DIAGNOSIS
AND MONITORING OF
Viral Hepatitis
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Chronic viral hepatitis

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  - Interpretation
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Treatment

- Acute hepatitis
- Chronic hepatitis
- Management of the main treatment-related side effects

Vaccination

Pregnant women

This paper was prepared with the kind co-operation of Doctor L Castéra (Hepato-gastro-enterology department, CHU, Bordeaux - France), and Professor JM Pawlotsky (Bacterio-virology department, Hôpital Henri Mondor, Créteil - France).
Incubation
2-7 weeks

Acute phase
several days-2 weeks

Convalescence
3-8 months

Cure
years

HAV Ag in feces

clinical signs

infectivity

contact

Anti-HAV IgM

Total Anti-HAV Ab

Anti-HAV IgM

Total Anti-HAV Ab

Increase in transaminase levels
HBV DNA
HBs Ag
HBe Ag
Anti-HBc IgM
Total Anti-HBc Ab
Anti-HBe Ab
Anti-HBs Ab
Increase in transaminase levels
<table>
<thead>
<tr>
<th>Incubation</th>
<th>Acute phase</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7 weeks</td>
<td>4-12 weeks</td>
<td>years</td>
</tr>
</tbody>
</table>

- **Incubation**:
  - HCV RNA
  - HCV Ag

- **Acute phase**:
  - HCV RNA
  - HCV Ag
  - Increase in transaminase levels
  - Anti-HCV Ab

- **Cure**:
  - Anti-HCV Ab

- **Clinical signs**:
  - Contact

- **Spontaneously resolvent**

- **Acute hepatitis C**
**Hepatitis A**

- **Transmission**: enteral (contaminated food and drink)
- **Clinical signs**: asymptomatic in 90% of cases
- **Cure**: 100% of cases
- **Complications**: fulminant forms (rare)
- **Development of chronic form**: NO
- **Prevention**: vaccination+++; hygiene; specific Ig
- **Main markers**: anti-HAV IgM, total anti-HAV Ab

**Hepatitis B**

- **Transmission**: sexual, parenteral, perinatal, direct contact between individuals
- **Clinical signs**: asymptomatic in 90% of cases
- **Cure**: 95% of cases (adults)
- **Complications**: cirrhosis and hepatocellular carcinoma
- **Development of chronic form**: YES (5% of adult cases)
- **Prevention**: vaccination+++; specific IgG
- **Main markers**: HBs Ag, anti-HBc IgM, total anti-HBc Ab, anti-HBs Ab, HBe Ag, anti-HBe Ab, HBV DNA

**Hepatitis C**

- **Transmission**: parenteral, nosocomial
- **Clinical signs**: asymptomatic in 90% of cases
- **Complications**: cirrhosis and hepatocellular carcinoma
- **Development of chronic form**: YES (80% of cases)
- **Prevention**: hygiene, no vaccination
- **Main markers**: anti-HCV Ab, HCV RNA, HCV Ag, genotyp
ACUTE VIRAL

Clinical signs

Determination of date of infection to orient diagnosis

- Non-specific or absent symptoms (90% of cases):
  - pain in right hypochondrium - fever
  - nausea and vomiting - arthralgia
  - urticaria
- Icterus (≤ 10% of cases)

First-line approach

Biological profile

- AST (or SGOT) and ALT (or SGPT) transaminase serum activity assay.
- Detection of A, B and C viruses (the most common causes). (1-5)
  - Anti-HAV IgM
  - HBs Ag
  - Anti-HBc IgM
  - Anti-HCV Ab

Interpretation (2, 3, 4)

<table>
<thead>
<tr>
<th>Transaminases</th>
<th>Acute Hepatitis A</th>
<th>Acute Hepatitis B</th>
<th>Acute Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HAV IgM</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBs Ag</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anti-HCV Ab</td>
<td></td>
<td></td>
<td>-/+ *</td>
</tr>
</tbody>
</table>

* In the initial phase of acute hepatitis C, anti-HCV Ab detection may be negative (serological window of 4 to 6 weeks): repeat the test for this marker in the weeks following acute infection to confirm seroconversion (1, 5).

Early diagnosis during serological window: HCV RNA detection using amplification techniques (e.g., Polymerase Chain Reaction) by specialized laboratories (6).
Hepatitis

- Severe form: fulminant hepatitis
  - Clinical signs: hepatic encephalopathy
  - Biological signs: prothrombin level (< 50%); transaminase level not correlated with the severity of fulminant hepatitis

Urgent hospitalization in a specialized ward

### Prognosis and follow-up

**Development of chronic forms**

- No risk for hepatitis A and E viruses.
- Possible progression to chronic hepatitis for B, C and \( \Delta \) viruses: risk of cirrhosis and hepatocellular carcinoma.

**Follow-up**

<table>
<thead>
<tr>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of chronic form</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Probability of cure</td>
<td>100%</td>
<td>90-95% (adults) 50% (children) 5% (newborns)</td>
</tr>
<tr>
<td>Indicator of cure</td>
<td>disappearance of anti-HAV IgM</td>
<td>disappearance of HBs Ag + appearance of anti-HBs Ab</td>
</tr>
<tr>
<td>Protective immunity</td>
<td>YES (Total anti-HAV Ab)</td>
<td>YES (anti-HBs Ab)</td>
</tr>
</tbody>
</table>

* The presence of anti-HCV antibodies does not ensure protective immunity.

**Specific cases**:

- **Delta superinfection** in chronic HBs Ag carriers (drug abusers): anti-\( \Delta \) IgM and IgG detection.
- **Hepatitis E** (subject returning from a stay in an endemic zone, Africa, Asia, South America): anti-HEV Ab detection.

**Other causes of acute hepatitis**

Epstein-Barr virus, Cytomegalovirus, Herpes virus, etc.
Clinical signs

Generally asymptomatic, no specific clinical signs (1)

 Detected in a routine blood test (chronic rise in transaminase level) or when donating blood.

First-line approach

Biological profile

1 • Test for signs of chronic hepatitis :
   Transaminase assay (at least 3 assays over a period of at least 6 months)(1).

2 • Test for signs of complications (1) :
   • Prothrombin level,
   • Serum protein electrophoresis (γ globulins)
   • Liver scan

3 • Test for the viral cause(1) :
   • HBV : HBs Ag, total anti-HBc Ab, anti-HBs Ab
   • HCV : anti-HCV Ab

4 • Test for other possible causes
   (in event of negative viral serologies)(1) :
   Alcoholism, administration of therapeutic drugs, steatosis, hemochromatosis, auto-immune hepatitis, etc.

Interpretation (3)

Hepatitis B

<table>
<thead>
<tr>
<th>Transaminases</th>
<th>HBs Ag</th>
<th>Total anti-HBc Ab</th>
<th>Anti-HBs Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated to 1 to 10 times the normal level</td>
<td>+ on 2 samples over more than 6 months</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

* Perform at least 3 assays over a period of at least 6 months.

Hepatitis C (4)

Confirm the presence of anti-HCV Ab on a 2nd sample :

• Present in 100% of immunocompetent subjects with chronic hepatitis C.
• May be undetectable in hemodialysis patients or immunocompromised subjects : a negative result for anti-HCV Ab does not eliminate a possible diagnosis.
AL HEPATITIS

Second-line approach (3-5)

Biological profile

Test for
- HBV and HVC: HBe Ag, Anti-HBe Ab, HBV DNA, anti-Δ IgM and total anti-Δ Ab
- HCV : HCV RNA

Interpretation (1,3)

<table>
<thead>
<tr>
<th>Hepatitis B</th>
<th>HBe Ag</th>
<th>Anti-HBe Ab</th>
<th>Viral replication (HBV DNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>«Wild» B virus</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>«Pre-core mutant» B virus (up to 50% of cases in some countries)</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Non-replicating B virus carriers (1/3 of chronic HBs Ag carriers)</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

Specific case for hepatitis B + Δ:
- Total anti-Δ Ab (+) and anti-Δ IgM (+ or -); RNA of Δ virus detectable.

Hepatitis C (4-6)

Test for HCV RNA
- If presence of anti-HCV Ab: active viral replication is confirmed by the presence of HCV RNA.
- If absence of anti-HCV Ab:
  - (hemodialysis patients or immunocompromised subjects): the presence of viral RNA confirms the diagnosis of chronic hepatitis C.

Liver biopsy

- Diagnosis of certainty of chronic hepatitis.
- To be envisaged systematically for any patient with a chronic rise in transaminase levels (over 6 months), irrespective of the extent of the rise.

Aim: to determine the severity of hepatic lesions on 3 criteria to decide on the administration of an antiviral treatment:
- Extent of necrosis and inflammation
- Degree of fibrosis
- Any associated lesions

Detected at the compensated or complicated cirrhosis stage (ascites, icterus, digestive hemorrhage).
Acute hepatitis

- No specific treatment of acute viral hepatitis.
- Symptomatic treatment: rest and elimination of alcoholic beverages until transaminase levels return to normal.

Hepatitis B

Interferon-α: 5 to 6 million units 3 times/week subcutaneously for 4 to 6 months. Disappearance of HBV DNA from serum, and of HBe Ag, with appearance of anti-HBe Ab (HBe seroconversion in approximately 20% of cases).

Current Nucleoside

<table>
<thead>
<tr>
<th>Nucleoside analogue</th>
<th>Dose</th>
<th>Reduction in serum HBV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine (3TC)</td>
<td>100 mg qd</td>
<td>4-6 log_{10}</td>
</tr>
<tr>
<td></td>
<td>500 mg tds</td>
<td>1-2 log_{10}</td>
</tr>
<tr>
<td>Famiciclovir</td>
<td>5-30 mg qd</td>
<td>4-8 log_{10}</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>0.5-2.5 mg qd</td>
<td>2-3 log_{10}</td>
</tr>
<tr>
<td>(bis-POM-PMEA)</td>
<td>(capsules) qd</td>
<td>2-4 log_{10}</td>
</tr>
<tr>
<td>Entecavir (BMS-200475)</td>
<td>200 mg (or 240 mg (24 mL) oral solution qd)</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine [5 fluorothiacytidine (FTC)]</td>
<td>300 mg qd</td>
<td>4-6 log_{10}</td>
</tr>
<tr>
<td>Tenoforv</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pegylated Interferon-α (subcutaneous route), associated with ribavirin (per os), for 6 to 12 months:

Management of the main type of side effect

<table>
<thead>
<tr>
<th>Type of side effect</th>
<th>Specific treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-like syndrome (70% of cases): within hours of injection; predominant at start of treatment (1st and 2nd months).</td>
<td>Paracetamol: (1g before each injection followed by 1 to 3g over the next 24 hours)</td>
</tr>
<tr>
<td>Leukopenia and thrombopenia (30% of cases): monitoring of CBC and platelet count</td>
<td>None</td>
</tr>
<tr>
<td>Hemolytic anemia: monitoring hemoglobin level</td>
<td>None</td>
</tr>
</tbody>
</table>

CBC: complete blood count;
Aims of treatment: prevention of viral replication and/or definitive elimination of virus from the body; prevention of progression to complications (cirrhosis, hepatocellular carcinoma).

Prevention of viral replication (>50% of cases); definitive cure in the majority of cases responding to the treatment.

Dosage adaptation
- NO: improvement if IFN is injected in evening before going to bed
- IFN dosage reduction
  - Discontinuation (<10% of cases) if PN<500/mm³ or pl<50,000/mm³

Discontinuation of treatment
- NO
- Rare

IFN: interferon; PN: polynuclear neutrophils; pl: platelets.

Prevention of viral replication (>50% of cases); definitive cure in the majority of cases responding to the treatment.

Chronic hepatitis (1,3,4,6)

Comments
- The «pre-core mutant» B virus is generally more severe and more resistant to treatment.
- Carriers of the non-replicating B virus do not require treatment.

Analogues (approved or in clinical trials)

<table>
<thead>
<tr>
<th>Proposed mechanism of action</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competitive inhibition with dCTP</td>
<td>Approved</td>
</tr>
<tr>
<td>Competitive inhibition with dGTP</td>
<td>Approved</td>
</tr>
<tr>
<td>Competitive inhibition with dATP</td>
<td>Approved</td>
</tr>
<tr>
<td>Competitive inhibition with dGTP</td>
<td>Approved</td>
</tr>
<tr>
<td>Competitive inhibition with dCTP</td>
<td>Approved</td>
</tr>
<tr>
<td>Competitive inhibition with dATP</td>
<td>Approved (Europe) Pending (US)</td>
</tr>
</tbody>
</table>

qd: once daily / tds: three times daily.
**Hepatitis A**

**Epidemiology**

Transmission: Enteral (contaminated food and drink) \(^{(2)}\).

At risk subjects \(^{(2)}\):
- travelers or army personnel in endemic zones
- healthcare and childcare personnel
- close family and friends of an infected subject
- children in institutional care
- catering personnel

Vaccination \(^{(1,2)}\): recommended for at-risk group

At risk subjects:
- Drug abusers
- Subjects exposed to nosocomial infection
- Healthcare personnel

Vaccination: None

**Hepatitis C**

**Epidemiology**

Transmission \(^{(4)}\):
- parenteral ++++
- nosocomial

At risk subjects:
- Drug abusers
- Subjects exposed to nosocomial infection
- Healthcare personnel

Vaccination: None
Hepatitis B

Epidemiology

Transmission:
- Parenteral +++ and percutaneous +
- Sexual +++ and perinatal +++
- Direct contact between individuals

At risk subjects:
- Drug abusers
- Hemodialysis patients
- Close family and friends of an infected subject
- Healthcare personnel
- Subjects with multiple partners
- Children born to mothers carrying HBV

Vaccination / at risk population:

<table>
<thead>
<tr>
<th>Vaccination strategy</th>
<th>Pre-vaccination serological profile *</th>
<th>Post-vaccination immunity test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns and children</td>
<td>Recommended by the WHO (universal vaccination program)</td>
<td>HBs Ag Anti-HBs Ab Total anti-HBc Ab</td>
</tr>
<tr>
<td>Adults</td>
<td>Compulsory for certain at risk groups in some countries</td>
<td>YES for at risk subjects Anti-HBs Ab protective titer &gt; 10 mIU/ml, 2 to 3 months after vaccination.**</td>
</tr>
</tbody>
</table>

* If HBs Ag (+) and/or total anti-HBc Ab (+), continue the profile.
If total anti-HBc Ab (+) and anti-HBs Ab (+), vaccination not necessary.

** At risk subjects: Recommend a booster injection for anti-HBs titers between 10 and 100 mIU/ml. (11)
Pregnancy not affected by the existence of chronic hepatitis during pregnancy.

**Hepatitis A**

- No specific risk or follow-up for pregnant women.

**Hepatitis B**

<table>
<thead>
<tr>
<th>Status of pregnant woman</th>
<th>Risk of contamination of newborn</th>
<th>Seroprophylaxis and vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic carriage of HBs antigen</td>
<td>+++ at childbirth</td>
<td>compulsory at birth: injection of anti-HBs immunoglobulins associated with the first vaccine injection.</td>
</tr>
</tbody>
</table>

- Mother-child contaminations during childbirth (+++ and the post-natal period
- Mother infected during pregnancy or, most frequently, mother is a chronic HBV carrier
- Vaccination possible during pregnancy

<table>
<thead>
<tr>
<th>Maternal status</th>
<th>Risk of transmission</th>
<th>Risk of progression of infection to chronic form in newborns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother infected during 1st trimester of pregnancy</td>
<td>Almost none</td>
<td></td>
</tr>
<tr>
<td>Mother infected during 2nd trimester of pregnancy</td>
<td>6%</td>
<td>95%</td>
</tr>
<tr>
<td>Mother infected during 3rd trimester of pregnancy</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Mother = chronic carrier of -HBV DNA</td>
<td>&lt; 10%</td>
<td></td>
</tr>
<tr>
<td>Mother = chronic carrier of +HBV DNA</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>
### Hepatitis C

<table>
<thead>
<tr>
<th>Status of pregnant woman</th>
<th>Risk of contamination of newborn</th>
<th>Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of hepatitis C</td>
<td>Low (5 to 10% of cases)</td>
<td>No vaccine available</td>
</tr>
<tr>
<td></td>
<td>Increased in the event of HIV co-infection (20%)</td>
<td>Breastfeeding recommended*</td>
</tr>
</tbody>
</table>

* C virus is not passed into breast milk.

### Hepatitis E

<table>
<thead>
<tr>
<th>Status of pregnant woman</th>
<th>Risk for newborn</th>
<th>Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulminant forms of hepatitis E during 3rd trimester</td>
<td>20% maternal-fetal mortality</td>
<td>Vaccine under development</td>
</tr>
</tbody>
</table>

Travel to HEV endemic zones not recommended for pregnant women.


Internet sites to consult

http://www.hepfi.org
http://www.hepatitis-central.com/
http://www.cdc.gov/ncidod/diseases/hepatitis/
http://www.who.int/topics/hepatitis/en
http://www.hepnet.com
**HEPATITIS Product Range**

**VIDAS® range**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kits</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis A parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIDAS HAV IgM</td>
<td>30 tests</td>
<td>30 307</td>
</tr>
<tr>
<td>VIDAS Anti-HAV Total</td>
<td>30 tests</td>
<td>30 312</td>
</tr>
<tr>
<td><strong>Hepatitis B parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIDAS HBs Ag Ultra*</td>
<td>60 tests</td>
<td>30 315</td>
</tr>
<tr>
<td>VIDAS HBs Ag confirmation</td>
<td>30 tests</td>
<td>30 317</td>
</tr>
<tr>
<td>VIDAS Anti-HBs total Quick</td>
<td>60 tests</td>
<td>30 238</td>
</tr>
<tr>
<td>VIDAS Anti-HBc Total II</td>
<td>60 tests</td>
<td>30 314</td>
</tr>
<tr>
<td>VIDAS HBc IgM II</td>
<td>30 tests</td>
<td>30 439</td>
</tr>
<tr>
<td>VIDAS HBe/Anti-HBe</td>
<td>30 tests</td>
<td>30 305</td>
</tr>
</tbody>
</table>

**VIDIA® range**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kits</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIDIA HBs Ag</td>
<td>100 tests</td>
<td>38 800</td>
</tr>
<tr>
<td>VIDIA HBs Ag confirmation</td>
<td>30 tests</td>
<td>38 802</td>
</tr>
<tr>
<td>VIDIA Anti-HBs Total</td>
<td>100 tests</td>
<td>38 801</td>
</tr>
<tr>
<td>VIDIA Anti-HBc Total</td>
<td>100 tests</td>
<td>38 803</td>
</tr>
<tr>
<td>VIDIA Anti-HBc IgM</td>
<td>50 tests</td>
<td>38 804</td>
</tr>
</tbody>
</table>

**Microtiter plate range**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kits</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPANOSTIKA® HBsAg Ultra</td>
<td>192 tests</td>
<td>28 4132</td>
</tr>
<tr>
<td>HEPANOSTIKA HBsAg Ultra</td>
<td>576 tests</td>
<td>28 4133</td>
</tr>
<tr>
<td>Confirmatory</td>
<td>25 tests</td>
<td>28 0253</td>
</tr>
<tr>
<td>HEPANOSTIKA anti-HBc</td>
<td>192 tests</td>
<td>28 4144</td>
</tr>
<tr>
<td>HEPANOSTIKA anti-HBc</td>
<td>576 tests</td>
<td>28 4147</td>
</tr>
</tbody>
</table>

**Immunochromatographic test range**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kits</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIKIA® HBs Ag*</td>
<td>25 kits</td>
<td>31 113</td>
</tr>
</tbody>
</table>

*This rapid test is only available in countries not applying IVD CE and FDA regulations.*
The information in this booklet is given as a guideline only and is not intended to be exhaustive. It in no way binds bioMérieux S.A. to the diagnosis established or the treatment prescribed by the physician.