Hepatitis B in Children

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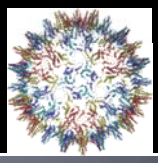


Disclosure

I have NO financial relationships with any commercial entity to disclose.

Learning Objectives

- Understand the ***natural history*** and the ***phases*** of HBV infection in children
- Discuss the recommendations for ***monitoring*** children with HBV infection
- Review the ***current therapies*** for patients with HBV infection

Description

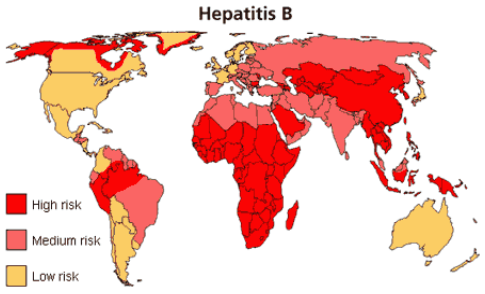
- Hepadnaviridae family
- Double-stranded DNA virus
  - Outer lipoprotein envelope (surface Ag)
  - Inner viral nucleocapsid (core)
- Eight genotypes
- All HBV subtypes share one common antigenic determinant – "a"

Epidemiology – International

- 350 million persons with infection
- 5% world's population has chronic infection
  - Leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma
- 500,000 – 1,000,000 persons die each year due to liver related diseases

Center for Diseases Control and Prevention – The Pink Book (May 2012)

Epidemiology



Epidemiology – United States

- 1.25 million chronic carriers
- 43,000 new infections each year
- 3,000 deaths annually
  - Cirrhosis
  - Hepatocelular carcinoma
- 22,000 HBV+ women give birth each year

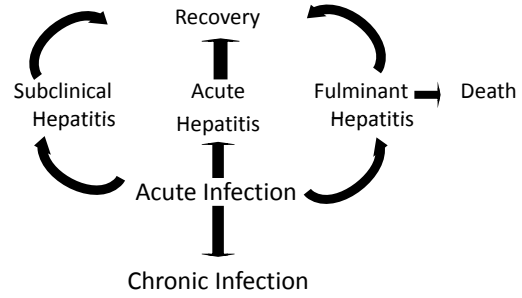
Center for Diseases Control and Prevention – The Pink Book (May 2012)

Epidemiology – United States

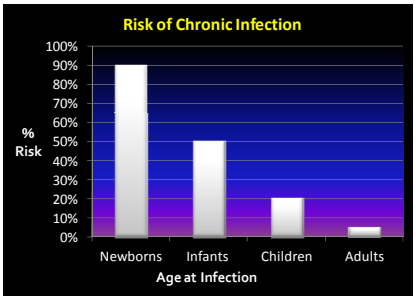
- 184 with hepatitis B
  - 67 % were female
  - median age 9 years (range 1 – 17)
  - 11% Caucasian, 7% African American, 79% Asian, 3% mixed race
  - 58% were international adoptees

Schwarz KB, Ling SC, Rosenthal P, Murray K, Rodríguez-Báez N, Teckman J, Schwarzenberg S, Cloonan YK and Li R for the Hepatitis B Research Network. Abstract AASLD 2012

Outcome of Hepatitis B Infection



Who Gets Chronic Hepatitis B?



Chronic Infection

- Four immunological phases
  - Immune Tolerant
  - HBeAg positive immune active
  - Inactive HBsAg "carrier"
  - Reactivation or HBeAg negative immune active

Jonas M, et al. Hepatology 2010, 52(6) , 2192-2205

Chronic Infection

- Immune Tolerant Phase
  - HBsAg and HBeAg detectable
  - HBV DNA > 20,000 IU/mL (> 10^5 copies/mL)
  - ALT normal
  - Absent or minimal liver inflammation and fibrosis
  - Most children are asymptomatic

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Chronic Infection

- Immune Tolerant Phase
  - Biopsy not generally indicated
  - Antiviral therapies are generally ineffective
  - Risk of drug resistance if treated with nucleos(t)ide analogs
  - Continued monitoring recommended

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Chronic Infection

- HBeAg positive Immune Active Phase
  - HBsAg and HBeAg remain detectable
  - HBV DNA > 20,000 IU/mL (>10^5 copies/mL)
  - ALT persistently abnormal

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Chronic Infection

- HBeAg positive Immune Active Phase
  - Most children are asymptomatic
  - Biopsy indicated
  - Appropriate testing should be considered to rule out other liver diseases
  - Treatment should be considered

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Chronic Infection

- Inactive HBsAg "carrier" Phase
  - HBsAg present
  - HBeAg undetectable; anti-HBe present
  - HBV DNA < 2,000 IU/mL (< 10^4 copies/mL)
  - ALT normal
  - Absent or minimal liver inflammation, fibrosis will regress with time
  - Age at seroconversion appears to be influenced by HBV genotype

Chronic Infection

- Inactive HBsAg "carrier" Phase
  - Risk of developing HCC
  - Risk of developing cirrhosis declines
  - Biopsy generally not recommended
  - Continued monitoring recommended

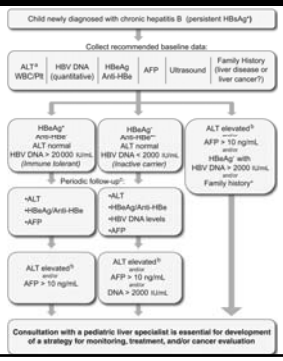
Chronic Infection

- Reactivation or HBeAg negative Immune Active Phase
  - Occurs in 20 – 30% of patients
  - HBsAg present
  - HBeAg remains negative; antiHBe positive
  - Called "e-antigen-negative" hepatitis B
  - Due to basal core promoter or precore mutation

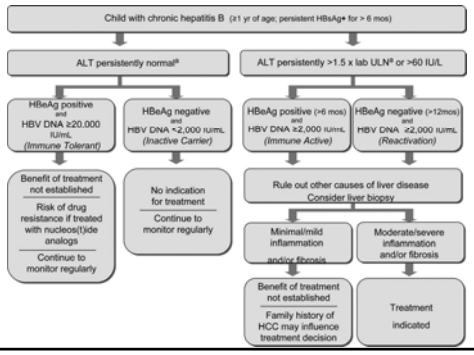
Chronic Infection

- Reactivation or HBeAg negative Immune Active Phase
  - HBV DNA > 2,000 IU/mL (> 10^4 copies/mL)
  - ALT normal or elevated
  - Active liver inflammation +/- fibrosis
  - Liver biopsy indicated, especially if ALT abnormal
  - Treatment should be considered if moderate or severe inflammation or fibrosis present
  - Treatment with nucleos(t)ide analog may long term

Evaluation and Monitoring



Evaluation and Monitoring



Treatment

- Prevention
- Prophylaxis
  - Possible exposure
- Medications
  - Chronic infection

Prevention

- In 1991, US started routine vaccination
  - Incidence of acute HBV infection has declined
- Offer vaccine to high risk individuals

Prophylaxis

- Hepatitis B immune globulin (HBIG) and vaccine
  - Patients with no history of vaccine
    - Percutaneous exposure (needle sticks)
    - Household contacts exposed to blood
  - Perinatal exposure
    - Prevents transmission in 95% of mothers HBsAg positive when given within 12 hours of birth

Goals of Treatment Chronic Hepatitis B

- Sustained suppression of HBV replication
  - HBV DNA undetectable in serum
  - HBeAg to anti-HBe seroconversion
  - HBsAg to anti-HBs seroconversion
- Remission of liver disease
  - Normalization of serum ALT levels
  - Improvement in liver biopsy
- Improvement in clinical outcome
  - Prevention of liver failure and cancer
  - Increased survival

Chronic Infection Who Should We Treat?

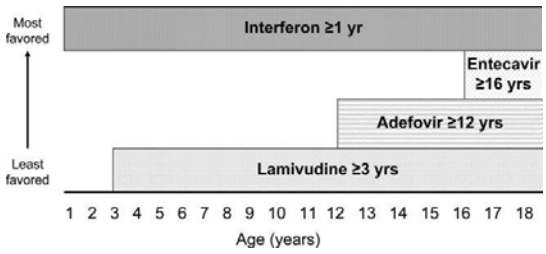
- Treat:
  - **HBeAg positive** with persistent infection and abnormal LFTs
- No treatment:
  - **HBeAg negative** and **carrier** (normal LFTs, viral load less than 10^5 and asymptomatic)
- Probably treat:
  - **HBeAg negative** with **chronic infection** (high viral load, abnormal LFTs)

Therapeutic Agents in Chronic Hepatitis B

Immune Modulators analogs	Nucleo(s)tide
Interferon*	**Lamivudine***
Peginterferon	**Adefovir***
	Entecavir*
	Tenofovir
	Telbivudine

* Approved for Children

Therapeutic Agents in Chronic Hepatitis B



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Interferon alfa

- Subcutaneous injection three times per week for 6 months
- 20 – 40% of patients had response
  - Seroconversion to HBe antibodies
  - Normalization of ALT
- Factors associated with response
  - ALT > 2 times ULN
  - Female gender; Young age
  - Low HBV DNA load
  - Active inflammation

Interferon alfa

- Multiple side effects
  - Fever, myalgia, thrombocytopenia, depression
- Contraindicated in advanced liver disease
  - 'Flairs' or elevation in LFT's occur at time of seroconversion to anti-HBe due to increased immune response
  - May precipitate overt liver failure

Lamivudine

- Oral medication
- Inhibits HBV DNA polymerase
- Usually given for 52 weeks or longer
- 23% of children had a successful response
- Factors associated with response
  - ALT >5 times normal -> 65% response rate
  - ALT 2-5 times normal -> 26% response
  - ALT <2 times normal -> 5% response
  - Active inflammation in liver biopsy

Lamivudine

- Use limited by resistance
  - At one year of treatment 15-20% of patients develop resistance
  - 40% at two years
  - 67% at four years
- However, the resistant virus is less hearty than the native virus resulting is lower replication rates than pretreatment

Adefovir

- Nucleotide analogue
- Inhibits viral polymerase
- Efficacy
  - Reduces viral load
  - Enhances HBeAg seroconversion
  - Results in histological improvement of liver
  - Improved LFTs
- Much lower rate of resistance than Lamivudine

Entecavir

- Guanosine nucleoside analog
- Activity against HBV polymerase
- Less effective for lamivudine-refractory HBV infection
  - Requires higher dose

Treatment Outcomes in Children with Hepatitis B

	IFN-a (Sokal)	Lamivudine (Jonas)	Adefovir dipivoxil (Jonas)
HBeAg clearance	23*	26*	16
HBeAg seroconversion	54 (7 years)	23*	16
Suppression of HBV DNA	29*	61*	23*
Side effects	yes	no	no
Resistance to antiviral agent	no	19%	no
HBsAg clearance	8.9% (7 years)	2%	0.5%

Predictors of Response to Treatment

Higher response rates
- < 5 years
- ALT >> normal
- Low HBV DNA
- Compensated liver disease
- HBV genotype A and B
- Low drug resistant mutant rates
- HBeAg + hepatitis
- Low HBsAg levels

Lower response rates
- > 5 years
- Normal ALT
- High HBV DNA
- Liver failure
- HBV genotype C and D
- High drug resistance mutant rates
- HBeAg negative hepatitis
- HDV
- High HBsAg levels

Approach To Treatment

- Unfortunately, studies are lacking to define what is the best approach.
- Interferon alfa, Adefovir and Entecavir are considered first line therapy.
- Unknown if benefit of using combination therapy.

Summary

- Hepatitis B is an important cause of liver disease worldwide.
- An effective vaccine is available and safe and is highly effective in preventing infection.
- Current treatments are effective in approximately 30% of patients with chronic infection.