Comments:

(1) **Introduction:** “It is one of five known human hepatitis viruses: A, B, C, D, and E.” should be replaced by “Hepatitis E is one of six known human hepatitis viruses: A, B, C, D, E and G”

(2) **Signs and symptoms: other organs**

Please add this extrahepatic manifestations of HEV infection:

- **Acute pancreatitis**
- **Haematological manifestations:**
  - Thrombopenia, haemolysis, aplastic anaemia, cryoglobulinemia, monoclonal gammopathy
- **Autoimmune phenomena:**
  - Membranous glomerulonephritis, Henoch-Schönlein purpura, arthralgia, skin rash
- **CNS neurological syndromes:**
  - Transverse acute myelitis
  - Acute meningoencephalitis
  - Aseptic meningitis
  - Amyotrophic neuralgia
  - Pseudotumour cerebri
  - Bilateral piramidal syndrome
- **PNS neurological syndromes:**
  - Guillain-Barré syndrome
  - Cranial Nerve paralysis
  - Peripheral neuropathy

Reference:

(3) **Virology: classification**

HEV is classified into the family *Hepeviridae*. This family is divided in two genera, *Orthohepevirus* (all mammalian and avian HEV isolates) and *Piscihepevirus* (cutthroat trout HEV). Species within the genus *Orthohepevirus* are designated *Orthohepevirus A* with isolates from human, pig, wild boar, deer, mongoose, rat, rabbit and camel; *Orthohepevirus B* with isolates from chicken; *Orthohepevirus C* includes isolates from greater bandicoot, Asian musk shrew, ferret and mink; and *Orthohepevirus D*, *with isolates from bat*. Within species *Orthohepevirus A*, there are currently five genotypes described that infect humans (Gt1, Gt2, Gt3, Gt4 and Gt7) and two genotypes (Gt5 and Gt6) that affect only animals (3). Genotype 1 (Gt1) includes the human Burma strain (prototype) and strains from Asia, Middle East and North Africa. Gt2 consists of a human Mexican strain (prototype) and several strains isolated in outbreaks from Africa. Gt3 comprises human and animal strains from USA, European countries, Argentina, Canada, New Zealand, and Asia. Gt4 includes human and animal strains identified in
Asia and Europe. Gt7 comprises human and animal (camel) strains. Data regarding the frequency of Gt7 affecting humans is scarce, however, it has been recently found in a liver transplant patient from Middle East, who consumed camel meat and milk (4). These data support Gt3, Gt4 and Gt7 having a zoonotic nature (5, 6).


(4) Transmission: Please, Indicate the meaning of DEFRA.

(5) Genomics: Delete this paragraph because it is classification: “The virus has since been classified into the genus Orthohepevirus, and has been reassigned into the Hepeviridae family.”

(6) Genomics: Add this paragraph about ORF3: “ORF3 and its corresponding function(s) have been largely elusive. The smallest ORF of the HEV genome, ORF3 is translated from a subgenomic RNA into a protein of 113–115 amino acids. ORF3 is proposed to play critical roles in immune evasion by HEV. Previous studies showed that ORF3 is bound to viral particles found in patient sera and produced in cell culture. Although in cultured cells ORF3 has not appeared essential for HEV RNA replication, viral assembly, or infection, it is required for particle release.”

Reference:
https://doi.org/10.1073/pnas.1614955114

(7) Diagnosis: Add virological markers for the diagnosis of HEV infection. For example:

| Anti-HEV-IgM<sup>a</sup> | Positive | Negative | | Anti-HEV-IgG<sup>b</sup> | Positive | Negative |
|--------------------------|----------|----------|--------------------------|----------|----------|
| HEV-RNA and/or HEV-Ag<sup>b</sup> | | | | | |
| Positive | Negative | | | Positive | Negative |
| Interpretation | Acute infection | Chronic infection (RNA+ >3 months) | Recent infection | Cross-reactivity<sup>c</sup> | Acute infection | Possible reinfection | Window period Chronic infection (RNA+ >3 months) | Past infection | Absence of infection |

<sup>a</sup> Serum and/or plasma.

<sup>b</sup> Serum, plasma, CSF, laces, urine, etc.

<sup>c</sup> Anti-HEV-IgM reactivity should be confirmed with immunoblotting and a subsequent seroconversion study.

Reference: