

We thank the editors and the reviewers for considering our manuscript and advising changes to further improve it. We have incorporated all the changes as suggested by the reviewers. We hope, you will find it appropriate for publication now. However, we will be happy to make any further changes you may suggest.

No.	Reviewer's comments	Authors reply	Changes made
#1	The authors provide a "meta summary" of liver failure induced by Dengue. Although a very common disease in certain parts of the world, and further spread anticipated, there is a lack of information re liver failure and particularly well documented cases. The authors were able to identify some 19 cases from the world literature. They rightly conclude that frequent severe damage is extremely rare. Estimated of nominators/denominators are hard to identify. They discuss various aspects of pathophysiology and speculate about multiple factors that could contribute. Not a single evidence based recommendation can be provided. Although this author has very limited expertise with Dengue (mostly practicing in non-endemic areas, a few years Africa), he has considerable experience with liver transplant and liver failure,. My reflections and questions: 1. When discussing liver failure, too often not too stringent criteria are in use What were the criteria the authors applied or were able to extract from their search? I would suggest a more critically review and or delineation of the evidence of acute liver failure as an entity with multi-organ failure # liver failure (often more functional than anatomical)	Thank you for your inputs. As this is a meta-summary of case reports from different authors, it may be possible that they might have used different definitions of ALF. However, all the authors have used internationally recognised definitions (including that described by O'Grady), and have attributed neurological dysfunction to ALF rather than dengue encephalitis.	No changes made

	vs a disease affecting multiple organs and causing damage. Acute liver failure is associated with multi-organ failure but it tends to have often a particular pattern. I refer the authors to the landmark article by O'Grady at all (Lancet 1981) re hyperacute, acute and subacute liver failure. In the limited documented series they are able to report, the onset of symptoms was so early (4.5 days median) with relatively low bilirubin values and INRs. (Or do we speculate a longer prodromal phase?) The question comes up: Is the encephalopathy here portosystemic # liver failure or are we for dealing with acute brain damage # dengue encephalitis. This postulate could have major impact on diagnosis and treatment (transplant even less likely to help). There may indeed be acute cytopathic damage to various organs (as also suggested in some case of acute hepatitis A as well) and explaining early damage and response.		
	Is there a role for acute anti-inflammatory agents like steroids? Will we ever be able to tests if so rare?	As discussed in our discussion section, even though steroids have been shown to improve outcomes in severe dengue, the role of steroids have not been studied in dengue associated ALF. Further, we agree with the reviewer that it may difficult to tests their utility in these patients because of rarity of this problem. That is why we need such meta-	No changes made

		summaries of case reports.	
	This brings me to another point that may deserve further highlighting, namely the recognition of liver failure vs significantly abnormal liver tests in the context of various infectious diseases not being viral hepatitis. Leptospirosis is an interesting example with high bilirubins with lower transaminases and usually not very prolonged INR etc. So the recognition of acute liver failure with laboratory data consistent with that is relevant (INR runs off, creatinine increases etc.). As another example: Acetaminophen toxicity and acute ischemic damage (shock liver) can be accompanied by high transaminases (5-10.000 or higher) but the pattern and evolution and association with INR and creatinine matter for disease outcome etc.) The Dengue pattern would be consistent with acute ischemic damage and/or viral cytopathic damage. Unfortunately, the extreme rarity, the limited numbers prevent any firm recommendations and liver failure as such is an extremely unusual event that speculation that liver transplant may help has -based on the current data - no merits. This brings me to the question as to for whom or with what purpose the article is written. Should it be more: Recognition of the rare occurrence of serious Dengue associated liver failure: common sense should guide us by lack of any evidence based data?	We agree with the reviewer that it is many times difficult to recognise liver failure in such a clinical scenario. That could be one of the reasons of under-reporting of ALF secondary to dengue infection. We feel it will be an interesting review article "Recognition of the rare occurrence of serious Dengue associated liver failure: common sense should guide us by lack of any evidence based data?" but it would not be possible to conduct a meta-summary on this title.	No changes made

#2	The article entitled "Dengue induced acute hepatic failure: A meta summary of case reports" has an interesting approach to this complication of infection caused by dengue. It is a well-written work, with clarity in its general objective. In fact, I was unable to do so and have never seen any work that compiled case reports, clinical approaches and prognoses of patients with this complication. Understanding that this work can be important for updating and alerting health professionals who work in emergencies and intensive care units to think about the profile of the patient suffering from this complication. As there are 19 cases included in the study, I suggest that the authors include a table with the 19 studies, describing the author, publication data, title, which diagnostic method was used and how many patients were included in each study. It is important for the reader to have an overview of the work carried out.	Thank you for your inputs. As per the suggestion, we have added a new table.	3rd table added (table no. 1)
	Regarding figure 2, I suggest using authorial figures, the DENV figure can be better represented in an illustrative way, the liver and hypoxia/ischemia as well. Redraw figure 2 and center the sentences.	We have made the suggested changes in the figure	Necessary changes made in figure 2.
#3	NAC has been the drug of choice for the treatment of acetaminophen related liver failure since the 1970s. NAC helps neutralize free oxygen radicals and replenishes cytoplasmic and mitochondrial glutathione stores by acting as a glutathione substitute and directly combining with reactive metabolisms. It serves as a source of sulfate, thus	Thank you for your inputs. As dengue induced ALF is rare, the data regarding utility of NAC has been extrapolated from studies in acetaminophen and non-acetaminophen induced ALF. Earlier reports suggested that	Have made the necessary changes in the discussion section.

	enhancing non-toxic sulfate conjugation and preventing hepatic damage. I ask some questions to author. Please let me know from what day and for how many days NAC should be administered after liver failure occurs.	NAC may be more useful in preventing rather than treating hepatic injury and hence it was recommended to start NAC early (within 8-12 hours) of acetaminophen overdose (doi: 10.1136/bmj.2.6198.1097). However, it is difficult to determine the exact time of hepatic insult in patients with non-acetaminophen induced liver failure and hence, it is recommended to initiate NAC in patients with significant acute liver injury as soon as ALF is detected. (Pulley JM, Jerome R. Acetylcysteine (N-acetylcysteine, NAC) for the management of non-acetaminophen-induced acute liver failure.)	
	What is the PT value to start NAC after acute liver failure?	The cut-off for PT has not been defined. In patients with non-paracetamol ALF, NAC is generally initiated at INR>1.5 (10.20524/aog.2021.0571). However, such values have not been defined for dengue induced ALF and hence, we cannot recommend any specific cut-off based on this meta-summary.	No changes made

	Please tell me the etiology of liver failure due to dengue fever.	The exact pathophysiology of liver failure due to dengue fever remains unknown. However, several mechanisms have been described but in most of the cases the cause may be multifactorial. Details have been mentioned in the 2nd paragraph of the discussion section.	No changes made
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