Acute and chronic viral hepatitis

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Discovery of aetiological agents of VH

- 1965 Hepatitis B surface antigen (HBsAg) isolated (Blumberg)
- 1973 Hepatitis A virus (HAV) identified (Feinstone)
- 1977 Delta agent (HDV) identified (Mario Rizzetto)
- 1985 recombinant DNA technology
- 1989 HCV identified (Houghton)
- 1990 HEV identified (Bradley)
- 1995 HGV identified

Etiological agent

<table>
<thead>
<tr>
<th>HA V</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>Picornaviridae</td>
<td>Hepadnaviridae</td>
</tr>
<tr>
<td>Genus</td>
<td>Hepatovirus</td>
<td>Orthohepadnavirus</td>
</tr>
<tr>
<td>Size</td>
<td>27-28 nm</td>
<td>42 nm</td>
</tr>
<tr>
<td>Genom</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Number of genotypes</td>
<td>4</td>
<td>&gt;6 main genotypes</td>
</tr>
<tr>
<td>Incub. period (days)</td>
<td>15-50</td>
<td>30-180</td>
</tr>
<tr>
<td>Transmission:</td>
<td>- fecal-oral</td>
<td>yes</td>
</tr>
<tr>
<td>- sexual contact</td>
<td>rarely</td>
<td>yes</td>
</tr>
<tr>
<td>- parenteral</td>
<td>rarely</td>
<td>yes</td>
</tr>
<tr>
<td>Chronicity</td>
<td>no</td>
<td>55-85%</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>anti-HAV IgM, anti-HAV IgG, anti-HAV IgM, anti-HAV RNA</td>
<td></td>
</tr>
<tr>
<td>Fulminant course</td>
<td>0.1%</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>Active and passive immunization</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Discovery of aetiological agents of VH

- 1965 Hepatitis B surface antigen (HBsAg) isolated (Blumberg)
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- 1989 HCV identified (Houghton)
- 1990 HEV identified (Bradley)
- 1995 HGV identified

Etiological agent

<table>
<thead>
<tr>
<th>HDV (delta agent)</th>
<th>HEV (swHEV)</th>
<th>GBV-C (HGV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>Hepatovirus</td>
<td>Hepevirus</td>
</tr>
<tr>
<td>Genus</td>
<td>Deltavirus</td>
<td>Hepevirus</td>
</tr>
<tr>
<td>Size</td>
<td>35-37 nm</td>
<td>27-34 nm</td>
</tr>
<tr>
<td>Genom</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Number of genotypes</td>
<td>3 (I, II, III)</td>
<td>4</td>
</tr>
<tr>
<td>Incub. period (days)</td>
<td>30-180</td>
<td>15-60</td>
</tr>
<tr>
<td>Transmission:</td>
<td>- fecal-oral</td>
<td>no</td>
</tr>
<tr>
<td>- sexual contact</td>
<td>yes</td>
<td>rarely</td>
</tr>
<tr>
<td>- parenteral</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Chronicity</td>
<td>no</td>
<td>80-90%</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>anti-HDV IgM, anti-HDV IgG, anti-HDV RNA</td>
<td></td>
</tr>
<tr>
<td>Fulminant course</td>
<td>1%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Active immunization</td>
<td>against HEV</td>
<td></td>
</tr>
</tbody>
</table>

HFV

- In December 1994, researchers published evidence for the transmission of the enteric agent responsible for sporadic non-A, non-E hepatitis to rhesus monkeys
- Virus-like particles (27-37 nm in diameter) were detected in human stool extracts from French patients and in the liver and stool of the inoculated animals
- The authors provisionally named agent hepatitis French (for origin) virus or HFV
- Analysis of the viral genome indicated that it contained double-stranded DNA
  (Journal of Gastroenterology and Hepatology 2001;16(2):124-131)
- We know now, that this discovery was not correct = HFV as well as HF do not exist

HEV resistance on heat I.

Heating the food to an internal temperature of 71 ºC for 20 min is necessary to completely inactivate HEV

HEV resistance on heat II.

<table>
<thead>
<tr>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Cooking methods</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 °C</td>
<td>30'-60'</td>
<td>medium rare</td>
<td>HEV is resistant</td>
</tr>
<tr>
<td>60 °C</td>
<td>60'</td>
<td>medium</td>
<td>HEV is residual but alive</td>
</tr>
<tr>
<td>66 °C</td>
<td>10'-60'</td>
<td>medium well-cooked</td>
<td>HEV inactivation</td>
</tr>
<tr>
<td>70-71 °C</td>
<td>10'-60'</td>
<td>well done</td>
<td>HEV inactivation</td>
</tr>
</tbody>
</table>

**Source:** AASLD, 2000
Acute VH in CR (Epidat)

(HC = acute HC + chronic HC firstly diagnosed)

<table>
<thead>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1195</td>
<td>904</td>
<td>933</td>
<td>614</td>
<td>325</td>
<td>127</td>
<td>114</td>
<td>70</td>
<td>322</td>
<td>132</td>
<td>128</td>
<td>1648</td>
<td>1104</td>
<td>862</td>
<td>264</td>
<td>284</td>
<td>348</td>
<td>673</td>
<td>724</td>
<td>930</td>
</tr>
<tr>
<td>B</td>
<td>564</td>
<td>575</td>
<td>636</td>
<td>604</td>
<td>457</td>
<td>413</td>
<td>370</td>
<td>392</td>
<td>361</td>
<td>307</td>
<td>307</td>
<td>306</td>
<td>247</td>
<td>244</td>
<td>192</td>
<td>154</td>
<td>133</td>
<td>105</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>C</td>
<td>273</td>
<td>448</td>
<td>634</td>
<td>637</td>
<td>798</td>
<td>858</td>
<td>846</td>
<td>868</td>
<td>840</td>
<td>801</td>
<td>812</td>
<td>1022</td>
<td>980</td>
<td>974</td>
<td>836</td>
<td>709</td>
<td>812</td>
<td>794</td>
<td>873</td>
<td>857</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>17</td>
<td>5</td>
<td>12</td>
<td>13</td>
<td>12</td>
<td>21</td>
<td>36</td>
<td>37</td>
<td>45</td>
<td>48</td>
<td>54</td>
<td>258</td>
<td>218</td>
<td>299</td>
<td>412</td>
<td>339</td>
<td>344</td>
<td>288</td>
<td>319</td>
</tr>
</tbody>
</table>

Previous theory about HE prevalence

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in > 25% of Population: Non-VBC Hepatitis

HE prevalence in the world

[Epidem. Mikrobiol. Imunol. 2015;64(2):72-78]
Hepatitis B: Some Sobering Facts

- 350 million people chronically infected
- 2 billion with evidence of past or present infection
- Country of origin is THE major risk factor

HBV Reactivation: Overview

- Clinical syndrome characterized by an increase in HBV DNA and ALT/AST with or without symptoms or jaundice
- Occurs in pts with active (HBsAg+) and resolved (HBsAg-, anti-HBc+) HBV infection
- Wide clinical spectrum
  - Ranges from silent to acute liver failure (fibrosing cholestatic hepatitis)
- Can occur during treatment with many immunosuppressive agents
  - May also occur up to 12 mos after treatment
- Preventable by antiviral prophylaxis

New nomenclature for the chronic states of HBV infection

- **Phase 1**: HBeAg-positive chronic HBV infection previously „immune tolerant” phase
- **Phase 2**: HBeAg-positive chronic hepatitis B
- **Phase 3**: HBeAg-negative chronic HBV infection previously termed „inactive carrier” phase
- **Phase 4**: HBeAg-negative chronic hepatitis B
- **Phase 5**: HBsAg-negative phase also known as „occult HBV infection” (J Hepatol 2017;67:370-98)
Effects of interferon alfa
- IFN alfa inhibits the synthesis of viral nucleic acids and structural and nonstructural viral proteins
- Immunomodulatory effect:
  - IFN alfa increases the activity of cytotoxic T lymphocytes (CTLs) and NK cells, stimulating T lymphocytes and macrophages to the production and secretion of next cytokines
  - IFN alfa increases the expression of HLA antigens of the 1st class on the health and viral infected cells and therefore infected hepatocytes are then more sensitive to CTLs

Nucleos(t)ide analogues
* Famiclovir – analogue of deoxycytidine
* Lamivudine (3TC, LAM) – analogue of deoxycytidine
* Adefovir dipivoxil (ADV) – analogue of dAMP
* Tenofovir – similar as ADV
  - TDF = tenofovir disoproxil fumarate
  - TAF = tenofovir alafenamide
* Entecavir (ETC) – analogue of deoxyguanosine
* Emtricitabine (FTC) – analogue of cytosine
* Clevudine (LFMAU) – analogue of pyrimidine
* Telbivudine (LdT) – analogue of L-deoxythymidine

Indication for the treatment of HBV infection (EASL 2017 Clinical Practice Guidelines)
- HBV DNA >2,000 IU/ml
- Elevated ALT and/or at least moderate histological lesions
  - i.e. HBeAg-positive or HBeA-negative chronic HB
- All cirrhotic patients with detectable HBV DNA
- The prevention of mother to child transmission in pregnant women with high viremia (i.e., > 200 000 IU/ml) – Czech recommendation (from SEP 2017) is to use tenofovir (TDF) from 24th to 28th week of gravidity and stop this prophylaxis during the next 12 weeks after the birth
- Prevention of HBV reactivation in patients requiring immunosuppression or chemotherapy
- Patients with HBeAg-positive chronic HBV infection with normal ALT and high HBV DNA (i.e. previously termed „immune tolerant” phase) if they are older than 30 years
- Patients with severe acute HB, characterised by coagulopathy or protracted course, should be treated with nucleos(t)ide analogue (NA) therapy and considered for liver transplantation
- Tenofovir (TDF) is recommended for pregnant women with CHB and advanced liver disease or cirrhosis

Duration of the therapy of chronic HB

<table>
<thead>
<tr>
<th></th>
<th>HBeAg pos.</th>
<th>HBeAg neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEG-IFN alfa</strong></td>
<td>48 wks</td>
<td>48 wks</td>
</tr>
<tr>
<td><strong>Nucleos(t)ide analogues</strong> (LAM, ADV, TDF, ETC)</td>
<td>To HBeAg disappearance and next 12 months</td>
<td>To HBsAg disappearance X HBsAg persistency very often to the end of the life</td>
</tr>
<tr>
<td><strong>Initiation of antiviral therapy</strong></td>
<td>HBV DNA &gt;2 000 IU/mL (&gt;10⁴ copies/mL)</td>
<td>HBV DNA &gt;2 000 IU/mL (&gt;10⁴ copies/mL)</td>
</tr>
</tbody>
</table>

Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), telbivudine (TBV), entecavir (ETV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naive patients with chronic HB (Hepatology 2014;60:313A-317A)
Long-term Oral HBV Therapy is Highly Effective

- Suppresses HBV DNA\(^1,2\)
- Normalizes ALT\(^3,4\)
- Prevents fibrosis progression\(^3,4\)
- Promotes fibrosis regression, even in cirrhosis\(^4\)
- Prevents and even reverses hepatic decompensation\(^3,4\)
- Reduces, but does not eliminate, the risk of HCC\(^2,4\)
- Long-term therapy is effective... but low rates of HBsAg loss\(^6\)


Long-term Oral HBV Therapy: Downsides

- Toxicity
  - Potential for renal, bone complications with TDF
- Resistance
  - High with lamivudine (not preferred by guidelines)\(^1\)
  - Very low with entecavir—unless already LAM resistant\(^2\)
- None with TDF in clinical trials (similar expected with TAF)\(^3\)
- Cost
- Adherence

PegIFN vs Nucleos(t)ide Analogues

<table>
<thead>
<tr>
<th>PegIFN</th>
<th>Nucleos(t)ide Analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro</td>
<td>Con</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>SC administration</td>
<td>PO administration</td>
</tr>
<tr>
<td>Frequent AEs</td>
<td>Infrequent AEs</td>
</tr>
<tr>
<td>Contraindicated in patients with cirrhosis, in pregnancy, with acute hepatitis B, and who are immunosuppressed*</td>
<td>Safe at all stages of disease, including decompensated cirrhosis*</td>
</tr>
<tr>
<td></td>
<td>Need for lifelong therapy/ lifelong therapy</td>
</tr>
<tr>
<td></td>
<td>Potential for drug resistance</td>
</tr>
</tbody>
</table>

*Particularly for HBsAg-positive patients with gynecologic A infection.
- Recent case report of lactic acidosis in several liver failures.

Estimated 70 Million Persons Living With HCV

Prevalence (Viremic)

- 0% to < 0.6%
- 0.6% to < 0.8%
- 0.8% to < 1.3%
- 1.3% to < 2.9%
- 2.9% to < 8.7%

HCV Infection Among Persons Who Inject Drugs (PWIDs)

- In most developing countries, injection drug use is primary source of new infections
- HCV treatment must be coupled with harm reduction measures to reduce total infections
13.1.2019

Global distribution of genotypes of HCV
(WHO Guidelines 2016)

Nearly Everyone With HCV Can Now Be Treated Successfully

- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every pt
- Treatment generally just 12 wks

Chronic Hepatitis C Is a Progressive Disease

- Few or no symptoms; can progress without signs for decades[1]
- Most pts asymptomatic until serious liver complications arise[2]

References in slide notes.

Nearly Everyone With HCV Can Now Be Treated Successfully

- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every pt
- Treatment generally just 12 wks

References in slide notes.

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13.1.2019

EASL 2018 HCV Treatment Guidelines

- Recommendations for treatment-naive patients and patients previously treated with pegIFN/RBV ± SOF or SOF + RBV, a compensated cirrhosis

**HCV Genotype**

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>SOF/VEL (Maviret™)</th>
<th>GLE/PIB (Epclusa™)</th>
<th>SOF/VEL/VOX (Vosevi™)</th>
<th>LDV/SOF (Harvoni™)</th>
<th>EBR/GZR (Zepatier™)</th>
<th>DOPT/VTVY + DSV (Viekirax™ + Exviera™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>1b</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5 or 6</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Triple combination effective but not needed because double combinations comparably effective.

- Tx naive ± compensated cirrhosis.
- Tx naive or tx experienced without cirrhosis or with compensated cirrhosis and HCV RNA ≤ 800,000 IU/mL.
- Tx naive or tx experienced with compensated cirrhosis.
- Treatment naive without cirrhosis or with compensated cirrhosis and HCV RNA ≤ 800,000 IU/mL.

Dostupné varianty IFN-free režimů pro jednotlivé genotypy HCV (DP ČHS ČLS JEP 2017)

- sofosbuvir + ledipasvir = HARVONI™ (Gilead)
- sofosbuvir = SOV ALDI™ (Gilead)
- sofosbuvir + velpatasvir = EPCLUSA™ (Gilead)
- daclatasvir = DAKLINZA™ (BMS)
- ombitasvir + paritaprevir = VIEKIRAX™ (AbbVie)
- simeprevir = OLYSIO™ (Janssen)
- dasabuvir = EXVIERA™ (AbbVie)
- grazoprevir + elbasvir = ZEPATIER™ (MSD)
- sofosbuvir + SOVARD™ (Gilead)
- daclatasvir = DAKLINZA™ (BMS)
- ombitasvir = VIEKIRAX™ (AbbVie)
- simeprevir = OLYSIO™ (Janssen)
- dasabuvir = EXVIERA™ (AbbVie)

University of Liverpool hepatitis drug interactions website (HEP Drug Interaction Checker)

http://www.hep-druginteractions.org/
Main extrahepatic manifestations in pts with HCV infection
(Ther Adv Infect Dis 2016;3(1):3-14)

Immune-related extrahepatic manifestations

• Mixed cryoglobulinemia
• Cryoglobulinemic vasculitis
• B-cell NHL (non-Hodgkin’s lymphoma)
• Sicca syndrome (Sjögren’s syndrome)
• Arthralgia/myalgia
• Autoantibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, antithyroid and anti-smooth muscle antibodies)
• Polyarteritis nodosa
• Monoclonal gammopathy
• Immune thrombocytopenia

Inflammatory-related extrahepatic manifestations

• Type 2 diabetes mellitus type 2
• Insulin resistance
• Glomerulonephritis (membranoproliferative)
• Renal insufficiency
• Fatigue
• Cognitive impairment
• Depression
• Impaired quality of life
• Polyarthritis/fibromyalgia
• Cardiovascular disorders (i.e. stroke, ischemic heart disease)