Trends in Hepatitis B and C

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Disclosures

• Research grant funding for clinical trials through Janssen Pharmaceuticals
Learning Objectives

• Review current understanding of the natural history of viral hepatitis B and C infections

• Discuss optimal medical treatments and effect of those treatments on prognosis

• Briefly describe treatments for complications such as hepatocellular carcinoma and cirrhosis, including prognosis following liver transplantation
Hepatitis B Historic Perspective

- Infectious hepatitis was described by Hippocrates as early as 4000 B.C.

- In the late 1800’s outbreaks of jaundice/hepatitis were associated with vaccines synthesized using human serum.

- By 1908, a viral etiology of infectious hepatitis was postulated

- In 1947 “viral hepatitis” was classified into 2 types:
  - “Infectious Hepatitis” (HAV)
  - “Serum Hepatitis” (HBV)

Mandell, Principles and Practice of Infectious Diseases, 7th Edition; Dienstag, Hepatitis B Infection, NEJM, 2008
Hepatitis B Historic Perspective

• The “Australia Antigen” was discovered in 1967 by Baruch Baumberg in blood samples from aborigines – turned out to be Hepatitis B surface Ag.

• The “Dane Particle” was discovered in 1971 on electron microscopy – turned out to be the HBV virus particle

• In 1979 the virus was able to be cloned and full sequence of DNA determined

Mandell, Principles and Practice of Infectious Diseases, 7th Edition
Dienstag, Hepatitis B Infection, NEJM, 2008
HBV Vaccination

- Available in the U.S. since 1981 and is made of recombinant proteins of the HBsAg
- In 1991, HBV vaccination was added to the routine childhood vaccination schedule by Advisory Committee for Immunization Practices (ACIP)
- In 1995, unvaccinated adolescents were added to the schedule
- By 1999, vaccine schedule expanded to include all persons 18 years and under
- Since 1991, the vaccine has been recommended to health care workers by Occupational Safety and Health Administration (OSHA), and provided free of charge
- This has resulted in a decline in incidence of acute HBV in the U.S. from 8.5 per 100,000 in 1990 to 2.8 per 100,000 in 2002; a reduction of 67%
- Due to reduction in liver cancer risk, this is considered the first “Anti-Cancer” vaccine in history

Mandell, Principles and Practice of Infectious Diseases, 7th Edition
~250-350 million chronic HBV infections worldwide

Ott et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity, Vaccine, 2012
Hepatitis B Epidemiology

- Worldwide, the estimate of chronic HBV infection is 350 million individuals, and HBV results in 600,000 deaths annually

- Approximately 1 million individuals in the U.S. have chronic HBV infection, a prevalence of 0.4%

- Vaccination has resulted in a decline in HBV prevalence in the U.S.

- 88% of the world’s population lives in regions where the prevalence is > 2%

- In highly endemic regions, up to 70% of adults have evidence of prior exposure

Mandell, Principles and Practice of Infectious Diseases, 7th Edition
Dienstag, Hepatitis B Infection, NEJM, 2008
MAP 3-4. PREVALENCE OF CHRONIC HEPATITIS B VIRUS INFECTION AMONG ADULTS

Hepatitis B Natural History

- Development of **acute vs chronic** inversely related to age at time of exposure
  - Percent of development of Chronic HBV:
    - 90% of infected infants
    - 30% of infected children aged <5 years
    - 2%–6% of persons who become infected as adults

Hepatitis B Diagnosis

• **Hepatitis B Surface Antigen**
  • The hallmark for active infection (acute or chronic) is **HBsAg**

• **Hepatitis B Surface Antibody**
  • **Anti-HBs** is a marker for immunity, either natural or vaccine related

• **Hepatitis B core Antibody**
  • Hepatitis B core antibody (**Anti-HBc**) is a marker for prior exposure
    • **Anti-HBc-IgM** implies early or acute infection
    • **Anti-HBc-IgG** occurs later in disease
Hepatitis B Serologies: HepB Surface

- **HBsAg** is the marker of active infection, acute or chronic
- **HBsAg** is the primary serum marker for screening of active disease
- **HBsAg** + individuals can transmit HBV to others
- **HBsAg** disappears in patients who recover from acute infection
  - Persistence > 6 months indicates chronic infection
- **Anti-HBs** – marker of immunity – from vaccination or from natural immunity
- **Anti-HBs** is a useful screening tool for effectiveness of HBV vaccine
Hepatitis B Serologies: HepB Core

- **HBcAg** is an intracellular antigen expressed in infected hepatocytes
- **HBcAg** is not detectable in serum, and is not a useful screen for infection
- **Anti-HBc** is a marker for acute, chronic, or prior infection
- **Anti-HBc** is not protective, and is not an indicator of immunity
- **Anti-HBc-IgM** is a marker of acute infection
- **Anti-HBc-IgM** may be present in the “window period” after the disappearance of HBsAg, and the appearance of Anti-HBs.
- **Anti-HBc-IgG** is a marker of prior exposure
Hepatitis B Serologies: HepBe Antigen/Antibody

- **HBeAg** is a secretory protein produced by HBV

- **HBeAg** is generally used as a marker of HBV reproduction and infectivity

- Previously used as a marker of whom to treat

- Now partially replaced by HBV PCR

- Development of **Anti-HBe** and disappearance of **HBeAg** is the marker of progression to the “inactive carrier” phase of chronic infection

- In acute infection, **Anti-HBe** appears prior to **Anti-HBs**, which confers immunity to infection
Hepatitis B: DNA

- A direct measure of HBV DNA in serum
- High levels of HBV DNA correlates with high HBeAg levels, and is another marker of infectivity
- The major use of HBV PCR is to monitor response to treatment
- HBV PCR is also useful in fulminant hepatitis because HBsAg may be absent on presentation
Hepatitis B Natural History: Acute

- Incubation period of 1-4 months after exposure

- Symptoms of acute HBV infection are non-specific and may include: Fatigue, malaise, nausea, vomiting, abdominal pain, anorexia, low grade fever, jaundice, or dark colored urine

- Acute infection is commonly asymptomatic or sub-clinical

- Laboratory findings include elevations in AST/ALT – frequently in the range of 1,000-2,000; ALT>AST

- Bilirubin may be normal (anicteric hepatitis) or elevated (icteric hepatitis)

- Prothrombin time (PT) is the best predictor of prognosis
Hepatitis B Natural History: **Acute**

- HBsAg becomes detectable in the blood after 4-10 weeks after exposure, followed by Ab to the core Ag (Anti-HBc)

- Acute HBV typically resolves after 2-4 months

- Clearance of infection is marked by normalization of AST/ALT, a decline in HBsAg and the appearance of Anti-HBs antibody

- Low levels of HBV DNA can sometime be detected in the blood for many years to life, even after clearance of HBsAg and the development of Anti-HBs antibodies

- Reactivation can rarely occur, even after recovery from acute disease – usually only with profound immunosuppression (HIV/AIDS, bone marrow transplantation)
Hepatitis B Natural History: Acute Fulminant

- Rare occurrence (0.1-0.5%)
- Causes < 10% of all fulminant liver failure in the U.S.
- Presents with rapidly progressive disease (encephalopathy, coagulopathy, cerebral edema) within 28 days of symptom onset
- May result in the need for urgent liver transplantation
- HBsAg may be negative, but Anti-HBc-IgM, and HBV DNA should be detectible
- Pathogenesis is unclear, but likely related to a massive immune response
Hepatitis B Natural History: Chronic

• Chronic infection is defined as signs of infection > 6 months
  • Positive Hepatitis Bs Antigen

• Chronic infection develops in a minority (<5%) of HBV exposed adults

• Chronic infection can result in cirrhosis (~20%), end stage liver disease, and Hepatocellular Carcinoma (HCC)

• The risk for HCC in individuals with HBsAg is 100 x higher than the general population
Hepatitis B Natural History: Chronic

- **Immunotolerant phase** – High levels of HBV antigens and HBV DNA, little immune response, so little elevation in AST/AST

- **Inflammatory phase** – Decreasing levels of HBV antigens and DNA; elevated AST/ALT

- **Inactive carrier state** – sero-conversion of HBeAg to Anti-HBe; decrease in HBV DNA and reduction in transaminases
  - HBsAg and HBV DNA persists, but at lower levels
  - May be accompanied by an acute “flare” with rises in AST/ALT
  - Incomplete seroconversion may happen; and recurrent “flares” might increase the risk for HCC

Fontana, Evaluation of the patient with chronic HBV, Clinical Liver Disease, 2013
Natural Course of Chronic HBV

HBV
DNA
ALT

HBeAg
Anti-HBe

Immune Tolerance
Immune Clearance
Inactive Carrier
Reactivation

Fontana, Evaluation of the patient with chronic HBV, Clinical Liver Disease, 2013
Hepatitis B Natural History: Treatment

- If there is evidence of **chronic HBV**, refer to a HBV expert to help guide decision for possible need for antiviral treatment (gastroenterologist, hepatologist, infectious disease)

- Indicated to treat active chronic HBV causing necro-inflammation

- Assess for stage by follow HepBe Ag status, LFTS, and DNA level. In some cases still require liver biopsy to make treatment decision.

- All patients with advanced fibrosis or cirrhosis with detectable DNA should be treated

Fontana, Evaluation of the patient with chronic HBV, Clinical Liver Disease, 2013
Management of Chronic HBV Infection*

HBsAg +
- HBeAg
  - Positive
    - ALT < 1 X ULN
      - Q 3-6 mo ALT
      - Q 6-12 mo HBeAg
    - ALT 1-2 X ULN
      - Q 3 mo ALT
      - Q 6 mo HBeAg
      - Consider biopsy if persistent or age > 40, Rx as needed
    - ALT >2 X ULN
      - Q 1-3 mo ALT, HBeAg
      - Treat if persistent
      - Liver bx optional
      - Immediate Rx if jaundice or decompensated

* HCC surveillance if indicated

AASLD Practice Guidelines, Chronic HBV, Hepatology, 2009
A

Management of Chronic HBV Infection*

HBsAg +

HBeAg

Positive

ALT < 1 X ULN

Q 3-6 mo ALT
Q 6-12 mo HBeAg

ALT 1-2 X ULN

Q 3 mo ALT
Q 6 mo HBeAg
Consider biopsy if persistent or age > 40,
Rx as needed

ALT > 2 X ULN

Q 1-3 mo ALT, HBeAg
Treat if persistent
Liver bx optional
Immediate Rx if jaundice or
decompensated

* HCC surveillance if indicated

AASLD Practice Guidelines, Chronic HBV, Hepatology 2009
# Hepatitis B Treatments

## Table 11. Comparison of Approved Treatments of Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Indications</th>
<th>IFNα</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
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<tr>
<td><strong>HBeAg+</strong>, normal ALT</td>
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<tr>
<td><strong>HBeAg+</strong> chronic hepatitis</td>
<td>Indicated</td>
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<table>
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<tr>
<th>Duration of treatment</th>
<th>IFNα</th>
<th>Lamivudine</th>
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<tbody>
<tr>
<td><strong>HBeAg+</strong> chronic hepatitis</td>
<td>4-12 months§</td>
<td>≥1 year**</td>
<td>≥1 year**</td>
<td>≥1 year**</td>
<td>≥1 year**</td>
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<td><strong>HBeAg-</strong> chronic hepatitis</td>
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<table>
<thead>
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<th>Route</th>
<th>IFNα</th>
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<td>Subcutaneous</td>
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<td>Oral</td>
<td>Many</td>
<td>Negligible</td>
<td>Potential Nephrotoxicity</td>
<td>Negligible</td>
<td>Negligible</td>
<td>Potential Nephrotoxicity</td>
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<table>
<thead>
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<th>Side effects</th>
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<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
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<tbody>
<tr>
<td>Drug resistance</td>
<td>~20%, year 1</td>
<td>None, year 1</td>
<td>~1% up to year 5‡</td>
<td>~25% up to year 2</td>
<td>None, year 1 na beyond 1 year</td>
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<tr>
<td>Cost*</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
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</tbody>
</table>

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*Based on treatment duration of 1 year.

**Treatment for at least 12 months continuing for at least 6 months after anti-HBe seroconversion.

†Not preferred drug due to high rate of resistance.

§PegIFN approved for 12 months.

‡Entecavir resistance reported within year 1 in patients with prior lamivudine resistance.

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AASLD Practice Guidelines, Chronic HBV, Hepatology, 2009
Hepatitis B: Duration of Treatment

• For HepBe Ag Positive Patients:
  • Goal “seroconversion”
    • HepBe Ag Positive → HepBe Ag Negative & HepBe Antibody Positive
  • Treat for another 6 months after seroconversion
  • Occurs in about 20% of patients at 1 year, 40% by year 5
  • Monitor closely after stop treatment given risk of relapse

• For HepBe Ag Negative Patients:
  • End point for treatment not defined
  • Continue until have loss of HepBs Ag (very rare)

• For Chronic HBV with Cirrhosis/Advanced Fibrosis:
  • Likely need lifelong treatment

AASLD Practice Guidelines, Chronic HBV, Hepatology, 2009
**Chronic Hepatitis B Prognosis: Cirrhosis**

- **Taiwan and Korea**
  - HBeAg negative
  - HBeAg positive

  **13% Incidence of Cirrhosis at 5 years in HepBeAg Negative**
  **8% Incidence of cirrhosis at 5 years in HepBeAg Positive**

- **Europe**

  **38% Incidence of Cirrhosis at 5 years in HepBeAg Negative**
  **17% Incidence of cirrhosis at 5 years in HepBeAg Positive**

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Fattovich et al, *Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors*, *Journal of Hepatology*, 2008
Hepatitis B Complications: Hepatocellular Carcinoma (HCC)

Fattovich et al, Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors, Journal of Hepatology, 2008

Cumulative Incidence of Hepatocellular Carcinoma

Taiwan, China, Singapore, Korea and Japan
- 17% incidence HCC cirrhosis
- 3% Incidence HCC in chronic hepatitis
- 1% incidence in inactive carrier

Europe and USA
- 10% incidence HCC in cirrhosis
- 1% incidence of HCC in chronic hepatitis
- 0.1% incidence in inactive carrier
Hepatitis B: Effect of Treatment on Prognosis

- Slows progression of fibrosis
- Reverse cirrhosis
- Prevents decompensation with cirrhosis
- With decompensated liver disease, improves overall morality and transplant free survival
Hepatitis B: Effect of Treatment on Prognosis

- Study of 707 patients with decompensated liver disease in Korea followed prospectively – 284 untreated vs 483 treated

Jang et al, Long-Term Effect of Antiviral Therapy on Disease Course After Decompensation in Patients With Hepatitis B Virus-Related Cirrhosis, Hepatology, 2015
Hepatitis B: Summary Points

• Wide spectrum of disease depending on age of exposure

• Most of cases in United States are adult exposure, which predominantly spontaneously clear

• Incidence decreasing with increased vaccination program

• If a patient has evidence of chronic infection, they should be evaluated by HBV specialist to help guide possible treatment with antiviral therapy to decrease rate of complication from chronic infection
Hepatitis C Historic Perspective

• In the 1970s Viral Hepatitis was considered infectious (Hepatitis A) and serum (Hepatitis B)

• After discovery of HBV antigen and then Hepatitis A antigen it became apparent that not all of the “serum hepatitis” were from these agents
  • “Non-A Non-B Hepatitis” or NANB

• Early studies used Interferon to treat patients with this entity of NANB – published in 1986

• By the 1989 HCV was identified as the causative agent for NANB Hepatitis

Hepatitis C Historic Epidemiology

- Total Global prevalence of HCV-Ab estimated about 1.6% = 115 million exposed to HCV
- “Viremic” Prevalence estimated about 1.1% = 80 million infected
- United States estimated prevalence of about 3-4 million
  - Approximately half are unaware of their status
  - Most common blood borne infection
  - More than 12,000 deaths annually in US from HCV-related disease
- Globally 360,000 deaths annually

Gonzalez and Davis, Demographics of Hepatitis C Virus Today, Clinical Liver Disease, 2012
Hepatitis C Epidemiology

Hepatitis C Natural History: **Acute Hepatitis C**

- Up to 4 million people are infected annually worldwide

- Acute HCV may present with icteric hepatitis, but typically very mild symptoms (malaise, fatigue, anorexia, nausea)
  - Most individuals exposed are asymptomatic
  - After exposure, about 2-3 weeks before detect HCV RNA

- Up to 18-34% will spontaneously clear

- No long term sequelae if clear spontaneously

- Prior exposure does not confer immunity

*Westbrook, Natural History of Hepatitis C, Journal of Hepatology, 2015*
Hepatitis C Natural History: Chronic Hepatitis C

• Majority of those exposed become chronic defined as + virus detected at > 6 months
  • ~ 60-85% become chronic
  • More precise estimate limited by retrospective nature of most studies
  • Reports vary depending on host factors (immune response, etc)

• Usually asymptomatic and many not aware they have chronic infection
  • Symptomatic infection probably more likely to clear

• Chronic HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma, and liver related deaths in the Western World

Hepatitis C Natural History: Chronic Hepatitis C

• Slow progression toward cirrhosis in ~10-20% of individuals over a 20-30 year time period
  • Although reports variable with range of cirrhosis of only 2-3% up to 51% over 22 years in the published literature

• Once develop cirrhosis:
  • 1-5% annual risk for hepatocellular carcinoma
  • 3-5% risk for decompensation

• Once have decompensation:
  • Risk of death within one year 15-20%

Hepatitis C Natural History: Chronic Hepatitis C

• Factors associated with increased risk of progressive fibrosis:
  • Age at infection
  • Male Gender
  • Alcohol consumption (>50 grams/day)
  • Obesity
  • Insulin resistance
  • Type 2 Diabetes
  • Co-infection with HBV or HIV
  • Immunosuppressive therapy
  • Genetic factors

• Progression of fibrosis is not necessarily linear – rates of fibrosis at 30 years estimated 3X that at 20 years (possibly related to age)

Hepatitis C Natural History: Chronic Hepatitis C

• The prevalence of cirrhosis in chronic HCV has doubled in the last 10 years

• Projected prevalence of cirrhosis in those with chronic HCV in 2030 is expected to approach 50%

• Even though the overall prevalence HCV will decline, with increased percent of advanced liver disease, the impact on public health will only increase

• Annual number of liver related deaths expected to double leading up to 2030

Gonzalez and Davis, Demographics of Hepatitis C Virus Today, Clinical Liver Disease, 2012
Davis et al, Aging of hepatitis C virus (HCV) infected persons in United States: a multiple cohort model of HCV prevalence and disease progression, Gastro, 2010
Hepatitis C Natural History: Treatment

- Sustained Viral Response (SVR)
  - Accepted as cure
  - Defined as undetectable HCV RNA in the serum at 12-24 weeks following completion of therapy

- Eradication of HCV reduces risk for portal hypertension, hepatic decompensation, and hepatocellular carcinoma
  - Decrease in progression of fibrosis
  - In those with compensated cirrhosis, decrease rate of varices development
  - Meta analysis: Decreased rate of HCC from ~3% per person year to 1.05% per person year
  - HALT-C Cohort: HCC decreased from 8.8% to 1.1% over 7 years of follow up with SVR

Hepatitis C Viral Genome

Rosen, NEJM, 2011
Hepatitis C Treatments

• Historically treated with Interferon (IFN) and Ribavirin, until new Direct acting antiviral (DAAs)
  • SVR with Peg-IFN and Ribavirin: Genotype 1 = 40-60% and Genotype 2-3 = 70-90%

• 1st generation of Boceprevir and Telaprevir available in 2011
  • “Triple Therapy” because both still required IFN and Ribavirin
  • Increased chance of cure (SVR) up to 80-90%, but increased the side effects
  • Complicated drugs with side effects

• 2nd generation are here and revolutionizing therapy for HCV
  • No need for Interferon, except in very rare cases
  • Many current regimens still need Ribavirin, but moving away with next generation
  • On average up to 90% chance of SVR with 12 weeks of therapy
# Hepatitis C Treatment: Currently Approved DAAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
</tr>
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<tbody>
<tr>
<td>Sofosbuvir</td>
<td>Nucleotide/side analogues</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>NS3-4A Protease Inhibitors</td>
</tr>
<tr>
<td>Paritaprevir/r</td>
<td>NS3-4A Protease Inhibitors</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>Non-nucleoside inhibitor of RNA Polymerase</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>NS5A inhibitor</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
</tr>
</tbody>
</table>
Hepatitis C Treatments: Genotype 1

- Harvoni (Sofosbuvir + Ledipasvir)
- Viekira Pak (paritaprevir/ritonovir + ombitasvir + dasabuvir)
- Olisio + Sovaldi (Simeprevir + Sofosbuvir)

Usually 12 weeks, extend to 24 in some populations (cirrhosis +/- tx ext)
Usually >90% chance of SVR

HCVguidelines.org
Hepatitis C Treatments: Genotype 2

• Sovaldi + Ribavirin (Sofosbuvir + Ribavirin)
• Daklinza + Sovaldi (Daclatasvir + Sofosbuvir)

Treat for 12 weeks, with possibly extend to 16 week in cirrhosis
Usually > 90% SVR

HCVguidelines.org
Hepatitis C Treatments: Genotype 3

• Daklinza + Sovaldi (Daclatasivir + Sosobuvir)
• Sovaldi + Ribavirin (Sofosbuvir + Ribavirin) + Interferon
• Sovaldi + Ribavirin (Sofosbuvir + Ribavirin)

Duration is variable based on cirrhosis/treatment experienced and ranges from 12 to 24 weeks +/- Ribavirin
Genotype 3 is now considered hardest to treat genotype

HCVguidelines.org
Liver Transplantation for Viral Hepatitis

• Indication for Liver transplant with viral hepatitis:
  • Decompensated Cirrhosis
    • Jaundice, ascites, varices, encephalopathy
  • Liver cancer
    • Same criteria for HCC for transplant for both HCV and HBV
    • HCC can occur in HBV without cirrhosis, so possible to consider resection
Liver Transplantation for Viral Hepatitis

• Chronic HBV previously was a contraindication for liver transplant

• Previously had severe recurrent HBV with liver failure

• With advent of HBV Immunoglobulin (HBIG) able to control reinfection and then maintain on antiviral therapy with great results
Liver Transplantation for Viral Hepatitis

• HCV Post-Transplant Recurrence: If have positive RNA detected pre-transplant, 100% recurrence
  • Within a few hours there is detectable virus circulating
  • Within a few weeks after transplant typically have higher viral counts than prior (typically 1 log higher)
  • Serologic chronic hepatitis established within 3 to 9 months
  • Rate of progression is more rapid with up to 30% rate of cirrhosis at 5 years
  • Small group (2-5%) can develop rapidly progressive form of recurrent HCV that can lead to death within the first 12 months

• New DAA agents have made standard practice to treat either pre-transplant or post-transplant to eradicate

HBV and HCV Hepatitis

- Very different natural history, but very similar outcomes with both cirrhosis, decompensated liver disease, and liver cancer occurring in chronic disease course

- HBV: still no cure, but able to suppress chronically and possibly eradicate with vaccination and public policy

- HCV: now have a cure for >90% of patients, but limited by cost burden
  - We will increasingly have patients with complications of cirrhosis, ESLD, and HCC with our aging population of HCV patients
Questions?