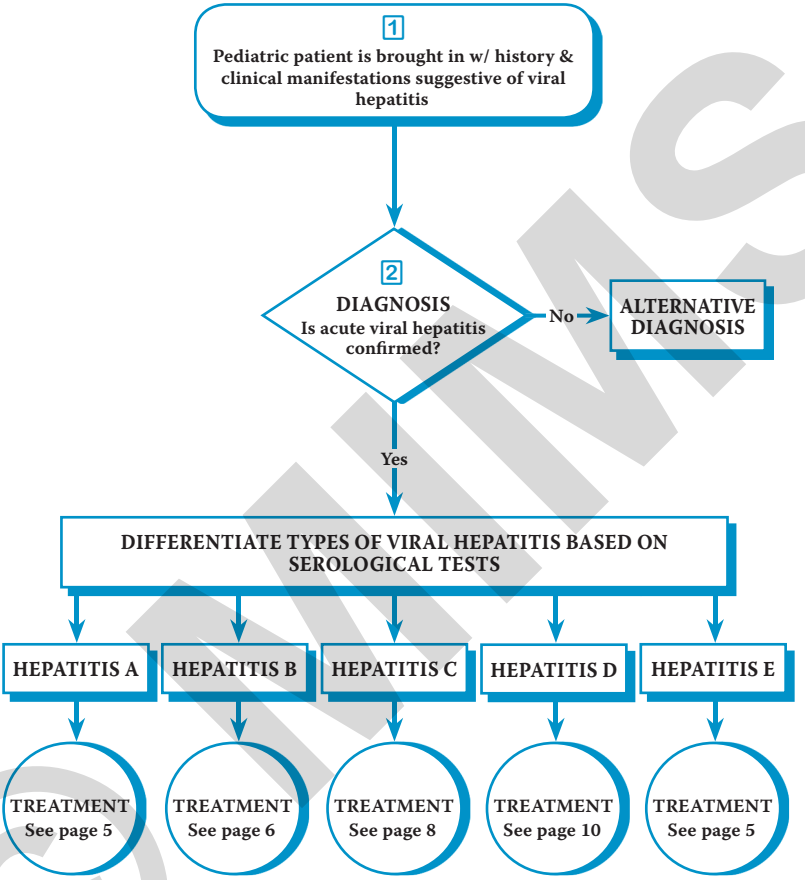
Hepatitis - Viral (1 of 20)



1 ACUTE HEPATITIS

Signs & Symptoms

- The majority of acute viral hepatitis infections are asymptomatic or they can cause an anicteric illness that may not be diagnosed as hepatitis

Preicteric Phase

- Nonspecific systemic symptoms (eg myalgia, nausea, vomiting, fatigue, malaise w/ discomfort in the right upper quadrant of the abdomen)
- Altered sense of smell or taste, coryza, photophobia, headache, cough, diarrhea, dark urine & serum sickness-like syndrome
- Hepatomegaly, splenomegaly & lymphadenopathy may be seen on physical exam

Icteric Phase

- Jaundice is usually noted after onset of fever or upon lysis of fever

Fulminant Hepatitis

- Development of symptoms of hepatic encephalopathy (eg confusion, drowsiness) w/in 8 wk of symptoms or w/in 2 wk of onset of jaundice
- Hypoglycemia, prolonged prothrombin time (PT)

Hepatitis A

- Generally causes minor illness in childhood w/ >80% of infections being asymptomatic
  - Adults are more likely to produce clinical symptoms
- Intestinal symptoms are usually misdiagnosed as gastroenteritis
- Jaundice & intestinal symptoms usually resolve 2-3 wk after onset
- A patient is infectious 1-2 wk prior to the clinical illness
- Atypical courses
  - Cholestatic jaundice: jaundice & severe pruritus last >12 wk
  - Relapsing hepatitis: a 2nd or 3rd recurrence of signs & symptoms occur after initial abatement
- Children may infect adults who may experience overt disease & higher risk of mortality

Hepatitis B, C & D

- May be asymptomatic
- Symptomatic hepatitis B will depend on the mode & time of transmission
  - Perinatal transmission from mother to child is the most common route for infants & almost always asymptomatic
  - Other routes of transmission are more likely to produce symptomatic disease (30% of cases transmitted by IV drug use are icteric)
  - Asian populations have a high rate of perinatal acquisition leading to high risk for chronicity
  - Westerners usually acquire HBV later in life
- Most acute & chronic HCV infections are clinically silent

Hepatitis E

- Accounts for >50% of acute hepatitis cases in Central & Southeast Asia, India, China & Africa
  - The most common cause of symptomatic hepatitis in children in these areas

History

Important points in the clinical history for patients w/ suspected viral hepatitis

- Contacts w/ jaundiced patients
- IV drug use
- History of blood transfusion
- Surgery or hospitalizations
- Family history of chronic liver disease
- Maternal history of hepatitis infection

Routes of Transmission of Hepatitis

Hepatitis A: Predominantly oral-fecal through person to person direct transmission & contaminated material or food

Hepatitis B: Perinatal, horizontal spread (infection acquired from living w/ a chronic HBV carrier), percutaneous, sexual, close person-to-person contact (ie by open cuts & sores)

Hepatitis C: Blood transfusions, percutaneous (ie IV drug use, sexual, perinatal)

- Majority of infections are identified in children w/ repeated exposure to blood products
- Conditions associated w/ HCV infection in pediatric population:
  - Thalassemia
  - Sickle cell disease
  - Hemophilia
  - History of malignancy
  - Hemodialysis
  - Solid organ transplants
  - IV drug use
  - Multiple sexual partners
  - Mother w/ chronic HCV
  - Household contact w/ HCV carrier

Hepatitis D: Sexual, percutaneous esp IV drug use

- Found only in patients w/ hepatitis B since it requires the hepatitis B outer coat

Hepatitis E: Primarily through contaminated drinking water & oral-fecal transmission

- Outbreaks often occur during rainy seasons

2 DIAGNOSIS

Serological Tests for Viral Hepatitis

Hepatitis A

- Anti-hepatitis A virus IgM has high sensitivity & specificity
  - This test remains positive for ≥6 mth

Hepatitis B

- Hepatitis B is usually characterized by the presence of hepatitis B surface antigen (HBsAg)
  - Recommended tests for HBsAg-positive pediatric patients:
    - HBeAg/anti-HBe status
    - HBV DNA
    - Anti-HBc IgM
    - Anti-HCV
    - Anti-HIV
    - Anti-HAV
    - Anti-HDV
- In the Asia-Pacific region, HBV infection is commonly found on routine blood testing
- Anti-HBc is the 1st antibody to appear in the serum & is a marker of natural infection
  - Presence of anti-HBc IgM (anti-core antibody) is diagnostic for acute hepatitis B virus (HBV) infection but may occur during a flare of chronic hepatitis B
  - Its presence indicates an immune response against HBV w/in liver cells & is a specific marker of acute hepatitis B infection
- Hepatitis B e antigen (HBeAg) is a marker of active viral replication
  - This may be negative at the time that the patient is evaluated for acute hepatitis B since viral replication may have already ceased
- Anti-HBs is usually produced following a resolved infection & is the only HBV antibody marker present after immunization
- Patients w/ seropositive HBsAg for >6 mth may be classified to have chronic HBV infection, & these patients should be tested for co-infection w/ hepatitis C virus (HCV), hepatitis D virus (HDV) & human immunodeficiency virus (HIV), if they are at risk for these infections
- Depending on local health services, the following groups should be tested for chronic HBV infection:
  - Persons born in hyperendemic areas, infants born to mothers w/ chronic HBV, w/ multiple sexual partners or history of STDs, IV drug users, dialysis patients, patients undergoing chemotherapy or immunosuppression, HIV positive individuals, & family or household members & sexual contacts of HBV-infected persons
    - Individuals who are seronegative should be vaccinated against HBV
    - HBsAg positive patients should be evaluated to assess progression of liver disease & need for antiviral therapy
    - Anti-HBs positive patients have developed natural immunity & do not need to be vaccinated
    - All pregnant women should be screened for HBsAg w/ appropriate treatment of newborn & immunization of infants

Hepatitis C

- Generally in clinical practice, acute hepatitis C is not commonly recognized & the majority of patients already have chronic hepatitis C
- Acute hepatitis C cannot be reliably diagnosed by antibody tests since these often do not become positive until 3 mth after infection
- Anti-HCV antibody
  - First-line serologic test for patients infected w/ acute Hepatitis C
  - Patients w/ positive anti-HCV antibody should be tested for HCV RNA
    - If results show negative HCV RNA even w/ a positive anti-HCV result, patient should be retested after 3 mth to confirm infection
  - A reactive HCV antibody & positive HCV RNA is conclusive of current Hepatitis C infection
- HCV RNA
  - If the clinical suspicion is high, the patient should be tested for HCV RNA to establish the diagnosis
  - Reverse-transcriptase polymerase chain reaction detects small amounts of HCV RNA w/in days of infection
  - Quantitative measurement of HCV RNA may be useful in prognosis or evaluating response to therapy
  - Both HCV RNA & anti-HCV antibody are needed to conclude diagnosis of chronic hepatitis C
- Recombinant immunoblot assay (RIBA) may be used to establish the cause of a positive anti-HCV test in a person w/ undetectable HCV RNA
  - A negative RIBA indicates that a positive anti-HCV immunoassay result showed a false positive result & no further testing is necessary
  - A positive RIBA & ≥2 subsequent tests in which HCV RNA cannot be detected suggests that HCV infection has resolved & no further testing is indicated

2 DIAGNOSIS (CONT'D)

Serological Tests for Viral Hepatitis (cont'd)

Hepatitis C (cont'd)

- HCV genotype should be determined, if possible, in all HCV-infected persons prior to treatment to determine duration of therapy & chances of response
  - Genotypes 2 & 3 are easier to treat, require shorter duration of therapy & a lower Ribavirin dose
- Liver biopsy may be done if it is thought that the results will influence clinical decision, but biopsy is not mandatory to start therapy in patients w/ genotypes 2 & 3
  - Liver biopsy may be obtained to provide prognostic information
- Depending on local health services, the following pediatric groups should be tested for HCV infection:
  - Persons who have in the recent or remote past used illicit IV drugs
  - Persons w/ conditions associated w/ high prevalence of HCV infection
    - Positive HIV, history of hemodialysis, unexplained abnormal aminotransferase levels
  - Persons who received blood/blood products or organ transplants prior to 1992, children born to HCV infected mothers, patients who had sexual encounters w/ HCV-infected persons
  - Infants born to HCV mothers who are HCV antibody positive & HCV RNA negative do not need to be tested
    - An HCV antibody test must be performed at 12 mth of age & thereafter to determine the majority of children who are not infected
    - Children born to mothers who are co-infected w/ HIV, & infants who are HCV antibody (positive) at 12 mth of age should have HCV RNA determination which must be confirmed, if positive, on a second sample
    - An HCV RNA test & repeat tests can be done at 2 mth of age in infants whose risk of HCV infection must be known before 12 mth of age
  - Children w/ chronically elevated transaminases
  - Children coming from regions w/ reported high incidence of HCV infection

Hepatitis D

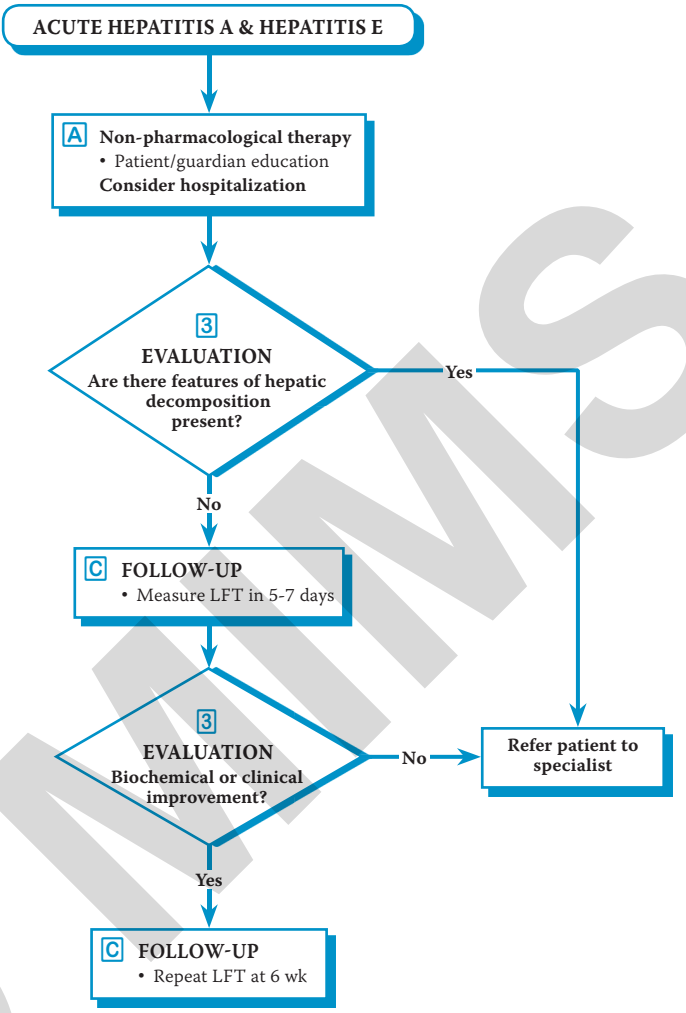
- Confirmed by positive anti-HDV antibody or HDV RNA test
- Hepatitis D only occurs as co-infection w/ Hepatitis B

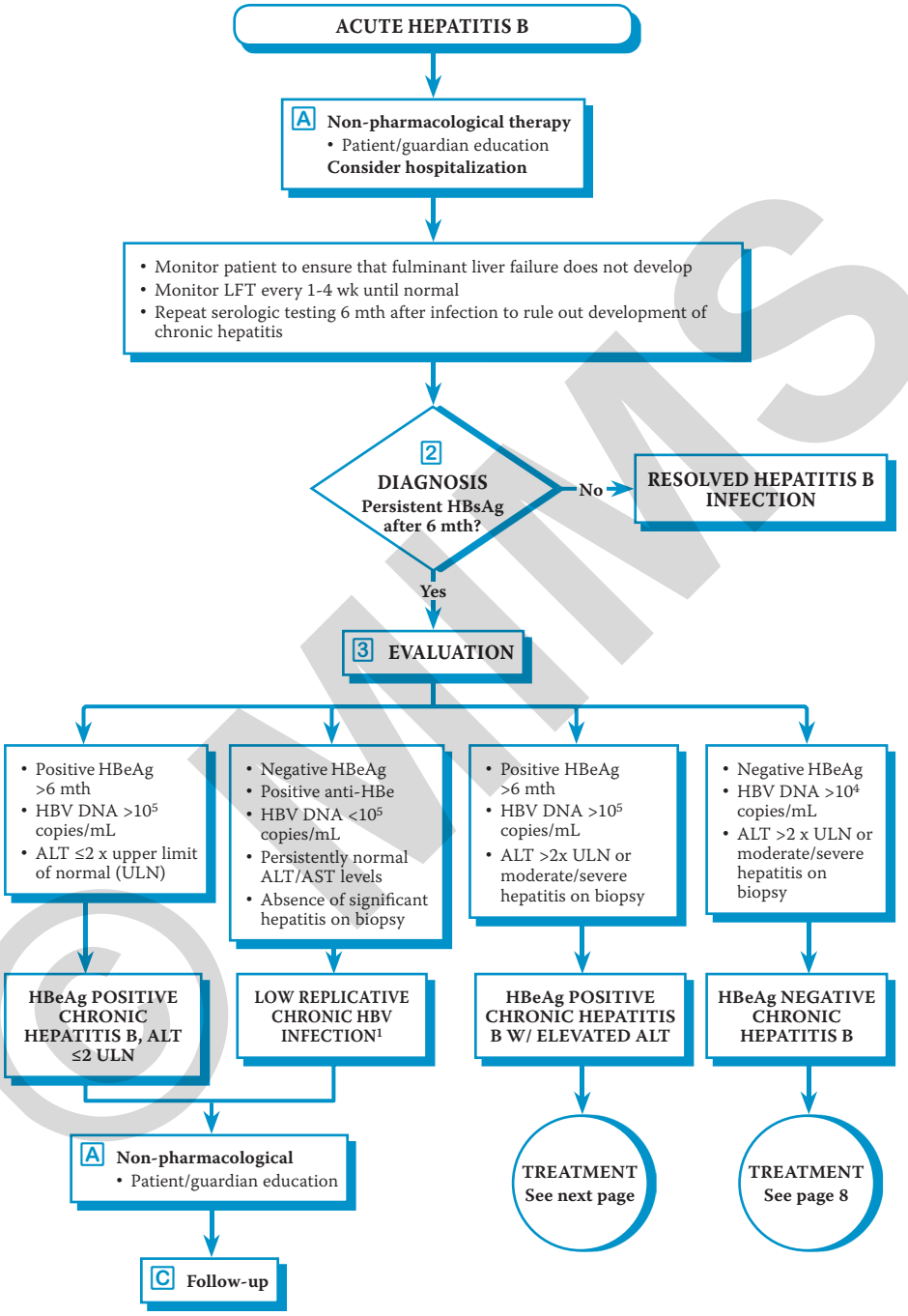
Hepatitis E

- Diagnosis is made in endemic populations by clinical symptoms & exclusion of other infectious agents like Hepatitis A, B, C, Epstein-Barr virus & cytomegalovirus
- Definitive diagnosis can be made by detection of IgM anti-HEV, IgG anti-HEV
- Hepatitis E virus (HEV) RNA from serum & stool of infected patients

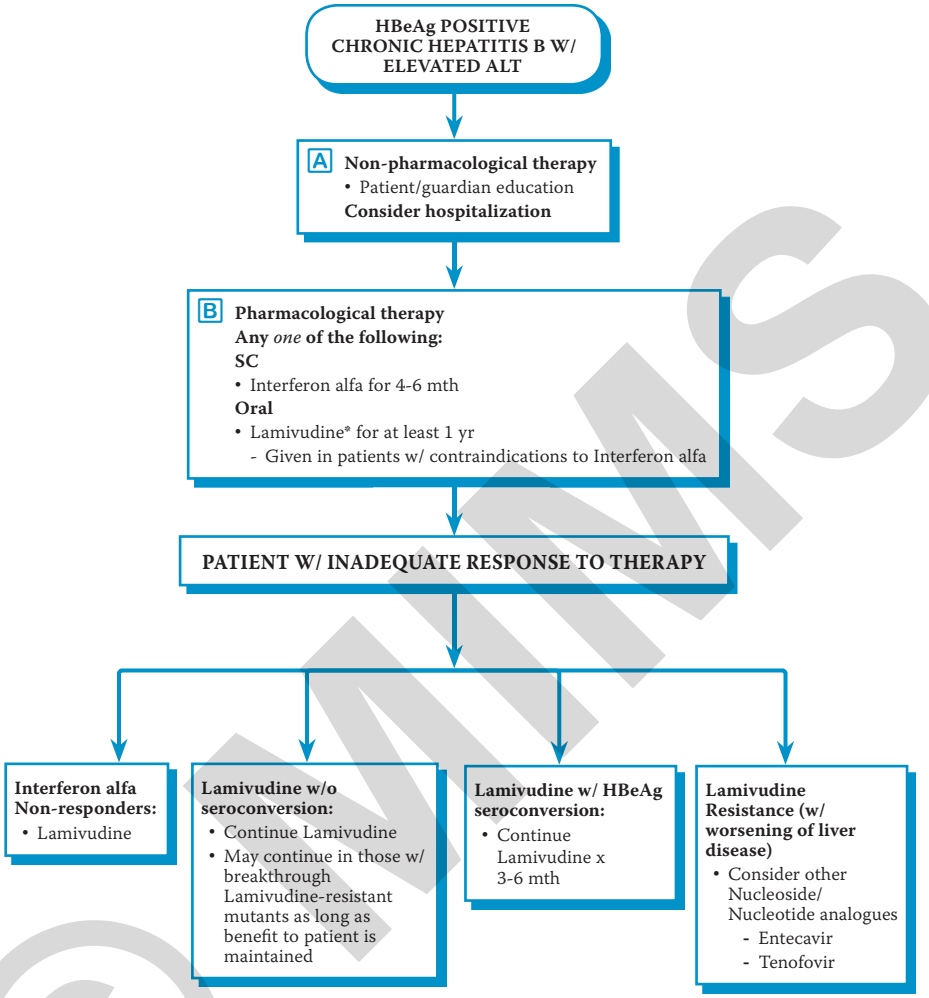
Other lab tests that are recommended in patients suspected to have viral hepatitis:

- Liver Function Tests (LFTs)
  - Aspartate aminotransferase (AST) & alanine aminotransferase (ALT) are usually increased (1.5-10 x)
  - Serum bilirubin, total bilirubin, alkaline phosphatase (ALP)
  - Complete blood count
- PT, international normalized ratio (INR)
- Liver biopsy
  - Reserved for pediatric patients suspected of having Hepatitis B infection, w/ HBV DNA of >2000 IU/ml, ALT ≥30 IU//L for boys & ≥19 IU/L for girls obtained twice & done 3 mth apart
- Tests for hepatocellular carcinoma (HCC), including liver ultrasound, alpha fetoprotein (AFP) for HBV-suspected pediatric patients





[1]Inactive chronic HBV infection - carrier state



*Continue treatment for 6 mth after anti-HBe seroconversion.

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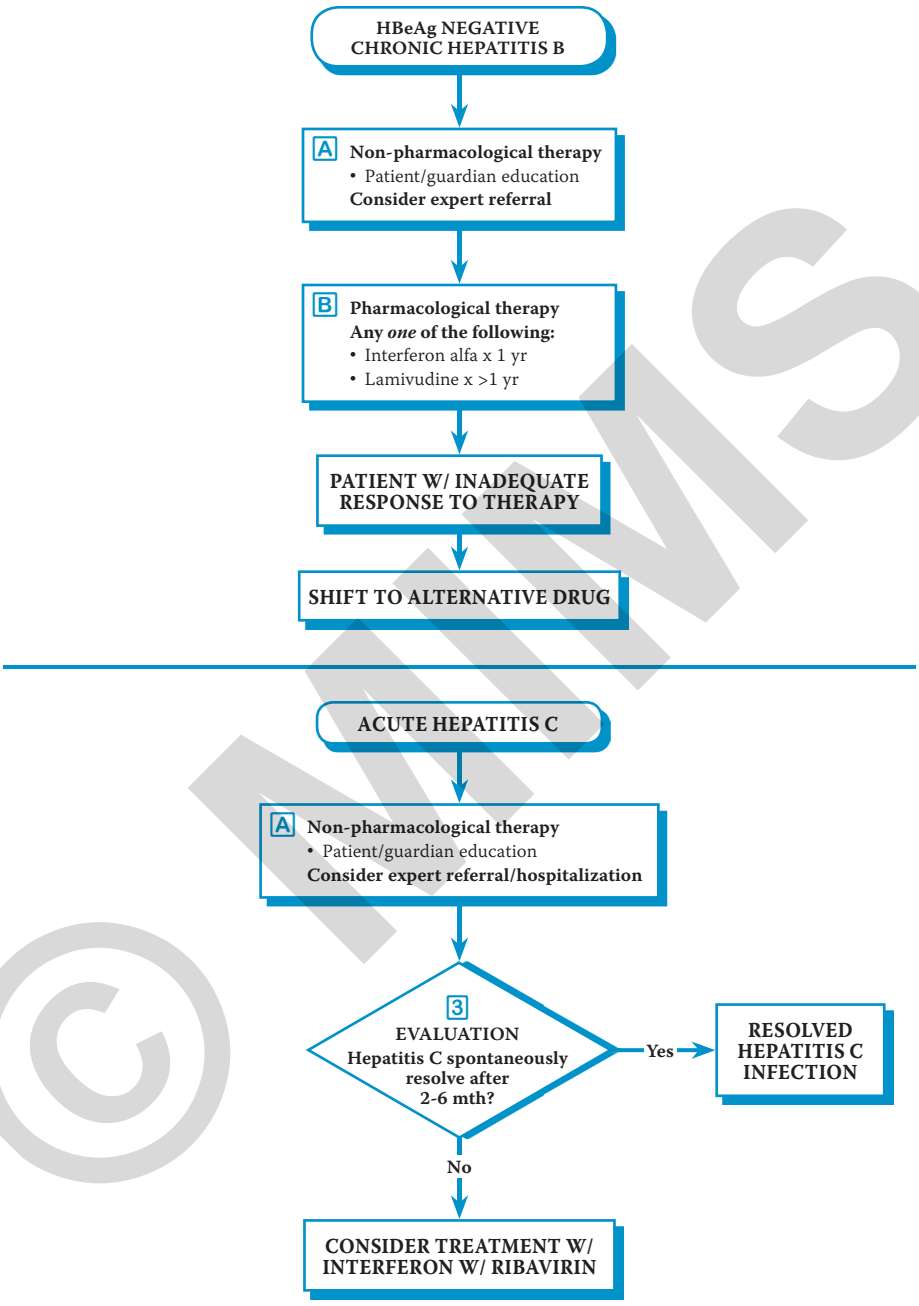
Specific prescribing information may be found in the latest MIMS.



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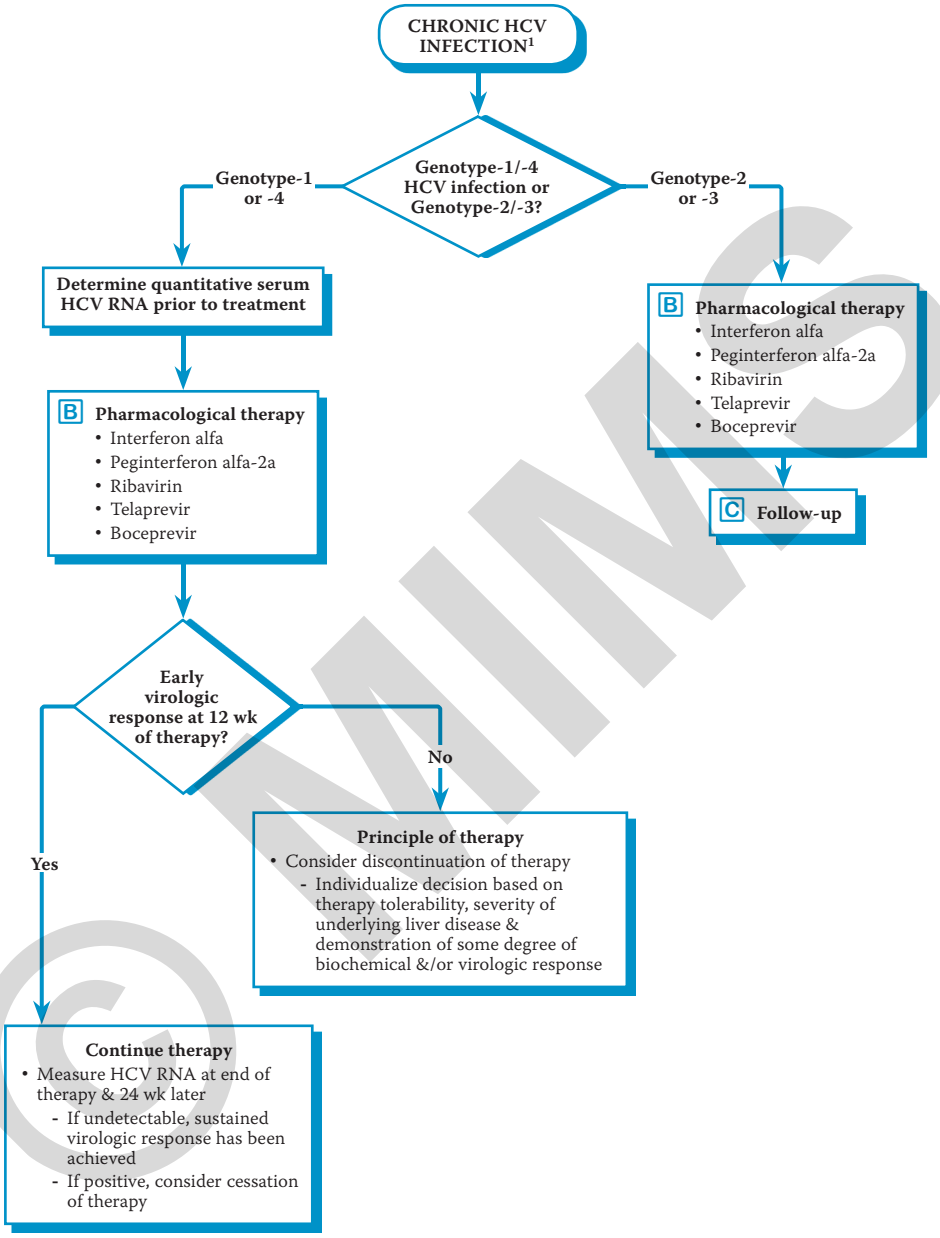
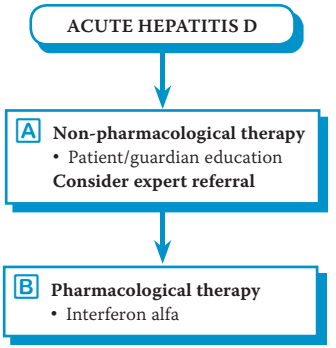


[1]Treatment is not recommended in patients <3 yr of age.



3 EVALUATION

- For Hepatitis A & B virus, the following are clues that hepatic decomposition may be present:
  - Mental dullness
  - Bilateral asterixis
  - Ascites
  - Hepatic encephalopathy
  - Clinical deterioration
  - PT is 3 sec longer than control
  - INR >1.5
  - Serum bilirubin >2.5x ULN

Acute Hepatitis B

- History & physical exam
- Measure HBeAg, anti-HBe, HBV DNA & ALT
- Complete blood count (CBC), PT
- Screen for hepatocellular carcinoma (HCC) in high-risk patients

If patient meets criteria for chronic hepatitis B

- Liver biopsy to grade stage of liver disease
  - The decision to perform biopsy in children should be guided by all factors considering its necessity & its benefits to the patient

PRINCIPLES OF THERAPY

Hepatitis B

- Children at high risk for disease progression or HCC development should be identified early so that therapy can be started, reducing the risk for antiviral resistance
- Initiate treatment in patients w/ chronic hepatitis B w/ evidence of fibrosis or ALT ≥30 IU/L for boys & ≥19 IU/L for girls obtained from 2 consecutive tests conducted 3 mths apart

Hepatitis C

- Antiviral therapy should be given to HCV-infected patients aged 3-17 yr
  - Treatment is contraindicated in patients <3 yr of age
- The benefits of treatment need to be weighed against the risk of side effects for children who have mild or no liver disease & are asymptomatic
- Treatment should start between 3 & 6 mth of diagnosis, if the infection has not resolved spontaneously

Consequences of HCV Infection

- More likely to resolve spontaneously in children
- Slower rate of progression to end-stage liver disease
- 50% of cases of HCV infection becomes chronic
  - 70% of transfusion acquired infections persist for >6 mth
- 5-20% of these patients may develop cirrhosis over the next 20-25 yr
  - HCV-related cirrhosis is associated w/ risk of developing end-stage liver disease (30% risk over 10 yr) as well as HCC
- HCV-infected children should be monitored to determine the minority who are at risk of progressive fibrosis during childhood & who may be candidates for treatment
- In patients w/ persistent infection, the evolution to cirrhosis is the primary concern
  - Usually occurs ≥20 yr after initial infection & occurs more often in patients at older ages (esp men), those who drink >50 g of alcohol/day, those who are obese or have substantial hepatic steatosis & in those w/ HIV infection

A NON-PHARMACOLOGICAL THERAPY

Hepatitis A & E

- Supportive care
- Consider hospitalization if there is vomiting, dehydration, signs of hepatic decompensation

Patient/Guardian Education

- Provide the parent &/or the patient w/ a detailed explanation of the patient's condition
- Patients must avoid food handling until they become noninfectious
- Good sanitary practices, drinking safe water, avoiding uncooked foods & vegetables & vigorous hand-washing help diminish the risk of infection
- A patient w/ Hepatitis A is infectious 1-2 wk prior to clinical illness during the prodromal stage
  - HAV infection of household contacts can be prevented by the administration of immune serum globulin

Acute Hepatitis B

- Supportive care
- Consider hospitalization if there is vomiting, dehydration, signs of hepatic decompensation

Patient/Guardian Education

- Provide the guardian/patient w/ a detailed explanation of his condition
  - Emphasize the disease's long-term implications for their & their partners' health
  - Provide clear, accurate, written information
- If appropriate, advise sexually-active adolescents to avoid unprotected sexual intercourse, emphasize condom use
- Screen for other STDs in cases of sexually-acquired hepatitis or if otherwise appropriate
- All non-immune sexual & household contacts must be screened & vaccinated

Chronic Hepatitis B

- 40-70% of HBV before 3 yr of age result in chronic carrier state
  - Persistent infection develops in 90% of neonates, 20-50% of young children, & 5% of adults who acquire HBV infection
- Course of infection in children depends mainly on age of acquisition of infection
  - Immunotolerant phase: High HBV DNA (>10^7 copies/mL), normal or minimally elevated ALT, typical in the Far East region, last for 10-30 yr after perinatal infection
  - Immunoactive phase: Decrease in HBV DNA, elevated ALT
  - Seroconversion of HBeAg to anti-HBe: May take place after a sudden, asymptomatic elevation of liver transaminases; spontaneous HBV remission, rare in children
  - Chronic hepatitis B infection: Persistence of HBsAg, elevated ALT, inflammatory & necrotic changes in the liver, elevated aminotransferases level & viremia
- Vaccination against hepatitis A for non-immune patients
- HBV infection has been linked to the development of HCC
  - HCC usually occurs >20 yr after onset of HBV infection
  - HBV-associated HCC cases may be seen in young children before the onset of cirrhosis
- Liver biopsy
  - Purpose is to assess the degree of liver damage, to rule out other causes of liver disease & to help predict prognosis
  - Recommended for chronic hepatitis B patients who are candidates for antiviral therapy
  - May be important when the administration of new therapy of chronic HBV becomes possible
  - The decision to perform biopsy should consider necessity & its benefits to the patient
- Screening for HCC in children

Patient/Guardian Education

- Provide the patient/guardian w/ a detailed explanation of the patient's condition
  - Emphasize the disease's long-term implications for their & their partners' health
  - Provide clear, accurate, written information
- Breastfeeding is encouraged for infants who have been properly immunized
  - Check for any open wound or bleeding in the nipple area prior to breastfeeding

A NON-PHARMACOLOGICAL THERAPY (CONT'D)

Chronic Hepatitis B (Cont'd)

Patient/Guardian Education (cont'd)

- Counseling regarding prevention of transmission of HBV
  - Sexual transmission: Protected sexual intercourse (ie condom use)
  - Perinatal transmission: Hepatitis B immune globulin (HBIg) & hepatitis B vaccine at delivery for babies of HBV-infected mothers
  - Inadvertent transmission via environmental contamination from a blood spill

Hepatitis C

- Supportive care
- Consider hospitalization if there is vomiting, dehydration, signs of hepatic decompensation
- Screen for other STDs in cases of sexually-acquired hepatitis or if otherwise appropriate

Patient/Guardian Education

- Provide the patient/guardian w/ a detailed explanation of the patient's condition
  - Emphasize the disease's long-term implications for their & their partners' (if any) health
  - Provide clear, accurate, written information
- Advise patient not to donate blood, semen or organs
- Advise patient to avoid sharing items of personal hygiene eg toothbrushes, shaving equipment
- Counsel patient to stop using illicit drugs
- Advise patient regarding sexual transmission
  - HCV is not considered to be a sexually transmitted disease, but sexual promiscuity, HIV & herpes simplex virus (HSV-2) co-infections are associated w/ sexual transmission of hepatitis C
  - Avoid unprotected sex during menstruation
- Advise patient regarding the potential deleterious effect of alcohol esp in association w/ development of HCC, progression of liver fibrosis & increase in HCV replication
- Advise adolescent patient against smoking which could accelerate disease progression

Hepatitis D

- Supportive care
- Consider hospitalization if there is vomiting, dehydration, signs of hepatic decompensation
- Screen for other STDs in cases of sexually-acquired hepatitis or if otherwise appropriate
- Consider expert referral

Partner Notification

- Partner notification for at-risk contacts

Patient/Guardian Education

- Provide the patient w/ a detailed explanation of the patient's condition
  - Emphasize the disease's long-term implications for their & their partners' health
  - Provide clear, accurate, written information
- Advise patients to avoid unprotected sexual intercourse

B PHARMACOLOGICAL THERAPY

Hepatitis B

Patients For Whom Treatment is Not Recommended

- Negative HBeAg, positive anti-HBe, HBV DNA <10^5 copies/mL, normal ALT (inactive HBV infection)
- Positive HBeAg, HBV DNA >10^5 copies/mL & normal ALT

Patients For Whom Treatment is Recommended

- Positive HBeAg, HBV DNA >10^5 copies/mL, persistent or intermittent elevations of ALT
- Negative HBeAg, HBV DNA >10^4 copies/mL, elevated ALT

Goals of Treatment

- Continued viral suppression is necessary to reduce or prevent hepatic disease & disease progression
- Primary goal of treatment is to permanently suppress HBV or to eliminate it
  - Short-term goal is the sustained suppression of HBV DNA, ALT normalization, to prevent decompensation & to decrease hepatic necroinflammation & fibrosis during & after therapy
  - Long-term goal of therapy is to avoid hepatic decompensation, reduce or prevent progression to cirrhosis &/or HCC & to prolong survival
- Endpoints used to assess response:
  - Biological response: Normalization of serum ALT
  - Virological response: Undetectable HBV DNA, loss of HBeAg in those initially HBeAg positive
  - Histological response: Decrease in histology activity compared to pretreatment liver biopsy
  - Complete response: Fulfill criteria of biochemical & virological response & loss of HBsAg
  - Anti-HBs positive on 2 consecutive annual tests
- Current treatments of chronic hepatitis B have limited long-term efficacy

Considerations Prior to Initiation of Treatment

- Age of patient
- Severity of liver disease
- Likelihood of response
- Potential adverse events & complications
- HBeAg positive chronic HBV patients w/ elevated ALT levels & compensated liver disease should be observed for 3-6 mth for spontaneous seroconversion from HBeAg to anti-HBe prior to initiation of treatment; initiation of therapy may be delayed
- Choice of therapy will depend on availability, cost of medication, necessary number of clinic visits, expected duration of treatment & patient/parent/guardian clinician preference
- Different genotypes may have different prognoses but currently do not imply difference in therapeutic management compared to hepatitis C

Monitoring During Therapy

- Monitor ALT, HBeAg &/or HBV DNA at least every 3 mth
  - Test for ALT levels every 24 wk in pediatric patients positive for HBeAg w/ normal ALT levels (<30 IU/L in boys, <19 IU/L in girls) w/o fibrosis in all diagnostic tests
- Monitor renal function if Adefovir is used
- Monitor for adverse effects if Interferons are used

Interferon alfa

- Interferons have antiviral, antiproliferative & immunomodulatory effects
- Therapy of choice for pediatric patients ≥1 yr old w/ chronic hepatitis B & compensated liver disease
- May be a preferred agent, in the treatment of HBeAg negative chronic hepatitis B & may be used as initial therapy for HBeAg positive chronic hepatitis w/ elevated ALT
- **Action:** Suppresses HBV replication & induces remission of liver disease
- **Effects:**
  - Efficacy is similar for adults & children
  - Relapse is a major problem in HBeAg negative chronic hepatitis B
  - Accelerates HBV DNA clearance & HBeAg/anti-HBe conversion
- Consensus guidelines on optimal selection for Interferon alfa treatment:
  - HBeAg & HBV DNA positive
  - Age >3 yr
  - Elevated ALT levels (at least 2x the normal or higher)
  - Intermediate & low levels of HBV DNA in serum (<1000 pg/mL)

B PHARMACOLOGICAL THERAPY (CONT'D)

Interferon alfa (cont'd)

- For HBeAg positive chronic hepatitis B, important predictors of response to therapy are high pretreatment ALT & lower levels of serum HBV DNA
- Obtain baseline CBC, LFTs (bilirubin, albumin, ALT), renal function tests (urea, electrolytes), thyroid function test, weight, height, prior to & during therapy
- Finite duration of therapy associated w/ Interferon alfa related flares of hepatitis
- Side effects include mood swings & depression; patient's mental health should be closely monitored by the clinician
- **Other Considerations**
  - In children w/ high viremia, delay the treatment until viremia decreases
  - Consider Interferon alfa in case of cirrhosis due to chronic HBV in children w/ Child-Turcotte-Pugh class A & persistent HBe antigenemia
  - Contraindicated in patients w/ decompensated cirrhosis, coexisting autoimmune diseases & in children w/ organ transplant, renal or cardiac failure, neurological diseases & severe function disturbances
  - Not recommended for patients w/ compensated cirrhosis because of risk of hepatic decompensation
  - Prednisone priming prior to Interferon alfa therapy is not recommended
  - Discontinue treatment when HBV DNA levels reach <2 $\log_{10}$ IU/ml &/or HBsAg >20,000 IU/ml
- **Response to therapy**
  - Seroconversion from HBeAg to anti-HBe antibody, normalization of serum ALT, HBV DNA clearance during the treatment or at 4, 12, & 24 wk after therapy is indicative of good treatment response
- Peginterferon, the pegylated form of Interferon, is currently being studied for the treatment of chronic hepatitis B infection in children

Nucleoside/Nucleotide Analogues

- Eg Adefovir, Entecavir, Lamivudine, Tenofovir
- Given to HBV DNA-positive pediatric patients unresponsive to Interferon alfa-48 wk treatment course
- Obtain baseline CBC, LFTs, renal function tests (w/ urine protein/creatinine ratio), blood clotting, HBV DNA & HBeAg levels in patients w/ compensated liver disease prior to & weekly after initiation of Lamivudine or Entecavir therapy
  - Add phosphate level measurement in patients w/ compensated liver disease who are to be given Tenofovir
- Adefovir
  - Alternative treatment for HBeAg-positive children >12 yr of age w/ persistently elevated LFTs
  - Studies showed that seroconversion can be achieved after a few yr of continuous Adefovir therapy
  - **Action:** Inhibits DNA synthesis through competitive reverse transcriptase inhibition & viral DNA incorporation
- **Entecavir**
  - Treatment option for HBeAg-positive HBV patients ≥16 yr of age w/ compensated liver disease intolerant or unresponsive to treatment w/ Interferon alfa or Tenofovir
    - May also be given if HBV DNA is still detectable despite a 96-wk treatment w/ Tenofovir & Lamivudine
    - Alternative treatment to Tenofovir in HBeAg-negative HBV patients w// compensated liver disease & w/ detectable HBV DNA even at 48 wk treatment duration
  - Alternative treatment for HBsAg-negative HBV patients w/ compensated liver disease previously given Interferon alfa w/ HBV <2 log IU/ml & HBsAg remains the same
  - Consider in HBV patients w/ possible HCV co-infection & w/o history of Lamivudine resistance
- **Lamivudine**
  - May be used as initial therapy for HBeAg positive chronic hepatitis w/ elevated ALT
  - Recommended in viremic patients (HBeAg positive & HBeAg negative patients) aged ≥2-3 yr w/ ALT >5x ULN esp if there is concern regarding decompensation
  - Good safety profile & ease of administration are its advantages over Interferon alfa
  - **Action:** Premature termination of viral DNA chain termination thereby inhibiting HBV DNA synthesis
    - Induces histologic improvement & reduction in rate of development of hepatic fibrosis
  - **Effects:**
    - Pretreatment ALT & active histological disease are the most important predictors of response
    - Response is greatest in patients w/ an ALT 2x the normal value

B PHARMACOLOGICAL THERAPY (CONT'D)

- **Lamivudine (cont'd)**
  - Treatment may be discontinued in patients who have completed 1 yr of treatment & have persistent HBeAg seroconversion to anti-HBe
  - Treatment may be continued in patients who have not achieved HBeAg seroconversion & have no evidence of breakthrough infection, because HBeAg seroconversion may occur w/ continued treatment
  - **Other Considerations**
    - Monitor HBV DNA levels, quantitative HBsAg, HBeAg levels at 12, 24, & 48 wk after initiation of therapy, & every 6 mth thereafter
    - Test for HBV DNA every 12 wk in HBeAg-negative patients on Lamivudine treatment for ≥5 yr
  - **Lamivudine-resistant HBV**
    - Emergence of Lamivudine-resistant HBV is increasingly common w/ prolonged treatment, together w/ a decreasing rate of remission
    - Associated w/ development of Lamivudine-resistant YMDD viral mutants, which appear to be less virulent than wild-type HBV, but have been associated w/ rapidly progressive liver disease in some patients
    - Lamivudine resistance is usually manifested as breakthrough infection, w/ reappearance of HBV DNA in serum
    - Factors that may correlate w/ the emergence of Lamivudine resistance: High pre-treatment HBV DNA levels, high pre-treatment ALT levels, male gender, high BMI
- **Tenofovir**
  - Drug of choice for HBeAg-positive HBV patients ≥12 yr old unresponsive or intolerant to Interferon alfa treatment
  - Alternative treatment for HBsAg-negative HBV patients w/ compensated liver disease previously given Interferon alfa w/ HBV <2 log IU/ml & HBsAg remains the same
  - Lamivudine may be added if HBV DNA is still detectable at 96 wk of treatment
  - Test for HBV DNA, quantitative HBsAg & HBeAg levels prior to, at 12, 24, & 48 wks during, & every 6 mth after initiation of treatment
  - May help evaluate patient's response & adherence to Tenofovir

Hepatitis C

- Peginterferon/Ribavirin combination therapy w/ either Telaprevir or Boceprevir is the treatment of choice for chronic hepatitis C genotype 1
- Assess liver disease severity prior to therapy

Goals of Treatment

- Prevent complications of HCV infection by eradication of the infection
- Treatment responses are usually characterized by HCV RNA testing (<15 IU/ml at 12 & 24 wk post-treatment
- Eradication of infection is considered when there is sustained virologic response (SVR)
  - SVR is defined as the absence of HCV RNA in serum by a sensitive test at the end of treatment & 6 mth later
- Early virologic response is defined as 2-log drop or loss of HCV RNA 12 wk into therapy
- End of treatment response is defined as continued absence of detectable virus at end of treatment
- Relapse is considered when HCV RNA becomes undetectable on treatment but is detected after discontinuation of therapy
- Patients in whom HCV RNA levels remain stable while on treatment are considered non-responders while those HCV RNA levels decline but never become undetectable are referred to as partial responders

Individualize treatment based on the following:

- Severity of liver disease
- Potential of serious side effects
- Likelihood of treatment response
- Presence of comorbid conditions

Boceprevir

- Addition to Interferon alfa/Ribavirin combination yields higher sustained virological response (SVR) rates
- Recommended triple therapy regimen for the following:
  - Patients w/ detectable HCV RNA at wks 8 & 24: stop treatment at 28 wk
  - Patients w/ detectable HCV RNA w/in 8-24 wk of therapy: stop Boceprevir at wk 36 of treatment, then continue Interferon alfa & Ribavirin regimen up to 48 wk

B PHARMACOLOGICAL THERAPY (CONT'D)

Hepatitis C (cont'd)

Interferon alfa w/ or w/o Ribavirin

- The use of Interferon alfa-2b combined w/ Ribavirin may be considered in patients w/ HCV infection

Peginterferon alfa-2a w/ Ribavirin

- Treatment of choice for treatment-naive chronic HCV patients aged 3-17 yr w/ genotype 2 or 3, & genotype 1 & 4 & high viral load

Ribavirin

- Assess HCV genotype prior to initiation of treatment

Telaprevir

- Added to Interferon alfa/Ribavirin regimen for patients w/ undetectable HCV RNA at wk 4 & 12 of therapy

Hepatitis D

- Interferon alfa may have a role

C FOLLOW-UP

Hepatitis A

- Considered a benign disease but may progress to fulminant liver failure & death
- HAV infection does not result in a carrier state nor chronic infection
- Exposure to Hepatitis A virus induces immune response that confers lifelong protection

Hepatitis B

End of Therapy

- Monitor ALT & HBV markers (including HBV DNA) mthly x 3 mth to detect relapse
- Then every 3 mth in patients w/ cirrhosis or HBeAg/HBV DNA positive
- May monitor every 6 mth in patients who responded to therapy
- Further monitoring in non-responders is recommended to recognize delayed response & to plan retreatment if required

HBeAg positive chronic hepatitis B w/ ALT ≤2x ULN

- Obtain LFT every 3-6 mth
  - If ALT >1-2x ULN, recheck every 1-3 mth
- If ALT >2x ULN x 3-6 mth, HBeAg positive & HBV DNA >105 copies/mL
  - Consider retreatment
- If persistent ALT at high normal values, w/ family history of hepatocellular carcinoma
  - Consider liver biopsy
  - Initiate pharmacotherapy if biopsy shows significant fibrosis or moderate to severe inflammation, & if viral DNA >20,000 IU/mL

Low Replicative Chronic HBV Infection

- Obtain LFT every 6-12 mth
  - If ALT >1-2x ULN, check serum HBV DNA level & exclude other causes of liver disease
  - Monitor CBC & LFTs annually
- Screen for HCC in relevant populations
  - Obtain an ultrasound scan & AFP levels every 6-12 mth & every 3 mth in high-risk patients w/ cirrhosis
  - Contrast-enhanced CT & MRI may be used to confirm lesions seen during ultrasound in high-risk cirrhotic patients

Chronic Hepatitis C

- Measure HCV RNA at 4 wk after start of therapy, at the end of therapy & 24 wk later
  - If undetectable, sustained virologic response has been achieved
  - Consider reduced duration of therapy of 12-16 wk
- Other laboratory tests used during monitoring may include CBC w/ prothrombin time, hepatic panel, FBS, thyroid function test, urinalysis

Hepatitis E

- Mortality is low in endemic groups except for the pregnant women
- Currently, no effective therapy exists
- Immune serum globulin does not prevent symptoms

PREVENTION & POST-EXPOSURE PROPHYLAXIS OF VIRAL HEPATITIS

Patient Group for Whom Prevention or Post-exposure Prophylaxis is Recommended	Recommended Prevention or Post-exposure Prophylaxis Regimen
Prevention	
Hepatitis A Susceptible persons traveling to HAV endemic areas Household contacts, day-care children & staff Healthcare personnel potentially exposed to HAV Patients who will undergo blood transfusion Immunocompromised children (suboptimal response) Illegal drug users (both injection & non-injection drug users) Persons w/ chronic liver disease, including persons w/ chronic HBV & HCV infection who have evidence of chronic liver disease	Hepatitis A Vaccine[1]
Hepatitis B Unvaccinated infants, children & adolescents Premature infants w/ immediate risk of HBV infection Persons w/ any of the following sexual risk factors: History of STD, multiple sex partners, sex w/ an injection drug user, victims of sexual assault Illegal IV drug users Household members, sex partners & drug-sharing partners of a person w/ chronic HBV infection[2] Persons on hemodialysis, or are receiving clotting factor concentrates, or who have occupational exposure to blood	Hepatitis B Vaccine • Infants should be given 1st dose w/in 24 hr after birth, then followed by 2-3 more doses based on the recommended immunization schedule • Older children & adolescents should receive 3 doses based on the recommended immunization schedule
Post-exposure Prophylaxis	
Hepatitis A Unvaccinated or non-immune persons exposed to hepatitis A virus (HAV) through eg household or sexual contact or by sharing illegal drugs w/ a person who has hepatitis A[3]	Administer a single IM dose of human immunoglobulin (Ig)[4] or hepatitis A vaccine[5] as soon as possible but not >2 wk after exposure
Hepatitis B Unvaccinated or non-immune sex partners of persons w/ acute hepatitis B Newborns of HBeAg-positive mothers	Administer Ig w/in 14 days after the most recent sexual contact Administer hepatitis B vaccine + Ig w/in 12-24 hr

Pre- or post-exposure prophylaxis is not recommended for hepatitis C.
[1]Postvaccination serologic testing is not indicated because most persons respond to the vaccine.
[2]Vaccination of household contacts (esp children & adolescents) of persons w/ acute HBV infection is also encouraged. Consider post-vaccination testing (anti-HBs) for sex partners of persons w/ chronic HBV infection. Those found to be antibody negative should receive a second, complete vaccination series.
[3]A person who has had 1 dose of hepatitis A vaccine at least 1 mth before exposure to HAV does not need Ig.
[4]Preferred for children <12 mth, immunocompromised persons, persons diagnosed w/ chronic liver disease, & those w/ contraindications to vaccines.
[5]Preferred over Ig for healthy individuals aged 12 mth - 40 yr.

Dosage Guidelines

IMMUNOGLOBULINS		
Drug	**Dosage**	**Remarks**
Hepatitis B Immunoglobulin (Hepatitis B Ig)	Individualize dose based on manufacturer's recommendations	**Adverse Reactions** • Post-inj local reactions, hypersensitivity reactions
Human Immunoglobulin	Single IM dose Individualize dose based on manufacturer's recommendations w/ in 2 wk of exposure to Hepatitis A	**Adverse Reactions** • Post-inj local reactions, hypersensitivity reactions

INTERFERONS W/ OR W/O RIBAVIRIN			
Drug	**Dosage**	**Duration**	**Remarks**
Interferon alfa-2b	**Chronic Hepatitis B:** 3-5 MIU SC/IM 3x/wk **Chronic Hepatitis C/ non-A non-B:** 3 MIU SC 3x/wk **Max dose:** 10 MIU SC 3x/wk	≤4 mth	**Interferons** **Adverse Reactions** • Influenza-like symptoms (fatigue, fever, headache, myalgia, arthralgia); Neuropsychiatric symptoms (depression, mood swings, irritability, somnolence); GI effects (abdominal pain, vomiting); Hematologic effects (neutropenia, granulocytopenia, thrombocytopenia) • Pain at inj site, dyspepsia, alopecia, thyroid function abnormalities • Decreased growth rate, absence of weight gain **Special Instructions** • Use w/ caution in patients w/ hepatic or renal impairment, depression or psychiatric disorders • Maintain adequate hydration during treatment • Withdraw drug if jaundice occurs **Ribavirin** **Adverse Reactions** • Hemolytic anemia, fatigue, itching rash, sinusitis, gout, birth defects **Special Instructions** • Do not give to patients w/ conditions that may be exacerbated by Ribavirin-induced hemolysis • Use w/ caution in patients w/ hepatic or renal impairment
Interferon alfa-2b + Ribavirin	**Chronic Hepatitis C in combination w/ Ribavirin** 3 MIU SC 3x/wk + **Ribavirin** **>75 kg:** 600 mg PO 12 hrly **≤75 kg:** 400 mg PO in the morning & 600 mg PO in the evening	6-12 mth	
Peginterferon alfa-2b + Ribavirin	**Chronic Hepatitis C in combination w/ Ribavirin** 60 mcg/m^2 SC once wkly + **Ribavirin** **≥27-35 kg:** 400 mg/day PO divided 12 hrly **36-49 kg:** 600 mg/day PO divided 12 hrly **50-65 kg:** 800 mg/day PO divided 12 hrly **>65 kg:** 1,000 - 1,400 mg/day PO divided 12 hrly	**Genotype-1 or 4:** 48 wk **Genotype-2 or 3:** 24 wk	

All dosage recommendations are for children w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.
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Dosage Guidelines

NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		
Drug	**Dosage**	**Remarks**
Adefovir	**Chronic Hepatitis B (w/ HBV replication & persistent elevation of LFTs)** **≥12 yr:** 10 mg PO 24 hrly	**Adverse Reactions** • GI effects (hepatomegaly, steatosis, GI upset, pancreatitis); Renal effects (nephrotoxicity, proximal renal tubulopathy, renal failure, Fanconi syndrome); Musculoskeletal effects (osteomalacia, myopathy); Metabolic effects (lactic acidosis, hypophosphatemia); Other effects (post-treatment hepatitis exacerbation, asthenia, headache, pruritus) **Special Instructions** • Use w/ caution in patients w/ renal impairment, HIV co-infection, hypertension, diabetes, obesity, liver disease, Lamivudine resistance, childn <12 yr • Obtain baseline ClCr, HIV Ab test prior to initiation of treatment
Entecavir	**Chronic Hepatitis B** **≥16 yr:** 0.5 mg PO 24 hrly **Patients ≥16 yr w/ prior HBV infection during Lamivudine treatment or w/ known Lamivudine resistance:** 1 mg PO 24 hrly on an empty stomach	**Adverse Reactions** • GI effects (abdominal pain, dyspepsia, N/V, diarrhea, increases in ALT/AST levels); CNS effects (headache, dizziness, somnolence, insomnia); Dermatological effects (rash, alopecia); Other effects (fever, malaise, cough, nasal symptoms, arthralgia, musculoskeletal pain, peripheral neuropathy) **Special Instructions** • Use w/ caution in patients w/ hepatomegaly & renal/ hepatic impairment
Lamivudine	**Chronic Hepatitis B** **≥2 yr:** 3 mg/kg PO 24 hrly x ≥1 yr **Max dose:** 100 mg/day	
Tenofovir	**Chronic Hepatitis B** **≥12 yr:** 300 mg PO 24 hrly	**Adverse Reactions** • GI effects (abdominal pain, dyspepsia, N/V, diarrhea, increases in ALT/AST levels); CNS effects (headache, dizziness, somnolence, insomnia); Dermatological effects (rash, alopecia); Other effects (fever, malaise, cough, nasal symptoms, arthralgia, musculoskeletal pain, peripheral neuropathy) **Special Instructions** • Use w/ caution in patients w/ lactic acidosis, severe hepatomegaly w/ steatosis, CrCl <50 ml/min, end-stage renal disease requiring dialysis, renal impairment, HIV-1 & HBV co-infection, autoimmune disorders, HBV-infected patients w/ decompensated liver disease • Assess estimated CrCl, serum phosphorus, urine glucose & protein prior to initiation & periodically during therapy

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Dosage Guidelines

OTHER ANTIVIRALS		
Drug	**Dosage**	**Remarks**
Inosine dimepranol acedoben (Inosine pranobex, Inosiplex, Methisoprinol)	**Hepatitis A & Acute Hepatitis B** **<1 yr/<9 kg:** 62.5 mg PO 4 hrly **1-3 yr/9-14 kg:** 125 mg PO 4 hrly **3-7 yr/14-21 kg:** 187.5 mg PO 4 hrly **>7 yr/>21 kg:** 250 mg PO 4 hrly	**Adverse Reactions** • Transient elevation of urine &/or serum uric acid levels; infrequent: Skin rashes &/or itching, Gl upsets, nausea, diarrhea, fatigue &/or malaise; rarely: Headache, vertigo, arthralgia, constipation, polyuria **Special Instructions** • Monitor serum uric acid levels in patients w/ gout, urolithiasis or renal dysfunction • Supervise administration to digitalized patients

VACCINES		
Drug	**Dosage**	**Remarks**
Hepatitis A vaccine	Individualize dose based on manufacturer's recommendations & local immunization guidelines	**Adverse Reactions** • Post-inj local reactions; Systemic symptoms (fever, headache, malaise); Hypersensitivity reactions **Special Instructions** • Give by SC route in patients w/ bleeding disorders
Hepatitis A & B vaccine	Individualize dose based on manufacturer's recommendations & local immunization guidelines	**Adverse Reactions** • Post-inj local reactions; Systemic symptoms (fever, headache, malaise); Hypersensitivity reactions • Abdominal pain, dizziness, sleep disturbance **Special Instructions** • Give by SC route in patients w/ impaired immunity or w/ bleeding disorders
Hepatitis B vaccine[1]	Individualize dose based on manufacturer's recommendations & local immunization guidelines	**Adverse Reactions** • Post-inj local reactions; Systemic symptoms (fever, headache, malaise); Hypersensitivity reactions • Abdominal pain, dizziness, sleep disturbance **Special Instructions** • The deltoid region as a site for inj is recommended for adults & the anterolateral thigh for infants • Inj in the gluteal region has been associated w/ diminished response

[1]Hepatitis B vaccine is also available in combination w/ diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B &/or polio vaccines. For available formulations, please refer to the latest MIMS.

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Please see the end of this section for the reference list.