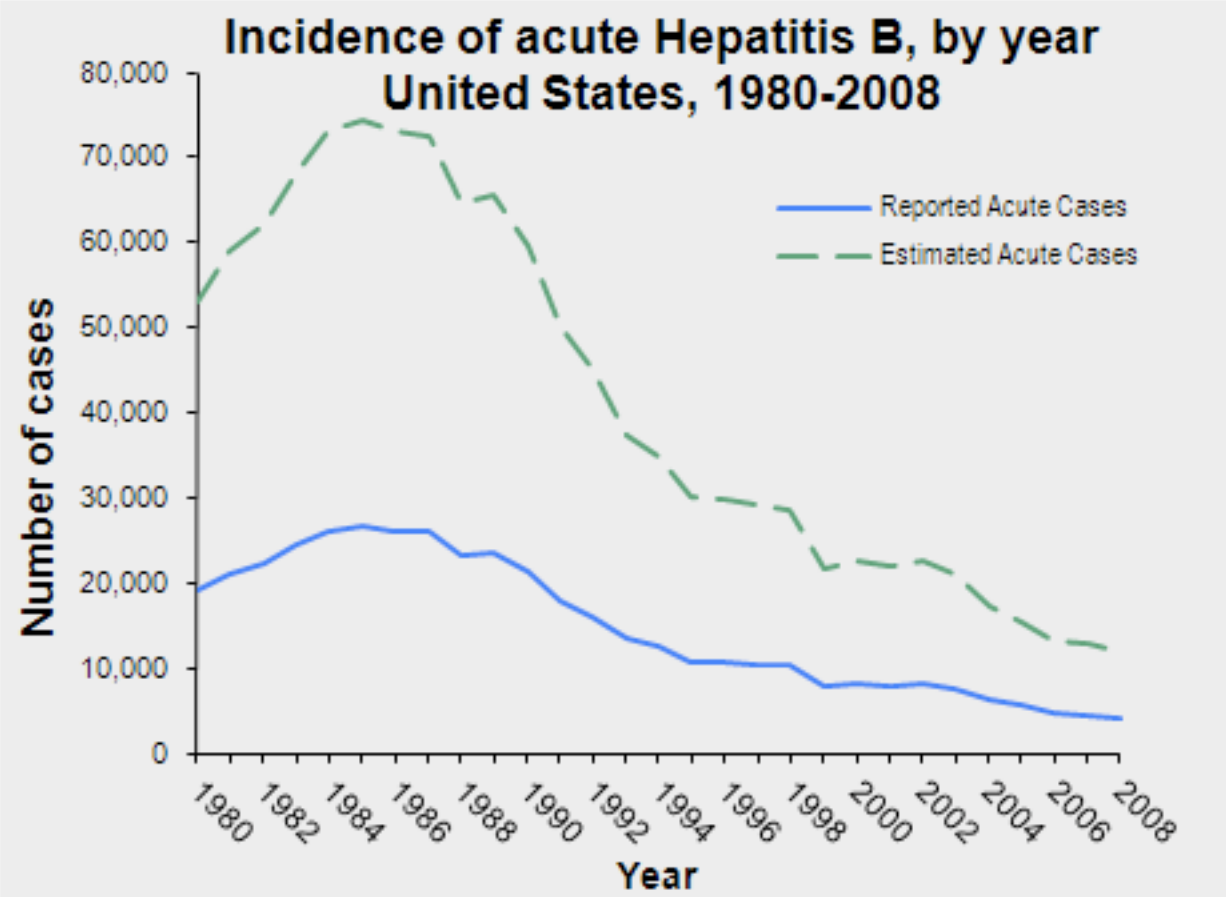
FIGURE 3. Geographic distribution of chronic hepatitis B virus (HBV) infection — worldwide, 2006*



* For multiple countries, estimates of prevalence of hepatitis B surface antigen (HBsAg), a marker of chronic HBV infection, are based on limited data and might not reflect current prevalence in countries that have implemented childhood hepatitis B vaccination. In addition, HBsAg prevalence might vary within countries by subpopulation and locality.

Source: CDC. Travelers' health; yellow book. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. Available at http://wwwn.cdc.gov/travel/yellowbookch4-HepB.aspx.

INCIDENCE OF ACUTE HBV



CDC

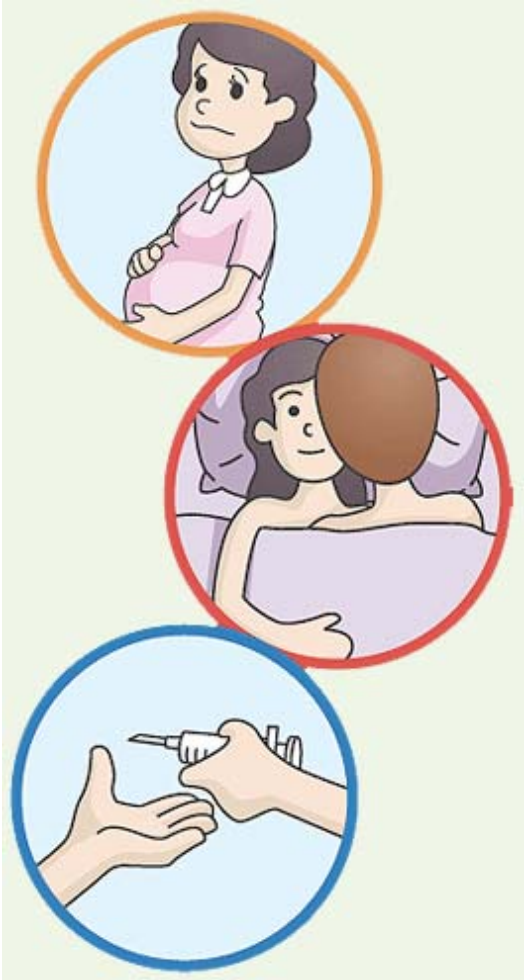
*Acute, Chronic, and Perinatal HBV are all reportable diseases.

HBV IN KY – INCIDENCE PER 100,000

State/Area	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Alabama	1.8	1.9	1.7	2	1.6	2	2.3	2.1	1.8	2	2.1	2.8	2.3
Alaska	2.6	2.5	2.1	2.9	2.1	1.6	1.9	1.2	1.7	1.2	1.2	1.3	1.5
Arizona	5.3	4.4	4	2.9	4.2	3.1	4.6	5.1	5	6.3	†	1.3	1.2
Arkansas	3.7	4.2	4.5	3.8	4.1	4	4.4	3.3	4.3	2.6	3.1	2.5	2.3
California	5.4	5.1	4.4	3.7	3.2	2.5	1.8	1.9	1.4	1.1	1.2	1.1	0.8
Colorado	3.5	3.8	2.6	2.4	2.5	2.3	1.8	1.8	1.2	1.3	0.7	0.7	0.7
Connecticut	2.5	1.7	1.2	1.2	1.4	1.4	2	2.8	3.1	1.4	1.4	1.1	0.9
Delaware	1.2	1	0.5	0.1	1.9	3.6	1.7	1.7	6.4	4.4	5.5	1.7	†
District of Columbia	5.9	5.7	3.6	4.8	6.1	2.3	3.9	2.3	3.4	2.4	1.5	†	†
Florida	4.6	4.4	3.5	3.9	3.8	3.1	3.3	3.7	2.9	2.7	2.3	1.8	1.9
Georgia	0.8	3	2.7	3	4.3	5.2	5.7	7.7	1.2	2.2	2.2	1.6	1.9
Hawaii	1.2	0.9	1.5	1.3	1	1.8	1	2.2	0.9	0.8	0.6	1.3	0.5
Idaho	7.4	4.5	4	2.3	0.8	0.8	0.5	0.6	1	1	1	1	0.8
Illinois	2.8	2.4	1.9	1.7	1.4	1.7	1.5	1	0.9	1.2	1	1	1.4
Indiana	2.5	1.7	2	1.3	1.4	1.2	1.4	1.1	1.3	0.9	1.3	1	1.1
Iowa	2.6	1.5	1.9	1.5	1.3	0.8	0.7	0.6	0.6	1.1	0.7	0.9	0.8
Kansas	1.2	1.2	1.1	0.6	1	0.5	0.9	0.7	0.7	1.2	0.4	0.3	0.3
Kentucky	2	1.1	1.2	1.3	2	1.6	1.6	2.3	2.1	1.6	1.6	1.8	2.4
Louisiana	4.8	4.8	5	3.9	3.5	2.8	3	2.6	1.5	1.5	1.5	2.3	2.1

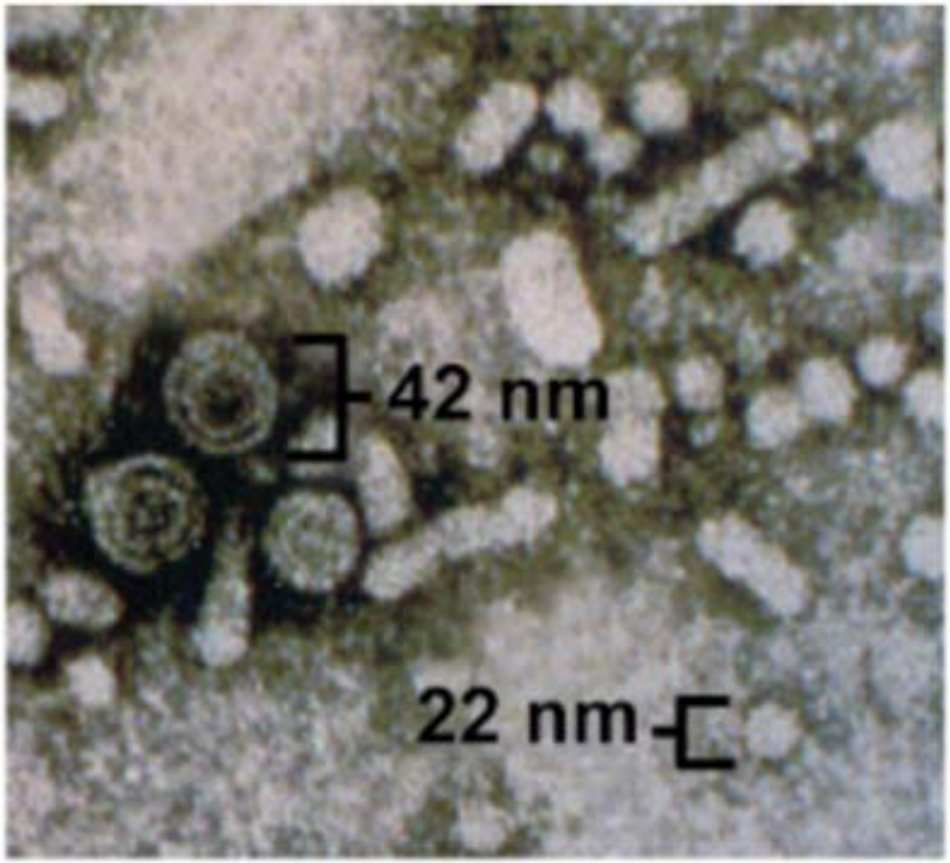
CDC

HBV TRANSMISSION



- Vertical Transmission
- Unprotected Intercourse
- IVDU
- Tattoos
- Blood transfusions
- Organ donation

THE VIRUS



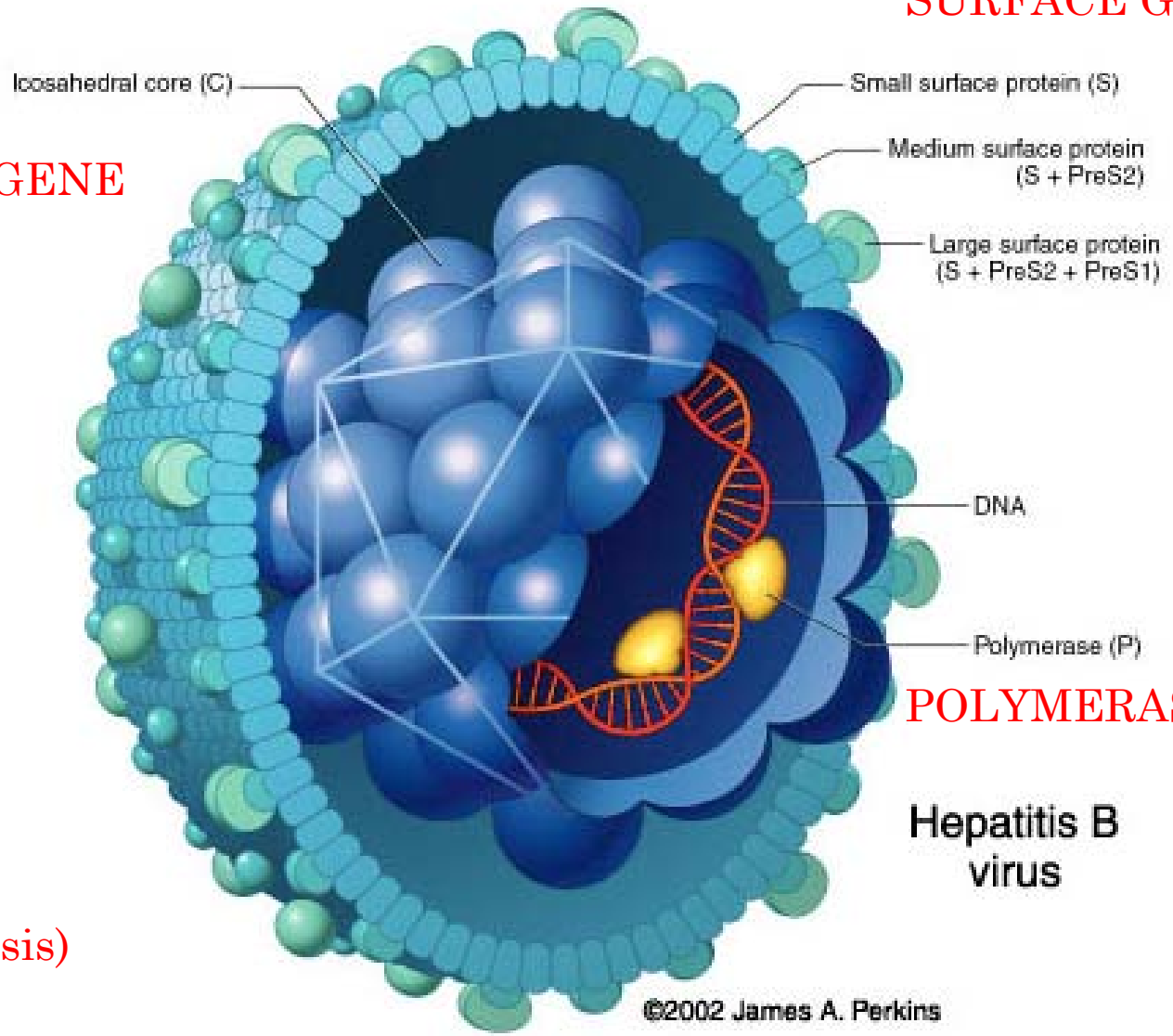
EM of HBV particles!

Hepatology. 2009 May ; 49(5 Suppl): S13–S21

VIRUS

SURFACE GENE

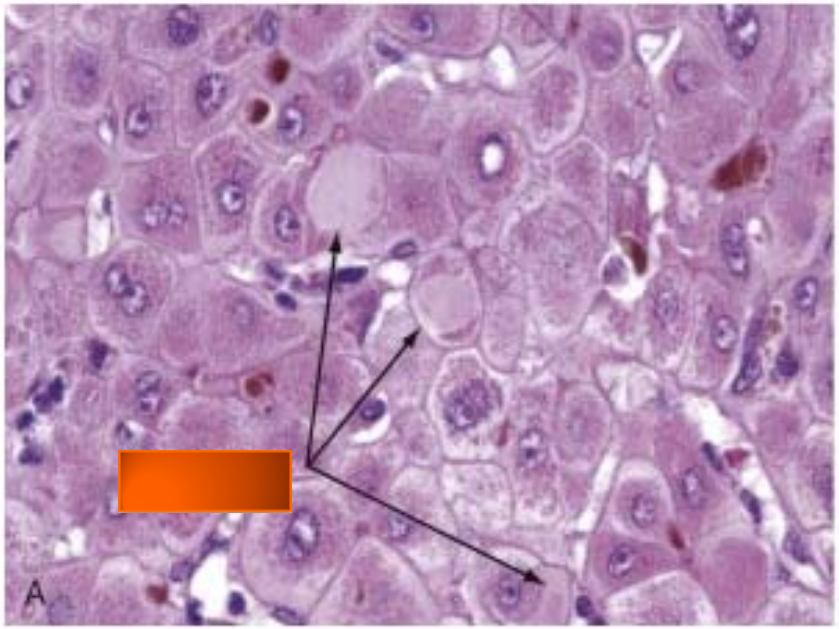
CORE GENE



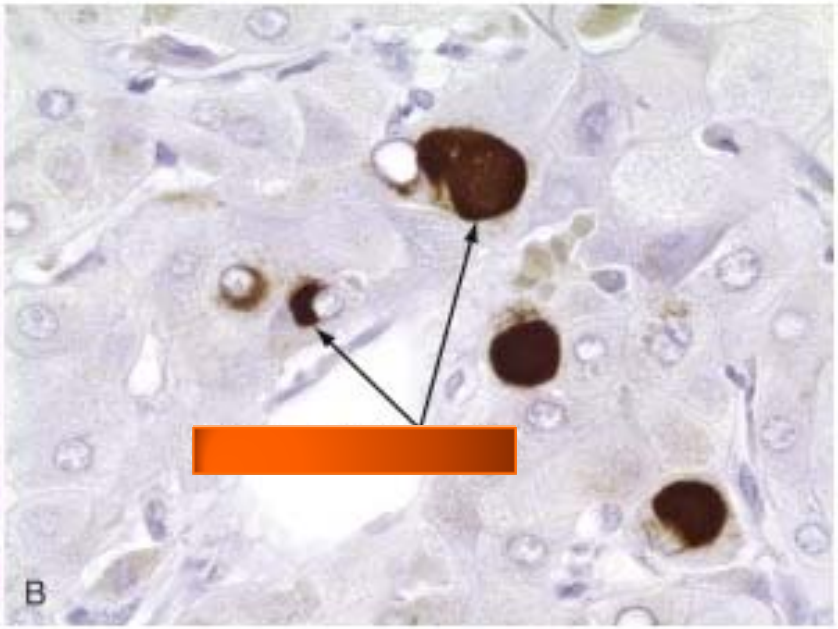
POLYMERASE GENE

X GENE
(possibly
carcinogenesis)

LIVER BIOPSY



H and E Stain



Immunohistochemical Stain

Sleisenger and Fordtran Figure 78-5.

THE MARKERS

- Hepatitis B Surface Antigen = **HBsAg**
  - protein that forms outer coat of HBV
  - high quantities during viral replication
  - presence = acute or chronic infection
  - disappearance = viral clearance
- Hepatitis B Surface Antibody = **HBsAb**
  - antibody directed against surface antigen
  - presence = past infection or vaccination (>10iu/ml)

THE MARKERS

- Hepatitis B Core Antigen
  - does not gain access to serum
  - unable to be detected in blood
- Hepatitis B Core Antibody = **HBcAb**
  - three forms: IgG, IgM, and total
  - IgM = acute HBV or viral reactivation
  - IgG = resolved past infection of chronic carrier state

THE MARKERS

- Hepatitis B e Antigen = **HBeAg**
  - soluble protein encoded by portion of core coding domain
  - presence = acute infection or actively replicat. chronic HBV
  - lose this in resolved acute infection or inactive HBV
  - not present in precore mutant HBV
- Hepatitis B e Antibody = **Anti-HBe**
  - seroconversion usually associated with decrease in DNA and liver disease
- HBV DNA

POP QUIZ

- What lab testing for HBV is performed on donated blood?
- What is the risk of HBV transmission by blood transfusion?

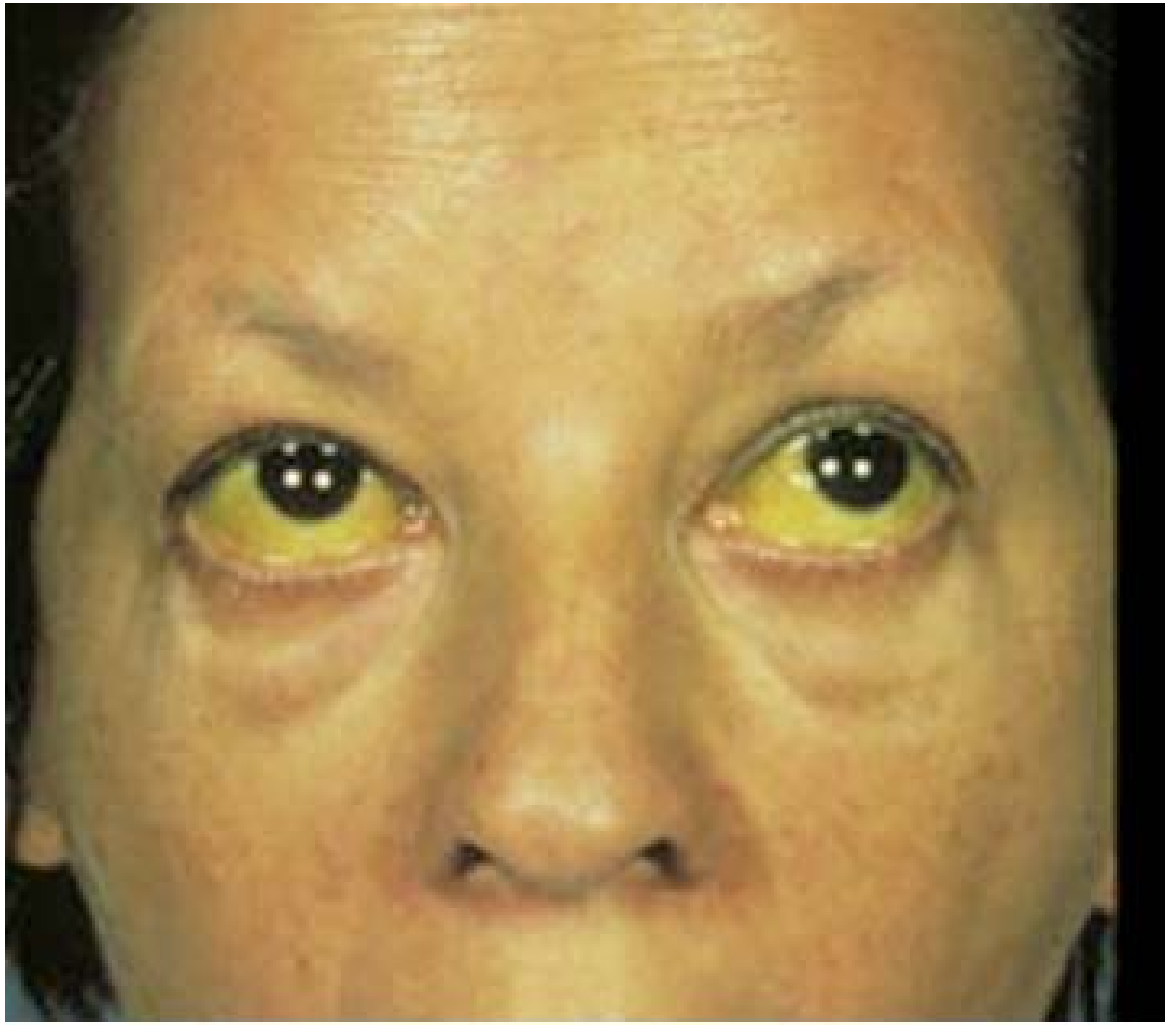
BLOOD TRANSFUSION

- Blood is tested for
  - HBsAg – 1971
  - Anti-HBc – 1986
  - HBV DNA – 2009
    (through nucleic acid testing)
- Transmission Risk
  - **1 in 200,000 - 500,000**

HCV Risk: 1 in 1.4M
HIV Risk: 1 in 2M

American Red Cross

CASE 1



CASE 1

- 52F with PMH HTN admitted to hospital with abd pain, low-grade fever, and jaundice. Mentation is normal. Lab work reveals:

ALT 2000	HBsAg positive
TB 6	Anti-HBc IgM positive
INR 1.1	HBV DNA 1500 IU/ml
Alb 4.0	

Other causes of liver disease are excluded. Risk factors include unprotected sex during foreign travel 12 weeks ago.

**What is your diagnosis?
**What is your treatment?

CASE 1 – ACUTE HBV

- Most likely acute HBV
- Could be reactivation of chronic HBV but in those cases VL >1M IU/ml (can check s:n ratio)
- Acute HBV is asx in 60-80% of cases

- Supportive care
- Given age and + jaundice, low risk chronic infection
- Risk of FHF < 1% in adults
  - Spontaneous survival in FHF = 20%
- Consider treatment in 'protracted hepatitis'
- Ensure resolution and education!

ACUTE HBV MARKERS

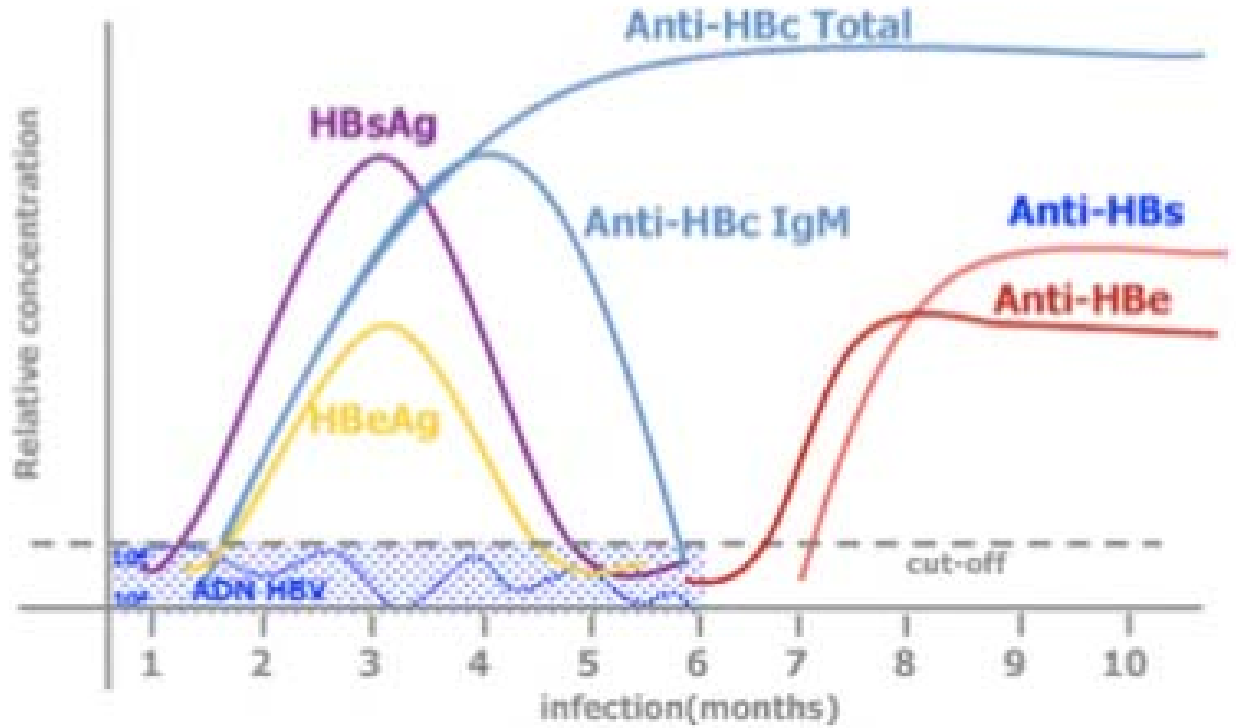
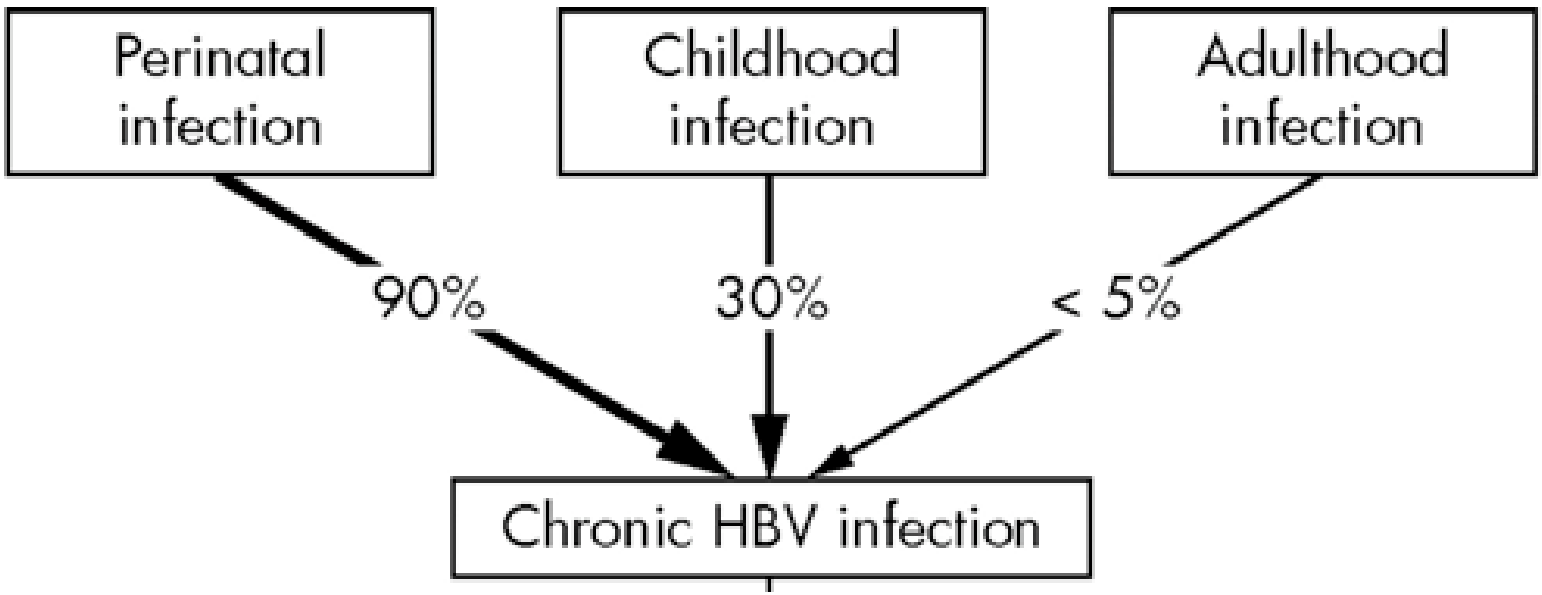


Fig. 3. Evolution of serological markers during resolved acute hepatitis B virus infection.

P. De´ ny, F. Zoulim / Pathologie Biologie 58 (2010) 245–253

PROGRESSION: ACUTE → CHRONIC

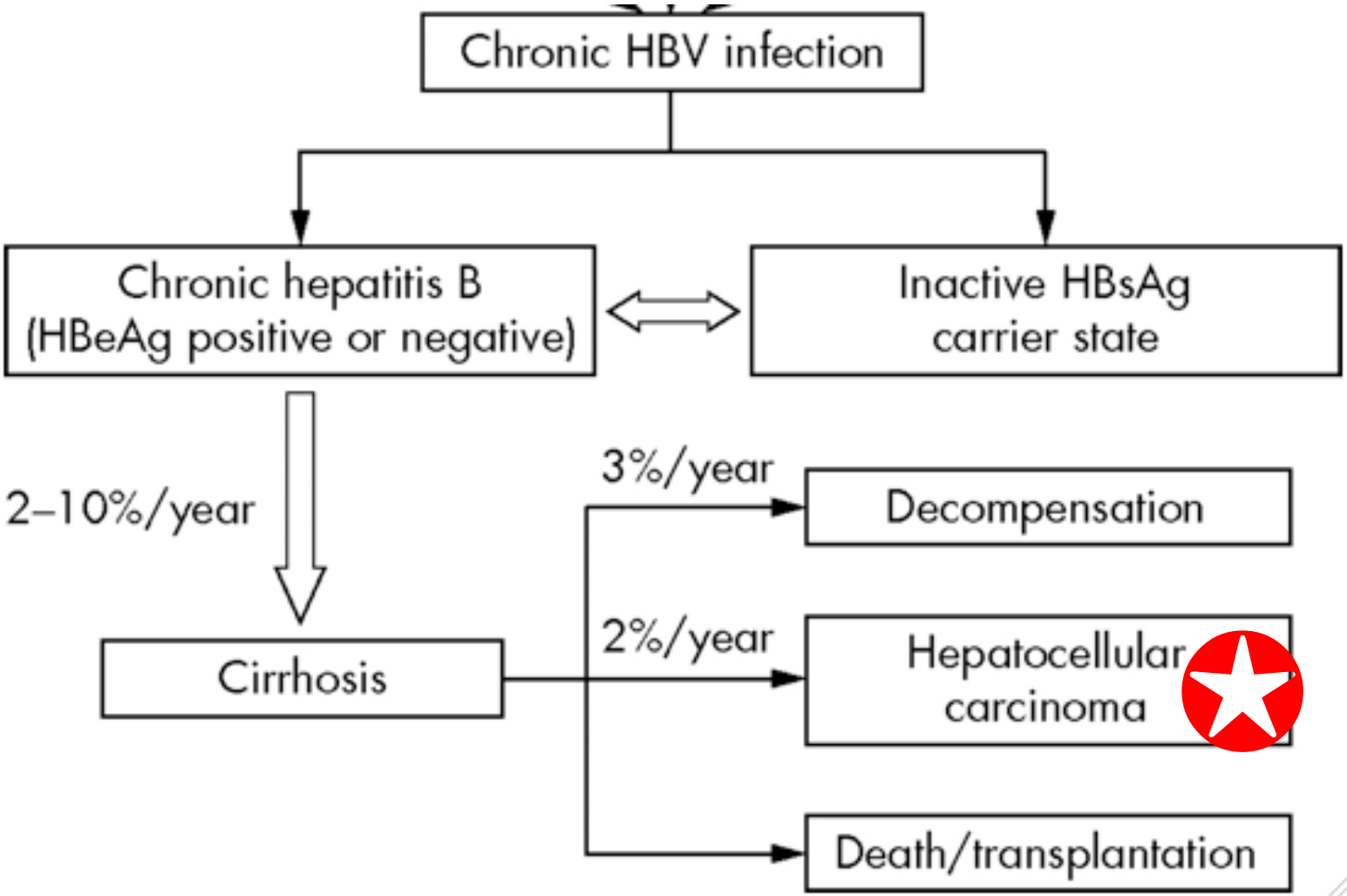


**Risk of Fulminant Failure < 1% (in adults)

*Ann Rheum Dis 2006;**65:983-989***

✪HBV non-cirrhotics also at risk for HCC

PROGRESSION OF HBV



*Ann Rheum Dis 2006;**65:983-989***

CHRONIC HEP B

Chronic hepatitis B

1. HBsAg-positive >6 months
2. Serum HBV DNA >20,000 IU/mL (10^5copies/mL), lower values 2,000-20,000 IU/mL (10^4-10^5 copies/mL) are often seen in HBeAg-negative chronic hepatitis B
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

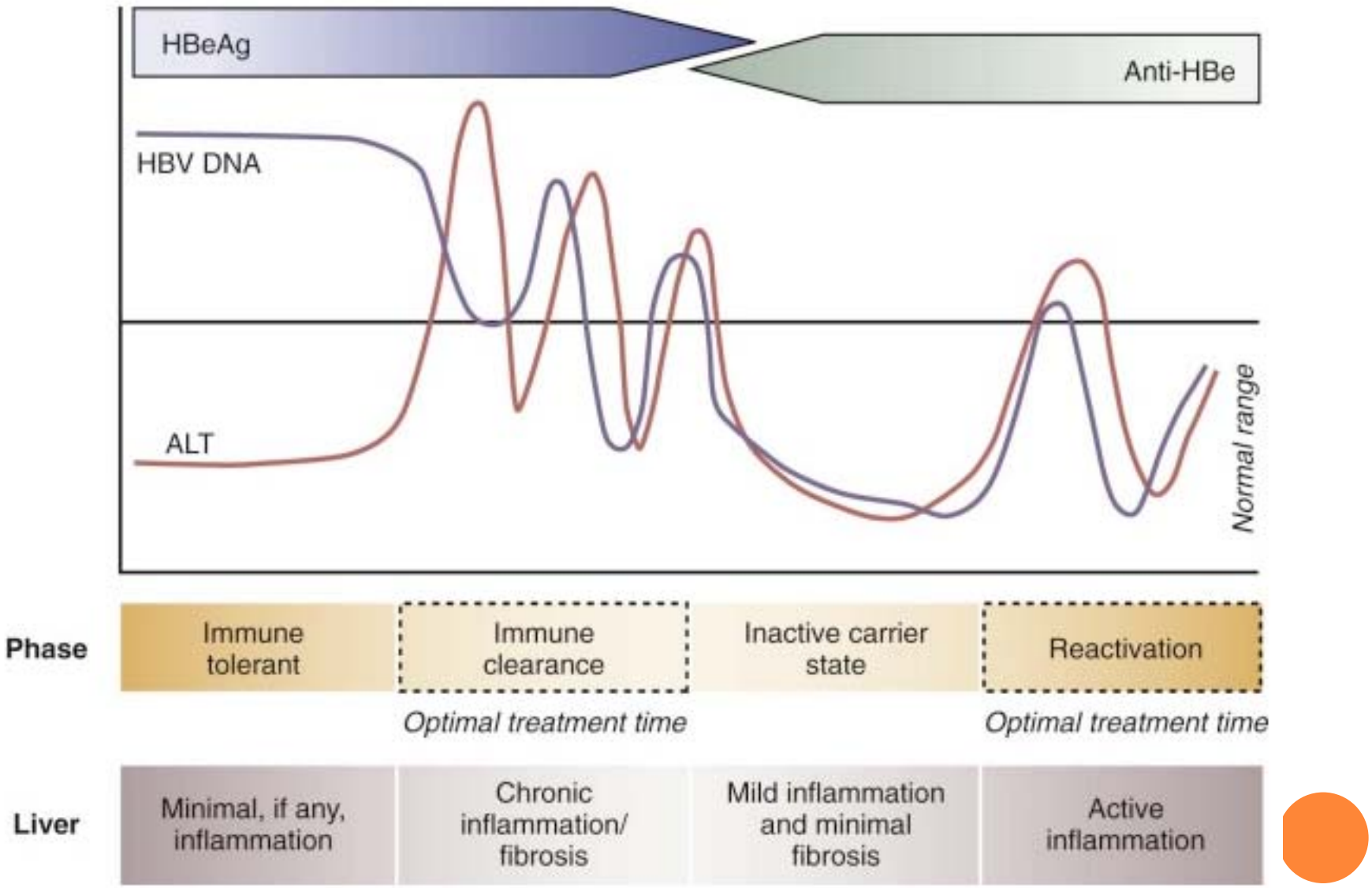
AASLD Practice Guidelines: Chronic Hepatitis B, 2009.

HBV MARKERS

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected

CDC

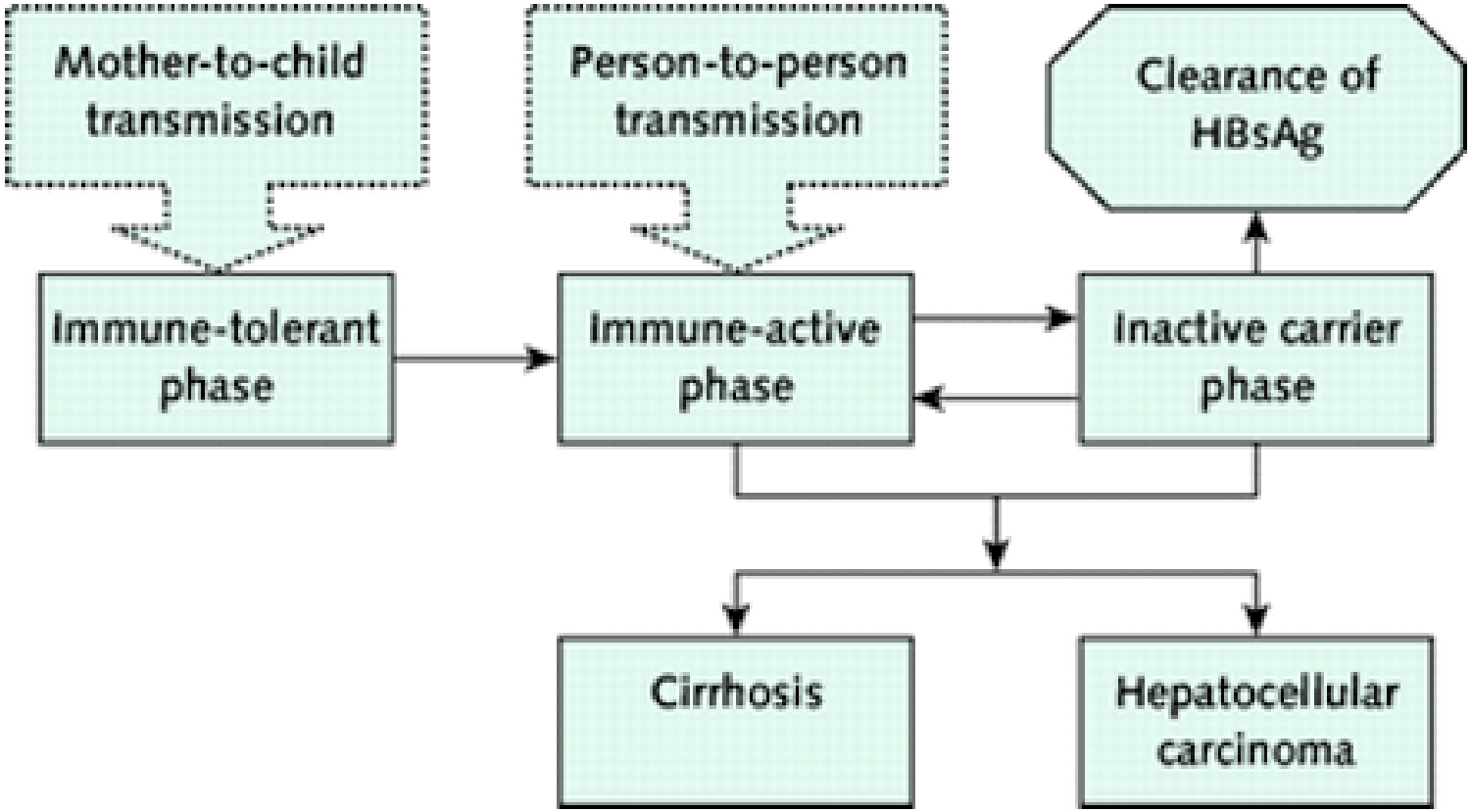
NATURAL HISTORY – CHRONIC HBV



Sleisenger and Fordtran Figure 78-5

NATURAL HISTORY

Figure. Natural history of chronic Hepatitis B Virus infection



NIH Consensus Development. Management of Hepatitis B. 2008.

NATURAL HISTORY

- Immune Tolerant State
  - active viral replications → HBeAg +, HBV DNA +, normal ALT
  - liver bx: no/little inflammation
  - lasts 1 to 4 decades
- Immune Active/Clearance
  - body recognizes HBV as foreign and starts fighting it, starting a robust immune response
  - clinically silent
  - Intermittent/persistent elevations in ALT and HBV DNA
  - liver bx: active inflammation, fibrosis, and cirrhosis (up to 20%)
  - this immune response can prompt seroconversion to inactive state
  - this is the TIME TO TREAT!!

NATURAL HISTORY

- Chronic Inactive State
  - anti-HBe, undetectable/low HBV DNA (<2000 iu/ml), normal ALT
  - can seroconvert to clearance or reactivate
  - can persist indefinitely
- Clearance
  - 1/2 of the chronic inactive will seroconvert to clearance over 25 years
  - seroconversion labs: HBsAg neg, anti-HBs+, HBV DNA undetectable
  - "occult" HBV still with DNA positive (usually <200 IU/ml, but can be up to 10,000 IU/ml)

INACTIVE CARRIERS

1. HBsAg-positive >6 months
2. HBeAg-, anti-HBe+
3. Serum HBV DNA <2,000 IU/mL
4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis

*What is **OCCULT HBV**?
HBsAg Negative
Anti-HBs Positive
Very low DNA levels (normally <200 iu/ml)

RESOLVED HBV

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs
2. HBsAg−
3. Undetectable serum HBV DNA*
4. Normal ALT levels

AASLD Practice Guidelines: Chronic Hepatitis B, 2009.

ISOLATED CORE POSITIVE

HBsAg negative
Anti-HBc positive
Anti-HBs negative

Resolved Acute HBV
Window Acute HBV (IgM)
False-positive test
Chronic HBV
Co-infection with HCV/HIV

~Prevalence in non-endemic areas 1-4% of population

~Overall, 0-30% of these patients have detectable HBV DNA

~OLT transmission risk: up to 50-70% w/o tx

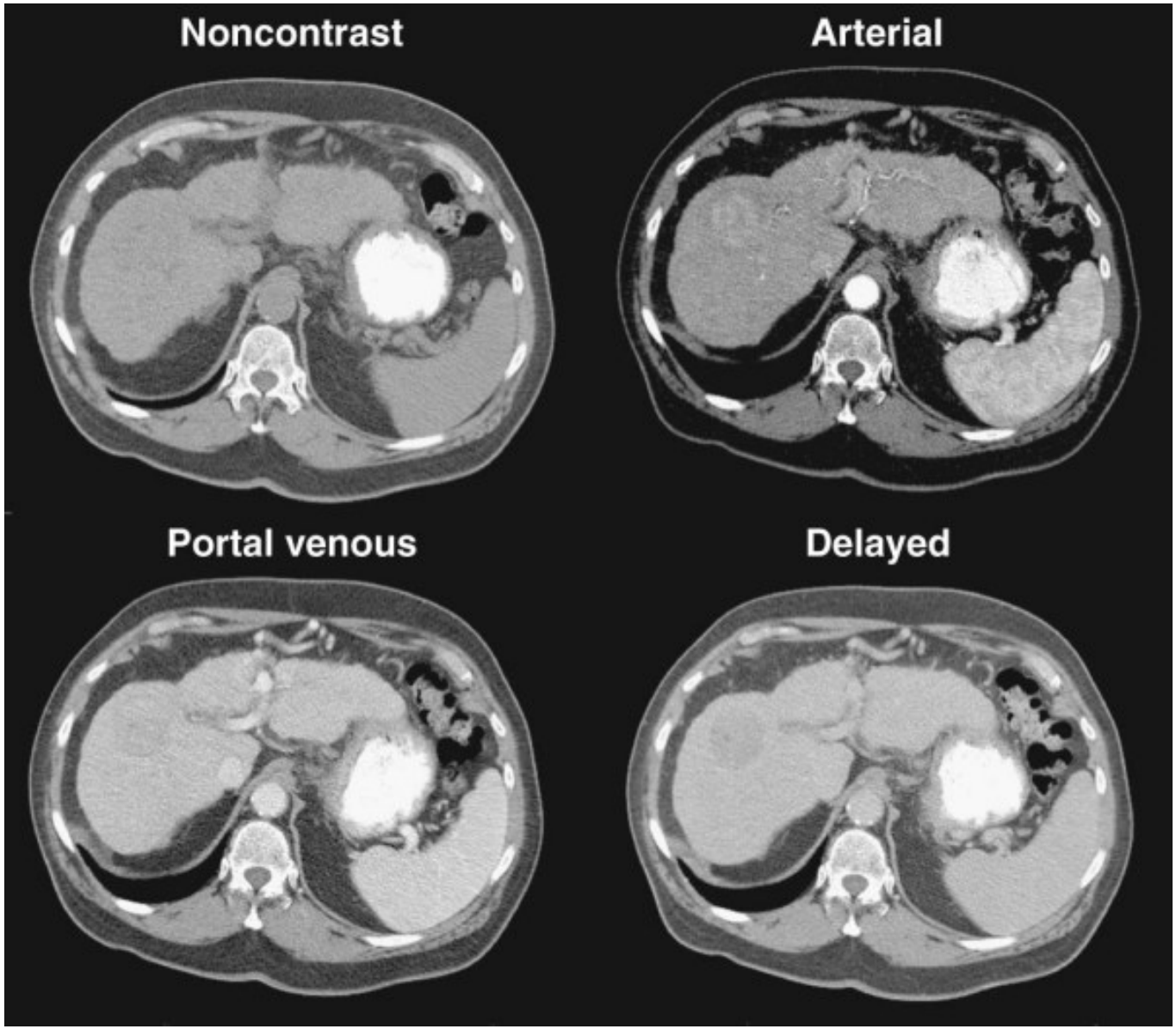
HBSAG AND ANTI-HBS CO-EXISTENCE

- Reported in 25% of HBsAg+ pts
- More commonly represents Chronic HBV, rather than acute HBV
  - Anti-HBS present in low-level, non-neutralizing, and heterotypic subtype of HBsAg
  - Related to minor variant of HBsAg protein

CIRRHOSIS RISK

- Duration of disease
- Persistently elevated VL
  - >2000 IU/ml ~ 10^4 copies
- Older age (>40)
- HBeAg +
- Male
- Alcohol and Tobacco
- Infection with genotype C or D
- Viral Co-infection
  - HCV, HDV, or HIV

HBV COMPLICATION



Sleisenger and Fordtran Figure 94-2.

HEPATOCELLULAR CARCINOMA

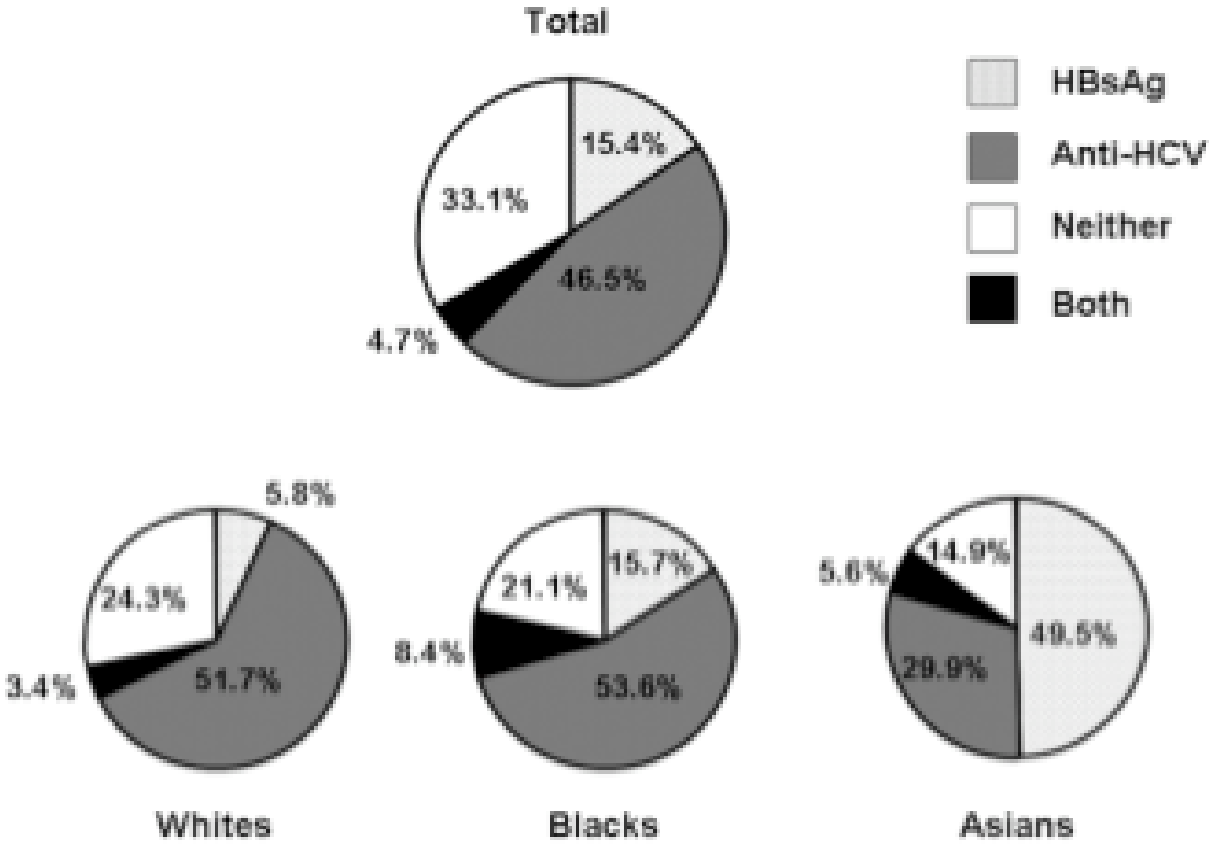


Fig. 1. Etiology of HCC in the United States: Survey of 691 patients with HCC from 13 referral centers. Abbreviations: HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus. Reprinted from American Journal of Gastroenterology.[8]

Hepatology, Vol 49, No 5, Suppl 2009

SCREENING FOR HCC

- Family h/o HCC
- Africans >20
- Asian men >40
- Asian women >50
- Cirrhotics
- Any carrier over 40 with intermittent/persistent ALT elevations or DNA >2000 iu/ml

*** 30-50% of HBV-associated HCC occurs in the ABSENCE of cirrhosis!**

***U/S every 6-12 months!**

AASLD Practice Guidelines: Chronic Hepatitis B, 2009.

CASE 2

- 32F with chronic HBV is pregnant with her first child. She wants to know how she can reduce the risk of transmission to her newborn.

  - What is your recommendation on
    - How to treat the mother?
    - Method of delivery?
    - How to treat the baby?
    - Feeding recommendations?

HBV AND PREGNANCY

- **90%** - Risk of vertical transmission without prophylaxis*
- **95%** - Risk that infected neonate will progress to chronic infection
- **95%** - Chance that neonate will not be infected if given HBIG and vaccination

*60-90% in HBeAg + moms
*15-20% in Anti-HBe + moms

HBV AND PREGNANCY

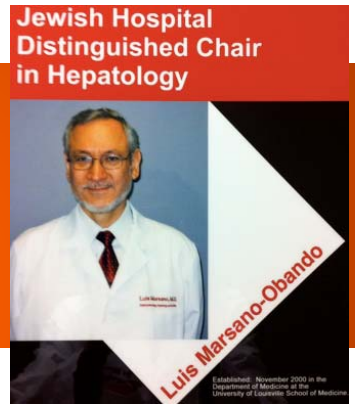
- Baby needs HBIG and vaccination
- If viral load is <100M
  - The risk of transmission is so low with HBIG and vaccination so C-section is not indicated
- If viral load > 100M – 200M
  - Risk of transmission even with HBIG/vaccination is still 30-40%
  - Unknown if c-section is helpful
  - Start oral anti-virals in last 8 weeks of pregnancy and continue 4 weeks post-partum
- Breastfeeding
  - recommended if baby has received HBIG and vaccination

MORE ABOUT BREASTFEEDING. . .

- Most vertical transmissions occur intrapartum
  - Blood transfusion during contractions, membrane rupture, and direct contact with infected secretions
- Risk of vertical transmission related to presence of HBV DNA in placenta and maternal viremia
- Breast milk: presence of HBsAg, HBeAg, and HBV DNA confirmed

IF MOTHER IS ON ANTI-VIRALS: SAFETY OF BREASTFEEDING DEPENDS ON WHO YOU TRUST. . .

Sleisenger and Fordtran



WHO, AAP

Which agent to use?
TENOFOVIR

WJG. Breastfeeding and Chronic HBV Infection: Clinical and Social Implications. 2010 Oct 28: 16(40): 5042-5046

CASE 2: HBV AND PREGNANCY

- How to treat the mother?

  Anti-virals if viral load high.

- Method of delivery?

  No indication for c-section.

- How to treat the baby?

  HBIG & Vaccination, Post-vaccination testing.

- Feeding recommendations?

  Breastfeeding.

PREGNANCY

HBV	HCV
1) Vertical transmission high without treatment	1) Vertical transmission uncommon <5%

2) No indication for c-section

3) No contraindication to breastfeeding

** Vertical transmission of HCV is much greater if high maternal viral load, co-infection with HIV, or IVDU

VACCINATION

- HBV Immune globulin (HBIG)
  - give to all neonates HBV mothers
  - useful for healthcare workers after exposure (though most are given active vaccination)
  - HBV OLT patients
- Plasma-derived Vaccine
  - made from pts with active Hep B
  - concern for communicable diseases, but cheaper
- Recombinant Vaccine
  - cloned s-genome into yeast to make HBsAb.

PASSIVE PROPHYLAXIS

ACTIVE VACCINATION

**Both vaccines result in high titers in >90% in 4-6 months after 3 doses.

VACCINATION

- All children and adolescents
- All high-risk groups
- Post-vaccination testing:
  - Health-care and public safety workers
  - Infants from HBsAg+ mothers (at 9-15 months)
  - Hemodialysis patients (1 month after 3rd dose, then yearly)
  - Sexual partners of HBsAg+ pts (1 month after 3rd dose)

BOOSTER SHOT?
HBsAb can decrease over time.
If level ever >100 Iu/ml, no need to revaccinate.
If less than 100, give booster shot and recheck in 3w.
If still less than 100, give full course of vaccination.

HIGH-RISK GROUPS

Heath care workers

Hemodialysis patients

Household contacts and sexual partners of HBV carriers or patients with acute hepatitis B

Injection drug users

Inmates of correctional facilities

International travelers to areas endemic for HBV who may have intimate contact with the local population or take part in medical activities

Men who have sex with men

Patients who are likely to require multiple transfusions with blood or blood products

Patients with chronic liver disease (other than chronic hepatitis B)

Potential organ transplant recipients

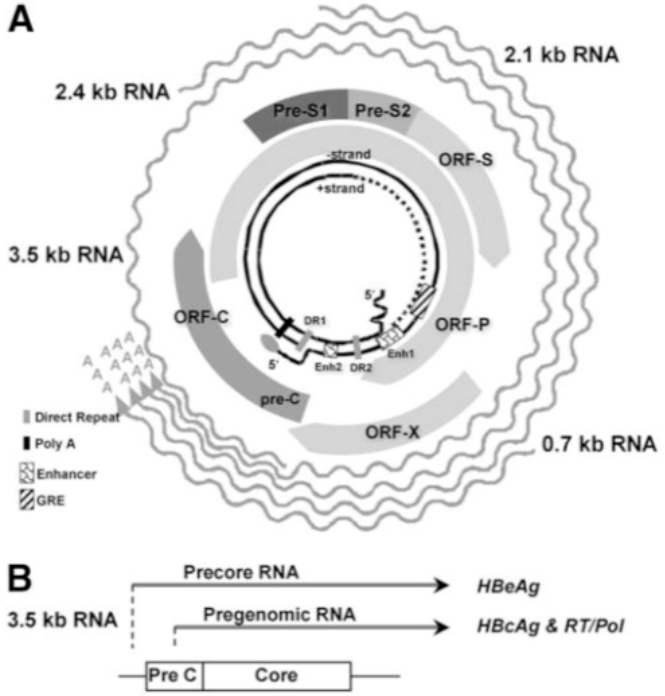
Public safety workers with likelihood of exposure to blood

Sexually active heterosexual men and women, if they have more than one partner

Staff and clients of institutions for developmentally disabled

Sleisenger and Fordtran Table 78-6.

MUTANT



- Precore
  - common
  - does NOT express HBe antigen
- Basal Core
  - decreases HBe antigen production ~70%
- Surface mutation
  - uncommon
- Polymerase mutations
  - drug resistance

Example: 45M with Chronic HBV has lost HBeAg. Still with elevated ALT and + DNA.

--Think precore mutant. Not in inactive carrier state, is actually in immune clearance phase! ie TREAT.

Precore and Basal Core Mutations:
are common, significantly increase HCC risk, implicated in severe/fulminant hepatitis

Hepatology. 2009 May ; 49(5 Suppl): S13–S21

INITIAL EVALUATION

1. History and physical examination
2. Family History of liver disease, HCC
3. Laboratory tests to assess liver disease—complete blood counts with platelets, hepatic panel, and prothrombin time
4. Tests for HBV replication—HBeAg/anti-HBe, HBV DNA
5. Tests to rule out viral coinfections—anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV in those at risk
6. Tests to screen for HCC–AFP at baseline and, in high risk patients, ultrasound
7. Consider liver biopsy to grade and stage liver disease - for patients who meet criteria for chronic hepatitis

AASLD Practice Guidelines: Chronic Hepatitis B, 2009.

GOALS OF THERAPY

- Improve QOL and survival by preventing progression of the disease to cirrhosis, ESLD, HCC, and death.
- Chronic HBV cannot be completely eradicated

IDEAL END POINT

- Sustained off-therapy loss of HBsAg
  - Infrequently achievable

REALISTIC END POINTS

- Sustained off-therapy virological/biochemical response in HBeAg Neg
  - HBeAg neg at baseline or seroconversion with treatment
- Maintained virological remission on therapy

EASL Clinical Practical Guidelines: Chronic HBV Infection 2012

TREATMENT

CONVERT ACTIVE INFECTION → INACTIVE STATE

suppress DNA level seroconversion to anti-HBe

Clear Benefit

- HBeAg POS WITH
  - Elevated ALT
  - HBV DNA >200K
  - Active hepatitis on bx
- HBeAg NEG WITH
  - Elevated ALT
  - HBV DNA >2000
  - Active hepatitis on bx

No Clear Benefit

- HBeAg POS/NEG
  - Normal ALT
  - Min inflammation on bx

CAVEAT: Pts with long-standing HBV may not have increased ALT levels. At age 40, do a LIVER BX to assess their disease state!

TREATMENT- LIFE-THREATENING DISEASE

Clear Benefit

- Acute Liver Failure ← (Well, some controversy here. . .)
- Decompensated Cirrhosis
- Severe Hepatitis Flare
- Compensated Cirrhosis

☑Oral agents
☒ Interferon

TREATMENT – ORAL AGENTS

PREFFERRED	LESS PREFFERRED
Entecavir (Baraclude)	Lamivudine
Tenofovir (Viread)	Adefovir
	Telbivudine

Lamivudine: highest resistance risk
Entecavir: lowest resistance risk
Adefovir: nephrotoxicity
Tenofovir: nephrotoxicity

WARNING: Do NOT believe DDSEP length of treatment recs!!

*Continue all oral antivirals for at least **6-12 months** post sero-conversion.

*Safe to use these in cirrhotics (adefovir safety in decompensated not studied)

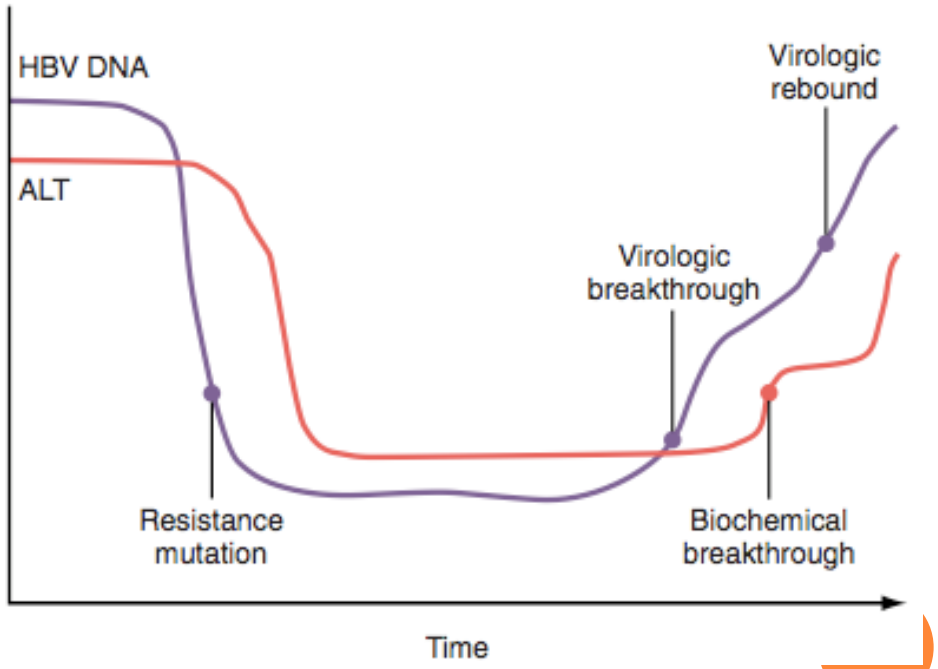
HBeAg	HBV DNA (PCR)	ALT	Treatment Strategy
+	>20,000 IU/mL	≤2 × ULN	Low efficacy with current treatment. Observe; consider treatment when ALT becomes elevated. Consider biopsy in persons > 40 years, ALT persistently high normal-2x ULN, or with family history of HCC. Consider treatment if HBV DNA >20,000 IU/mL and biopsy shows moderate/severe inflammation or significant fibrosis.
+	>20,000 IU/mL	>2 × ULN	Observe for 3-6 months and treat if no spontaneous HBeAg loss. Consider liver biopsy prior to treatment if compensated. Immediate treatment if icteric or clinical decompensation. IFNα/pegIFNα , LAM, ADV, ETV, TDF or LdT may be used as initial therapy. ADV not preferred due to weak antiviral activity and high rate of resistance after 1st year. LAM and LdT not preferred due to high rate of drug resistance. End-point of treatment – Seroconversion from HBeAg to anti-HBe. Duration of therapy: ● IFN-α: 16 weeks ● PegIFN-α: 48 weeks ● LAM/ADV/ETV/LdT/TDF: minimum 1 year, continue for at least 6 months after HBeAg seroconversion IFNα non-responders / contraindications to IFNα → TDF/ETV.
−	>20,000 IU/mL*	> 2 x ULN	IFN-α/peg IFN-α, LAM, ADV, ETV, TDF or LdT may be used as initial therapy. LAM and LdT not preferred due to high rate of drug resistance ADV not preferred due to weak antiviral activity and high risk of resistance after 1st year. End-point of treatment – not defined Duration of therapy: ● IFN-α/pegIFN-α: 1 year ● LAM/ADV/ETV/LdT/TDF: > 1 year IFNα non-responders / contraindications to IFN-α → TDF/ETV.
−	>2,000 IU/mL	1->2 x ULN	Consider liver biopsy and treat if liver biopsy shows moderate/severe necroinflammation or significant fibrosis.
−	≤2,000 IU/mL	≤ULN	Observe, treat if HBV DNA or ALT becomes higher.
+/−	detectable	Cirrhosis	Compensated: HBV DNA >2,000 IU/mL–Treat, LAM/ADV/ETV/LdT/TDF may be used as initial therapy. LAM and LdT not preferred due to high rate of drug resistance; ADV not preferred due to weak antiviral activity and high risk of resistance after 1st year. HBV DNA <2,000 IU/mL–Consider treatment if ALT elevated. Decompensated: Coordinate treatment with transplant center, LAM (or LdT) +ADV, TDF or ETV preferred. Refer for liver transplant.
+/−	undetectable	Cirrhosis	Compensated: Observe. Decompensated: Refer for liver transplant.

AASLD Practice Guidelines: CHB, 2009.

HBV TREATMENT

- Check HBV DNA q3 months
- Primary Treatment Failure:
  - Less than 1-log decline in DNA at 12 weeks
  - Switch to a different agent
- If sudden rise in DNA
  - Medication compliance?
  - Virological breakthrough? (ie drug resistance)

* To avoid drug resistance, don't treat patients who are unlikely to respond!



Sleisenger and Fordtran Figure 78-6

Results of **HBeAg Pos** Patients

	Nucleoside analogues			Nucleotide analogues	
	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Dose*	100 mg	600 mg	0.5 mg	10 mg	245 mg
[Ref.]	[63, 65-68]	[68]	[67]	[69, 70]	[70]
Anti-HBe seroconversion (%)	16-18	22	21	12-18	21
HBV DNA <60-80 IU/ml (%)	36-44	60	67	13-21	76
ALT normalisation# (%)	41-72	77	68	48-54	68
HBsAg loss (%)	0-1	0.5	2	0	3

Results of **HBeAg Neg** Patients

	Nucleoside analogues			Nucleotide analogues	
	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Dose*	100 mg	600 mg	0.5 mg	10 mg	245 mg
[Ref.]	[68, 90-92]	[68]	[92]	[70, 93]	[70]
HBV DNA <60-80 IU/ml (%)	72-73	88	90	51-63	93
ALT normalisation# (%)	71-79	74	78	72-77	76
HBsAg loss (%)	0	0	0	0	0

EASL Clinical Practical Guidelines: Chronic HBV Infection 2012

FOLLOW-UP FOR PTS NOT BEING TREATED

HBeAg+, HBV DNA >20,000 IU/mL and normal ALT

- ALT q 3-6 months, more often if ALT becomes elevated
- If ALT levels are between 1-2 × ULN, recheck ALT q1-3 months; consider liver biopsy if age >40, ALT borderline or mildly elevated on serial tests. Consider treatment if biopsy shows moderate/severe inflammation or significant fibrosis
- If ALT > 2 × ULN for 3-6 months and HBeAg+, HBV DNA > 20,000 IU/mL, consider liver biopsy and treatment
- Consider screening for HCC in relevant population

Inactive HBsAg carrier state

- ALT q 3 months for 1 year, if persistently normal, ALT q 6-12 months
- If ALT > 1-2 × ULN, check serum HBV DNA level and exclude other causes of liver disease. Consider liver biopsy if ALT borderline or mildly elevated on serial tests or if HBV DNA persistently ≥2,000 IU/mL. Consider treatment if biopsy shows moderate/severe inflammation or significant fibrosis
- Consider screening for HCC in relevant population

AASLD Practice Guidelines: Chronic Hepatitis B, 2009.

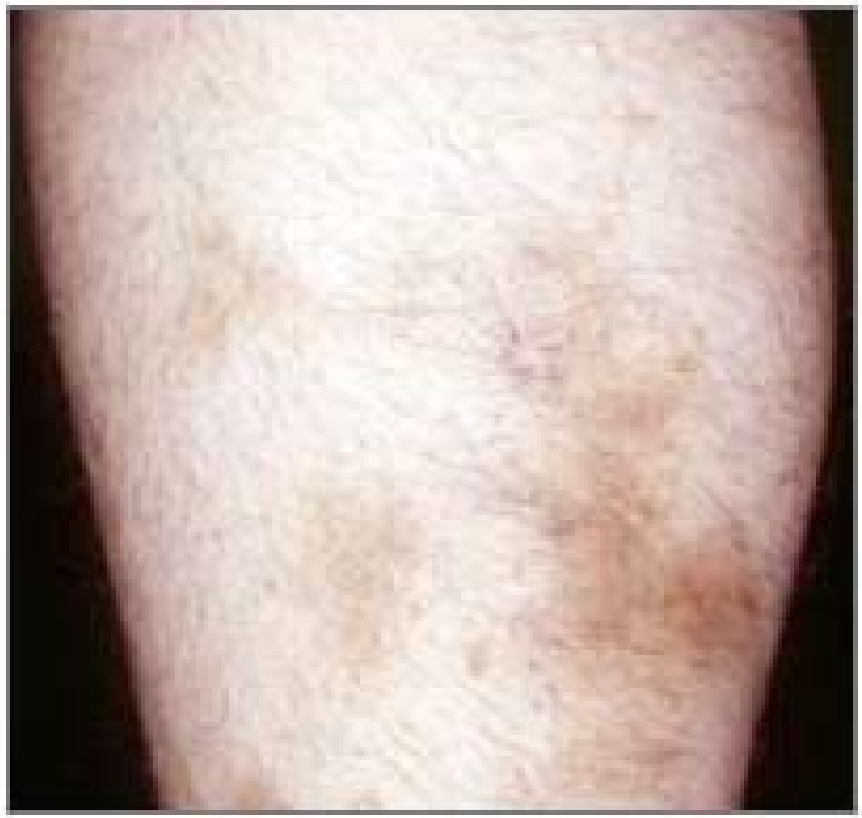
CASE 3

- 52M with no sig PMH admitted with fever, large-joint arthritis, abd pain, and numbness of the R arm and L lower leg. Pt is sick-appearing and has a skin lesion. HTN is noted.

Labs significant for mild anemia, normal LFTs and elevated Cr. Urine studies show mild proteinuria. EMG shows asymmetric nerve involvement.

Due to clinical suspicion, HBsAg is ordered and found to be positive.

CASE - CUTANEOUS LESION

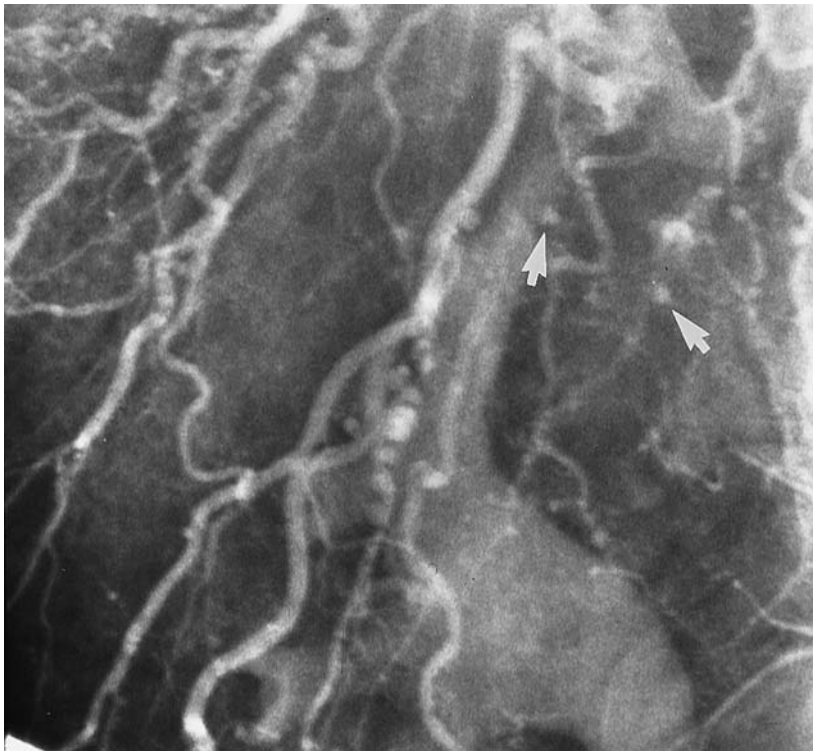


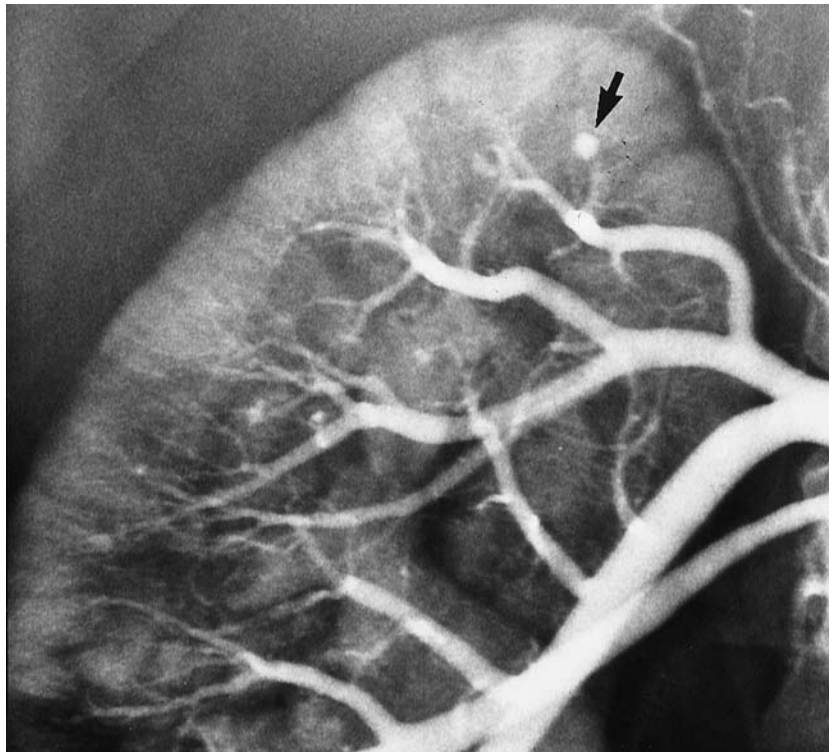
Firm, subcutaneous nodules on the shin

Jacobs-Kosmin. Medscape.

WHAT ARE YOU THINKING? WHAT IS YOUR NEXT TEST?

CASE 3





Angiograms of the Liver (left) and Kidney (right)

Stanson A W et al. Radiographics 2001;21:151-159

CASE 3 – HBV-ASSOCIATED PAN

- Vasculitis affecting small and medium arteries of the body
  - Microaneuryms, thrombosis, ischemia/infarcts, hemorrhage
  - Multiorgan involvement: kidney, liver, mesenteric arteries, nerves, joints
- Diagnosis
  - Clinical presentation with angiogram showing multiple vascular aneurysm and corkscrewing of blood vessels
  - 'Gold standard': tissue bx showing medium-sized vasculitis
- Treatment
  - Poor prognosis without aggressive therapy – overall 5-year survival is 50-70%
  - Anti-virals
  - Plasmapheresis

EXTRAHEPATIC MANIFESTATIONS

- Polyarteritis nodosa
- Cryoglobulinemia
- Glomerulonephritis
  - Membranous
  - Membranoproliferative
  - Mesangial proliferative
- Arthritis-Dermatitis (acute HBV)
- Aplastic Anemia (acute HAV and acute HBV)

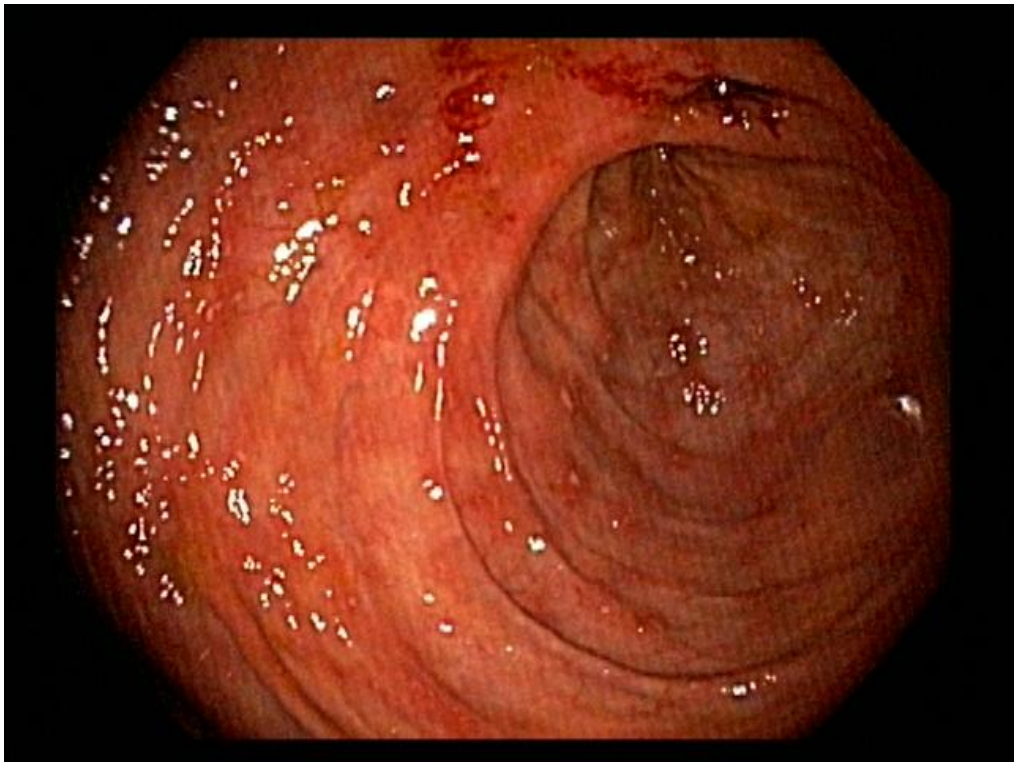
Much more frequent with HCV!

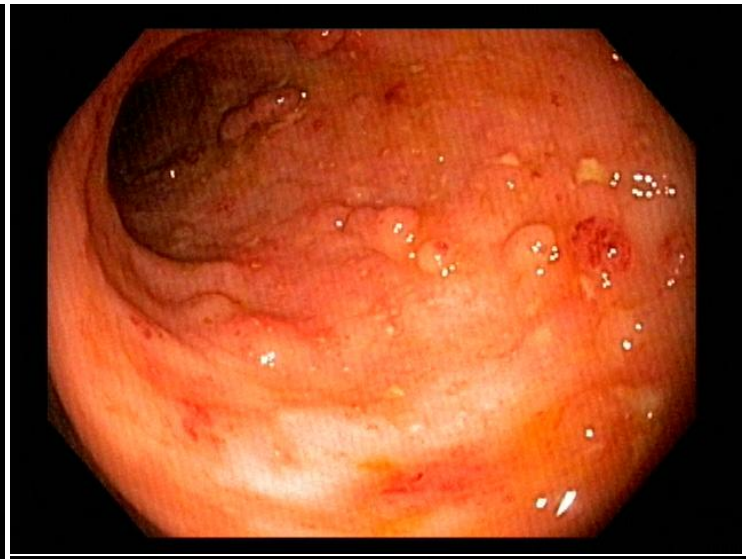
*HBV-GNs often present with nephrotic syndrome

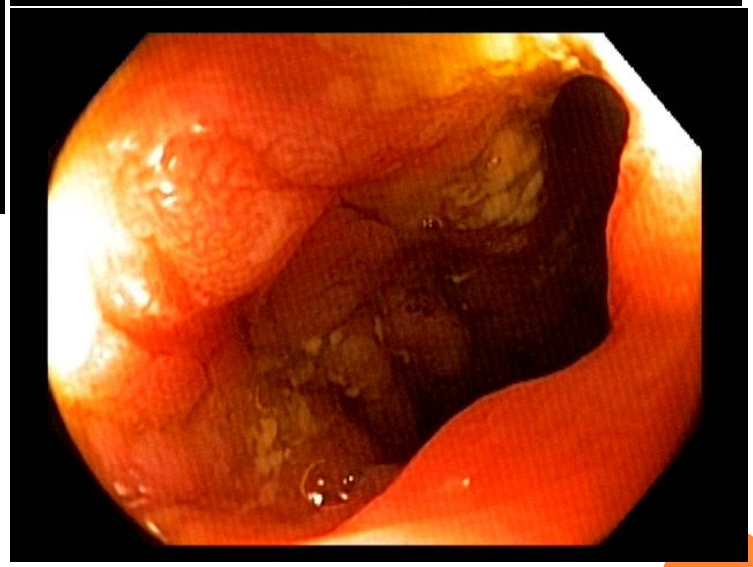
CASE 4

- A 33cMwith PMH EtOH/tobacco abuse diagnosed initially with UC 10 years ago, then later changed to Crohn's. Infrequently sees MD, seen for first time in GI clinic with worsened abd pain and increase #BMs. Placed on steroids and colonoscopy ordered. Endoscopy shows. . .

CASE 4 – COLONOSCOPY FINDINGS







1) What do you think he will need?

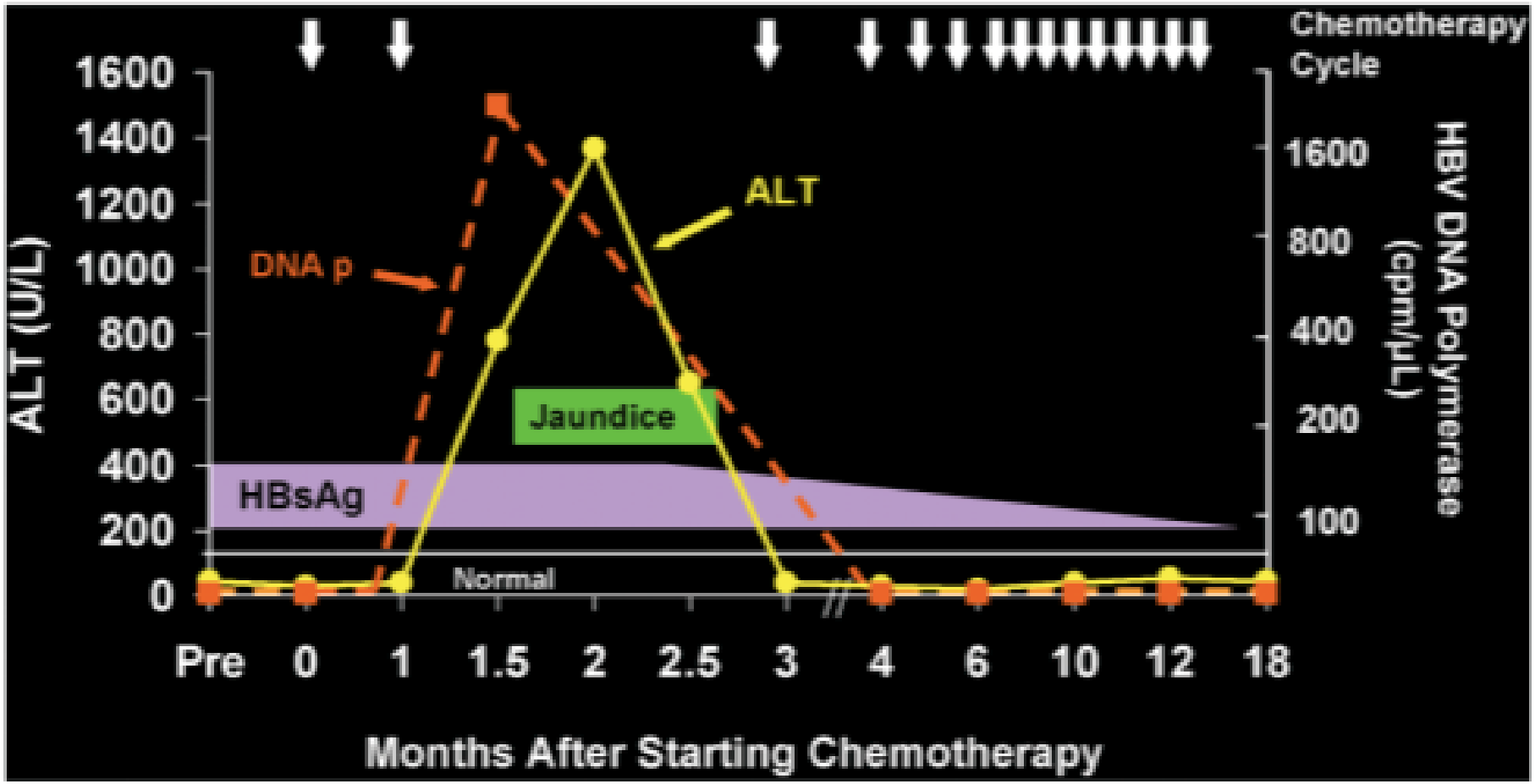
2) What do you worry about with these treatments?

3) What lab tests do you need to order before starting such treatment?

REACTIVATION OF HBV

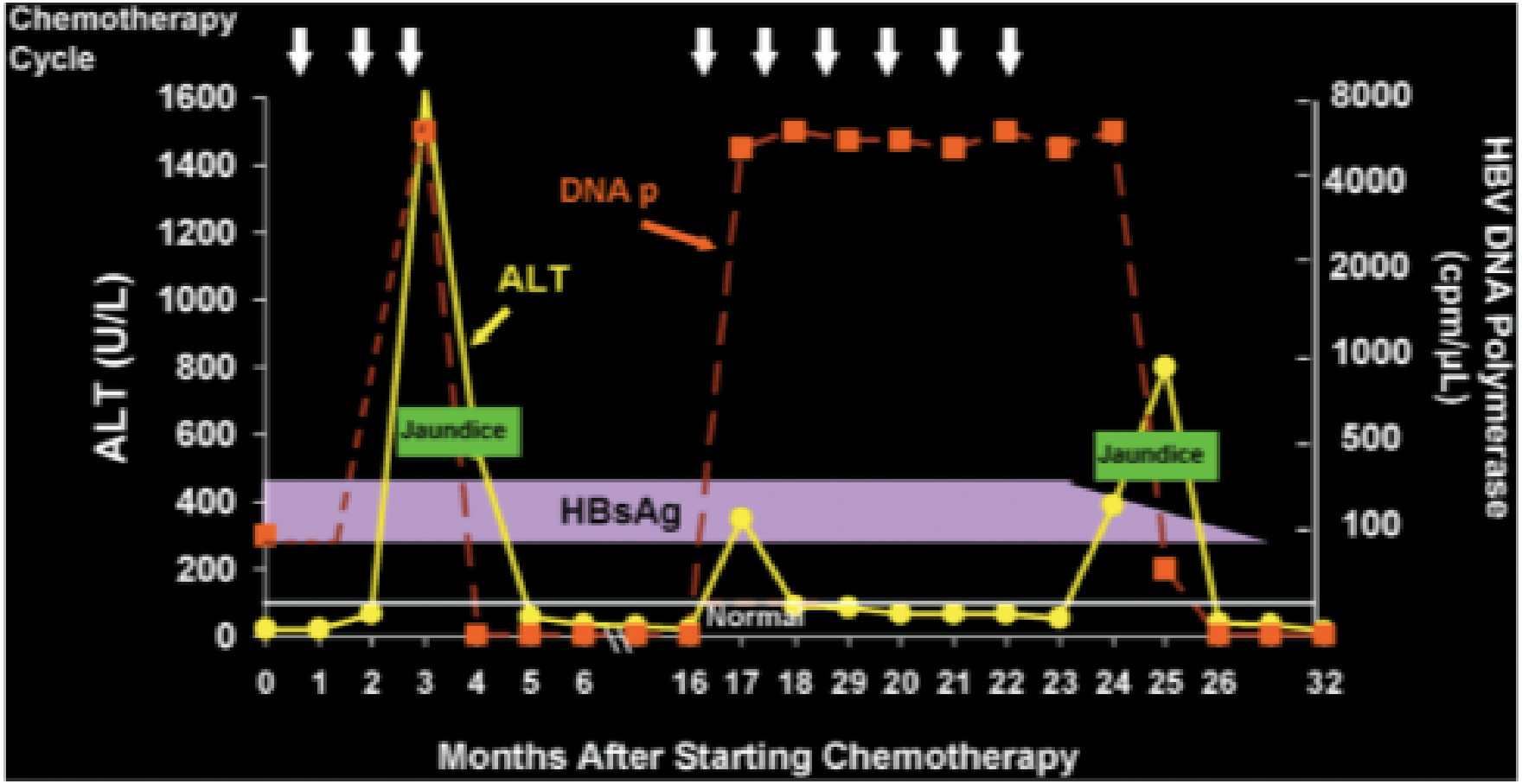
- Abrupt increase in HBV replication in an inactive carrier or a pt with resolved HBV
- Can be spontaneous or triggered
- Can be clinically silent or lead to liver failure/death

TYPICAL REACTIVATION



Hoofnagle. Hepatology, Vol 49, No 5, Suppl., 2009. Figure 1A.

TYPICAL REACTIVATION



Hoofnagle. Hepatology, Vol 49, No 5, Suppl., 2009. Figure 1B.

HBV REACTIVATION

Table 1. Three Phases of HBV Reactivation

Phase	Feature	Diagnostic Markers	Comments
1	Increase in Viral Replication	HBV DNA HBeAg HBsAg	Rise of $\geq$ 1 $\log_{10}$ IU/mL In HBeAg negative Reverse seroconversion
2	Appearance of Disease Activity	ALT Symptoms Jaundice	Rise of $\geq$ 3 times baseline Indicative of more severe injury
3	Recovery	HBV DNA ALT HBsAg	Fall to baseline values Fall to baseline values May be cleared late

Hoofnagle. Hepatology, Vol 49, No 5, Suppl., 2009. Table 1.

CAUSES OF HBV REACTIVATION

Table 2. Different Causes and Forms of HBV Reactivation

Spontaneous
Progressive Immunodeficiency (HIV Infection)
Sudden Withdrawal of Antiviral Therapy
Cancer Chemotherapy
Immunosuppression for Autoimmune or Allergic Conditions
Solid Organ Transplantation (Kidney, Heart, Lung)
Liver Transplantation (Reactivation in Graft)
Bone Marrow Transplantation

Hoofnagle. Hepatology, Vol 49, No 5, Suppl., 2009. Table 2.

HBV REACTIVATION

HIGHER FREQUENCY

- Bone Marrow Transplant (*reactivation can be years later)
- Treatment of leukemia/lymphoma
- Rituximab and fludrabine
- Use of concomitant steroids with chemo

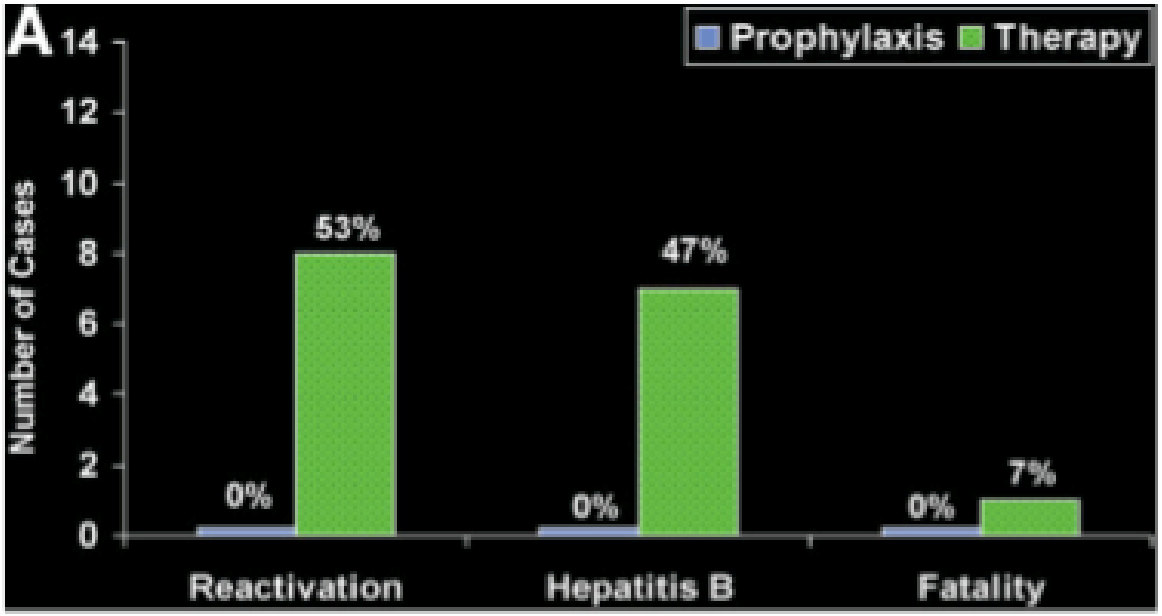
LOWER FREQUENCY

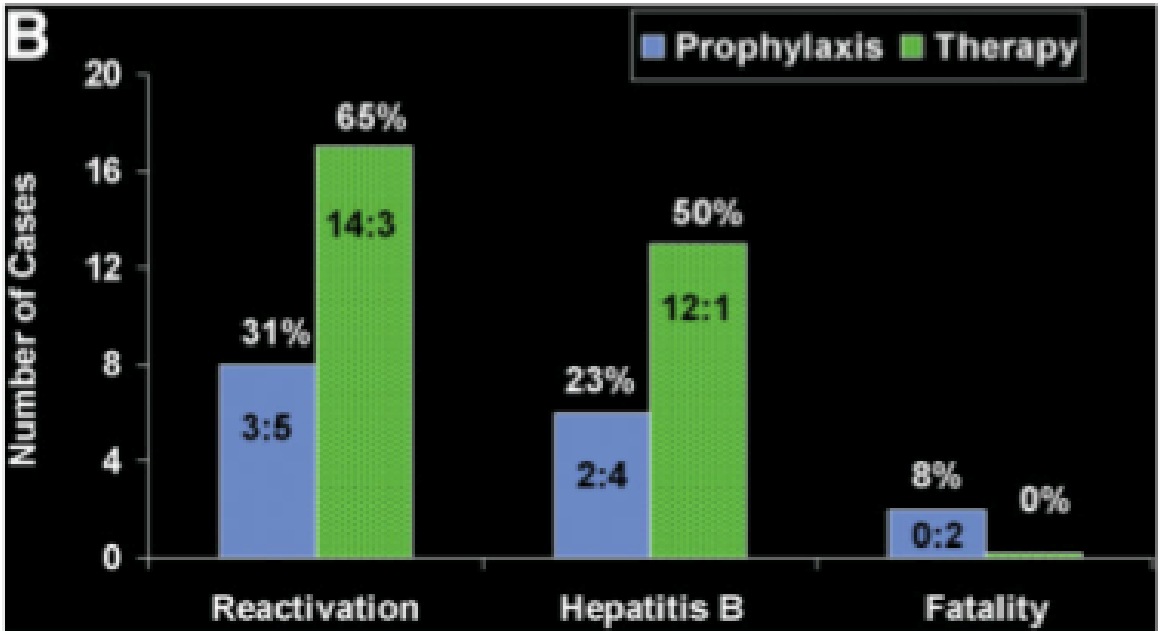
- Azathioprine/6-MP
- Low-dose steroids
- Rare reports with long-term methotrexate
- Anti-TNF agents
- HCC intra-arterial chemo

MORTALITY

Higher than >10%

Significantly higher than typical acute HBV





PROPHYLAXIS:

- HBV Reactivation
- Clinical Hepatitis
- HBV-assoc death

Hoofnagle. Hepatology, Vol 49, No 5, Suppl., 2009. Figure 4.

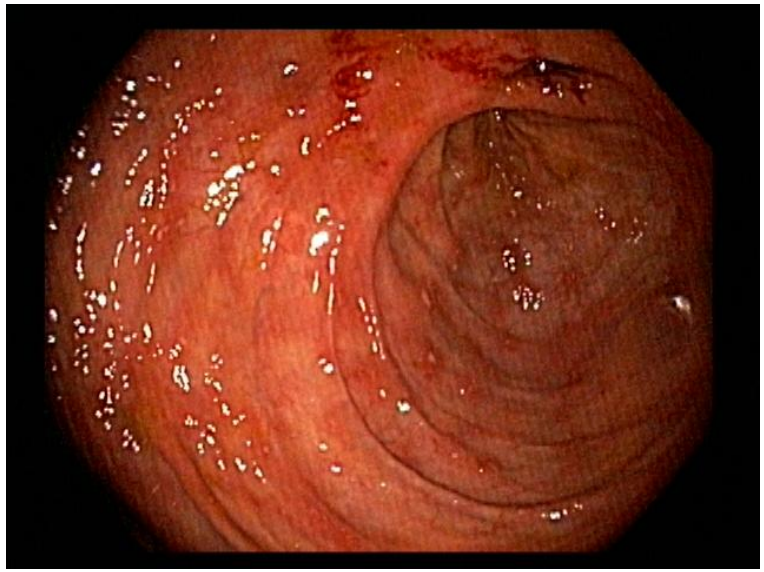
PROPHYLAXIS OF REACTIVATION - AASLD

- Screen any high-risk pt prior to starting chemo or immunosuppression
- Prophylactic anti-viral therapy for HBV carriers before CA chemo or finite course of immunosuppressants
- Use lamivudine or telbivudine if treatment <12 months and baseline DNA undetectable
- Use tenofovir or entecavir if treatment > 12 months
- Treat for at least 6 months post-immunosuppressive therapy
- No role for Interferon

PROPHYLAXIS B  &  !

- Need >10,000 IU/ML HBV DNA to develop resistance.
- In cases of prophylaxis, lamivudine is fine to use if DNA level is low - even LONG-TERM.
- Screen everyone & vaccinate HBV naïve pts!

CASE 4



- What do you think he will need?

Immunomodulative therapy to include possibly azathioprine and/or anti-TNF

- What do you worry about with these treatments?

Reactivation of Hep B

- What lab tests do you need to order?

HBsAg
Anti-HBc
HBsAb

REVIEW

- Understanding the Markers
- Natural History
- Pregnancy
- Vaccination
- Treatment
- Extrahepatic Manifestations
- Reactivation

RECOMMENDED READING

- Wong and Heathcote. "Management of Hepatitis B." Clinical Gastroenterology and Hepatology 2011: 9:385-391.

- Hoofnagle. Hepatology. "Reactivation of Hepatitis B." Vol 49, No 5, Suppl., 2009. Table 2.
  - NIH Consensus Development Conference 2009

- Morisco et al. Digestive and Liver Disease. "Hepatitis B Virus Infection and Immunosuppresive Therapy in Patients with Inflammatory Bowel Disease." 43S (2011) S40-48.