Peer Review File

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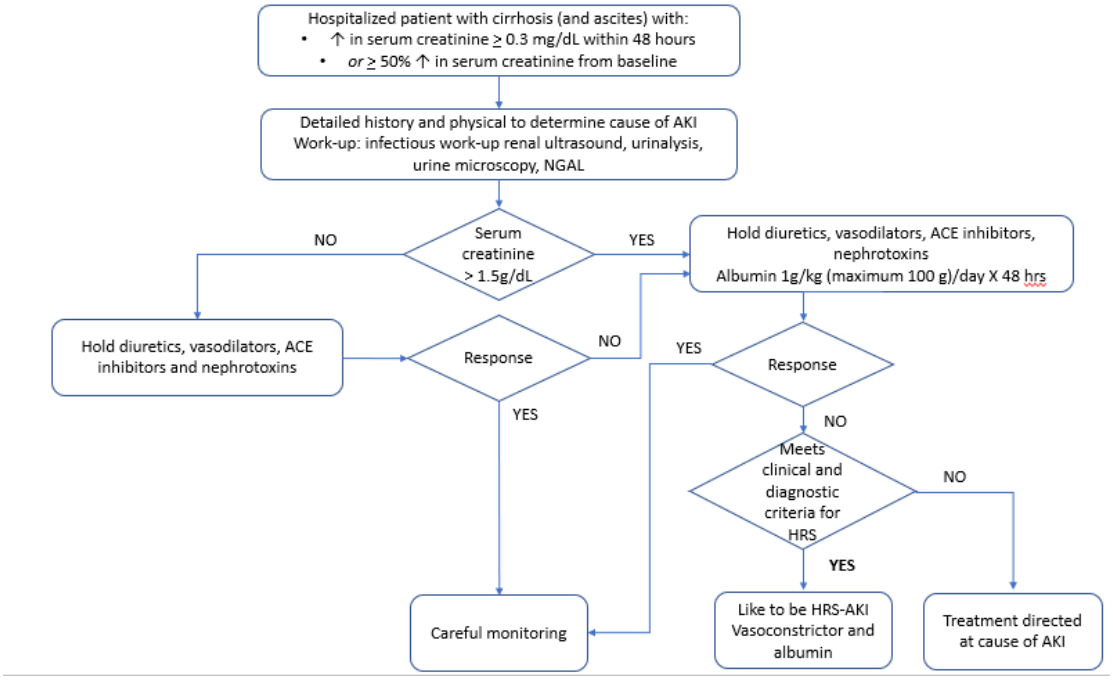
Reviewer A

Hantzidiamantis et al performed an interesting case based clinical guide addressing hepatorenal syndrome. I particularly found the selected case very illustrative of daily practice.
Reply: We thank Reviewer A for their encouraging comments.

Comment 1: I would like to suggest for the authors to add tables or charts regarding the main concepts of the syndrome, for example the diagnosis criteria and the treatments available.
Reply 1: We agree with the reviewer, and we have added the following figure and table.
Changes in the text:
We have added the following figure:
Figure 1. Approach to diagnosis and management of patients with cirrhosis and AKI. Early diagnosis and treatment of AKI in cirrhosis is critical for better outcomes. This figure shows the suggested approach for diagnosis and management AKI in cirrhosis in the first 48 hours of presentation. The focus is on simultaneous work-up to determine cause the AKI, withdrawal of diuretics, vasodilators, ACE inhibitors and other nephrotoxic agents and volume expansion with albumin.
Figure 1.



We have added the following table:

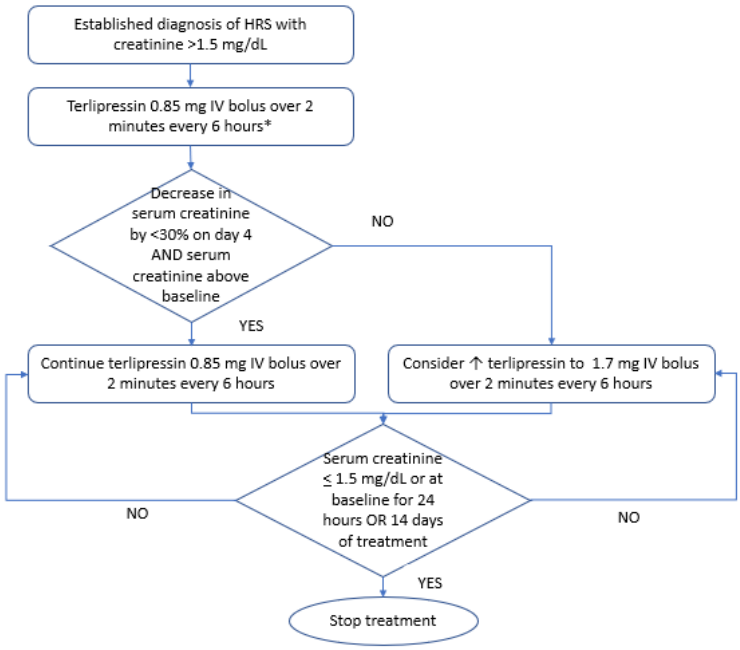
Table 1. Drugs, dosage and route, and goal of drugs used in management of HRS-AKI

Drug	Dosage and Route	Goal	Side effects

Octreotide and Midodrine	Octreotide: 100 -200 µg every 8 hours subcutaneously Midodrine: 7.5-15 mg three times a day orally	Increase in MAP by 15 mm Hg	Mild and rare, transient decrease in heart rate and cardiac output, hypoglycemia
Noradrenaline	0.5 mg/hour titrated to 3 mg/hour (infusion)	Increase in MAP by 10 mm Hg or increase in urine output by 200 mg in 4 hours	Bradycardia, cardiac arrhythmia, cardiomyopathy, peripheral vascular insufficiency, Anxiety, transient headache, dyspnea
Terlipressin	2 mg/day titrated to 12 mg/day (infusion)	Improvement in serum creatinine to <1.5 mg/dL	Hyponatremia, abdominal ischemia), circulatory overload, myocardial ischemia, peripheral ischemia, skin necrosis, arterial hypertension, arrythmias and persistent diarrhea.

Comment 2: For the doses of terlipressin, I suggest adding an algorithm explaining how to increase or decrease the doses according to the creatinine levels.
Reply 2: We have added this algorithm
Changes in the text:
Figure 2. Algorithm for administration of terlipressin. *Terlipressin should not be started in patients with 1) severe cardiovascular disease such as unstable angina, pulmonary edema, congestive heart failure or symptomatic peripheral vascular disease 2) serum creatinine > 5 mg/dL 3) acute on chronic liver failure stage 3 or greater 4) SpO2 < 90%. 5) pregnancy Patients on terlipressin should be constantly monitored for coronary ischemia and respiratory deterioration. These may require dose interruption or discontinuation.

Figure 2



Comment 3: Concerning the case itself, I suggest the authors to specify the reasons for not performing liver transplantation on this patient.
Reply 3: We have added this.
Changes in the text: The statement now reads “The transplant team determines that the patient is not a good candidate for liver transplant, due to various reasons *including comorbidities and lack of good social support*.”

Comment 4: The manuscript is well-written, however some minor English corrections are necessary.
Reply: The manuscript has been reviewed again to correct grammatical errors.

For example:
4(a)- “A 65-year-old man with cirrhosis secondary TO chronic alcohol use, decompensated (…)” (Line 41)
Reply 4(a): This change has been made. The line now reads “A 65-year-old man with cirrhosis secondary to chronic alcohol use….”

4(b)- “A large of redness and increased warmth in left shin is noted” (line 47) – this sentence is confusing.
Reply 4(b): This statement has been changed to “A large area of erythema and increased warmth is noted in the left lower extremity”.

4(c)- “In a small 59 group of patients may have AKI due to other intrinsic causes(…)” (Line 58)
Reply 4(c): This statement has been changed to “*A* small group of patients may have AKI due to other intrinsic causes….”

4(d)- “For EASIER readability, HRS-AKI(...) (line 64).
Reply 4(d): This statement has been changed as suggested. It now reads “For *easier* readability…”

4(e)- “ (…) in nature (i.e. due to 73 hypovolemia or HRS) (…)” (lines 72-73)
Reply 4(e): This statement has been changed to “Most cases of AKI in decompensated cirrhosis with ascites are pre-renal *caused by hypovolemia or HRS*.”

4(f)- “(…) renal vasoconstriction and decreased in renal blood flow 79 leading TO THE development of hepatorenal syndrome(…) (lines 78-79)
Reply 4(f): This statement has been corrected. It now reads “…renal vasoconstriction and decrease in renal blood flow leading *to* development of hepatorenal syndrome.”

4 (g)- “Any factor that DECREASES effective (…) (line 79)
Reply 4(g): This statement has been corrected. This now reads “Any factor that *decreases* effective arterial volume such as intravascular volume depletion…”

4 (h)- “(…) A comprehensive infectious work-up including a diagnostic paracentesis IS imperative(…) (lines 83-84)
Reply 4(h): This statement has been corrected. It now reads “A comprehensive infectious work-up including a diagnostic paracentesis *is* imperative”

4 (i)- - “(…) determine if the fluid IS depleted or overloaded and thus guide paracentesis (…)” (Line 135)
Reply 4(i): This statement has been corrected. It now reads “…by point-of-care ultrasound can used to determine *if the patient is fluid depleted or overloaded* and thus guide paracentesis.”

Reviewer B

This is a very interesting and educational case of HRS. It has been well managed, and the option for palliative care instead of dialysis is correct. You have mentioned the inflammatory hypothesis, which is good.
Reply: We thank Reviewer B for their constructive comments.

Comment 1. I would just suggest you discussing the role of institutional protocol for management of these patients:
Reply 1. We have added the following statement as the recommended reference "*An evidence-based protocol for diagnosis and treatment has been associated with lower mortality, easier recognition, and earlier initiation of treatment. Institutional protocols may allow for earlier diagnosis and treatment initiation*.[35]
https://www.elsevier.es/en-revista-gastroenterologia-hepatologia-english-edition--382-articulo-evidence-based-protocol-for-diagnosis-treatment-S2444382422000086

Reviewer C

The authors reported a patient hepatorenal syndrome in detail. This article is of great clinical value. However, I think the current version of the manuscript is better suited to be published as Case Report, not a Review Article (with only one case). Please see more details at Instructions for Authors:https://dmr.amegroups.com/pages/view/guidelines-for-authors#content-2-3
Then, please revise the Abstract structured with Background, case description and Conclusion. The content in the Abstract may better suit the Introduction. The text also should be arranged as follows: Introduction, Case Presentation, and Discussion.

Please fill out and submit the "CARE Checklist". The relevant page/line and section/paragraph number in the manuscript should be stated for each item in the checklist. And add a statement "We present the following case in accordance with the CARE reporting checklist" in the Introduction.

Reply: We respectfully disagree with the reviewer. While we use a representative case to explain the course of a typical patient hospitalized with cirrhosis and hepatorenal syndrome, this is not a real case. The case history is a representation of our clinical experience in taking care of patients with HRS.

We use a simulated case to present diagnostic conundrums commonly faced by clinicians. We then address these conundrums with relevant literature and guidance on diagnosis and management.

This is an uncommon format for a review article, but it is more likely to be more useful to physicians and trainees on wards taking care of such patients as it clearly states the clinical questions. Comments by reviewer 1 and 2 attest to the value of this approach.

We request the Review 3 to see the value in our approach and provide us with the "artistic liberty' to present a review article in this practical format.

We are unable to fill the CARE Checklist as this is not a real case.

Comment 1:
Please consider a more informative title. The recommendations include the elements of PICO (patient, intervention, control, outcome). Please also add 3-5 keywords after Abstract. Meanwhile, identify the manuscript as a case report in the title and keywords.
Reply 1: We have changed the title to 'A Practical, Simulated Case-Based Review of Hepatorenal Syndrome'. PICO format is not applicable to this review as the case is simulated. The keywords are hepatorenal syndrome, AKI, cirrhosis, decompensated cirrhosis, terlipressin

Comment 2:
In the Abstract and Introduction, please highlight the unique point of this manuscript based on comparison with existing evidence/similar cases.
Reply 2. The case presented in this review article is a simulated case. The case represents a typical case of HRS. Our approach to writing a review article is unique, but as this is not original research there is nothing unique in comparison to existing evidence.

Comment 3:
In these sections, 'Does this patient have hepatorenal syndrome?', 'What factors can precipitate AKI in this patient?', 'What should be the next steps?', 'Does this patient have ATN?'. Some statements should be in the Introduction, such as in page 4, 'AKI is common in hospitalized patients with decompensated cirrhosis and … or post-renal obstruction.'. And retain the statements about the clinical findings, diagnosis, progression of disease in the 'Case presentation' section, such as 'This patient has acute kidney injury (AKI) as defined … increase in 50% from baseline.' in page 4.
Reply 3: Please see first reply to reviewer 3

Comment 4: Please give details of the time of the case, specifically to the month and year.
Reply 4: This is a simulated case. The month and year will not any relevance to this article.

Comment 5:
Are there any other side effects or complications? If not, add a statement that there were no other side effects or complications.
Reply 5. We have added side -effects to table 1 titled "Drugs, dosage and route, goal and side-effects of drugs used in management of HRS-AKI"

Comment6:
What is the outcome of the patient? Is the patient still followed alive? If available, please add more details of the follow-up. All these key information should be added in the case presentation.
Reply 6. This is a simulated case. We have modified the statement to reflect that the patient died "The patient was eventually transitioned to comfort measures *and died with family members at bedside*"

Comment 7:
In page 6, 'Terlipressin in not available in US and Canada'. This information is not important.

Reply 7: This statement has been removed.

Comment 8:
The authors should define the abbreviation ‘SBP’ when its first used in page 7.
Reply 8: The abbreviation has bee expanded to spontaneous bacterial peritonitis.

Comment 9: Timeline
We suggest the authors adding a timeline. The timeline should present relevant events in the patient’s history in chronological order in a figure or table, enabling the core elements of the case report standing alone. Please see the example: https://tlcr.amegroups.com/article/view/35939/24197
Reply 9: As this is a case simulation and not a true case, we have not added a timeline.

Comment10:
Please add a Discussion section, In the discussion, the authors could compare with similar cases and discuss in detail. It is also necessary to transparently discuss BOTH the STRENGTHS AND LIMITATIONS of the study in the Discussion. A separate paragraph is highly suggested.
Reply 10: This is a case simulation of a typical case of hepatorenal syndrome. As this is not a research study, there are no strengths and limitations. As this is a review article and not a case report, we did not add a discussion section.