**Supplementary Material- 9 Acute HEV case histories**

Short clinical summaries of the 9 new, incremental cases of acute hepatitis E infection are provided in this supplement. Clinical, laboratory and histologic data are provided followed by the initial clinical assessment and the results of HEV testing with conclusions on the likelihood that HEV infection occurred (definite, highly likely or probable) and whether HEV was the cause of the liver injury (definite, highly likely, probable or only possible). The material also includes a flow sheet of relevant liver test results and a clinical commentary. Results of anti-HEV IgG and IgM testing are expressed as S/C values indicating the ratio of sample to control, the cutoff for positive varying from lot to lot, but borderline values were generally 0.90 to 1.49 and positive values 1.50 and above. Similar summaries of the initial 9 cases are provided in the appendix of reference 9.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alk P, alkaline phosphatase; ULN, upper limit of the normal range; *R*, ratio of ALT to Alk P both expressed as the ULN; INR, international normative ratio; BMI, body mass index; ANA, antinuclear antibody; SMA, smooth muscle antibody; AMA, antimitochondrial antibody; HCV, hepatitis C virus; HEV, hepatitis E virus; CT, computerized tomography; MRI, magnetic resonance imaging; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; S/C, sample to control ratio for anti-HEV results; HIV, human immunodeficiency virus; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.

**Case 10. Levofloxacin [2009]**

A 50-year-old white man was treated with levofloxacin for symptoms of abdominal discomfort, fever and dysuria but developed worsening abdominal pain, fever and hematuria. Six days after starting levofloxacin, he was seen in an emergency room and found to have jaundice and abnormal liver tests including total bilirubin of 3.5 mg/dL, ALT 743 U/L, AST 843 U/L, alkaline phosphatase 236 U/L (*R*=7.0: hepatocellular), serum albumin 3.0 g/dL and INR 1.4. He had a history of pancreatic carcinoma and underwent a Whipple procedure 5 years previously and resection of a metastasis 3 years before. He had no previous history of liver disease, alcohol abuse, drug allergies or risk factors for viral hepatitis. His other medications included replacement pancreatic enzymes, insulin and zolpidem. He had received a two-day course of ampicillin 2 for a dental procedure 2 weeks before presentation. On admission he was jaundiced but had no rash, fever or signs of chronic liver disease. Laboratory tests for hepatitis A, B and C (including HCV RNA) were negative as were ANA, SMA and AMA. Abdominal imaging by ultrasound and CT scan showed evidence of the previous surgery and mild biliary dilation with no obvious obstructing mass or lesion. He was followed on no specific therapy and his bilirubin rose to a peak of 7.9 mg/dL 5 days later and then began to fall. He did not undergo liver biopsy. He was discharged after a week in the hospital and in follow up his liver tests rapidly improved and were normal except for minor elevations in alkaline phosphatase (1.1 to 1.4 times ULN). Initially, the liver injury was considered highly likely due to levofloxacin. Retrospective testing of a stored serum sample taken 11 days after onset revealed IgG [S/C 8.05] and IgM [S/C 4.62] anti-HEV without detectable HEV RNA. Results of testing a follow up specimen at 7 months after onset was still reactive for IgG anti-HEV [S/C 10.58] but negative for IgM anti-HEV [S/C 0.75] and HEV RNA. Based upon the serologic testing, the patient was judged to have highly likely had acute HEV infection which was highly likely the cause of the liver injury, while levofloxacin was considered unlikely.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| Pre | -69 days | 19 | 91 | 0.7 |  |
| -3 days | -8 days | 93 | 99 | 1.2 |  |
| 0 | -5 days |  |  |  | *Levofloxacin started* |
| 5 days | 0 | 743 | 236 | 3.5 | *Symptoms & jaundice* |
| 6 days | 1 day | 660 | 221 | 3.2 | *Levofloxacin stopped* |
| 7 days | 2 days | 604 | 215 | 4.2 |  |
| 8 days | 3 days | 689 | 229 | 6.6 |  |
| 9 days | 4 days | 575 | 208 | 7.9 |  |
| 10 days | 5 days | 483 | 209 | 7.6 |  |
| 11 days | 6 days | 294 | 183 | 5.0 | *IgG & IgM anti-HEV+, RNA-* |
| 12 days | 7 days | 243 | 189 | 4.4 | *Discharged* |
| 27 days | 3 weeks | 20 | 109 | 1.4 |  |
| 33 days | 4 weeks | 11 | 100 | 0.8 |  |
| 48 days | 6 weeks | 13 | 117 | 0.8 |  |
| 60 days | 8 weeks | 15 | 145 | 0.7 |  |
| 81 days | 3 months | 18 | 116 | 0.8 |  |
| 118 days | 4 months | 25 | 99 | 0.8 |  |
| 158 days | 5 months | 20 | 97 | 0.5 |  |
| 193 days | 6 months | 19 | 105 | 0.7 |  |
| 223 days | 7 months | 25 | 111 | 0.8 | *IgG Anti-HEV+, IgM -, RNA -* |
|  |  |  |  |  |  |
| ***Normal*** |  | ***< 50*** | ***<90*** | ***<1.2*** |  |

**Comment:** This 50-year-old man with a past medical history of pancreatic cancer and a Whipple procedure developed abdominal pain and urinary symptoms which were attributed to a urinary tract infection and treated with levofloxacin. His symptoms worsened and he developed jaundice which led to the discontinuation of levofloxacin and search for a cause of acute hepatitis. None was found and a diagnosis of levofloxacin-induced liver injury was made. In retrospect, he probably had acute hepatitis E and his urinary symptoms (dark urine) and abdominal pain may have been early symptoms of hepatitis. He was tested for HEV markers within 2 weeks of onset and was strongly positive for both IgG and IgM anti-HEV but HEV RNA was not detectable. In follow up, after he had recovered, he was still IgG anti-HEV positive but no longer positive for IgM anti-HEV. The source of the hepatitis E was unclear, but the pattern of abnormalities and hepatitis E serology were typical of this disease.

**Case 11. Lovastatin [2009]**

A 75-year-old man with hypercholesterolemia and asthma on long-term therapy with lovastatin (20 mg daily), niacin and montelukast developed fatigue followed by pruritus and jaundice. When he sought medical care approximately 10 days after onset of symptoms, he was jaundiced and serum bilirubin was 11.3 mg/dL, ALT 597 U/L, AST 651 U/L, and alkaline phosphatase 245 U/L (*R* = 5.4: hepatocellular). His liver tests were not being routinely followed but had been normal in the past. He had no history of liver disease, drank alcohol moderately (averaging 1 drink per day), and had no recent foreign travel or risk factors for viral hepatitis. His active medical conditions included diabetes, hypercholesterolemia, obesity (BMI 31.2), hypothyroidism, asthma, allergic rhinitis and gastroesophageal reflux. His other medications included aspirin, cetirizine, diphenhydramine, eszopiclone, fluticasone, guaifenesin, glyburide, levothyroxine, metformin, omeprazole, pioglitazone and vitamin D. He had a history of an allergic reaction to cephalexin (hives) but not drug-induced liver injury. He also had a history of low-grade B cell lymphoma and prostate cancer, both of which were in long term remission. When first seen, lovastatin was stopped, and he was monitored as an outpatient. Serum albumin was 3.3 g/dL and INR 1.0. Tests for hepatitis A, B and C (including HCV RNA) were negative as were ANA, SMA and AMA. Imaging of the liver by CT scan showed a small gallstone, but no evidence of biliary obstruction or hepatic masses. Over the next two weeks his serum bilirubin rose to 26.2 mg/dL (Table) while serum albumin fell to 2.6 g/dL and INR rose slightly to 1.2. His other medications were stopped. He was not admitted to the hospital but did undergo percutaneous liver biopsy which showed bile duct injury with marked hepatocellular and canalicular cholestasis, as well as steatohepatitis with mild to moderate steatosis, moderate inflammation, mild ballooning injury and both perisinusoidal and bridging fibrosis. The changes suggested a second process superimposed on pre-existing NASH. Eventually, symptoms began to resolve, and bilirubin fell slowly, jaundice persisting for more than 2 months and serum enzyme elevations for 3 months. In follow up, at 5, 6 and 7 months after onset, however, all tests were normal. This case was initially adjudicated as possibly drug induced liver injury, possibly due to lovastatin but unlikely due to montelukast or niacin. Retrospective testing of a stored serum sample taken 2 months after onset revealed the presence of both IgG [S/C 8.31] and IgM [S/C 4.59] anti-HEV, but without HEV RNA. A follow up specimen from 7 months after onset revealed stable levels of IgG anti-HEV [S/C 8.05] and a borderline IgM reactivity [S/C 1.16]. HEV RNA was again negative. Based on HEV serology, this case was judged as highly likely HEV infection as well as highly likely the cause of the liver injury, the diagnosis of drug-induced liver injury and the role of lovastatin were considered unlikely.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| 0 | Pre | ***Lovastatin started (20 mg daily)*** | | | |
| 4.2 years | Pre | 24 | 74 | 0.6 | *Routine testing* |
|  | -10 days | ***Symptom onset*** | | | |
| 5.4 years | 0 | 597 | 245 | 11.6 | *Lovastatin stopped, R = 5.4* |
|  | 6 days | 563 | 301 | 27.8 | *CT scan normal* |
|  | 10 days | 251 | 272 | 25.7 | *R=1.9, Other drugs stopped* |
|  | 14 days | 100 | 233 | 26.2 |  |
|  | 21 days | 67 | 185 | 15.9 | *INR 1.2, albumin 2.6 g/dL* |
|  | 41 days | 77 | 248 | 8.5 | *Liver biopsy (day 31)* |
|  | 50 days | 71 | 283 | 6.8 |  |
|  | 58 days | 77 | 290 | 4.3 |  |
|  | 65 days | 88 | 360 | 3.0 | *IgG & IgM anti-HEV+, RNA -* |
|  | 80 days | 47 | 194 | 2.0 |  |
| 6.0 years | 5 months | 32 | 110 | 0.9 |  |
|  | 6 months | 27 | 90 | 1.1 |  |
| 6.2 years | 7 months | 37 | 98 | 0.8 | *IgM Anti-HEV borderline* |
| ***Normal*** |  | ***< 55*** | ***<130*** | ***<1.2*** |  |

**Comment:** This elderly man with diabetes, hypercholesterolemia and asthma developed jaundice and acute hepatocellular injury while on long-term lovastatin, niacin, montelukast, glyburide, metformin and pioglitazone therapy. The injury was initially attributed to lovastatin but when bilirubin levels continued to climb, his other medications were stopped. Testing at the time revealed no other cause for acute liver disease. While initially hepatocellular, the injury rapidly became cholestatic, and he recovered slowly. Retrospective testing revealed evidence of acute hepatitis E (IgM anti-HEV in moderately high titers). HEV RNA was not detectable but the sample was taken more than 2 months after onset. Symptomatic acute hepatitis E is most common in elderly men and can be mistaken for acute drug-induced liver injury. Exposures and the source of the hepatitis E are rarely identified. While usually resembling acute viral hepatitis with marked elevations in ALT and AST and modest increases in alkaline phosphatase, acute hepatitis E can present with a more “mixed” enzyme pattern and cholestatic course, particularly in patients with pre-existing liver disease. While lovastatin has been linked to rare instances of drug-induced liver injury, the appearance of acute hepatitis 5 years after starting the medication and without recent dose escalation is atypical. The latency to onset also spoke against the role of the other medications that can cause liver injury (niacin, montelukast, pioglitazone, metformin and glyburide). Niacin typically causes an acute hepatic necrosis with very high serum ALT levels and modest bilirubin elevations that resolves rapidly with stopping. The other medications are extremely rare causes of liver injury and generally cause a cholestatic or mixed pattern of injury.

**Case 12. Protein Shakes [2010]**

A 33-year-old obese Hispanic man developed acute hepatitis with jaundice while taking several over-the-counter products for weight loss including “protein shakes”. He had no history of liver disease, alcohol abuse, risk factors for viral hepatitis or known drug allergies. He had no other significant medical problems and was not taking any prescription medications. During the previous 9 months he had taken several products recommended by friends for weight loss and body building, but none on a regular basis. The constituents of the protein shakes were unknown, and no product was provided for testing. He was not taking any prescription medications. On presentation he was symptomatic with itching, mild rash, fatigue, nausea, vomiting, dark urine and jaundice. He denied fever. On examination he was obese (BMI 37.5 kg/m2) and mildly jaundiced but without fever or obvious skin rash. Laboratory testing showed a total bilirubin of 3.5 mg/dL, ALT 1116 U/L, AST 620 U/L, and alkaline phosphatase 357 U/L (*R* = 10.2: hepatocellular). Serum albumin was 4.5 g/dL while INR was not done initially but was 0.94 when performed one week later. Tests for hepatitis A, B and C (including HCV RNA) were negative. ANA was positive (1:160) but SMA and AMA were negative. Abdominal ultrasound showed gallstones and fatty liver, but no evidence of biliary obstruction or hepatic masses. He was hospitalized briefly but did not undergo liver biopsy. Liver tests worsened for a few days initially (Table) but then improved rapidly with resolution of jaundice within 4 weeks. He never received corticosteroids. When seen in follow up 8 months after onset, he was asymptomatic and, while serum ALT was minimally elevated (1.1 times ULN), all other liver tests were normal. On initial review, this case was judged to be highly likely liver injury due to the protein shakes. Retrospective testing of a stored serum sample taken 5 weeks after onset revealed the presence of both IgG [S/C 7.9] and IgM [S/C 4.12] anti-HEV, but without HEV RNA. A follow up specimen taken 6 months later, showed the persistence of IgG anti-HEV [S/C 7.1] but absence of both IgM anti-HEV [S/C = 0.12] and HEV RNA. Based upon serologic testing results, this case was re-evaluated and judged to be highly likely acute HEV infection which was highly likely the cause of the liver injury, the protein shakes being considered as an unlikely cause of the injury.

**Table**

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| 0 | -9 months | ***Protein shakes started, taken on an irregular basis*** | | | |
| 9 months | 0 | ***Symptom onset, nausea and anorexia. Protein products stopped*** | | | |
|  | 16 days | 1116 | 357 | 3.5 | *Jaundice, admitted, R=10.2* |
|  | 19 days | 3091 | 324 | 9.5 | *Ultrasound, fatty liver* |
|  | 20 days | 2216 | 260 | 7.4 |  |
|  | 25 days | 659 | 201 | 3.8 | *INR = 0.94* |
|  | 39 days | 80 | 127 | 1.6 | *IgG & IgM anti-HEV +, RNA -* |
| 16 months | 7 months | 45 | 108 | 0.7 | *IgG anti-HEV+, IgM -, RNA -* |
| ***Normal*** |  | ***< 40*** | ***<130*** | ***<1.2*** |  |

**Comment:** This 32-year-old man developed an acute, self-limited hepatitis while taking unidentified protein and vitamin supplements for weight loss and body building. The acute injury was entirely compatible with acute hepatitis E, although the source of the infection was not clear. The protein products being taken were initially thought to be the cause of the acute injury, but their identity and composition could not be identified, so that they could only be suspected of being causative. The serologic testing done in retrospect suggested that the acute injury was due to HEV infection. In follow up, he had mild elevations in ALT levels, most likely due to nonalcoholic fatty liver disease rather than a residual of the acute hepatitis E.

**Case 13. Atorvastatin [2010]**

A 62-year-old Syrian-born woman with hypercholesterolemia and diabetes treated with atorvastatin on and off for several years developed an acute, severe and protracted hepatitis 4 weeks after restarting the medication. She had been treated with atorvastatin for several years, generally in doses of 20 mg daily. At that dose, her serum aminotransferase levels had been normal (Table). However, several months after increasing the dose to 40 mg daily, she was found to have mild elevations in ALT (219 U/L) and AST (111 U/L) with normal bilirubin and alkaline phosphatase. Atorvastatin was stopped and serum aminotransferase levels returned to normal. Atorvastatin was then restarted at 20 mg daily. Approximately 4 weeks later she had the insidious onset of fatigue, nausea and anorexia which was followed by jaundice. At this point serum bilirubin was 5.2 mg/dL, ALT and AST above 2600 U/L and alkaline phosphatase 446 U/L (*R* > 47: hepatocellular). Atorvastatin was stopped and she was admitted at a local hospital for evaluation and monitoring. She had no known previous liver disease, alcohol abuse, risk factors for viral hepatitis, recent foreign travel or drug allergies. She had no other major medical illnesses and her only other medications were omega-3 fatty acids and occasional acetaminophen. Tests for hepatitis A, B and C (including HCV RNA) were negative. The ANA and anti-LKM were negative and SMA weakly positive (1:20) but immunoglobulin levels were normal. Imaging using ultrasound and CT scan showed a contracted gallbladder without stones and no evidence of biliary obstruction or hepatic masses. Despite stopping atorvastatin, she continued to worsen, serum bilirubin rising to 30.2 mg/dL and ALT to as high as 4279 U/L and AST to 2759 U/L. Serum albumin fell to 2.9 g/dL and INR rose to 1.4. A liver biopsy showed an acute hepatitis with diffuse necroinflammatory changes, prominent portal inflammation with lymphocytes and occasional plasma cells, but no fibrosis. Recuts available for central review had very little tissue, but the acute hepatitis with severe inflammation was confirmed. The biopsy was considered compatible with either severe drug-induced liver injury or autoimmune hepatitis. She was referred for evaluation for possible liver transplantation. Corticosteroids were started and she began to improve but she remained jaundiced for 3 months and serum enzyme levels were persistently abnormal and fluctuated during rapid tapering of prednisone. A repeat liver biopsy, not available for central review, showed chronic hepatitis and evidence of cirrhosis. Azathioprine was added and the dose of prednisone increased. At the time of final follow up 9 months after onset, all liver tests were normal, although she was still on low doses of prednisone (10 mg daily) and azathioprine (75 mg daily) raising the possibility of autoimmune hepatitis. This case was initially adjudicated as probably drug-induced liver injury due to atorvastatin. Retrospective testing of stored serum samples revealed IgG [S/C 8.31] and IgM [S/C 1.67] anti-HEV but no detectable HEV RNA on a specimen taken 58 days after onset. Follow up 6 months later showed persistence of IgG [S/C 9.30] but loss of IgM [S/C 0.81] anti-HEV and continued absence of HEV RNA. Based upon the serologic testing, HEV infection was considered highly likely, but only possibly the cause of the liver injury because both spontaneous autoimmune hepatitis and atorvastatin were also considered possible causes.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| 0 | Pre | ***Atorvastatin started (20 mg daily)*** | | | |
| 1.7 years | Pre | 24 | 74 | 0.6 | *Atorvastatin (20 mg/d)* |
| 2.1 years | - 6 months | 219 | 220 | 0.5 | *Atorvastatin (40 mg/d) stopped* |
| 2.2 years | - 5 months | 20 | 73 | 0.5 |  |
| 2.4 years | - 51 days | 22 | 64 | 0.6 | *Atorvastatin (20 mg/d) restarted* |
| 2.6 years | 0 | >2600 | 446 | 5.2 | *Atorvastatin stopped, R >47* |
|  | 6 days | 4560 | 359 | 14.8 | *1st liver biopsy: acute hepatitis* |
|  | 9 days | 3465 | 264 | 16.3 | *Prednisone started* |
|  | 13days | 4279 | 236 | 27.5 | *R=38.6* |
|  | 20 days | 2572 | 207 | 29.5 |  |
|  | 27 days | 1167 | 235 | 30.2 |  |
|  | 34 days | 660 | 310 | 23.6 |  |
|  | 48 days | 262 | 489 | 12.7 | *IgG & IgM anti-HEV+, RNA -* |
|  | 55 days | 152 | 330 | 7.9 |  |
|  | 76 days | 708 | 489 | 4.1 | *2nd biopsy: chronic hepatitis* |
|  | 90 days | 1169 | 512 | 4.1 | *Prednisone increased and azathioprine started* |
|  | 104 days | 773 | 427 | 3.0 |  |
|  | 4 months | 505 | 288 | 1.6 |  |
| 3.0 years | 5 months | 81 | 140 | 0.8 |  |
|  | 6 months | 40 | 140 | 0.8 |  |
|  | 7 months | 26 | 72 | 0.7 | *IgG Anti-HEV+, IgM -, RNA -* |
|  | 9 months | Normal | Normal |  | *Prednisone 10 mg, Aza 75 mg* |
| ***Normal*** |  | ***< 55*** | ***<130*** | ***<1.2*** |  |

**Comment:** This 60-year-old woman with hypercholesterolemia treated with atorvastatin for several years developed minor, asymptomatic serum enzyme elevations when the dose was increased from 20 to 40 mg daily. Atorvastatin was stopped and the enzyme abnormalities resolved rapidly. However, when she was restarted at the dose of 20 mg daily that she had previously tolerated well, she developed an acute hepatitis that was severe and prolonged. Because of concerns over autoimmune hepatitis, perhaps triggered by the atorvastatin injury, she was treated with prednisone and had a delayed but seemingly positive response. Her liver test abnormalities eventually resolved but she remained on low dose corticosteroids and azathioprine. The case was complex but was judged as probably due to atorvastatin induced liver injury. Retrospective testing demonstrated the presence of IgG and IgM anti-HEV during the acute episode. HEV RNA was not detectable, but the serum sample was drawn almost two months after disease onset. In follow up, anti-HEV was still detectable but IgM anti-HEV and HEV RNA were negative. The serologic results were compatible with an acute HEV infection. However, the timing of the injury in relation to starting and stopping atorvastatin and the unusual pattern of injury led to the opinion that it was still possibly due to the medication and therefore only possibly due to the acute HEV infection. One possibility is that the injury was due to both mild atorvastatin hepatotoxicity and a concurrent acute HEV infection.

**Case 14. Finasteride [2011]**

A 70-year-old man with stable cirrhosis due to alcoholic liver disease was found to be jaundiced on a routine follow up examination 53 days after starting finasteride (5 mg daily) for benign prostatic hypertrophy. He had a complex past medical history with suspected cirrhosis due to alcoholic liver disease that was, nevertheless, stable without previous episodes of jaundice, ascites, variceal hemorrhage or hepatic encephalopathy. His other medical problems included coronary artery disease with angina pectoris, obesity, diabetes, hypertension, hypercholesterolemia, prostate hypertrophy and obstructive sleep apnea His other medications include aspirin, metformin, nadolol, furosemide, pantoprazole, rosuvastatin, and tamsulosin which he had been taking at stable doses for more than one year. Laboratory testing showed a serum bilirubin of 6.0 mg/dL, ALT 567 U/L, AST 1265 U/L, and alkaline phosphatase 196 U/L (*R* = 9.0: hepatocellular). Results of previous liver tests were not available. He no longer drank alcohol, having been abstinent for more than one year. He denied recent foreign travel or risk factors for viral hepatitis. He had a history of an aversive reaction to atorvastatin (headaches) but not drug-induced liver injury. Finasteride was stopped and he was monitored as an outpatient. A liver biopsy 14 days after onset showed cirrhosis with prominent pseudoxanthomatous change and copper accumulation along with moderate inflammation and canalicular and hepatocellular bile stasis. He remained largely asymptomatic although bilirubin rose to 8.1 and serum albumin fell to 2.6 g/dL with an INR of 1.3. Tests for hepatitis A, B and C (including HCV RNA) were negative as were ANA, SMA and AMA. Abdominal imaging by ultrasound and MRI showed a contour suggesting presence of cirrhosis. There was no ascites. Jaundice resolved within 6 weeks, but liver tests remained mildly abnormal with persistent mild elevations in alkaline phosphatase and bilirubin. Retrospective testing of a stored serum sample taken 24 days after onset revealed the presence of both IgG [S/C 8.31] and IgM [S/C 4.62] anti-HEV with borderline low levels of HEV RNA [2.57 log GE/mL]. In follow up, 8 months later IgG anti-HEV was still present [S/C 9.80] but IgM anti-HEV was negative [S/C = 0.46] as was HEV RNA. Based upon the serologic testing, this case was considered definitely acute hepatitis E and the liver injury highly likely due to HEV, while finasteride was judged to be only possibly related to the liver injury.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| 0 | Pre | ***Finasteride started (5 mg daily)*** | | | |
| 53 days | 0 | 567 | 196 | 6.0 | *Finasteride stopped* |
| 56 days | 3 days | 898 | 233 | 8.1 | *INR 1.3, albumin 2.9 g/dL* |
| 67 days | 14 days | 194 | 184 | 7.6 | *Liver biopsy (day 5)* |
| 70 days | 17 days | 128 | 154 | 6.1 |  |
| 76 days | 24 days | 94 | 165 | 4.0 | *IgG & IgM anti-HEV +, RNA+* |
| 3 months | 43 days | 32 | 106 | 2.3 |  |
| 5 months | 87 days | 21 | 124 | 2.0 |  |
| 7 months | 133 days | 22 | 148 | 1.7 |  |
| 8 months | 176 days | 22 | 132 | 1.6 |  |
| 10 months | 240 days | 26 | 124 | 1.5 | *IgG anti-HEV +, IgM -, RNA -* |
| ***Normal*** |  | ***< 50*** | ***<120*** | ***<1.2*** |  |

**Comment:** This elderly man with cirrhosis, obesity, hypertension, diabetes, coronary artery disease and benign prostate hypertrophy was found to be jaundiced 2 months after starting finasteride. He was remarkably asymptomatic but developed an acute hepatitis that was initially attributed to the newly started finasteride. He had an underlying, rather stable cirrhosis which became obvious from the imaging studies done during the acute episode of jaundice. However, he did not really develop signs and symptoms of hepatic decompensation, although serum albumin fell considerably and INR levels rose. He recovered but laboratory tests were slow to improve and were mildly abnormal when he was last seen 8 months after onset probably due to the underlying cirrhosis. Retrospective testing revealed evidence of acute hepatitis E with IgG and IgM anti-HEV as well as low levels of HEV RNA. After resolution of the hepatitis, IgM anti-HEV and HEV RNA were no longer detectable. A common mode of presentation of acute hepatitis E is “acute-on-chronic” liver injury arising in an elderly man with pre-existing but stable cirrhosis. While the cirrhosis in this patient was attributed to alcohol, he had the metabolic syndrome with obesity, hypertension, hyperlipidemia, and diabetes, the major risk factors for nonalcoholic fatty liver disease. A striking finding during the acute episode of liver injury was the height of the AST elevations in comparison to those of ALT, an AST/ALT ratio of greater than 1.0 suggesting alcoholic liver disease but also being found in patients with inactive cirrhosis due to other causes.

**Case 15. Isoniazid [2013]**

A 63-year-old man with human immunodeficiency (HIV) infection on long-term therapy with atazanavir, abacavir, tenofovir, emtricitabine and ritonavir developed fatigue, nausea, anorexia, abdominal pain and low-grade fever and chills 3 to 4 months after starting isoniazid (300 mg daily) for latent tuberculosis. His liver tests were elevated with ALT 464 U/L, AST 420 U/L, alkaline phosphatase 120 U/L (*R* = 7.7, hepatocellular) and total bilirubin 2.9 mg/dL. Serum enzymes had been normal when tested one month earlier although his serum bilirubin was known to have been elevated chronically (2.1 to 2.5 mg/dL) which was attributed to therapy with atazanavir. He had a complex medical history which included known HIV infection for 9 years, history of cryptococcal meningitis, toxoplasmosis and oral thrush, hypercholesterolemia, anxiety, and peptic ulcer disease. Medications also included aspirin, niacin, lorazepam, fish oil, L-carnitine, spirulina and vitamins B6 (pyridoxine), C, D, and E most of which he had taken for several years. He had no history of liver disease, jaundice, previous drug reactions, alcohol abuse, recent travel, or known exposures to viral hepatitis. Isoniazid was stopped, antiretroviral therapy was held, and he was monitored closely (Table). Complete blood counts including eosinophils were normal, and INR was 0.91. He tested negative for IgM anti-HAV, anti-HBc, HBsAg, anti-HCV and HCV RNA. Test results for routine autoantibodies were not available. Ultrasound showed mild splenomegaly and increased hepatic echotexture suggestive of hepatic steatosis. His BMI was low normal (21.3 kg/m2). A liver biopsy was not done. ALT levels rose over the next two weeks to a peak of 4726 U/L (73 times ULN), AST to 2463 U/L (60 times ULN) and alkaline phosphatase to 401 (3 times ULN) while bilirubin peaked at 5.4 mg/dL and INR at 1.2. Thereafter, his symptoms began to resolve spontaneously without corticosteroid therapy, and bilirubin fell to its previous levels (1.6-2.9 mg/dL). He was restarted on antiretroviral therapy, and in follow up 7 months after onset, all liver tests were normal except for the persistent, mild indirect bilirubin elevations. Testing of stored serum samples revealed presence of IgG [S/C 3.86] and IgM [S/C 8.08] anti-HEV and HEV RNA [4.85 GE/mL] during the acute episode (day 20) and rise in IgG [S/C 9.40] and loss of IgM [S/C 0.16] and HEV RNA on follow up 6 months later. This case was initially judged to be highly likely isoniazid-induced liver injury. Based on the HEV serology, however, the case was judged as definitely HEV infection which was highly likely the cause of the liver injury, whereas isoniazid was re-adjudicated as only possibly the cause of the liver injury.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| 0 | Pre | ***Isoniazid (INH) 300 mg daily started*** | | | |
| 1 month | Pre | 29 | 88 | 2.1 |  |
| 3 months | Pre | 36 | 79 | 2.5 |  |
| 3.5 months | 0 | 464 | 120 | 2.9 | *Symptoms, INH stopped, R=7.7* |
| 4 months | 6 days | 1449 | 194 | 2.6 | *US: fatty liver, splenomegaly* |
|  | 8 days | 2191 | 226 | 1.4 |  |
|  | 11 days | 3782 | 287 | 4.0 |  |
|  | 13 days | 4726 | 392 | 5.4 | *R=24.6* |
|  | 15 days | 3467 | 401 | 4.6 |  |
|  | 18 days | 1772 | 344 | 2.5 |  |
| 4.5 months | 20 days | 1140 | 306 | 1.6 | *IgM & IgG a-HEV+, HEV RNA+* |
| 11 months | 7 months | 29 | 117 | 2.9 | *IgG a-HEV+, IgM-, HEV RNA -* |
|  |  |  |  |  |  |
| ***Normal*** |  | ***< 60*** | ***<125*** | ***<1.2*** |  |

**Comment:** This 63-year-old man with chronic HIV infection maintained on a 5-drug antiretroviral regimen developed an acute hepatitis three and a half months after starting isoniazid for a positive tuberculin test. At the time, the liver injury was attributed to isoniazid hepatotoxicity and indeed, after stopping the drug and a two week delay, the hepatitis began to resolve and liver enzymes were normal 7 months later. The hepatitis E test results performed on stored serum samples came as a surprise, but the serology, course and outcome were entirely compatible with an episode of acute hepatitis E. The source of the infection was unknown. Acute and chronic liver injury are not uncommon in patients with HIV infection and thorough evaluation should include testing for hepatitis E. Such testing is particularly important because immune deficiency can be associated with development of chronic hepatitis E which can be severe and lead to progressive fibrosis and cirrhosis.

**Case 16. Co-Enzyme Q10 [2015]**

A 71-year-old India-born woman with hypercholesterolemia and cerebrovascular disease on long-term therapy with simvastatin developed fatigue, anorexia, nausea and vomiting followed by dark urine and jaundice approximately 3 months after starting an over-the-counter preparation of Co-Enzyme Q10 (Qunol Liquid Co-Q10 Superior Absorption). She had no previous history of liver disease, drug allergies, exposure to hepatitis or alcohol abuse. She had recently returned from an annual 2 month visit to India and her symptoms first developed on the return flight. Her other medications included levothyroxine (for hypothyroidism) and losartan (for hypertension). She had been taking simvastatin for 3 years in a dose of 20 mg daily with a recent decrease to 10 mg daily. She was seen and found to be jaundiced but without physical evidence of chronic liver disease. Laboratory tests showed a total bilirubin of 4.0 mg/dL, ALT 2259 U/L, AST 1256 U/L, alkaline phosphatase 205 U/L (*R* = 24.5: hepatocellular) and INR 1.28. She was hospitalized for evaluation and monitoring (Table). Tests for hepatitis A, B and C (including HCV RNA) were negative as were ANA, SMA and AMA. A liver ultrasound was normal. ALT levels decreased minimally over the next ten days and serum bilirubin rose to a peak of 12.5 mg/dL, INR to 1.4 and albumin levels fell to 2.7 g/dL. A liver biopsy showed severe acute hepatitis with moderate cholestasis and prominent plasma cell infiltrates. The changes suggested autoimmune hepatitis, for which reason she was started on prednisone. Because of her history of recent travel to India, blood and stool samples were sent to the CDC for HEV serology. Serum was reported to be reactive for both IgG and IgM anti-HEV but not HEV RNA. A stool sample taken the same day, however, was positive for HEV RNA (4.56 GE/mL). While she was initially thought to have drug induced autoimmune hepatitis, the HEV testing results indicated that the injury was more likely due to acute HEV infection acquired during her trip to India. Based upon the HEV results, prednisone was discontinued. Her liver tests improved, jaundice cleared within a month, and serum enzymes fell into the normal range shortly thereafter. In follow-up at 6 and 8 months after onset, all liver tests were normal and repeat testing showed persistence of IgG anti-HEV [initially S/C = 7.50, at 8 months = 10.90] while IgM anti-HEV became undetectable [initially, S/C = 9.1, at 8 months = 0.53] and HEV RNA was still undetectable in serum. She had restarted simvastatin and liver tests remained normal. On the basis of the HEV serology, the case was adjudicated as highly likely HEV infection which was highly likely the cause of the liver injury while the role of Co-Enzyme Q10 and simvastatin were judged to be unlikely.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| 0 | Pre | ***Co-Enzyme Q10 started*** | | | |
| 3 months | 0 | 2259 | 205 | 4.0 | *Symptomatic for 4 days* |
|  | 1 day | 1695 | 169 | 3.3 | *Ultrasound normal* |
|  | 2 days | 1211 | 157 | 4.5 |  |
|  | 6 days | 1668 | 253 | 12.5 |  |
|  | 8 days | 1686 | 208 | 11.3 |  |
|  | 9 days | 1826 | 206 | 11.5 | *Liver biopsy* |
|  | 10 days | 1419 | 181 | 10.0 | *Prednisone started* |
|  | 13 days | 571 | 180 | 6.9 | *Stool sample HEV RNA +* |
|  | 16 days | 278 | 186 | 4.2 |  |
|  | 20 days | 152 | 161 | 3.0 |  |
|  | 24 days | 94 | 161 | 2.6 | *IgM & IgG anti-HEV +, RNA -* |
| 4 months | 34 days | 37 | 137 | 1.7 | *Prednisone discontinued* |
|  | 48 days | 34 | 127 | 0.9 |  |
| 5 months | 2 months | 30 | 122 | 0.7 |  |
|  | 3 months | 27 | 102 | 0.5 |  |
|  | 4 months | 19 | 114 | 0.6 |  |
|  | 6 months | 16 | 99 | 0.4 |  |
| 11 months | 8 months | 21 | 113 | 0.7 | *IgG anti-HEV+, IgM -, RNA -* |
|  |  |  |  |  |  |
| ***Normal*** |  | ***< 35*** | ***< 130*** | ***< 1.2*** |  |

**Comment:** This 71-year-old woman developed an acute hepatitis while on chronic therapy with simvastatin and 3 months after starting Co-Enzyme Q10. At the time, the liver injury was attributed to hepatotoxicity and indeed, after stopping the drug and a one-week delay, the hepatitis began to resolve, and liver enzymes were normal 2 months later. The hepatitis E test results were obtained because of the history of recent travel to India and provided evidence of acute hepatitis E with IgM anti-HEV in serum HEV RNA detectable in stool (20 days from onset). The serology, course and outcome were entirely compatible with an episode of acute hepatitis E. This case appeared to be an imported case of HEV, most likely from genotype 1. Most instances of HEV infection detected in the United States, however, are autochthonous and due to genotype 3, a strain that is common in domestic swine. The importance of the serologic testing was demonstrated by the unnecessary use of corticosteroids for what was believed to be an autoimmune hepatitis triggered by the cholesterol lowering agents. Corticosteroid use, particularly in the elderly, can be associated with clinically important adverse events. Furthermore, the diagnosis of hepatitis E allowed for restarting the lipid lowering agents.

**Case 17. Red Yeast Rice [2015]**

A 53-year-old white man developed fatigue, dark urine and jaundice approximately 4 months after starting an over-the-counter preparation of red yeast rice for its purported cholesterol lowering effects. He had switched preparations of red yeast rice 3 weeks before developing symptoms. He had been found to have hypercholesterolemia in the previous year but had not received lipid lowering prescription medications and had no other significant medical conditions. He denied a history of liver disease, drug allergies or exposure to hepatitis. He did, however, have a long history of moderate to excess alcohol use and admitted to drinking an average of 8 beers daily for the previous 9 years. He denied taking other medications or dietary supplements except for the red yeast rice. On examination he was jaundiced but had no signs of chronic liver disease or cirrhosis. The BMI was 25.3 kg/m2. Laboratory testing showed a total bilirubin of 6.5 mg/dL, ALT 1977 U/L, AST 1456 U/L, alkaline phosphatase 140 U/L (*R*=20: hepatocellular), total protein 9.0 g/dL, albumin 2.8 g/dL and INR 1.29. Serum enzyme levels had been normal on a routine blood test taken 5 months earlier (Table). He was hospitalized for evaluation and monitoring. Tests for hepatitis A, B and C (including HCV RNA) were negative. The ANA was strongly positive (1:1280) and SMA was detected (1:125). An abdominal CT scan showed enlargement of the liver and spleen, and MRCP showed no evidence of biliary obstruction or gallstones. A liver biopsy showed acute cholestatic hepatitis with minimal steatosis but no changes of alcoholic liver injury. Serum IgG was elevated at 2,680 mg/dL, and IgA at 432 mg/dL, while IgM levels were normal at 61 mg/dL. He was started on prednisone (60 mg daily) 2 days later. Serum enzyme levels improved lowly and were still elevated 6 months later while on 10 mg of prednisone daily (ALT 128 U/L, AST 91 U/L). He was still drinking alcohol but at a lower amount (3 beers daily). A biopsy done about 9 months after onset showed persistent moderately active chronic hepatitis with bridging fibrosis. During long term follow up his liver tests gradually fell into and remained in the normal range. Azathioprine was added and prednisone was gradually withdrawn. At one year, prednisone had been recently stopped and liver enzymes were borderline normal. He continued to drink alcohol.

While he was initially thought to have drug induced autoimmune hepatitis due to red yeast rice, HEV testing results at 61 days after onset revealed both IgG anti-HEV [S/C 6.59] and borderline low levels of IgM [S/C 1.14] with no detectable HEV RNA in serum. In follow up at 6 months, and 1 and 2 years, he remained positive for IgG anti-HEV [S/C 3.09, 3.73 and 2.92] but negative for IgM anti-HEV [S/C all <0.60] and HEV RNA. Based on the HEV serology, this case was adjudicated as highly likely acute HEV infection which was highly likely the cause of the acute liver injury, while the role of red yeast rice was judged as only possible. The evidence of chronic liver injury found during follow up was thought to be due to chronic alcohol associated injury but also possibly due to autoimmune hepatitis.

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| **Time**  **After**  **starting** | **Time After stopping** | **ALT (U/L)** | **Alk P (U/L)** | **Bilirubin (mg/dL)** | **Other** |
| Pre | - 5 months | 43 | 49 | 1.4 |  |
|  | - 4 months | *Red Yeast Rice started (NOW)* | | | |
|  | - 3 weeks | *Red Yeast Rice switched to another source (Weider)* | | | |
| 4 months | 0 | 1977 | 140 | 6.5 | *Red Yeast Rice Stopped* |
|  | 1 day | 2934 | 135 | 7.4 | *CT scan hepatomegaly* |
|  | 2 days | 1710 | 119 | 5.8 | *MRCP normal* |
|  | 3 days | 1650 | 124 | 4.0 | *Liver biopsy* |
|  | 5 days | 1720 | 126 | 3.4 | *Prednisone (60 mg/d) started* |
|  | 15 days | 1060 | 113 | 1.9 |  |
| 5 months | 35 days | 623 | 113 | 1.1 |  |
|  | 43 days | 543 | 115 | 0.8 |  |
|  | 50 days | 460 | 110 | 0.9 |  |
| 6 months | 61 days | 220 | 166 | 0.8 | *IgG & IgM anti-HEV +, RNA -* |
|  | 3 months | 589 | 103 | 0.7 |  |
|  | 4 months | 435 | 104 | 0.7 |  |
|  | 5 months | 191 | 91 | 0.6 |  |
|  | 6 months | 589 | 87 | 0.7 | *On prednisone (10 mg/d)* |
| 12 months | 8 months | 62 | 90 | 0.9 | *IgG anti-HEV+, IgM -, RNA -* |
|  | 1 year | 50 | 61 | 1.2 | *Azathioprine alone* |
|  | 2 years | 24 | 73 | 1.2 | *Azathioprine (75 mg/d)* |
| ***Normal*** |  | ***< 50*** | ***< 130*** | ***< 1.2*** |  |

**Comment:** This 53-year-old man developed an acute hepatitis while on chronic therapy with red yeast rice, 21 days after switching to a new brand of the over-the-counter botanical product. A liver biopsy done within a week of onset suggested an acute hepatitis with autoimmune features which was supported by the finding of high titers of ANA and SMA and elevations in serum globulins. The response to starting corticosteroids however was only partial and he continued to have serum aminotransferase elevations 6 and 8 months after initial presentation while still on low doses of prednisone. The serologic results for HEV infection added a complexity to the case but was considered probably the cause of the acute liver injury. HEV infection, however, did not explain the evidence for chronic liver injury after recovery from the acute hepatitis. The finding of evidence of HEV infection argues for an attempt at withdrawal of corticosteroid therapy. The continued elevations in serum enzymes argues for repeat liver biopsy once corticosteroids are stopped. Red yeast rice has been implicated in rare instances of acute drug-induced liver injury (typically hepatocellular as in this case), but the component believed to be responsible (monacolin which is structurally identical to lovastatin) is usually removed from red yeast rice preparations at the insistence of the FDA which has banned commercial red yeast rice products that contain the monacolin.

**Case 18. Doxycycline [2019]**

A 76-year-old man was treated for 8 days with doxycycline for a suspected sinus and upper respiratory infection but developed worsening symptoms, abdominal pain, nausea and vomiting followed by dark urine and jaundice. He stopped the doxycycline and when seen 5 days later had markedly abnormal liver tests with ALT 2173 U/L, AST 1076 U/L, alkaline phophatase 177 U/L (*R*= 34.5: hepatocellular), bilirubin 17.3 mg/dL, albumin 2.1 g/dL and INR 2.0. He was admitted for evaluation and management. He had no previously known disease but had a long history of diabetes and excessive alcohol consumption. His only medication was metformin. In the few days before presentation, he had taken 2 grams of acetaminophen daily for symptomatic relief. Physical examination revealed atrial fibrillation and jaundice. Tests for hepatitis A, B and C were negative as were ANA, SMA and AMA. An abdominal ultrasound showed hepatomegaly and a nodular liver suggestive of cirrhosis. An MRI demonstrated further evidence of cirrhosis as well as a 2.6 cm mass with features of hepatocellular carcinoma. He was enrolled into the prospective DILIN study for suspected doxycycline hepatotoxicity before tests for hepatitis E done locally were received that reported the presence of both IgG and IgM anti-HEV. Central testing of stored serum taken on day 7 after onset of symptoms revealed both IgG [S/C 10.7] and IgM [S/C 2.6] anti-HEV as well as low levels of HEV RNA [1.93 GE/mL]. He recovered rapidly but further evaluation of the hepatic mass demonstrated hepatocellular carcinoma. Follow up specimens for HEV serology were not available. This case was judged to be unlikely doxycycline-induced liver injury, and definitely acute hepatitis E virus infection which was highly likely the cause of the acute liver injury.

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| --- | --- | --- | --- | --- | --- |
| **Time After**  **starting** | **Days After**  **stopping** | **ALT**  **(U/L)** | **Alk P**  **(U/L)** | **Bilirubin**  **(mg/dL)** | **Other** |
| Pre | Pre | 35 | 62 | 0.9 |  |
| 7 days | -1 day | 27 | 58 | 0.6 |  |
| 13 days | 5 days | 2173 | 177 | 17.3 | *Admission, INR 2.0, US: Cirrhosis* |
| 15 days | 7 days | 1203 | 163 | 20.0 | *IgG & IgM anti-HEV+, RNA +* |
| 4 weeks | 3 weeks | 31 | 59 | 0.7 |  |
|  | 2 months | 30 | 62 | 0.6 |  |
|  | 3 months | 25 | 60 | 0.6 |  |
|  | 4 months | 26 | 136 | 0.7 | *Liver biopsy: HCC* |
|  |  |  |  |  |  |
| ***Normal*** |  | ***< 45*** | ***< 125*** | ***< 1.2*** |  |

**Comment:** This elderly man with cirrhosis probably due to fatty liver disease either from alcoholic or nonalcoholic steatohepatitis (or both) presented with an acute hepatitis that was initially thought to be due to doxycycline. The diagnosis of hepatitis E was made locally once HEV testing results were returned and was confirmed by repeat testing on a stored serum sample. The sample was also positive for low levels of HEV RNA. Evaluation of the acute injury also demonstrated evidence of a previously unsuspected cirrhosis as well as a 2.4 cm mass. In follow up three months later, a liver biopsy demonstrated that the mass was hepatocellular carcinoma. The clinical presentation and course are compatible with acute-on-chronic liver injury due to hepatitis E. The rapidity of onset and recovery suggest that acetaminophen or cardiac arrhythmias and ischemic injury may have contributed to the clinical presentation.