

Acute HEV on Chronic Hepatitis C

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- A 53-year-old patient
- Mixed alcoholic and HCV related liver cirrhosis diagnosed in 2013.
- No alcohol consumption since 2013
- CHILD-PUGH A
- HCV genotype 3
- HBV status : HBs-Ag negative, anti-HBc ab positive, anti-HBs ab negative
- 2013 : Interferon – ribavirin : relapse

- 2013 : diagnosis of cirrhosis
 - 2015 :
 - AST/ALT 105/85
 - Prothrombin index 61%
 - Normal bilirubin level
 - Treatment : interferon-Sofosbuvir-Ribavirin
 - October 2015 : AST/ALT 75/60 – HCV RNA undetectable
- HCV eradication

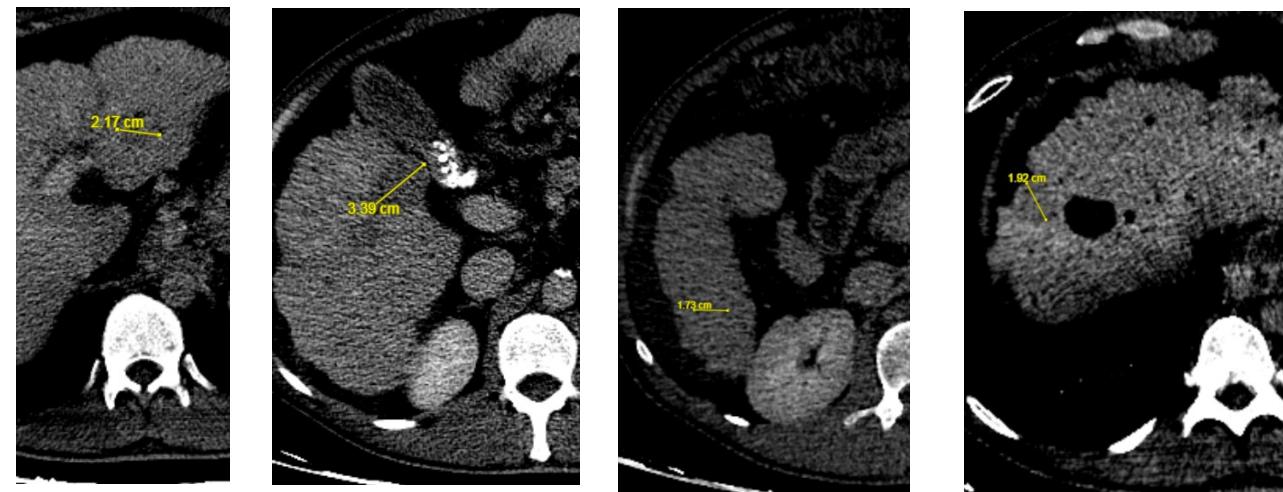
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 - 2 cm liver nodule on US examination
 - CT-scan :

CT-scan examination

Arterial phase



Portal phase



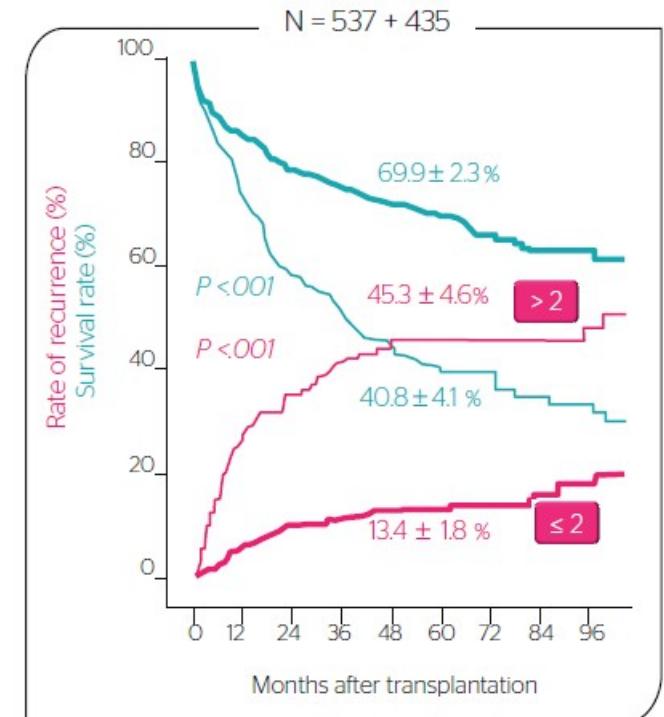
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 - 4 HCC nodules.
 - Largest : 33 mm.
 - AFP <10 ng/mL
 - Proposal?

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 - Proposal?

Score AFP

| | Score |
|-------------------|-----------------------------|
| Diamètre max (cm) | |
| ≤ 3 | 0 |
| 3-6 | 1 |
| > 6 | 4 |
| Nombre de nodules | |
| 1-3 | 0 |
| ≥ 4 | 2 |
| AFP (μg/l) | |
| ≤ 100 | 0 |
| 100-1000 | 2 |
| > 1000 | 3 |
| Score AFP | = Σ Scores variables |

→ Risque de récidive
 Score : ≤ 2 = faible
 > 2 = élevé



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Score AFP

- June 2016 :
 - 2 cm liver nodule on US examination
 - CT-scan :
 - 4 HCC nodules 2 points.
 - Largest 33 mm 1 point.
 - AFP <10 ng/mL
 - AFP score = 3

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- evaluation for liver transplantation
- necessity for downstaging
- transarterial chemoembolization is decided.

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- **June 2016** : TACE is scheduled but ...
 - Liver decompensation : jaundice, ascitis
 - Biology :
 - Total Bilirubin 150 µmol/L
 - AST/ALT : 950 / 780 UI/L
 - Prothrombin index 43 % (INR 2,2)
 - Creatinine 98 µmol/L

- **2013** : diagnosis of cirrhosis
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- **June 2016** : TACE is scheduled but ...
 - Liver decompensation : jaundice, ascitis
 - Biology :
 - Total Bilirubin 150 µmol/L
 - AST/ALT : 950 / 780 UI/L
 - Prothrombin index 38 % (INR 2,2)
 - Creatinine 98 µmol/L

→ Possible diagnosis ?

- Alcoholic hepatitis
- Acute viral hepatitis
- Progression of liver cancer
- Acute portal vein thrombosis or budd chiari syndrome
- Other

- No alcohol consumption or new drug introduction
 - US examination : No vascular abnormality
 - AFP level <10 ng/mL.
-
- HAV : IgM negative
 - HBV : HBsAg negative, HBV DNA undetectable
 - CMV, Herpes : past contamination
-
- HEV serology :
 - IgM positive (ratio 10.1), IgG positive (ratio 3.2)

→ Acute HEV infection?

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→ Acute HEV infection?

Recommendations

- EASL recommends using a combination of serology and NAT testing to diagnose HEV infection. (A1)
- EASL recommends NAT testing to diagnose chronic HEV infection. (A1)

Table 3. Laboratory diagnosis of HEV infection.

| Infection status | Positive markers |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Current infection - acute | <ul style="list-style-type: none"> • HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen |
| Current infection - chronic | <ul style="list-style-type: none"> • HEV RNA (\pm anti-HEV) \geq3 months • HEV antigen |
| Past infection | <ul style="list-style-type: none"> • Anti-HEV IgG |

* Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive. HEV, hepatitis E virus.

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 - US examination : No vascular abnormality
 - AFP level <10 ng/mL.
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- HEV serology :
 - IgM positive (ratio 10.1), IgG positive (ratio 3.2)
 - HEV RNA undetectable
 - HEV RNA could be detected retrospectively in a serum sample collected three weeks before decompensation.

→ Acute HEV infection

- **2013** : diagnosis of cirrhosis
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- **June 2016** : acute HEV infection
 - Severe liver dysfunction
 - Serum HEV RNA undetectable at time of diagnosis

→ Treatment ?

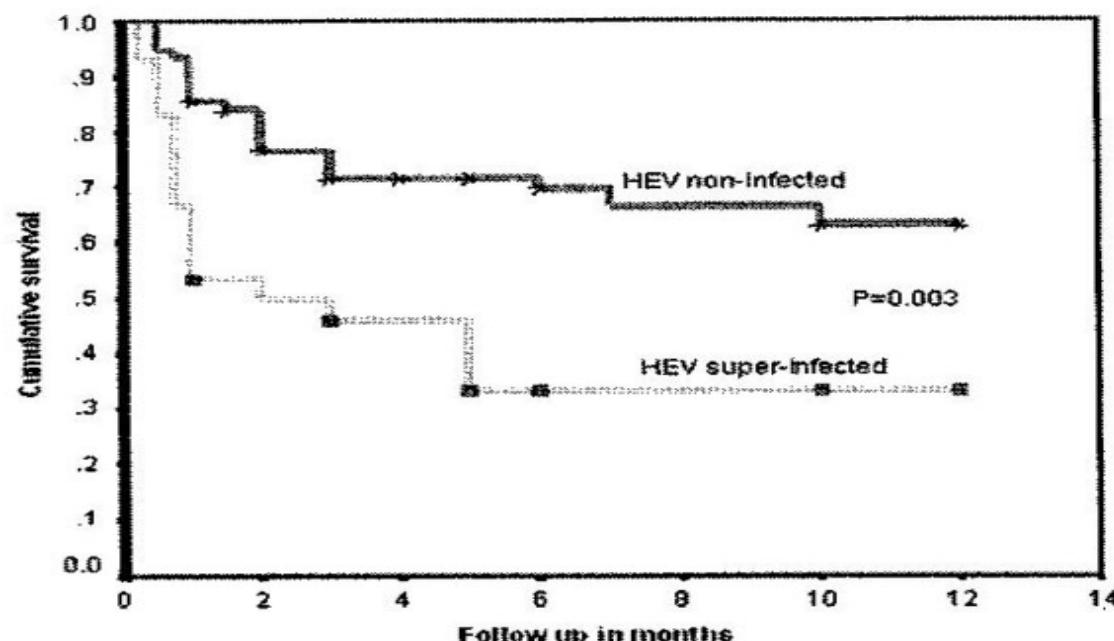
Hepatitis E virus as a cause of liver decompensation

Table 1 Etiology of acute exacerbation of previously unrecognized asymptomatic patients with hepatitis B virus-related chronic liver disease ($n = 43$)

| Etiology | HBeAg positive ($n = 21$) | HBeAg negative ($n = 22$) | Total ($n = 43$) |
|----------------------------------|-----------------------------|-----------------------------|--------------------|
| Acute exacerbation of HBV per se | 19 (90.5%) | 11 (50%) | 30 (69.8%) |
| Superinfection | 2 (9.5%) | 11 (50%) | 13 (30.2%) |
| HAV superinfection | 2 (9.5%) | 3 (13.6%) | 5 (11.6%) |
| HEV superinfection | 0 | 6 (27.3%) | 6 (13.9%) |
| HAV and HEV superinfection | 0 | 2 (9.1%) | 2 (4.7%) |

Data are expressed as number (percentage).

HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HEV, hepatitis E virus.



Locally acquired hepatitis E in chronic liver disease

| Age and sex | Clinical details | Bilirubin ($\mu\text{mol/L}$) | ALT (U/L) | AP (U/L) | Albumin (g/L) | INR | HEV IgM | Rising HEV IgG | HEV PCR | Liver biopsy | Outcome |
|-------------|-----------------------------|---------------------------------|-----------|----------|---------------|-----|---------|----------------|---------|---------------------|-----------------------------|
| 70M | Jaundice, malaise, anorexia | 314 | 1761 | 173 | 33 | 1·6 | + | + | - | Idiopathic fibrosis | Encephalopathy: recovered |
| 59M | Jaundice, fever, malaise | 160 | 1381 | 188 | 32 | 1·3 | + | + | +* | Alcoholic cirrhosis | Liver failure: died week 18 |
| 76M | Jaundice, abdominal pain | 86 | 2286 | 128 | 34 | 1·7 | - | + | - | Alcoholic cirrhosis | Liver failure: died week 24 |

ALT=alanine aminotransferase, AP=alkaline phosphatase, INR=international normalised ratio. Laboratory values are those at presentation.
 Hepatitis E case definition: ALT >500 U/L and HEV IgM positive, or a rising HEV IgG or HEV PCR positive.³ *Viral sequencing showed this to be HEV genotype 3.

Table: Clinical details and laboratory findings in three patients with locally acquired hepatitis E and underlying cirrhosis

Possible true fulminant hepatitis E

Table 1 Epidemiological, clinical and biological features of patients with fulminant or sub-fulminant hepatitis E.

| Patient | Date of HEV diagnosis | Delay from hepatitis onset to ALF (weeks) | Gender/age | Known associated disease | On-going drug therapy | Outcome | Liver histology | ALT (IU/L) | AST (IU/L) | Bilirubinemia (μ mol/L) | PI (%) | Factor V (%) | Anti-HEV IgG* | Anti-HEV IgM* | HEV RNA load (\log_{10} copies/ml) at time of LT or death |
|---------|-----------------------|-------------------------------------------|------------|---------------------------------------------------------------|--------------------------------|------------------|------------------------------------------------------------------------|------------|------------|------------------------------|--------|--------------|---------------|---------------|--------------------------------------------------------------|
| No. 1 | 06/2006 | 2 | M/58 | Non insulin dependent diabetes mellitus; hypercholesterolemia | Statins, metformin | LT; death | Severe acute hepatitis with massive necrosis; no pre-existing fibrosis | 2274 | 415 | 314 | 36 | 46 | 4.9 | 9.8 | 6.5 |
| No. 2 | 03/2008 | 4 | M/37 | Crohn's disease | Azathioprine, acetylsalicylate | Death on LT list | Pre-existing fibrosis | 374 | 149 | 635 | 21 | 23 | 7.3 | 9.7 | 5.6 |
| No. 3 | 09/2009 | 4 | M/29 | None | None | LT; survival | No pre-existing fibrosis | 2500 | 1700 | 400 | 24 | 21 | 3.3 | > 10 | Neg. |
| No. 4 | 03/2010 | 1 | M/41 | Excessive alcohol consumption | None | Death | Pre-existing fibrosis | 860 | 2360 | 243 | 16 | 18 | 2.8 | > 10 | 5.9 |

Test/cut-off optical density ratios; ALF: acute liver failure; ALT: alanine aminotransferases level; AST: aspartate aminotransferases level; HEV: hepatitis E virus; IgG: immunoglobulin G; IgM: immunoglobulin M; LT: liver transplantation; M: male; Neg.: negative; PI: prothrombin index.

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- **June 2016** : acute HEV infection
 - Severe liver dysfunction
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→ Treatment ?

Recommendations

- Ribavirin treatment may be considered in cases of severe acute hepatitis E or acute-on-chronic liver failure. (C2)

Table 1. Patients' characteristics at baseline

| | Patients n° | Age (years) | Gender | Comorbidities |
|-----------------------------------------------|-------------|-------------|--------|-------------------------------------------------|
| Cirrhosis (PT >60%) | 2 | 75 | M | Old age |
| | 18 | 50 | M | |
| | 20 | 69 | M | |
| Immunosuppressive therapy | 11 | 30 | F | Juvenile arthritis |
| | 12 | 62 | M | Psoriatic arthritis |
| | 15 | 50 | F | Ankylosing arthritis |
| | 3 | 70 | M | Old age and Rheumatoid arthritis |
| Chemotherapy | 10 | 54 | F | Breast cancer |
| | 19 | 71 | F | Cholangiocarcinoma and old age |
| PT ≤60% | 1 | 47 | M | Cirrhosis |
| | 5 | 46 | M | Cirrhosis |
| | 21 | 50 | M | Cirrhosis |
| | 6 | 62 | M | |
| | 7 | 44 | M | |
| | 8 | 61 | M | |
| | 13 | 64 | M | |
| | 17 | 63 | F | |
| | 4 | 70 | M | Idiopathic Thrombocytopenic Purpura and old age |
| | | | | |
| Others (haematological malignancy or old age) | 9 | 77 | F | Chronic myeloid leukaemia and Old age |
| | 14 | 50 | F | Chronic lymphocytic leukaemia |
| | 16 | 85 | M | Old age |

Table 2. Liver biochemical tests and virological parameters at baseline

| Patient n° | Liver parameters | | | | | Virological parameters | | Genotype |
|-------------------|------------------|-----------------|---------------|--------------------|-----------------|-------------------------------|-----|----------|
| | AST (IU/L) | ALT (IU/L) | γ-GT (IU/L) | Bilirubin (μmol/L) | PT (%) | HEV RNA levels Copies/mL | Log | |
| 1 | 2593 | 2724 | 1383 | 84 | 49 | 11 800 | 4.1 | ND |
| 2 | 784 | 1656 | 284 | 42.7 | 70 | 10 700 | 4.0 | ND |
| 3 | 1182 | 2157 | 182 | 13.2 | 91 | 1270 | 3.1 | 3c |
| 4 | 2938 | 2374 | 606 | 72 | 18 | 5 720 000 | 6.8 | 3f |
| 5 | 1829 | 1415 | 344 | 387 | 27 | ND | ND | ND |
| 6 | 1588 | 2124 | 1294 | 74.5 | 48 | ND | ND | 4 |
| 7 | 6218 | 7771 | 327 | 218 | 21 | ND | ND | 3f |
| 8 | | 4565 | | 550 | 38 | ND | ND | 3f |
| 9 | 90 | 140 | 152 | 14 | 100 | 368 000 | 5.6 | 3f |
| 10 | 883 | 1099 | 243 | 8 | 81 | 23 600 | 4.4 | 3f |
| 11 | 826 | 1118 | 357 | 20.5 | 100 | 471 000 | 5.7 | 3f |
| 12 | 584 | 1190 | 738 | 28 | 99 | 1 330 000 | 6.1 | 3c |
| 13 | 7477 | 6219 | 372 | 33 | 34 | 190 000 000 | 8.3 | 3f |
| 14 | 201 | 308 | 319 | 25 | 71 | 2 090 000 | 6.3 | 3f |
| 15 | 72 | 142 | 87 | 8 | 91 | 1610 | 3.2 | ND |
| 16 | 719 | 833 | 125 | 269 | 63 | 14 700 | 4.2 | 3f |
| 17 | 3339 | 4266 | 134 | 366 | 60 | 5 510 000 | 6.7 | 3f |
| 18 | 168 | 128 | 904 | 173 | 75 | 6650 | 3.8 | ND |
| 19 | 2078 | 1299 | 1180 | 89 | 90 | 322 000 | 5.5 | 3c |
| 20 | 1513 | 1482 | 565 | 59 | 81 | 125 000 | 5.1 | 3f |
| 21 | 153 | 136 | 411 | 502 | 41 | ND | ND | ND |
| Median (range) | 883 (72–7477) | 1415 (128–7771) | 500 (87–1383) | 80.5 (8–550) | 70% (18–100) | 233 500 (1270–190 000 000) | | |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma glutamyl transpeptidase; ND: not determined; PT, prothrombin time.

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→ Ribavirine 800 mg/d

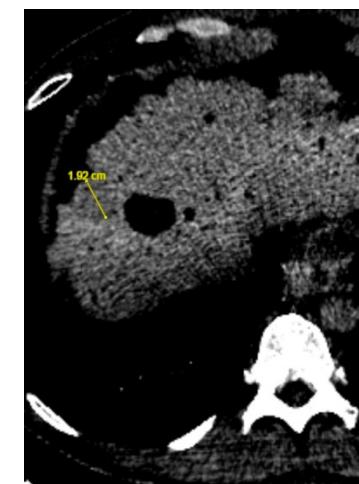
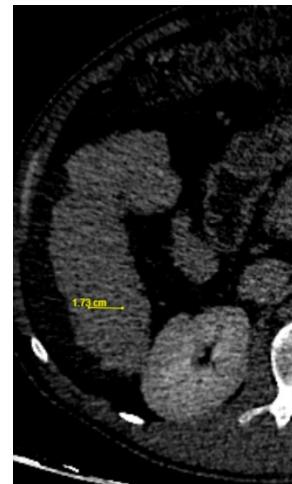
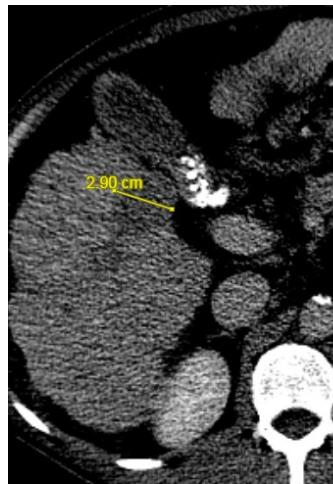
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- **July 2016**
 - Deterioration of liver function
 - Total Bilirubin 250 µmol/L
 - INR 3,8
 - Creatinine 145 µmol/L
- MELD score 39
→ ?

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→ Liver transplantation?

Body CT-scan reassessment

Absence of extrahepatic localisation
4 liver nodules, max 30 mm.

Portal phase



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- **July 2016**
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 - Body CT-scan reassessment
 - Absence of visible metastatic disease
 - Liver : 4 nodules up to 30 mm. AFP score 2.

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- **July 2016**

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- INR 3,8
- Creatinin 145 µmol/L



Liver transplantation

Histology :
severe cirrhosis with mononuclear infiltration
4 nodules of grade II HCC.
Largest nodule 28 mm.

- Body CT-scan reassessment
 - Absence of visible metastatic disease
 - Liver : 4 nodules up to 30 mm. AFP score 2.

