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Learning Objectives

- Review screening, counseling, and prevention strategies
- Differentiate specialized virological and serological tests
- Describe the major distinguishing characteristics of the unique viral disease, Hepatitis B.

AASLD 2018

- This AASLD 2018 Hepatitis B Guidance is intended to complement the AASLD 2016 Practice Guidelines for Treatment of Chronic Hepatitis B and update the previous Hepatitis B Virus guidelines from 2009.
- This 30-page document is support by 273 referenced articles.
- “In Contrast, this guidance document was developed by consensus of an expert panel, without formal systematic review or use of the Grading of Recommendation, Assessment,, Development and Evaluation system.”

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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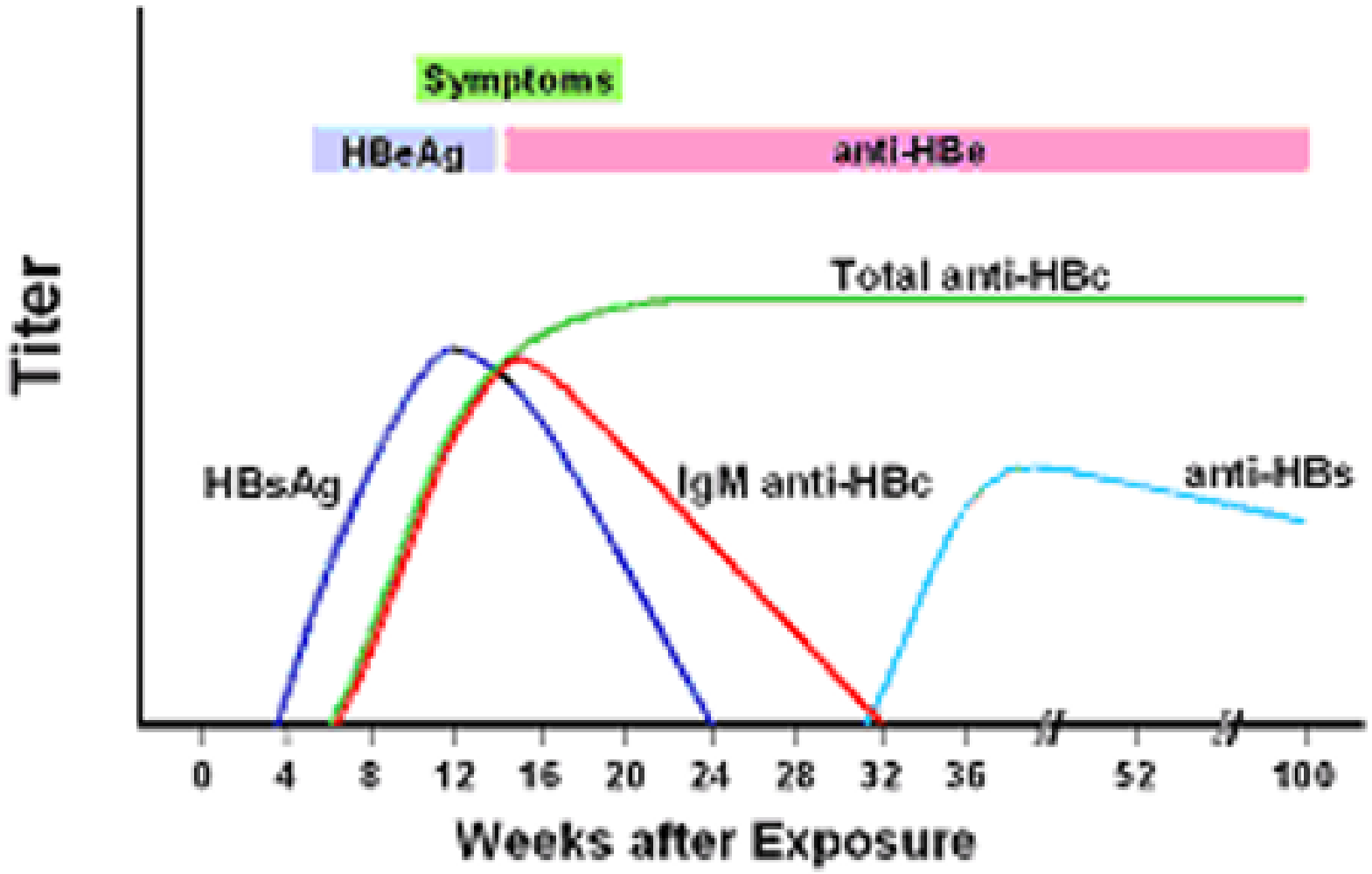
HBV Disease is Nuanced if not Complicated

- HBV is not directly cytopathic
- The host responses to the virus-infected hepatocytes are believed to mediate liver cell injury
- Long-term chronic liver inflammation and ineffective immune-mediated viral clearance, contribute to the development of cirrhosis and liver cancer.
- CHB is a dynamic disease with individuals transitioning through different clinical phases with variable levels of serum ALT activity, HBV DNA, and HBV antigens.
- A negative HBV DNA result does not rule out low levels of HBV DNA and HBV reactivation can occur (Reactivation is basically loss of immune control)
- Seroconversion and
- Seroreversion

Risk of Developing Chronic HBV Infection

- HBV can survive outside the body for prolonged periods.
- The risk of developing chronic HBV infection after acute exposure ranges from:
  - 90% in newborns of HBeAg-positive mothers to
  - 25%-30% in infants and children under 5 to
  - Less than 5% in US adults.
- In addition, immunosuppressed persons are more likely to develop chronic HBV infection after acute infection

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



HBV Serological Markers

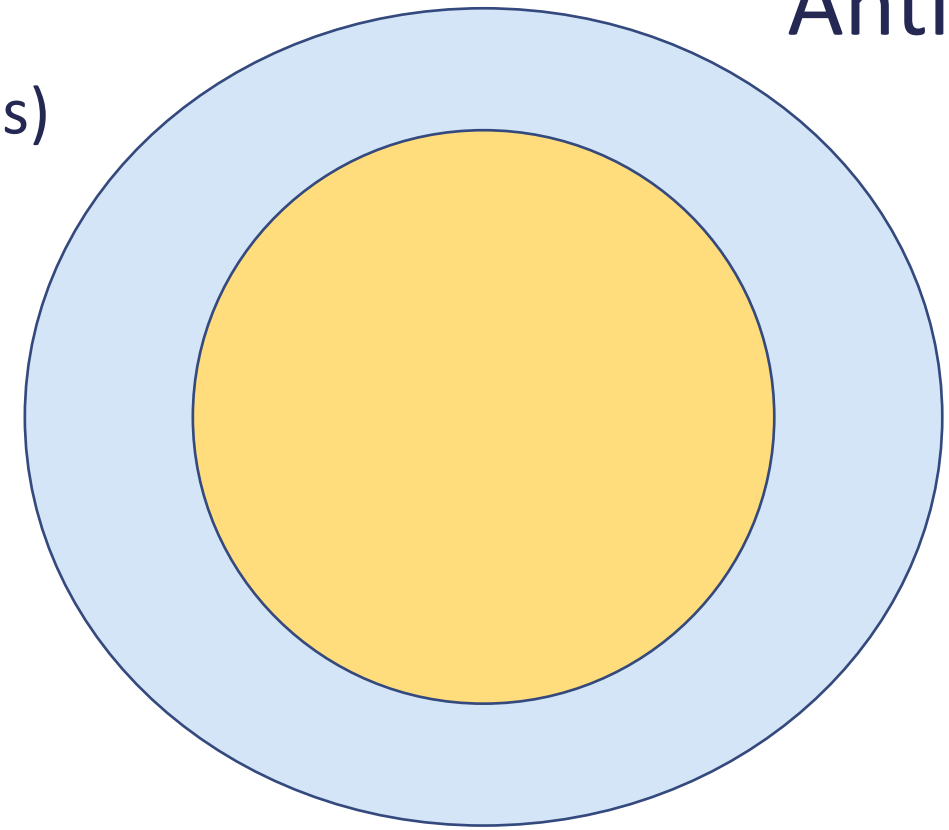
Antibodies

Surface Antibody (anti-HBs)

E Antibody (anti-HBe)

Core Antibody (anti-HBc)

- IgM
- Total



Antigens

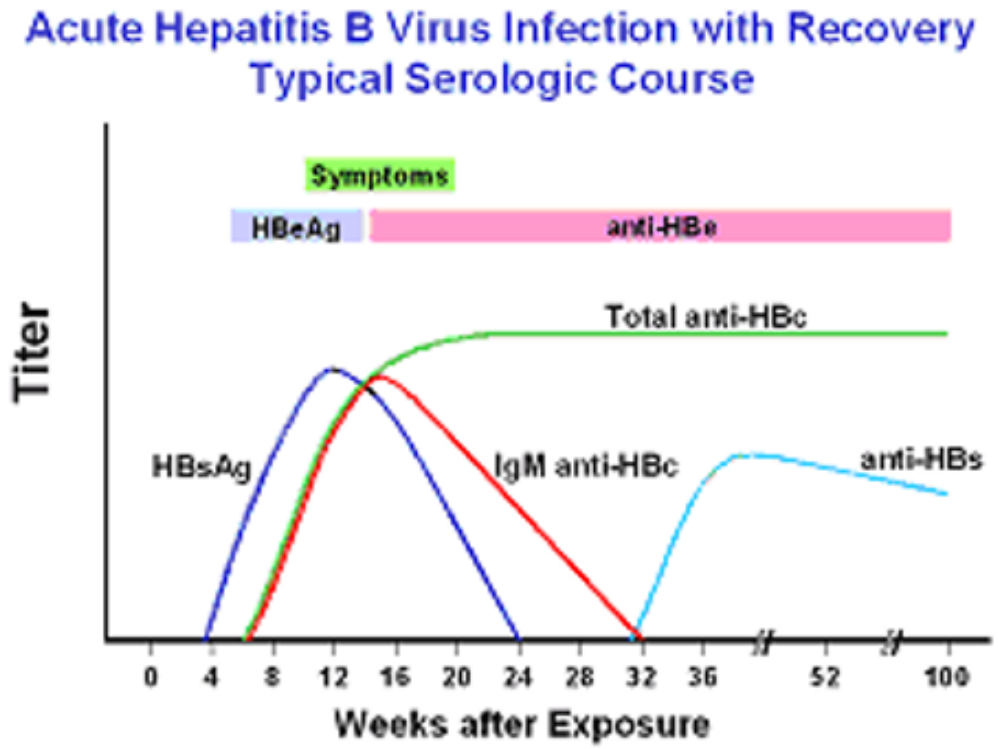
Surface Antigen (HBsAg)

E Antigen (HBeAg)

Core Antigen (HBcAg)

HBV DNA (Viral Load)

HBV Serology of Infection With Recovery



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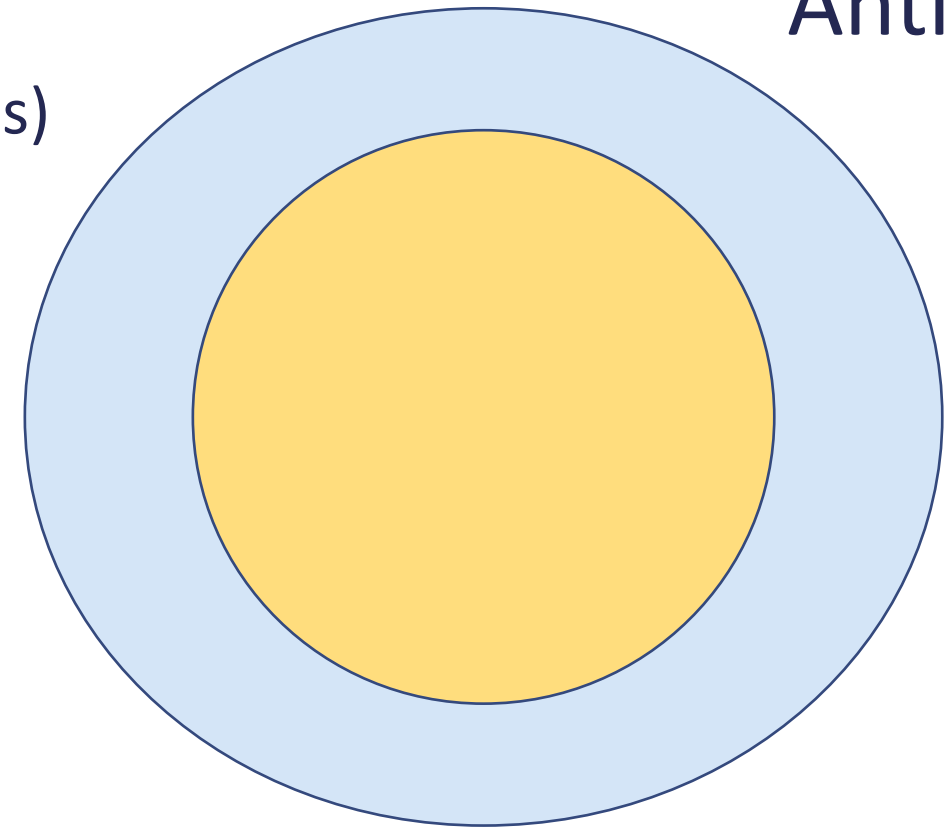

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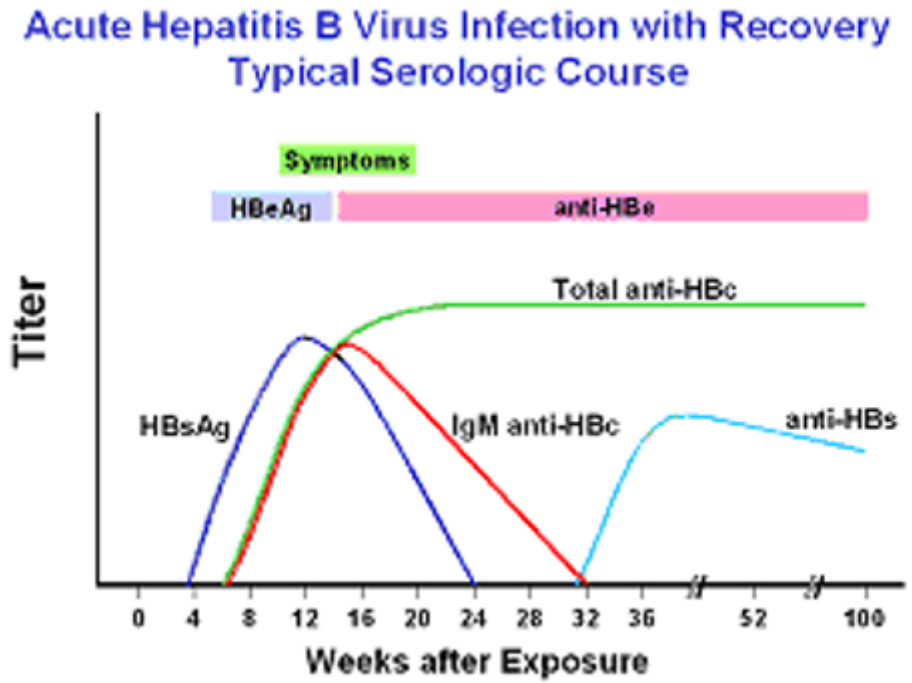

Interpreting Serology

Tests	Results	Interpretation
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible to HBV infection
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to HBV vaccination
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Recovered from HBV; immune due to natural infection
HBsAg anti-HBc anti-HBs	Positive Positive Negative	Chronic HBV

CDC Map of Worldwide Rates of Chronic Hepatitis B

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Vaccinations

- HBV vaccines have an excellent safety record and are given as a 3-dose series at 0, 1, and 6 months (with or without hepatitis A vaccine).
- There is a two step/dose option which is significantly more expensive.

Veterans Administration's Treatment Decision Guide

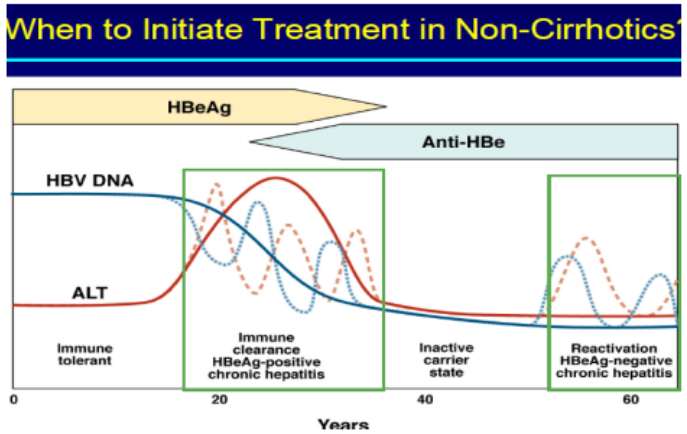
Table 2. Summary of AASLD HBV Treatment Criteria

ALT*	HBV DNA (IU/mL)	HBeAg	Other factors which should be present	Treatment Recommended per AASLD HBV Guideline**
≥ 2x ULN	>2,000	negative		yes
≥ 2x ULN	>20,000	positive		yes
>ULN but <2x ULN	>2,000	negative	Evidence of histological disease	yes
>ULN but <2x ULN	>20,000	positive	Evidence of histological disease	yes
>ULN but <2x ULN	<2,000 <20,000	negative positive	Any **one** of the following: Age>40 Family history of HCC Previous HBV therapy Extrahepatic manifestations	yes
Normal or elevated	>2,000	negative or positive	Cirrhosis	yes
Normal or elevated	>100,000	positive or negative	Age>40	yes
Normal or elevated	positive or negative	positive or negative	Immunosuppressants	yes
Normal	Any detectable	positive or negative		No (Immune Tolerant)

*ULN for men = 30 U/L; ULN for women = 19 U/L

**HBV treatment: entecavir 0.5mg-1mg/day or tenofovir 300 mg/day

AASLD HBV guidelines available at: www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf



Source: Anna Lok, DDW 2016 (Yapali S, et al. Clin Gastro Hepatol 2014)

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Treatment and Monitoring CHBV

- Patients not meeting criteria for antiviral therapy require regular monitoring to assess the need for future therapy per the AASLD 2016 HBV Guidelines.
- Complicated and nuanced and requires CDS from experience practitioner

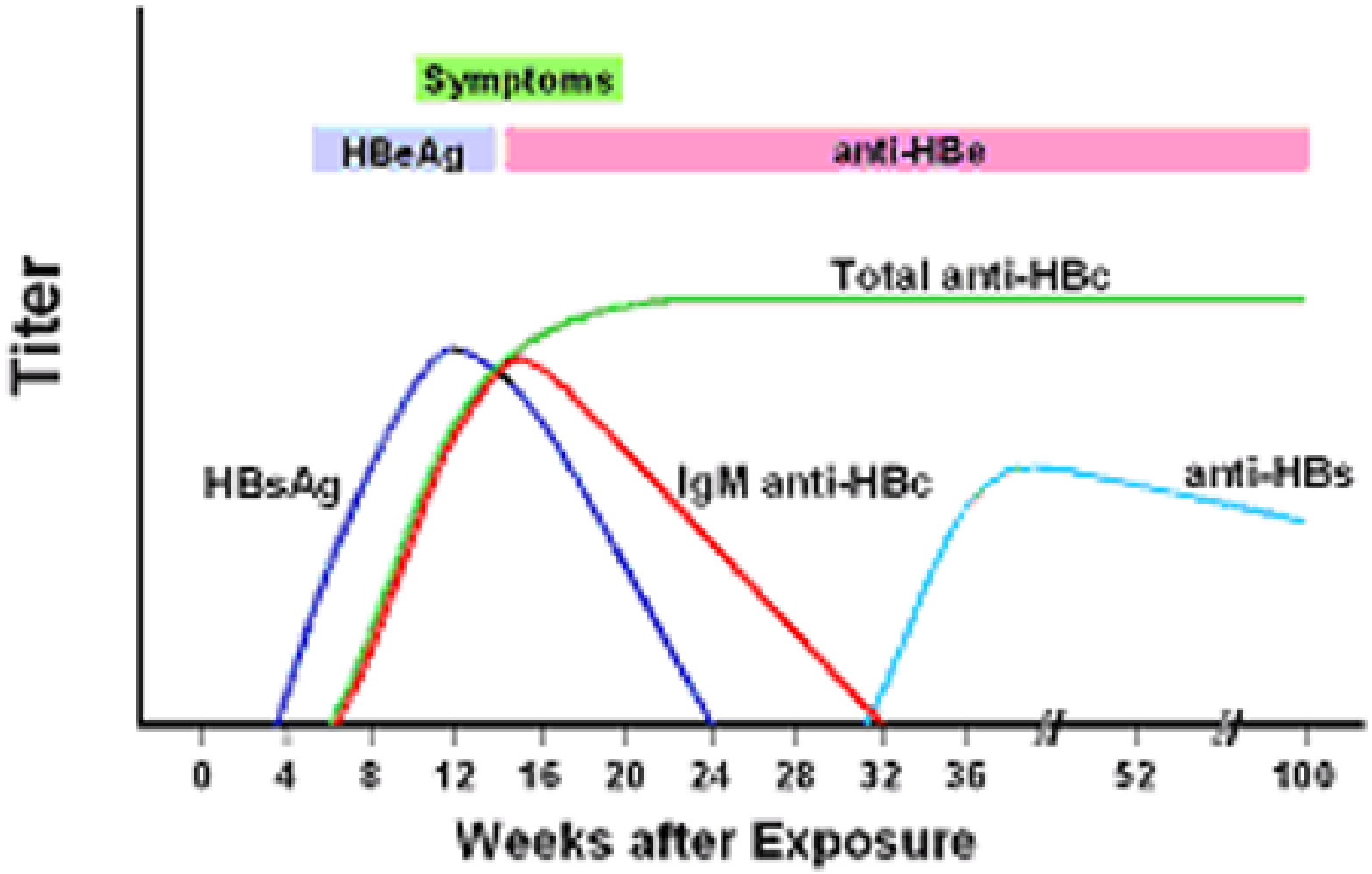
Monitoring on nucleos(t)ide therapy (TDF, TAF or Entecavir)

- Draw an HBV viral load every three months until undetectable for at least two consecutive visits and then decrease the frequency to every six months.
- Draw aminotransferases every three months. The frequency can be decreased to every six months in patients with normalized ALT or an undetectable viral load.
- HBeAg and anti-HBe every 12 months in patients who are HBeAg positive to determine if seroconversion has occurred. If seroconversion has occurred redraw HBeAg and anti-HBe to confirm the results.
- HBsAg should be tested yearly in patients with an undetectable viral load.
- Patients on TDF should have a creatinine and phosphate drawn every 3 to six months.

Screening for HCC

- Of the 2 tests prospectively evaluated as screening tools for HCC, alpha-fetoprotein (AFP) and ultrasonography (US), the sensitivity, specificity, and diagnostic accuracy of US are higher than those of AFP.
- The guideline for HCC recommends surveillance of persons at high risk of HCC with US every 6 months
- All HBsAg-positive patients with cirrhosis should be screened with US every 6 months.
- HBsAg-positive adults at high risk for HCC (including Asian or black patients over 40 years and Asian women over 50 years of age), persons with a first-degree family member with a history of HCC

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



Screening

- There are 21 “bullets” identifying groups of patients at “high risk” for HBV infection and
- 10 geographical regions identified as high or intermediate HBV endemicity, which appears to include over 100 countries
- AASLD recommend screening for all in this group; which includes “incarceration” as a risk factor requiring screening

Risk Stratification: Priority 1

- Potential reactivation if they have preexisting HBV
  - Individuals with HIV infection
  - Those about to undergo HCV treatment,
  - Those about to undergo chemotherapeutic, or immunosuppressive therapy
- Dialysis patients
- Pregnancy

Moderate Risk Screening Priority 2 and 3

Priority 2 (Patient request or Clinician Judgement)

- IVDU
- Tattoo from non-regulated source
- Men who have sex with men

Priority 3 (Annual Health Assessment)

- Incarceration

Counseling Patients with Chronic HBV Infection

- Patients with chronic HBV infection should be counseled regarding lifestyle modifications and prevention of transmission as well as the importance of lifelong monitoring
- Abstinence or only limited use of alcohol is recommended in HBV-infected persons.
- Optimization of body weight and treatment of metabolic complications, including control of diabetes and dyslipidemia, are recommended to prevent concurrent development of metabolic syndrome and fatty liver.

Transmission Prevention

TABLE 5. Recommendations for Infected Persons Regarding Prevention of Transmission of HBV to Others

Persons Who Are HBsAg Positive Should:

- Have household and sexual contacts vaccinated
- Use barrier protection during sexual intercourse if partner is not vaccinated or is not naturally immune
- Not share toothbrushes or razors
- Not share injection equipment
- Not share glucose testing equipment
- Cover open cuts and scratches
- Clean blood spills with bleach solution
- Not donate blood, organs, or sperm

Children and Adults Who Are HBsAg Positive:

- Can participate in all activities, including contact sports
- Should not be excluded from daycare or school participation and should not be isolated from other children
- Can share food and utensils and kiss others

Pregnancy

- All pregnant women should be screened for HBsAg.
- Pregnant women with CHB should be encouraged to discuss with their obstetrician and/or pediatrician the prevention of mother-to-child transmission.
- Hepatitis B immune globulin (HBIG) and HBV vaccine should be administered to their newborn < 12 hours after delivery
- Antiviral therapy in the third trimester is recommended for pregnant women with serum HBV DNA >200,000 IU/mL
- TDF is the preferred choice owing to its antiviral potency and concerns for resistance with the other antiviral agents.
- Breastfeeding is not prohibited.

Guidance Statements on Counseling of Women in Pregnancy

- Women who meet standard indications for HBV therapy should be treated. Women without standard indications but who have HBV DNA >200,000 IU/mL in the second trimester should consider treatment to prevent mother-to-child transmission.
- HBV-infected pregnant women who are not on antiviral therapy as well as those who stop antiviral at or early after delivery should be monitored closely for up to 6 months after delivery for hepatitis flares and seroconversion. Long-term follow-up should be continued to assess need for future therapy.

HBV Reactivation

- While persons who are positive for anti-HBc, but negative for HBsAg, are at very low risk of HBV reactivation, the risk can be substantial when chemotherapeutic or immunosuppressive drugs are administered

- Screening for anti-HBc to determine prior exposure is not routinely recommended but is an important test in patients who have HIV infection, who are about to undergo HCV or anticancer and other immunosuppressive therapies or renal dialysis, and in donated blood

Guidance Statements for Patients Undergoing Immunosuppressive and Cytotoxic Therapy

- HBsAg and anti-HBc (total or immunoglobulin G) testing should be performed in all persons before initiation of any immunosuppressive, cytotoxic, or immunomodulatory therapy.

- HBsAg-positive, anti-HBc–positive patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy.

- HBsAg-negative, anti-HBc–positive patients could be carefully monitored with ALT, HBV DNA, and HBsAg with the intent for on demand therapy, except for patients receiving anti-CD20 antibody therapy (e.g., rituximab) or undergoing stem cell transplantation, for whom anti-HBV prophylaxis is recommended.

Guidance Statements for Patients Undergoing Immunosuppressive and Cytotoxic Therapy

- When indicated, anti-HBV prophylaxis should be initiated as soon as possible before or, at the latest, simultaneously with the onset of immunosuppressive therapy. Once started, anti-HBV prophylaxis should continue during immunosuppressive therapy and for at least 6 months (or for at least 12 months for patients receiving antiCD20 therapies) after completion of immunosuppressive therapy.

- Anti-HBV drugs with a high resistance barrier (entecavir, TDF, or TAF) should be preferred over low-barrier agents.

- For patients being monitored without prophylaxis, HBV-DNA levels should be obtained every 1-3 months. Patients should be monitored for up to 12 months after cessation of anti-HBV therapy.

HBV-DNA QUANTITATION

- Quantification of serum HBV DNA is a crucial component in the evaluation of patients with CHB and in the assessment of the efficacy of antiviral treatment.
- Some patients with CHB have widely fluctuating HBV-DNA levels that may vary from undetectable to >2,000,000 IU/mL.
- Thus, serial monitoring of HBV-DNA levels is more important than any single arbitrary cut-off value in prognostication and in determining the need for treatment.

Diagnostic Criteria, Definitions and Phases for CHB

- **Chronic Hepatitis B (CHB)**
  - HBsAg present for 6 months
  - Serum HBV DNA varies from undetectable to several billion IU/mL
  - Subdivided into HBeAg positive and negative. HBV-DNA levels are typically >20,000 IU/mL in HBeAg-positive CHB, and lower values (2,000-20,000 IU/mL) are often seen in HBeAg-negative CHB
- **Immune-Tolerant CHB**
  - HBsAg present for 6 months
  - HBeAg positive
  - HBV-DNA levels are very high (typically >1 million IU/mL).

Diagnostic Criteria and Definitions for Chronic Hepatitis B

- **Immune-Active CHB**
  - HBsAg present for 6 months
  - Serum HBV DNA >20,000 IU/mL in HBeAg-positive CHB and >2,000 IU/mL in HBeAg-negative
- **Inactive CHB**
  - HBsAg present for 6 months
  - HBeAg negative, anti-HBe positive
  - Serum HBV DNA <2,000 IU/ml

Resolved Chronic Hepatitis B

- Sustained loss of HBsAg with
- Undetectable HBV DNA and
- Absence of clinical or histological evidence of active viral infection

Reminders:

- HBV is not cytotoxic
- Host response medicate cell injury
- Ineffective immune mediated viral clearance
- Reactivation and
- Dynamic disease
- HBeAg seroconversion: loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative
- HBeAg seroreversion: reappearance of HBeAg in a person who was previously HBeAg negative

References

- Reference 1: www.uptodate.com
- Reference 2: www.aasld.org
- Reference 3: www.cdc.gov
- Reference 4: www.hepatitis.va.gov
- Reference 5: www.bop.gov
- Reference 6: www.hepb.org