Author's response to reviews

Title: New foe treated with old guns - supportive role of steroids in the treatment of acute severe hepatitis E

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Author's response to reviews: see over
Dear Editor,

thank you for considering a revised version of our manuscript for publication in BMC Gastroenterology. We are grateful for the comments that guided us to significantly improve our case report. Please find the point-by-point reply to comments below.

Sincerely yours,

Marcial Sebode and Henning Wege

Reviewer #1

1) As discussed, though not very extensively, this could also have been spontaneous clearance of HEV. I would like this point to be more clear, both from the title and the conclusion. Stating on one patient that steroid therapy might be used in developing countries (other genotypes, other health care systems), is too strongly put.

We now emphasize both in the revised manuscript and its title that clearance of HEV in the presented case could also have been spontaneous and that the role of steroids in HEV may have been only supportive. We agree with the reviewer that it was too ambitious to propose steroid treatment of HEV in developing countries just based on our case and removed the statement from the manuscript.

2) Why did the authors decide to do a second round of HEV testing? In the manuscript this is phrased as "we suspected acute HEV"; suspected based on what? And if there was such a strong suspicion why was ribavirin not started as well?

With the goal of avoiding a further deterioration of liver function, we decided to start steroid treatment on the basis of the initially suspected immune-mediated drug-induced or toxic hepatitis. This procedure is in line with the reviewer’s comment. However, we could not detect a likely agent in the patient’s history that could explain his acute hepatitis. Therefore, we reconsidered other differential diagnoses and decided to repeat tests. We suspected HEV (despite initial negative testing) because of the risk profile for acute hepatitis E in this patient (male patient of older age, moderate but regular alcohol consumption, living in the countryside) and the typical clinical course (acute hepatitis with impaired liver function). Because of the beneficial course (improved liver function, drop in transaminases) and progressive viral clearance under steroid treatment, we decided not to add ribavirin. The decision making process in this case has been clarified in the revised manuscript.
3) Moreover, since the chain of events normally is that a patient with ALF presents at the hospital, you do diagnostic tests, and in the time awaiting results have to decide whether or not to treat a patient depending on the most likely diagnosis at the time. For this patient, the pathology report was toxic/medication induced. As clearly discussed, in ALF there is a sort of immunological phenomenon ongoing which responds well to steroids. So this case highlights in my view that starting prednison for ALF (without a diagnosis at the time) does not hamper (spontaneous or steroid induced) viral clearance of acute HEV infection.

We thank the reviewer for this comment and entirely concur – we added this important aspect to our conclusion: The course of our case points out that steroid treatment should not be delayed in patients with severe hepatitis and liver failure if test results for HEV are pending.

Reviewer #2

Major compulsory revisions:

1. Given the fact that this patient did not present with overt hepatic encephalopathy as stated in the manuscript, the diagnostic criteria of acute liver failure are not met. The authors should use the term acute liver injury instead. Of course, it may be speculated that the development of encephalopathy and hence acute liver injury could be prevented due to the use of corticosteroids. On the other hand, absence of encephalopathy is linked to a better prognosis per se which might support the notion that the favourable clinical outcome described here is the result of spontaneous resolution.

We fully agree with the reviewer that not all diagnostic criteria of acute liver failure are fullfilled and have revised our manuscript accordingly. Indeed, we cannot exclude the fact that absence of hepatic encephatholopathy in this case reflects a benign spontaneous course and is not a result of steroid treatment.

2. What is risk of chronic HEV infection in the course of acute HEV under sustained corticosteroid treatment? In the discussion the authors should clearly indicate why they thought from the very beginning that the potential benefits of maintenance of steroid therapy outweighed the risks of HEV chronification and also the infectious risks in the light of a clinical scenario in which patients are highly susceptible to bacterial threats. In the present form it is not fully comprehensive why this approach
was chosen. Was Ribavirin considered once the diagnosis of HEV was established? Please provide a more-depth rationale for the use of steroids.

The decision for steroid treatment was based on the initial assumption of an immune-mediated, probably drug-induced or toxic hepatitis. Because of the significant immune cell infiltration verified by liver histology, we started steroids. Until HEV infection was confirmed by a second PCR, the clinical and laboratory course of the acute liver injury was favourable (under steroid treatment). Therefore, we did not switch to ribavirin when HEV infection was affirmed. Indeed, every steroid treatment implies the risk of serious, opportunistic infections. However, in this patient, the risk was acceptable because liver cirrhosis and serious secondary diagnoses were absent.

Minor essential revisions:

1. Are there any hints for the possible route of transmission and/or source of infection in this case. Please comment on this.

The patient denied an exposure to game meat. He had no history of travelling or blood transfusions. The only remarkable exposure was his hobby of breeding poultry.

2. Did the patient receive high-dose acetylcysteine as it may be applied in acute liver injury/failure due to a non-acetaminophen cause (Lee et al., Gastroenterology, 2009)

Acetylcysteine was not applied in this case but could be an additive option for severe acute hepatitis E infection.