Project ECHO®

Chronic Liver Disease Foundation
New Jersey

# HBV Alliance:

## Expert Recommendations on Managing Patients with Chronic Hepatitis B

Accredited by

Rehoboth McKinley Christian Health Care Services

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CLDF
Chronic Liver Disease Foundation

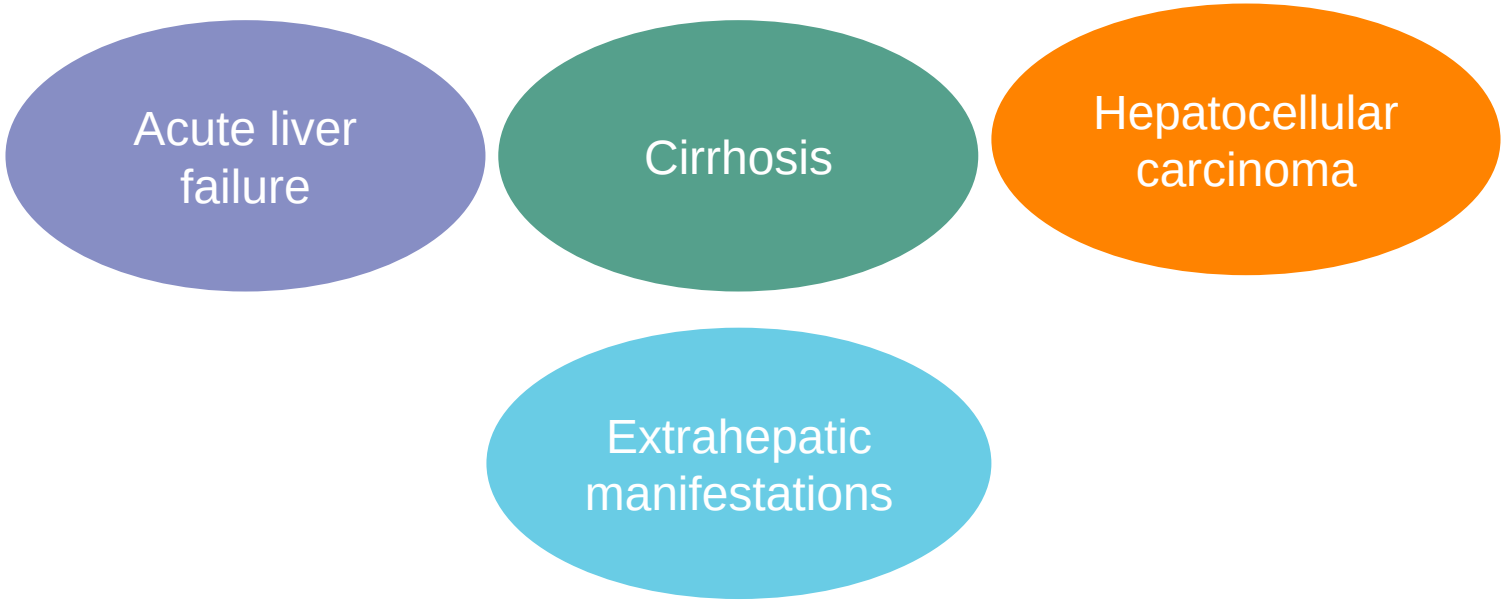
# Extrahepatic Manifestations of Hepatitis B

# Learning Objectives HBV ECHO Series

Upon completion of this activity, participants should be able to:

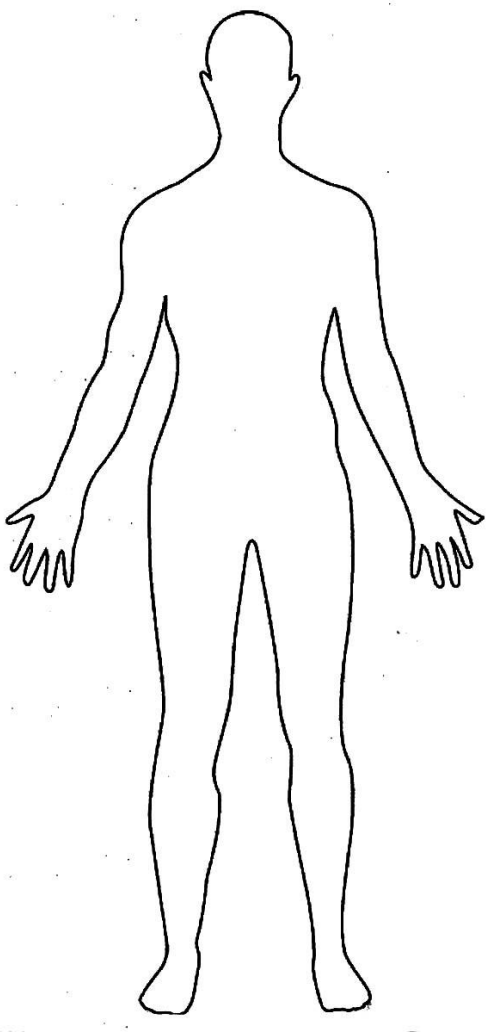
- Review data on the prevalence and transmission of HBV
- Define the risk of HBV among different patient populations, highlighting high-risk settings
- Describe the detrimental effects of untreated, chronic HBV to emphasize the need for diagnosis and treatment
- Demonstrate strategies to incorporate various diagnostic and treatment guidelines into clinical practice
- Analyze approved and emerging treatment options for HBV
- Identify patients that are likely to benefit from emerging treatment options versus currently available therapies

# Hepatitis B Complications



# Extrahepatic Manifestations of HBV

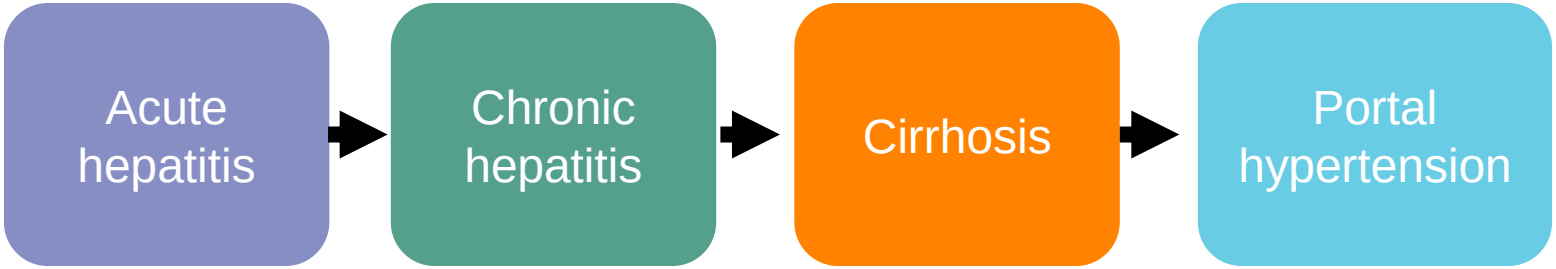
- Serum sickness-like syndrome
- Glomerulonephritis
- Polyarteritis nodosa
- Cryoglobulinemia



Kappus MR, Sterling RK. *Gastroenterol Hepatol*. 2013.

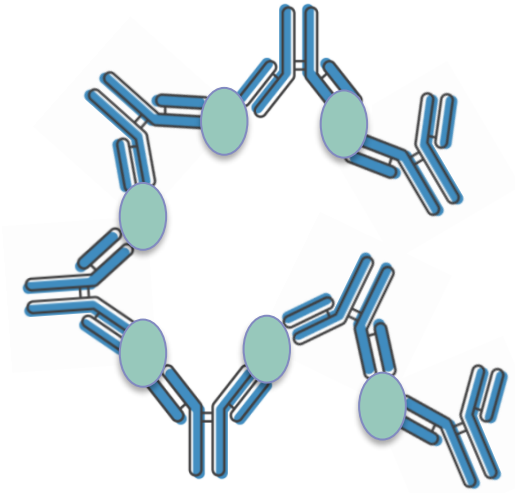
# Extrahepatic Manifestations of HBV

Across the spectrum of the natural history of HBV



# Why Do Extrahepatic Manifestations Develop?

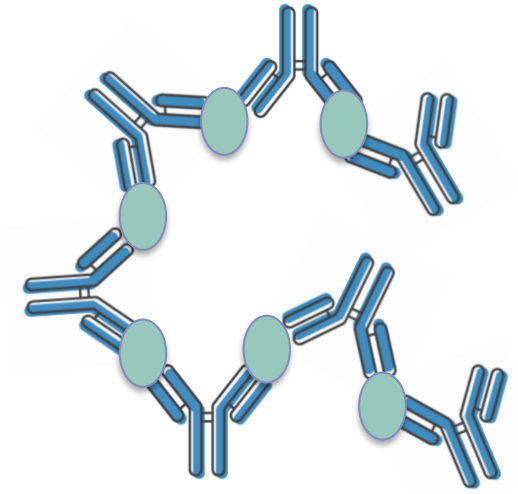
- Immune complex formation
- Immune complex deposition
- Immune complex-mediated inflammation



Chauhan AK. *Front Immunol*. 2017.

# Why Do Extrahepatic Manifestations Develop?

- Immune complex formation common with viral infections
  - Hepatitis B
  - Hepatitis C
  - HIV
  - Cytomegalovirus
  - Epstein-Barr virus
  - Human parvovirus B19



Belizna CC. *Rheumatology*. 2009.

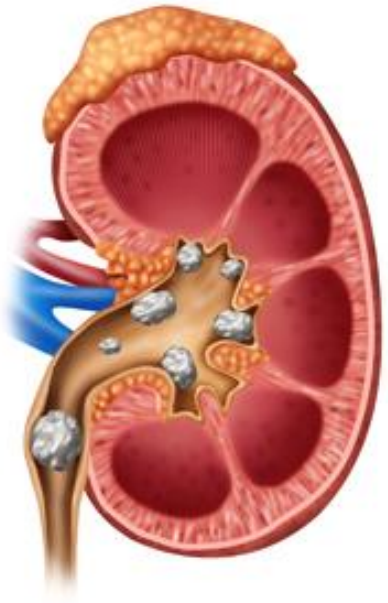
# Serum Sickness-Like Syndrome

- Acute hepatitis B,10-20% of cases
- Prior to onset of jaundice, then subsides
- Presentation
  - Fever (<39$^{o}$ C)
  - Skin rash
    - Erythematous, macular, maculopapular, urticarial, nodular, or petechial lesions
  - Myalgias, arthralgias
  - Fatigue, malaise

Kappus MR, Sterling RK. *Gastroenterol Hepatol*. 2013.

# Renal Manifestations

- Most common in HBV infection
  - Membranous nephropathy
  - Membranoproliferative glomerulonephritis (MPGN)
  - Polyarteritis nodosa (PAN)
- Less common (and in some cases debated)
  - Mesangial proliferative glomerulonephritis
  - Immunoglobulin A (IgA) nephropathy
  - Crescentic glomerulonephritis
  - Focal segmental glomerulosclerosis (FSGS)
  - Minimal change disease
  - Amyloidosis



Chan TM, Lok ASF. Renal disease associated with hepatitis B virus infection. UpToDate.

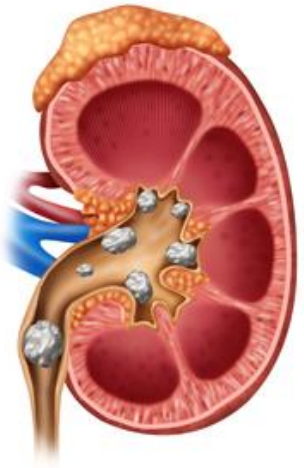
# Renal Manifestations

- Membranous nephropathy
  - Presents with proteinuria, can be nephrotic range
  - Microscopic hematuria
  - Lower complement levels
- Membranoproliferative glomerulonephritis (MPGN)
  - Hematuria, red blood cell casts
  - Variable degrees of proteinuria
  - Reduced glomerular filtration rate (GFR)
  - Hypertension
- Polyarteritis nodosa (PAN)

Chan TM. UpToDate; Li P. *Clin Nephrol.* 2012.

# Renal Manifestations

- Diagnosis
  - Kidney biopsy



Can you be sure of the link between HBV and the kidney disorder?

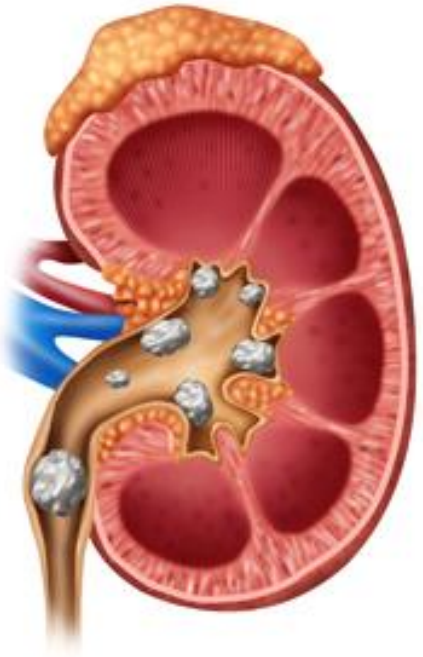
If antiviral therapy improves the kidney disorder

Important to consider these diagnoses in the right clinical setting. Standard treatment of these disorders would be immunosuppression and cytotoxic agents that might exacerbate HBV infection.

Chan TM. UpToDate; Li P. *Clin Nephrol*. 2012.

# Renal Manifestations

- Recommendation for antiviral therapy:
  - HBV-associated renal disease with
    - Detectable serum HBV DNA or
    - Positive hepatitis B e antigen (HBeAg)
  - Observational studies and uncontrolled trials:
    - Antiviral therapy associated with reduced proteinuria



Chan TM. UpToDate.

# Renal Manifestations

- Meta-analysis
  - 10 studies
    - 4 randomized controlled trials
    - 2 cohort studies
    - 4 self-controlled studies
  - 325 patients with HBV-associated glomerulonephritis
  - Nucleoside/nucleotide monotherapy
    - Entecavir (5)
    - Lamivudine (4)
    - Adefovir (1)

Wang WN. *Clin Nephrol*. 2016.

# Renal Manifestations

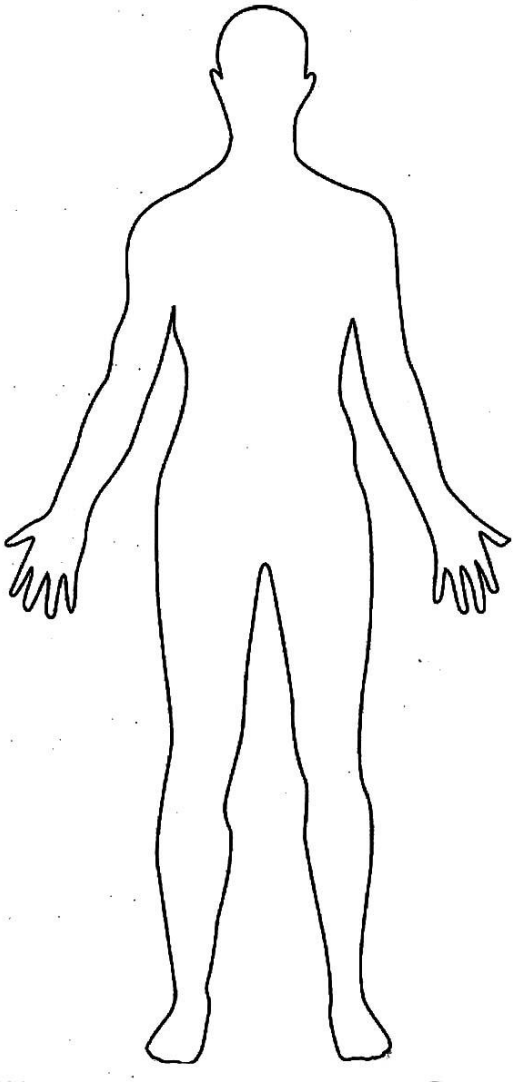
| Outcome | Relative Risk in NA group | 95% CI |
|---|---|---|
| Proteinuria remission to <0.3 g/24 hrs | 3.6 | 1.99 – 6.50 |
| HBV-DNA negative conversion rate | 2.20 | 1.55 – 3.13 |
| HBeAg clearance | 4.49 | 1.29 – 15.67 |

| Outcome | Mean difference | 95% CI |
|---|---|---|
| ALT (U/L) | - 56.60 | 50.41 – 62.79 |
| Serum creatinine (mmol/L) | - 25.25 | 17.11 – 67.61 |

Wang WN. *Clin Nephrol*. 2016.

# Polyarteritis Nodosa (PAN)

- Necrotizing vasculitis affecting small- and medium-sized blood vessels
- Typically within 4 months of onset of HBV infection
- Organs involved
  - Kidneys, skin, joints, muscles, nerves, and GI tract
- Etiology
  - Most idiopathic
  - Hepatitis B, Hepatitis C
  - Hairy cell leukemia



Guillevin L. *Medicine*. 2005. Merkel PA, UpToDate.

# Polyarteritis Nodosa (PAN)

- Renal
  - Hypertension common
  - Urine: minimal proteinuria, modest hematuria, RBC casts usually absent
- Skin
  - tender erythematous nodules, purpura, livedo reticularis, ulcers, and bullous or vesicular eruption
- Neurologic system
  - Motor and sensory deficits
  - Mononeuropathy multiplex (or asymmetric polyneuropathy) up to 70%
  - CNS involvement 5-10%

Guillevin L. *Medicine*. 2005. Merkel PA, UpToDate.

# Polyarteritis Nodosa (PAN)

- GI tract
  - Abdominal pain early symptom, esp. after meals; N/V
  - GI bleeding
  - Weight loss if ↓ food intake or malabsorption
  - Bowel infarction with perforation if advanced, ischemia
  - Rare: pancreatic infarction, splenic infarction
- Muscles
  - Common, myalgias and muscle weakness

Guillevin L. *Medicine*. 2005. Merkel PA, UpToDate.

# Polyarteritis Nodosa (PAN)

- Diagnosis
  - Clinical presentation has broad differential and so biopsy confirmation of affected organs recommended
- Alternatives
  - Mesenteric or renal arteriography: multiple aneurysms and irregular constrictions in larger vessels with occlusion of smaller arteries
  - MR and CT angiography

Guillevin L. *Medicine*. 2005. Merkel PA, UpToDate.

# Polyarteritis Nodosa (PAN)

- Treatment in setting of HBV and HCV therapy
  - Mild PAN: antiviral therapy
  - Persistent PAN despite antiviral therapy
    - Consider immunosuppressive therapies

Guillevin L. *Arthritis Rheum*. 2004

# Polyarteritis Nodosa (PAN)

- Treatment in setting of HBV and HCV therapy.
  - Severe PAN:
    - French series.
    - Multicenter, prospective, observational trial.
    - 10 patients with previously untreated HBV-related PAN.
    - Regimen.
      - Oral prednisone (1 mg/kg/day) was given for 1 week, then tapered and withdrawn within 1 week.
      - Lamivudine then started for a maximum of 6 months.
      - Plasma exchange performed simultaneously 3x/week for 3 weeks, 2x/week for 2 weeks, then 1x/week until HBeAg to HBeAb seroconversion obtained or until 2-3 months of clinical recovery sustained.
    - Results:
      - One death due to catheter-related septicemia.
      - 6 months: 9 achieved clinical recovery with seroconversion in 6/9 (67%).

Guillevin L. *Arthritis Rheum*. 2004

# Cryoglobulinemia

| Cryoglobulin | Immunoglobulins | Associated conditions |
|---|---|---|
| Type I<br>Single | Monoclonal IgG or IgM | Multiple myeloma<br>MGUS<br>Waldenström macroglobulinemia<br>CLL |
| Type II<br>Mixed | Mixture of monoclonal IgM (or IgG or IgA) with RF and polyclonal Ig | Hepatitis C<br>HIV<br>Hepatitis B<br>Autoimmune diseases |
| Type III<br>Mixed | Polyclonal IgG (all isotypes) and polyclonal IgM | Hepatitis C<br>Hepatitis B<br>Autoimmune diseases |

Kappus MR, Sterling RK. *Gastroenterol Hepatol*. 2013.

# Cryoglobulinemia

- Presentation for mixed cryoglobulinemias (types II/III)
  - Waxing and waning symptoms
  - Fatigue
  - Arthralgias, myalgias
  - Palpable purpura, legs or diffuse
  - Peripheral neuropathy
  - Membranoproliferative glomerulonephritis 20-30%

Monti G. *QJM*. 1995; Dispenzieri A. *Hematol Oncol Clin North Am*. 1999.

# Cryoglobulinemia

- Laboratory evaluation
  - Cryoglobulin testing requires planning!
  - Great risk of false negative result
  - Syringes and collection tubes must be prewarmed to 37ºC without anticoagulants
  - Blood is allowed to clot at 37ºC for 30-60 minutes and then serum separated by centrifuge and then refrigerated to allow precipitation of the cryglobulins
  - Cryocrit: measure of the packed volume of precipitate over the original serum volume
  - Negative result does not rule out the di suspicion high

Talk to your lab before ordering!

# Cryoglobulinemia

- Other tests
  - Complement: ↓ CH50, C1q, C2, and C4
  - Rheumatoid factor: usually present in type II
  - Erythrocyte sedimentation rate (ESR) ↑
  - C-reactive protein (CRP) ↑
  - Hypergammaglobulinemia: IgM, IgA, and/or IgG

# Cryoglobulinemia

- Treatment

Treat the underlying disorder

# Extrahepatic Manifestations of HBV

- Serum sickness-like syndrome
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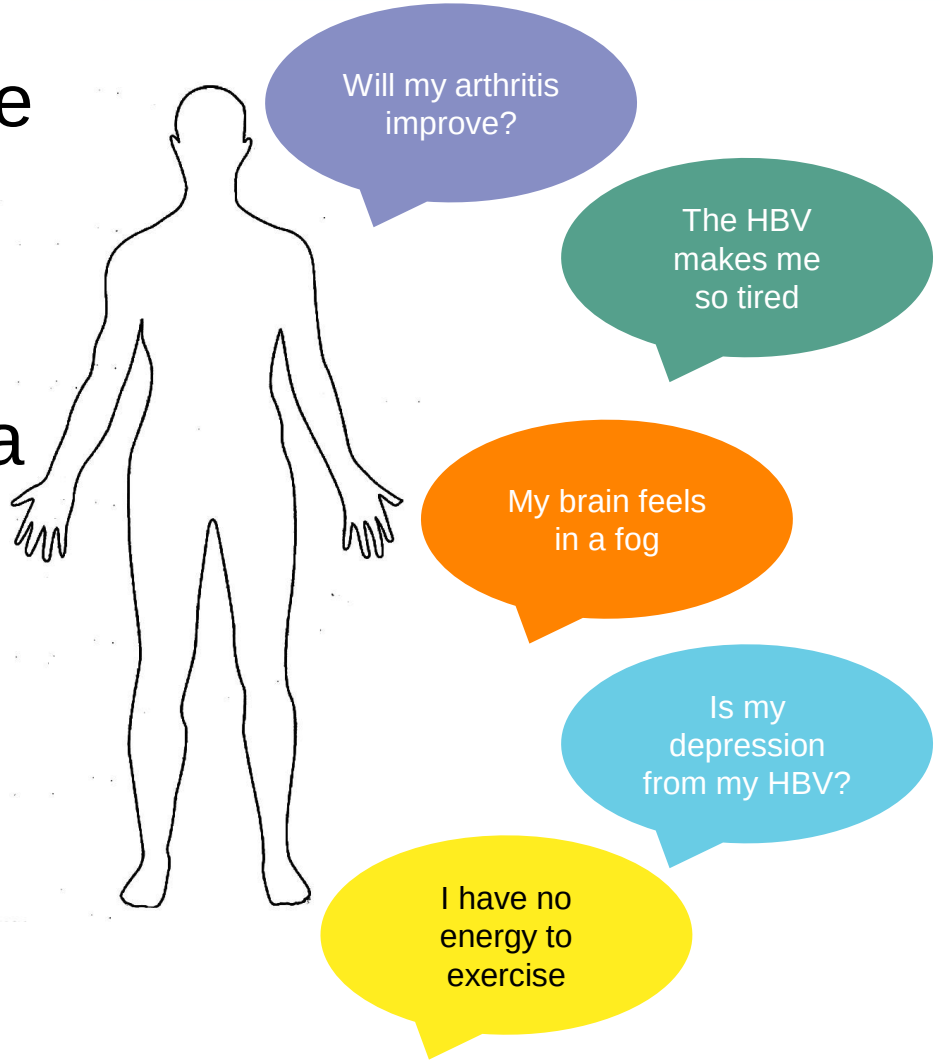



Kappus MR, Sterling RK. *Gastroenterol Hepatol*. 2013.

# Treatment Guidelines

- AASLD guidelines

The AASLD recommends antiviral therapy for adults with immune-active CHB (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications

Immune-active CHB is defined by
- ↑ ALT 2x the ULN or evidence of significant histologic disease plus
- ↑ elevated HBV DNA > 2,000 IU/mL (HBeAg negative) or > 20,000 IU/mL (HBeAg positive)

There is insufficient evidence for or against use of ALT criterion other than ALT 2x the ULN.

Additional factors included in the decision to treat persons with immune-active CHB but ALT < 2x the ULN and HBV DNA below thresholds are as follows:
- Age: older age (>40 years) is associated with a higher likelihood of significant histological disease
- Family history of cirrhosis or HCC
- Previous treatment history
- Serological and virological benefits of peg-IFN occur after treatment discontinuation (delayed)
- Past NA exposure is a risk for drug resistance
- Presence of extrahepatic manifestations: indication for treatment independent of liver disease severity
- Presence of cirrhosis

Terrault NA. *Hepatology*. 2018.

When do I start antiviral therapy for extrahepatic manifestations?

Clinical picture consistent with one of the extrahepatic manifestations and positive HBV DNA or positive hepatitis B e antigen

Which antiviral therapies do I use in these situations?

- Entecavir
- Tenofovir disoproxil fumarate
- Tenofovir alafenamide

- Not peginterferon alfa

# HBV antivirals need dose modification with renal impairment

## Entecavir

**Table 2: Recommended Dosage of BARACLUDE in Adult Patients with Renal Impairment**

| Creatinine Clearance (mL/min) | Usual Dose (0.5 mg) | Lamivudine-Refractory or Decompensated Liver Disease (1 mg) |
|---|---|---|
| 50 or greater | 0.5 mg once daily | 1 mg once daily |
| 30 to less than 50 | 0.25 mg once daily[a] **OR** 0.5 mg every 48 hours | 0.5 mg daily **OR** 1 mg every 48 hours |
| 10 to less than 30 | 0.15 mg once daily[a] **OR** 0.5 mg every 72 hours | 0.3 mg once daily[a] **OR** 1 mg every 72 hours |
| Less than 10 Hemodialysis or CAPD | 0.05 mg once daily[a] **OR** 0.5 mg every 7 days | 0.1 mg once daily[a] **OR** 1 mg every 7 days |

## Tenofovir disoproxil fumarate

**Table 3: Dosage Interval Adjustment for Adult Patients with Altered Creatinine Clearance**

| | Creatinine Clearance (mL/min)[a] | | | Hemodialysis Patients |
|---|---|---|---|---|
| | 50 or greater | 30-49 | 10-29 | |
| **Recommended 300 mg Dosing Interval** | Every 24 hours | Every 48 hours | Every 72 to 96 hours | Every 7 days or after a total of approximately 12 hours of dialysis[b] |

## Tenofovir disoproxil fumarate

**2.3 Dosage in Patients with Renal Impairment**

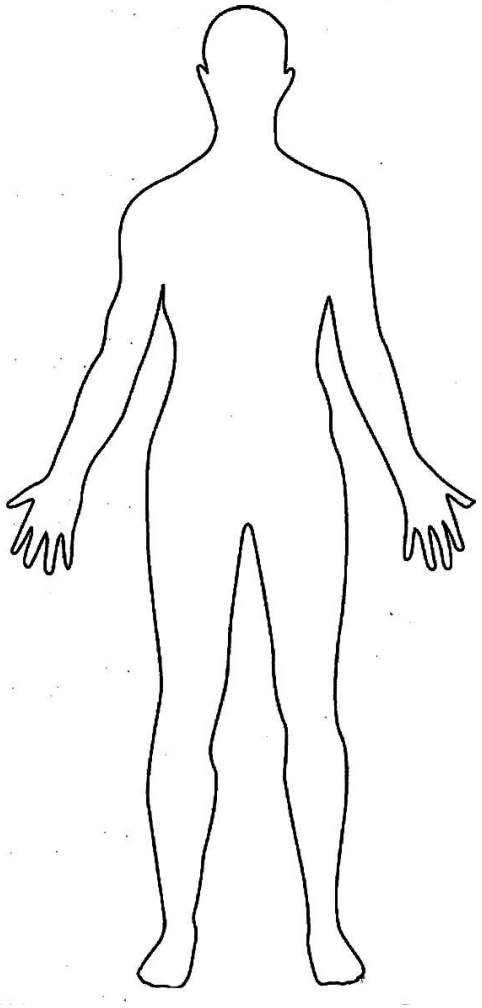
No dosage adjustment of VEMLIDY is required in patients with estimated creatinine clearance greater than or equal to 15 mL per minute, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL per minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer VEMLIDY after completion of hemodialysis treatment.

VEMLIDY is not recommended in patients with ESRD who are not receiving chronic hemodialysis *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

a. Calculated using ideal (lean) body weight
b. Generally once weekly assuming 3 hemodialysis sessions a week of approximately 4 hours' duration. VIREAD should be administered following completion of dialysis.
Baraclude FDA package insert; Viread FDA package insert; Vemlidy FDA package insert.

# Take Home Points

- Extrahepatic manifestations in HBV can affect most organ systems.
- The course of HBV extrahepatic manifestations can wax and wane with severe exacerbations.
- HBV extrahepatic manifestations can be challenging to diagnose. The diagnosis requires clinical judgment and focused a diagnostic evaluation.
- Antiviral therapy for HBV should be first-line treatment for HBV extrahepatic manifestations regardless of other indications for therapy.
- Antiviral therapies for HBV require dose modification for renal impairment.



# References


- Belizna CC, Hamidou MA, Levesque H, Guillevin L, Shoenfeld Y. Infection and vasculitis. *Rheumatology*. 2009;48(5):475.
- Chan TM, Lok ASF. Renal disease associated with hepatitis B virus infection. UpToDate. www.uptodate.com
- Chauhan AK. Immune Complexes in Disease Pathology. *Front Immunol*. 2017.
- Dispenzieri A, Gorevic PD. Cryoglobulinemia. *Hematol Oncol Clin North Am*. 1999;13(6):1315.
- Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, Cohen P, French Vasculitis Study Group. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore*). 2005;84(5):313.
- Guillevin L, Mahr A, Cohen P, Larroche C, Queyrel V, Loustaud-Ratti V, Imbert B, Hausfater P, Roudier J, Bielefeld P, Petitjean P, Smadja D, French Vasculitis Study Group. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. *Arthritis Rheum*. 2004;51(3):482.
- Kappus MR, Sterling RK. Extrahepatic manifestations of acute hepatitis B virus infection. *Gastroenterol Hepatol (NY).* 2013 Feb;9(2):123-6.
- Li P, Wei RB, Tang L, Wu J, Zhang XG, Chen XM. Clinical and pathological analysis of hepatitis B virus-related membranous nephropathy and idiopathic membranous nephropathy. *Clin Nephrol*. 2012 Dec;78(6):456-64.
- Merkel PA. Clinical manifestations and diagnosis of polyarteritis nodosa in adults. UpToDate. www.uptodate.com
- Monti G, Galli M, Invernizzi F, Pioltelli P, Saccardo F, Monteverde A, Pietrogrande M, Renoldi P, Bombardieri S, Bordin G. Cryoglobulinaemias: a multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. GISC. Italian Group for the Study of Cryoglobulinaemias. *QJM*. 995;88(2):115.
- Terrault NA, Lok ASF, McMahon BJ, Chang K, Hwang JP, Jonas MM, Brown RS, Bzowej NH, Wong JB. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. *Hepatology*. 2018; 67 (4): 1560-1599.
- Wang WN, Wu MY, Ma FZ, Sun T, Xu ZG. Meta-analysis of the efficacy and safety of nucleotide/nucleoside analog monotherapy for hepatitis B virus-associated glomerulonephritis. *Clin Nephrol*. 2016;85(1):21.

# Thank you!