MANAGEMENT OF HBV & HCV INFECTION---SIMILARITIES & DISSIMILARITIES---PAST AND PRESENT

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HEPATOTROPIC VIRUSES

HAV, HEV

HBV, HCV, HDV
HGV, TTV
Points to cover

1. **HBV infection**
   a. Diagnosis
   b. Treatment
      I) Past
      II) Present

2. **HCV infection**
   a. Diagnosis
   b. Treatment
      I) Past
      II) Present
Both HBV and HCV causes acute and chronic hepatitis

- Acute hepatitis due to HBV approximately 22% and due to HCV approximately 3%.
- Chronic hepatitis due to HBV approximately 80% and due to HCV approximately 4%.
Development of chronicity

Hepatitis B
only 5% develop chronicity in adult

Hepatitis C
75% - 85% develop chronicity.
Complication of acute hepatitis (hepatitis B and C)

Acute liver failure
Cholestatic hepatitis
Aplastic anaemia
Chronic liver disease and Cirrhosis
Relapsing hepatitis
HBV is a member of the hepadnaviridae (hepatotrophic DNA) family

Main routes of transmission of HBV are parenteral, sexual and perinatal
In 1965, Dr. Baruch S. Blumberg discovered the virus.

- Named “Australia antigen”
- Received the Nobel Prize in Medicine in 1976
- Australia antigen is now called hepatitis B surface antigen (HBsAg).
Hepatitis B – A Global Healthcare Concern

• CHB is a healthcare concern globally, particularly in Asia

• More than 400 million people are chronic carriers

• 15–40% of these will develop serious outcomes, such as cirrhosis, liver failure and hepatocellular carcinoma

• Disease from chronic infection accounts for >1 million deaths/year (10th leading cause of death worldwide)

• Liver cancer is the sixth most common cancer worldwide
Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- ≥8% - High
- 2-7% - Intermediate
- <2% - Low
5.4% healthy individuals.
7.5% healthy job seekers.
19-29% professional blood donors.
5.4% in slum population (BMRC).
CLD: 40% and HCC: 47% - due to HBV.
Consequences of HBV infection

Acute HBV infection

>90% of children

<5% of adults

Recovery protective immunity

Chronic HBV infection

Hepatocellular carcinoma (HCC)

Cirrhosis

30–40% risk

Transplant or death

Liver disease progression over time

Normal  →  Cirrhosis  →  Cirrhosis  →  HCC

HBV  →  ACUTE / CHRONIC HEPATITIS B  →  CIRRHOSIS  →  ESLD  →  HEPATOCELLULAR CARCINOMA

Liver damage = the result of attempts, usually unsuccessful, to clear infected hepatocytes as part of the immunoclearance stage of disease
### Course of CHB Infection

<table>
<thead>
<tr>
<th>Immuno-tolerant phase</th>
<th>Immune clearance phase</th>
<th>Low replicative phase</th>
<th>Reactivation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-positive</td>
<td>HBeAg-negative</td>
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#### HBV-DNA

- **HBeAg-positive CHB**
- **HBeAg-negative CHB**

#### ALT

- **Normal/mild CHB** → **Cirrhosis**
- **Moderate/severe CHB** → **Inactive cirrhosis**
- **Moderate/severe CHB** → **Cirrhosis**

#### Notes

- **Inactive carrier state**
- **Precore mutant**
In this “HBsAg-negative phase” after HBsAg loss, low-level HBV replication may persist with detectable HBV DNA in the blood (Occult HBV).
MANAGEMENT OF ACUTE HBV INFECTION

Rest
Dietary advice
Symptomatic management
Management of complications
Indication of oral antiviral in acute HBV

S. bilirubin more than 10 mg/dl.
Prothombin time: INR more than 1.5.
Presence of Ascites.
Associated with any malignancy.
Plan for chemotherapy
Treatment goals of Chronic Hepatitis B

- Clear the virus
- Suppress the virus
- Reduce liver injury
- Prevent fibrosis

Prevention of cirrhosis, and HCC
THE FIRST BRANCH POINT IN CHOOSING WHAT TO TREAT WITH

Decision to treat

- IFN (Peg IFN alfa-2a)
- Nucleos(t)ide analogues
Who should be treated with what?

Interferon-based
- Immunocompetent
- Compensated liver disease
- Younger patients
- NA-failures/resistant
- Patient/physician preference
- Consider risk of drug resistance
- Length of treatment
- Side effects

Direct antivirals
- Immunosuppressed
- Advanced liver disease
- IFN/PEG-IFN non-responders
- High ALT
- Low HBV DNA
- Liver lesions
All HBV carriers are potential treatment candidates; it is only a matter of time before they reach the criteria generally set for initiation of treatment.
Factors to Consider in Initiating Anti-HBV Therapy?

- ALT levels
- HBeAg status
- HBV DNA levels
- Histological grade and stage
- Cirrhosis vs no cirrhosis
- Compensated vs decompensated disease
Chronic Hepatitis B

Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus >6 months.

Diagnostic Criteria of CHB

1. HBsAg +ve >6 months

2. Serum HBV DNA >20,000 IU/ml (10⁵ copies/ml) in HBeAg +ve,
   > 2,000 IU/ml (10⁴ copies/ml) in HBeAg - ve CHB

3. Persistent or intermittent elevation in ALT/AST levels

4. Liver biopsy showing chronic hepatitis with moderate or severe necro inflammation
HBV Drugs evolution

1992
1998
2002
2005
2006
2008 and beyond…

IFN alfa
LAM
ADV
ETV
LdT
Tenofovir Clevudine Combination Rx?

“The New Era”
Oral therapy

PegIFN alfa-2a
Treatment Algorithm Update

HBeAg Positive Without Cirrhosis

HBeAg positive

- HBV DNA <10^5 copies/mL
  - ALT normal
    - No treatment
    - Monitor every 6–12 months

- HBV DNA ≥10^5 copies/mL
  - ALT normal/<2 times normal
    - Monitor every 3–12 months (immune tolerant)
    - Consider biopsy, if age >35–40 years; treat if significant disease
  - ALT elevated >2 times normal
    - Liver biopsy optional
    - Treat
Detectable DNA require urgent antiviral treatment with NA(s).

Significant improvement associated with control of viral replication.

Antiviral therapy not sufficient to rescue some patients with very advanced liver disease and considered for liver transplantation.
PEG- IFN is contraindicated during pregnancy.

Lamivudine, adefovir and entecavir are listed by the FDA as category C drugs.

Telbivudine and tenofovir as category B drugs.
Combining HBsAg & HBV DNA decline for early identification of non-response

Analysis of 102 patients with available HBV DNA and HBsAg levels (80% genotype D)

WEEK 12

ANY HBsAg decline

HBV DNA decline (copies/mL)

Sustained response*

*HBV DNA <10,000 copies/mL and ALT normal 6 months post-treatment

Rijckborst et al. Hepatology 2010
New milestones are needed to cure HBV infection with agents which:
- Act on all possible sites of viral replication cycle – from entry into hepatocytes to release into circulation
- Act on host immune system to clear up virus

Immune modulator is one of the options
Antiviral effect of HBsAg/HBcAg vaccine in CHB patients

HBV DNA positive in the sera

HBV DNA undetectable (<500 copies/ml) in the sera

No. of patients

Before vaccination

After 5 nasal vaccinations

After 10 vaccinations

12 months after end of vaccinations

N=18

N=5

N=6

N=9

18

12

6
Hepatitis B virus is a common problem for Bangladesh as well as globally.

Concept of management of hepatitis B is continuously changing and improving.

Peginterferon is one of the best treatment option, because of definite duration, no resistance, durable off treatment response.

Newer NUCs of high genetic barrier are next possible approach.

Immune modulator is one of the future options.
HCV

the silent killer

- 4 times more prevalent than AIDS worldwide
- Increases the risk for HCC by 25 fold
- Causes 3-4 times more liver related death than HBV
- No vaccine available to prevent Hepatitis-C
Identified and genome cloned in 1989

Family: Flaviviridae

Genus: Hepaciviruses

Spherical, enveloped, single-stranded RNA virus

Replication -> 1 trillion per day
Hepatitis-C: A global health problem

170-200 million Carriers Worldwide

Source WHO 1999
HCV: Prevalence in Bangladesh 0.8%

Total area: 1,47570sq. km
Population: 158.8 mil
Population density/sq. km: 1090

World bank, 2007
In acute infection:

- 20% may clear the virus spontaneously
- Symptomatic patients are more likely to clear
- Most patients do so within 12 weeks
- 80% of patients develop chronic infection
Enzyme immunoassay (EIA) detects 95% of infections

Recombinant immunoblot assay (RIBA)

Molecular tests - HCV RNA (qualitative and quantitative)

Genotype testing
Recommended Testing Sequence for Identifying Current HCV Infection

- **Nonreactive**
  - No HCV antibody detected
    - Stop*

- **Reactive**
  - HCV antibody
    - HCV RNA
      - Detected
        - Current HCV infection
          - Link to care
      - Not detected
        - No current HCV infection
          - Additional testing as appropriate†
Goals and endpoints of HCV therapy

- To prevent hepatic cirrhosis, decompensation of cirrhosis, HCC and death.

- The endpoint of therapy is undetectable HCV RNA in a sensitive assay (<15 IU/ml) 12 and 24 weeks after the end of treatment (i.e. an SVR).

- In patients with cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued.
Liver disease severity

Identifying patients with cirrhosis

Fibrosis stage

Presence of ascites
Pre-therapeutic assessment.

HCV RNA detection

The HCV genotype

IL28B genotyping
EVOLUTION OF HCV TREATMENT

- Discovery of HCV genome
- Treatment with IFN alfa for 24 or 48 weeks – 3x weekly dosing – Poor outcomes
- Addition of RBV to IFN alfa improved outcomes
- Development of Peg-IFN – once-weekly dosing – Outcomes improved further
- Peg-IFN alfa plus RBV becomes gold standard
- Response-guided therapy emerging
- New antivirals enter development

1989 - 2007
Available drugs

- Pegylated IFN-α2a - 180 μg/week
- Pegylated IFN-α2b - 1.5 μg/kg/week
- Ribavirin - 1000 or 1200 mg/day based on body weight (<75 kg or ≥75 kg, respectively)
- Sofosbuvir - 400 mg (one tablet)/day
- Simeprevir - 150 mg (one capsule) once per day

- Daclatasvir - 60 mg /day (Only recommended by EASL)
IFN ineligible

IFN ineligible is defined as one or more of the below:

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression, or clinical features consistent with depression
- A baseline neutrophil count below 1500/µL, a baseline platelet count below 90,000/µL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease
Sofosbuvir is a prodrug of a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase.

Approved By FDA In DEC 2013.
Sofosbuvir
Pharmacology

- Directly acts on HCV to inhibit HCV NS5B RNA-dependent RNA polymerase, an enzyme essential for viral replication and acts as a chain terminator.
Indications:
- Genotypes 1→4 chronic HCV
- Hepatocellular carcinoma with HCV
- HCV/HIV co-infection

Place in therapy:
- Considered first-line therapy for patients with HCV in combination with ribavirin and peg-interferon
Sofosbuvir
Clinical Application

Contraindications:
- Pregnancy and use in male partners of pregnant women
- All contraindications applicable to ribavirin and peg-interferon

Warnings and Precautions
- Use with potent P-gp inducers (Rifampicin)
- Pregnancy when used with ribavirin or peg-interferon
- Use as monotherapy
Pregnancy:
- US FDA pregnancy Category B (single use, not recommended)
- Category X when used in combination with ritonavir or peg-interferon/ribavirin

Lactation:
- Excretion in breast milk is unknown; use is not recommended
Dosing:
400mg daily with ribavirin with/without peg-interferon alfa
Simeprevir (150 mg daily), a specific inhibitor of the HCV NS3/4A serine protease
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>IFN eligible</strong>: SOF + PEG/RBV x 12 weeks</td>
<td><strong>IFN eligible</strong>: SMV x 12 weeks + PEG/RBV x 24 weeks*</td>
</tr>
<tr>
<td></td>
<td><strong>IFN ineligible</strong>: SOF + SMV ± RBV x 12 weeks</td>
<td><strong>IFN ineligible</strong>: SOF + RBV x 24 weeks</td>
</tr>
<tr>
<td>2</td>
<td>SOF + RBV x 12 weeks</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>SOF + RBV x 24 weeks</td>
<td>SOF + PEG/RBV x 12 weeks</td>
</tr>
<tr>
<td>4</td>
<td><strong>IFN eligible</strong>: SOF + PEG/RBV x 12 weeks</td>
<td>SMV x 12 weeks + PEG/RBV x 24-48 weeks</td>
</tr>
<tr>
<td></td>
<td><strong>IFN ineligible</strong>: SOF + RBV x 24 weeks</td>
<td></td>
</tr>
<tr>
<td>5 or 6</td>
<td>SOF + PEG/RBV x 12 weeks</td>
<td>PEG/RBV x 48 weeks</td>
</tr>
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</table>
Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A
Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

Rating: Class I, Level C

If the decision to treat has been made, the recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. This regimen should be used only by highly experienced HCV providers.

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks.

Rating: Class IIb, Level B
Patients with Renal Impairment

Severe Renal Impairment (CrCl <30 mL/min)

or

ESRD Requiring HD or PD
<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>eGFR/CrCl level (mL/min/1.73 m²)</th>
<th>Interferon</th>
<th>Ribavirin</th>
<th>Sofosbuvir</th>
<th>Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>50-80</td>
<td>180 µg PEG (2a); PEG (2b) 1.5 µg/kg</td>
<td>Standard</td>
<td>Standard</td>
<td>Standard</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-50</td>
<td>180 µg PEG (2a); PEG alfa-2b1 µg/kg or 25% reduction</td>
<td>Alternating doses 200 and 400 mg every other day</td>
<td>Standard</td>
<td>Standard</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30</td>
<td>135 µg PEG (2a); PEG (2b)1 µg/kg or 50% reduction</td>
<td>200 mg/d</td>
<td>Data not available</td>
<td>Standard</td>
</tr>
<tr>
<td>ESRD/HD</td>
<td></td>
<td>PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk</td>
<td>200 mg/d</td>
<td>Data not available</td>
<td>Data not available</td>
</tr>
</tbody>
</table>
Recently the treatment of HCV infection is dramatically improved.

Peoples are now using Interferon free regime in all Genotypes.

The oral DAA are now being used even in decompensated stage of the liver disease.

With the newer regime HCV infection is now claimed to be eradicated from the planet.

We hope that the cost of the recent drugs will be come down and easily available in our country.
THANK YOU