Diagnostisches und therapeutisches Vorgehen bei Hepatitis B

Current Management of Hepatitis B and C
Swiss MedLab 2012 Bern

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Diagnostisches und therapeutisches Vorgehen bei Hepatitis B

- Epidemiology/Natural history
- Diagnosis
- Treatment
Global HBV Distribution

Chronic infection prevalence
- ≥ 8% - High
- 2-7% - Intermediate
- < 2% - Low

Past infection prevalence
- 40-90%
- 16-55%
- 4-15%

Predominant age at infection
- Perinatal and early childhood
- Early childhood
- Adult

CDC, 1991
HBV Distribution in CH

Chronic hepatitis B: 0.3% (20'000)

History of hepatitis B: 4–8%
HBV Life cycle

Viral Reverse transcriptase

Host RNA polymerase

Natural History of HBV Infection

- 8-20%/5yr, 2-5%/yr
- Acute Hepatitis → Chronic Hepatitis → Cirrhosis → HCC → Death
- Recovery

- In the West, 95% of those infected in adolescence, will fully recover
- In Asia Pacific, 90% of those perinatally HBV infected will remain chronically infected to adulthood
Natural History of chronic HBV

HBe-Ag +

No Treatment

DNA PCR 2000IU/ml

ALT

HBs-Ag positiv

Immun-tolerance

HBe-Ag pos CHB

Inactive carrier

HBe-Ag neg CHB

Treat-ment

No Treat-ment

Treat-ment

No Treat-ment

Treat-ment
HBV-DNA and HCC Risk

Chen et al Gastroenterol 2011;141:1240-48

HR: 16.8

HR: 8.85

HR: 3.61

HR: 3.12

HR: 2.25

Group of Long-term HBV DNA Change

- Group I: Persistence at $>10^7$
- Group G-H: Decrease to/Persistence at $10^5-10^7$
- Group E-F: Decrease to/Persistence at $10^5-10^6$
- Group D: Persistence at $10^5-10^3$
- Group A-B-C: Decrease to $<10^4$
- Control Group: $<10^4$ at enrollment

Cumulative incidence of HCC, %

Year of Follow-up

Chen et al Gastroenterol 2011;141:1240-48
Vaccination

Yearly HCC incidence per 100'000 children aged 6-14 years

<table>
<thead>
<tr>
<th>Year</th>
<th>HbsAg +ve %</th>
<th>Vacc. coverage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981-86</td>
<td>10.1</td>
<td>0</td>
</tr>
<tr>
<td>1986-90</td>
<td>4.3</td>
<td>13</td>
</tr>
<tr>
<td>1990-94</td>
<td>.85</td>
<td>58</td>
</tr>
</tbody>
</table>


B.M. 09.06.2012

Hepatitis B Swiss MedLab 2012
Vaccination Effect CH

![Graph showing vaccination effect in CH]

- **1995**
- **1999**
- **2002**
54j Pat

- **HBe-Ag pos CHB**
  - 1998 INF 3x4.5 Mio U
  - Liver Bx 6/01: Ishak Score 3
  - 2002 Entecavir Phase 3 Studie
Indication for treatment

Replicating HBV-Infection:
HBeAg pos or neg., HBV-DNA pos. (>2000IU/ml)
and/or
Chronic Hepatitis: ALT >ULN for >6 mo.
and
Histology: >A2, >F2 nach Metavir

EASL Guidelines Journal of Hepatology 2009:50;227-42
Treatment Goals

Virological Response
- HBV-DNA neg
- Sustained HBe-Seroconversion

Complete Response
- Sustained HBs-Ag loss or seroconversion

Biochemical Response
- Normalisation of liver enzymes

Histological Response
- Decrease in histological activity by 2 pts
Therapy Monitoring & Response

Primary Non-Response: \( \downarrow \) HBV DNA <1 log\(_{10}\) IU/mL

Partial Virological Response

Virological Breakthrough: \( \uparrow \) HBV DNA ≥1 log\(_{10}\) IU/mL

Modify Therapy

HBV DNA negative

Wk. 12 HBV DNA
Wk. 24 HBV DNA HBe-Ag
Wk. 48 HBV DNA HBe-Ag

IFN: DNA <2,000 IU/mL
NUC: DNA negative

EASL Guidelines Journal of Hepatology 2009:50;227-42
Treatment Options HBV

Lamivudin  PEG-IFN2a  Telbivudin  Tenofovir
IFN  Adefovir  Entecavir

HBe-Ag pos CHB

HBe seroconversion

Undetectable HBV DNA

EASL Guidelines Journal of Hepatology 2009:50;227-42
HBe-Ag neg CHB

Undetectable HBV DNA

EASL Guidelines Journal of Hepatology 2009:50;227-42
## INF - NUC

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Pegylated interferon</th>
<th>NUCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finite duration</td>
<td>Absence of resistance</td>
<td>Potent antiviral effect</td>
</tr>
<tr>
<td>Absence of resistance</td>
<td>Higher rates of HBeAg</td>
<td>Good tolerance</td>
</tr>
<tr>
<td>Higher rates of HBeAg</td>
<td>and HBs seroconversion</td>
<td>Oral administration</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Moderate antiviral effect</th>
<th>Indefinite duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor tolerance</td>
<td>Subcutaneous injections</td>
<td>Risk of resistance</td>
</tr>
<tr>
<td>Lower rates of HBeAg and HBs seroconversion</td>
<td></td>
<td>Lower rates of HBeAg and HBs seroconversion</td>
</tr>
</tbody>
</table>
Hepatitis B: INF response

Genotype A: ~ 30% of patients in Europe
Pretreatment Predictors

PEG:
- HBe-Ag pos:
  - Low viral load (<2x10^8 IU/ml)
  - ALT>2-5ULN
  - A2 liver biopsy
  - Genotype A, B

Nuc:
- HBe-Ag pos:
  - Low viral load (<2x10^8 IU/ml)
  - ALT>2-5ULN
  - A2 liver biopsy
On treatment predictors

PEG:
- HBe-Ag pos:
  - HBs-Ag <1500 at wk 12
- HBe-Ag neg:
  - No HBs decline and <2log HBV DNA decline at wk 12

PEG:
- Undetectable HBV DNA at wk 24 (Lam, LdT) or 48 (ADV)
Praedictive factors for PEG-INF response in HBe-Ag pos CHB

Buster et al Gastroenterology 2009;137:2002-2009
# Resistance Pattern

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
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<tbody>
<tr>
<td><strong>Wild-type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>L180M ± M204I</strong></td>
<td><strong>R</strong></td>
<td></td>
<td><strong>I/R</strong></td>
<td><strong>S</strong></td>
<td><strong>S</strong></td>
</tr>
<tr>
<td><strong>L180M ± M204V</strong></td>
<td><strong>R</strong></td>
<td><strong>S</strong></td>
<td><strong>I</strong></td>
<td><strong>S</strong></td>
<td><strong>S</strong></td>
</tr>
<tr>
<td><strong>A180T/V</strong></td>
<td><strong>I</strong></td>
<td></td>
<td></td>
<td><strong>R</strong></td>
<td><strong>S</strong></td>
</tr>
<tr>
<td><strong>N236T</strong></td>
<td><strong>S</strong></td>
<td><strong>S</strong></td>
<td></td>
<td><strong>R</strong></td>
<td><strong>I</strong></td>
</tr>
<tr>
<td><strong>L180M + M204V/I ± I169T ± V173L ± M250V</strong></td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td><strong>S</strong></td>
<td><strong>S</strong></td>
</tr>
<tr>
<td><strong>L180M + M204V/I ± T184G ± S202I/G</strong></td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td><strong>S</strong></td>
<td><strong>S</strong></td>
</tr>
</tbody>
</table>

**Nucleoside**  **Nucleotide**
Entecavir in patients with decompensated liver cirrhosis

16 Pat. with decomp. cirrhosis

5 Pat. with severe lactic acidosis

4-240 after starting therapy

All Meld >20

Mortality 20%

Lange et al Hepatology 2009;50:2001-6
Chronic hepatitis B
HBsAg + >6 months, HbeAg + or -
HBV-DNA >2000 IE/ml
Liver biopsy: >A2, F2

HBe-Seroconversion likely
Viral load < 2x10^6 IU/ml, ALT > 3xULN
Aim: Treatment of finite duration with PEG-INF or NUC

Information about pro’s and con’s
Treatment decision

PEG-Interferon for 48 weeks
Consider stopping NUC 6-12 months after HBe-Ag Seroconversion

Achieve Seroconversion/SVR → Stop therapy
No Seroconversion No Suppression of viral replication

Evaluate:
Alternative therapy Add-on therapy

HBe-Seroconversion unlikely
Viral load > 2x10^6 IU/ml, ALT < 3x ULN
Aim: long-term treatment with NUC

Most potent agent with highest barrier of resistance
HBV-DNA every 3-6 months to detect HBV resistance as early as possible

Most potent agent with highest barrier of resistance. Consider de novo combination.
Watch for lactic acidosis
HBV-DNA every 3 months to detect HBV resistance as early as possible

Existing cirrhosis
Aim: Suppression viral replication and prevention of decompensation

No Seroconversion
No Suppression of viral replication

No suppression of viral replication after 6-12 months
>1log rise in viral load → check for viral resistance/compliance

No suppression of viral replication after 6-12 months
Regression of cirrhosis
Entecavir

N=57

3-7 yrs

Chang et al. Hepatology 2010;52:886-893
Regression of cirrhosis
Tenofovir

- 344/348 patients had liver biopsy data available at all three time points
- Percentage of the population with cirrhosis (Ishak Score ≥5) progressively decreased from 28% at baseline to 8% at Year 5

Marcellin, P, et al. AASLD 2011; Poster #1375.
Regression of cirrhosis
Tenofovir

- 96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and Year 5 biopsies
- 74% (n=71) of patients had cirrhosis reversed (Ishak fibrosis score <5) at Year 5, and 73%

Marcellin, P, et al. AASLD 2011; Poster #1375.
HBV-Elimination Improves Outcome?

Therapy of Hepatitis B: Special Groups

<table>
<thead>
<tr>
<th>Condition</th>
<th>TreatmentStrategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>NUCs with low risk of resistance: Tenofovir, Entecavir</td>
</tr>
<tr>
<td>Post-OLT</td>
<td>HBV-Immunoglobulin (HBIG) + NUC</td>
</tr>
<tr>
<td></td>
<td>Reinfection &lt;10%</td>
</tr>
<tr>
<td>Coinfection</td>
<td>Tenofovir + Emtricitabine / third HIV-agent</td>
</tr>
<tr>
<td>HIV</td>
<td>(PEG-)Interferon-α (&gt; 48 wks): NUCs ineffective</td>
</tr>
<tr>
<td>HDV</td>
<td>PEG-Interferon-α + Ribavirin; risk of HBV reactivation</td>
</tr>
<tr>
<td></td>
<td>after HCV clearance → NUCs</td>
</tr>
<tr>
<td>Acute severe</td>
<td>NUCs with low risk of resistance: Tenofovir, Entecavir</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>(Bilirubin &gt;10x ULN, Quick &lt;60%?)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Lamivudine, Adefovir, Entecavir (FDA Class C), Telbivudin (Class B); Tenofovir (B; large experience)</td>
</tr>
<tr>
<td>Immunosuppr./Chemotherapy</td>
<td>HBs-Ag positive: NUCs → 12 mo. after cessation</td>
</tr>
<tr>
<td></td>
<td>Anti-HBc Only: HBV-DNA f/u; NUC prophylaxis before ALT↑</td>
</tr>
</tbody>
</table>
Viral Eradication  
Rare

Viral Control  
Sustained Control

Maintained Control

INF

Nuc