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Journal Name:	British Microbiology Research Journal
Manuscript Number:	Ms_BMRJ_23625
Title of the Manuscript:	A new Antibiotic Adjuvant Entity (Ceftriaxone + sulbactam + disodium edetate): a safer alternative to carbapenems for ICU infection management
Type of the Article	Original Research Articles

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline>)



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PART 1: Review Comments

	Reviewer's comment	Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<u>Compulsory</u> REVISION comments	Overall I think this is a helpful descriptive study examining a treatment strategy for multidrug resistant bacteria. This study is timely and has high clinical implications for certain areas of the world with high rates of resistance. However, because of study design, it is very hard to draw any meaningful conclusions from as the authors simply describe whether treatment with the different modalities was successful or failed. Without controlling for other factors such as severity of illness, it is difficult to say this should be used in place of carbapenems in this population. Would consider softer wording when making conclusions. Phrases such as “equivalent efficacy” should be avoided, as this was not a non-inferiority study. The authors can instead state that AAE appears to have similar efficacy to carbapenems, or something similar. Overall, the aim of the paper is unclear. Are the authors trying to show that AAE are an acceptable alternative to carbapenems? If so, in what situations? Based on the results of the study, what are the author's personal conclusions? (I.e. Should AAE be used in place of carbapenemss in all situations versus only certain situations? Should it only be used with isolates show carbapenem resistance?). I would also recommend mentioning that further studies should be conducted to fully elucidate what the place in therapy should be.	
<u>Minor</u> REVISION comments	Title I think the title is too strongly worded – based on the study, it cannot be concluded that AAE is safer than carbapenems. The authors state that there were no major adverse drug events with either carbapenems or AAE. Additionally, based on the study design, it is not possible to conclude that AAE is more effective than carbapenems.	Title I think the title is too strongly worded – based on the study, it cannot be concluded that AAE is safer than carbapenems. The authors state that there were no major adverse drug



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	Abstract Pg 1, Ln 9: recommend changing “check the efficacy” to “assess the efficacy” Significantly more results were provided for the single-organism infections versus multiple bacterial infections – would recommend reconciling this to show similar amount of data for both groups. Again, conclusion is too strongly worded. Based on the current study, it is not possible to conclude that AAE is equivalent in efficacy to other carbapenems in susceptible cases. The only conclusion that can be made is that patients experienced similar rates of clinical response. I would also include that in susceptible cases, some patients who failed carbapenem therapy responded to AAE treatment. Introduction Page 2, Ln 33: would also add bacteremias, as many of the patients in this study had concomitant bacteremia as well Page 2, Ln 46: I would change this to “few compounds...will be available” as several new compounds targeting CREs have either been developed or are in the development process (ie. Ceftazidime/avibactam, imipenem/sulbactam/relebactam) Materials and Methods Based on the title, it seems that all patients are in the ICU but this is not mentioned in the methods. It is important to state which population is being studied. Pg 3 Ln 66: More information should be provided regarding which patients were included in the study (as, I’m sure not ALL patients with IAI/UTI/LRTI were included). Thus, were only patients with multidrug resistant bacteria included? Pg 3, Ln 68-70 Unclear why the population was categorized by source of infection, as these categories were not used again during the manuscript Pg 4 Ln 80: Why were patients who expired during course of treatment excluded? Wouldn’t you want to know who potentially expired secondary to infection progression/antimicrobial failure? Would include anyone who received at least 48h of the antimicrobial regimen.	events with either carbapenems or AAE. Additionally, based on the study design, it is not possible to conclude that AAE is more effective than carbapenems. Ans: Title has now been re-worded. And other changes have also been made. Abstract Pg 1, Ln 9: recommend changing “check the efficacy” to “assess the efficacy” Significantly more results were provided for the single-organism infections versus multiple bacterial infections – would recommend reconciling this to show similar amount of data for both groups. Again, conclusion is too strongly worded. Based on the current study, it is not possible to conclude that AAE is equivalent in efficacy to other carbapenems in susceptible cases. The only conclusion that can be made is that patients experienced similar rates of clinical response. I would also include that in susceptible cases, some patients who failed carbapenem
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	Pg 4 Ln 89: doses were already mentioned on Pg 3, consider omitting. Colistin dosing should be mentioned at Pg 3 Ln 76. Pg 4 Ln 91-93: Unclear why these patients were split into two separate groups. How does having a mono vs polymicrobial infection impact patient outcome? Pg 4 Ln 98: Would recommending adding more objective measures of how clinical improvement was assessed, especially since this was a retrospective analysis. Who determined whether clinical improvement was achieved? Pg 5 Ln 107: This may be because I am based in the US and we do not use ceftriaxone/sulbactam/EDTA, but how was susceptibility determined? As far as I know, the CLSI does not have defined breakpoints for this combination Pg 5 Ln 107: Significant description of microbiological methods could be omitted. Authors may consider referring readers to a reference for microbiologic procedures. Pg 5, Ln 107: Was any testing done to detect presence of beta-lactamases such as MBLs? Pg 5 Ln 110: was sensitivity to colistin tested? Pg 5 Ln 126: Were patients evaluated prospectively or retrospectively at day 3? Unclear if this was done for all patients during the course of therapy or if authors just retrospectively evaluated for clinical cure at day 3. Results Pg 6, Ln 137: Unclear what the purpose of table 1, table 2 or Lns 137-155. Would be more helpful to see a comparison of patients who received a carbapenem vs AAE, along with p values to assess for baseline differences between the groups. Demographics of the patients who were clinically cured does not help the reader. If the authors do not wish to compare the use of carbapenems to AAE, then this recommendation can be ignored, however direct comparisons between the two treatment modalities should also be avoided in the body of the manuscript. Pg 6, Ln 40: The title states that this study was performed in ICU	therapy responded to AAE treatment. Ans: The “check the efficacy” has been changed to “assess the efficacy”. Now, similar amount of data has been presented for both single organism infection and multiple bacterial infection. Conclusion has now been changed. Introduction Page 2, Ln 33: would also add bacteremias, as many of the patients in this study had concomitant bacteremia as well Page 2, Ln 46: I would change this to “few compounds...will be available” as several new compounds targeting CREs have either been developed or are in the development process (ie. Ceftazidime/avibactam, imipenem/sulbactam/relebactam) Ans: Bacteremia has now been added into revised manuscript. New compounds will be available has been changed to few compounds...will be available. Materials and Methods
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	patients but the results state that almost a quarter of the patients were from ward floors. Please reconcile. Pg 9 Ln 182: treatment duration seems short, especially since this study is focused in ICU patients, many of which have pneumonia (per IDSA guidelines, pseudomonas and acinetobacter pneumonia is treated for 14 days). Is this because EDTA should not be administered for >5 days secondary to toxicity? Discussion Authors should include a brief review of prior studies that have been performed utilizing ceftriaxone/sulbactam/EDTA - A Combination Strategy of Ceftriaxone, Sulbactam and Disodium Edetate for the Treatment of Multi-Drug Resistant (MDR) Septicaemia: A Retrospective, Observational Study in Indian Tertiary Care Hospital. J Clin Diagn Res. 2015 Nov;9(11):FC29-32. - Bhatia P. Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: a new way to spare carbapenems. <i>Res J Infect Dis</i>. 2015; 3:2. http://dx.doi.org/10.7243/2052-5958-3-2 Pg 10 Ln 218: this may be the case in India, but not worldwide. In the US, the most common causes of carbapenem resistance are carbapenem efflux pumps and loss of porin channels. Pg 10 Ln 221-223: with these types of resistance, this EDTA combination therapy would not be affected – please state this limitation. Pg 11 Ln 239-240: Please explain the statement “significantly high percentage of...false in vitro susceptibility results”? How do the authors know this? Could the failure rates just be due to failure of the drug or progression of infection despite adequate treatment? Pg 11, Ln 249: again, would use softer wording with regards to “superiority” – would change to “treatment success with AAE in the setting of meropenem failure”. Conclusion Pg 12 274-277: multiple conclusions are drawn that cannot be extrapolated from the study results alone.	Based on the title, it seems that all patients are in the ICU but this is not mentioned in the methods. It is important to state which population is being studied. Ans: Changes have now been made. Pg 3 Ln 66: More information should be provided regarding which patients were included in the study (as, I’m sure not ALL patients with IAI/UTI/LRTI were included). Thus, were only patients with multidrug resistant bacteria included? Ans: Only 84 patients of ICU were included in the study and 24 were excluded from the study. Details of the patients have now been mentioned in the materials and method section. Pg 3, Ln 68-70 Unclear why the population was categorized by source of infection, as these categories were not used again during the manuscript Ans: This was just to present how many of the patients were of
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	Pg 12 Ln 278: agree with this conclusion and would recommend making this a bigger focus of the manuscript Pg 13, Ln 284: Need data to support this. Change in carbapenem susceptibility is not presented in the manuscript. Recommend omitting Table 3 and instead adding %s and Group names to the boxes in Figure 1. Tables 5-8 seem unnecessary given the fact that isolated pathogens and group breakdown are provided in Figure 1 and Table 4.	different infections. Pg 4 Ln 80: Why were patients who expired during course of treatment excluded? Wouldn't you want to know who potentially expired secondary to infection progression/antimicrobial failure? Would include anyone who received at least 48h of the antimicrobial regimen. Ans: None of the patients has been reported to be expired. Pg 4 Ln 89: doses were already mentioned on Pg 3, consider omitting. Colistin dosing should be mentioned at Pg 3 Ln 76. Ans: Changes have now been done as suggested. Pg 4 Ln 91-93: Unclear why these patients were split into two separate groups. How does having a mono vs polymicrobial infection impact patient outcome? Ans: This was to show that out of
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		84 patients how many of patients were diagnosed with single bacteria and how many of patients were diagnosed with multiple bacterial infection. And also to study the responses of both of the drugs against both types of infections. Pg 4 Ln 98: Would recommending adding more objective measures of how clinical improvement was assessed, especially since this was a retrospective analysis. Who determined whether clinical improvement was achieved? Ans: Doctor determined the clinical improvement. Pg 5 Ln 107: This may be because I am based in the US and we do not use ceftriaxone/sulbactam/EDTA, but how was susceptibility determined? As far as I know, the CLSI does not have defined breakpoints for this combination Ans: Agreed with you. This is the innovative product of Venus Remedies Limited. The
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		susceptibility study was carried out according to the method defined by CLSI. Breakpoints to define susceptibility, resistance and intermediate we have established by Venus remedies Limited following the methods described by CLSI. Pg 5 Ln 107: Significant description of microbiological methods could be omitted. Authors may consider referring readers to a reference for microbiologic procedures. Ans: We have now been ommitted the method in the revised manuscript. Pg 5, Ln 107: Was any testing done to detect presence of beta-lactamases such as MBLs? Pg 5 Ln 110: was sensitivity to colistin tested? Ans: No test was carried out for MBL detection. Similarly, colistine sensitivity was carried out and all the isolates were found to be susceptible to colistine. However,
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		colistine result has not been included in this manuscript as our aim was to compare AAE with meropenem. Pg 5 Ln 126: Were patients evaluated prospectively or retrospectively at day 3? Unclear if this was done for all patients during the course of therapy or if authors just retrospectively evaluated for clinical cure at day 3. Ans: patients have been evaluated retrospectively. Results Pg 6, Ln 137: Unclear what the purpose of table 1, table 2 or Lns 137-155. Would be more helpful to see a comparison of patients who received a carbapenem vs AAE, along with p values to assess for baseline differences between the groups. Demographics of the patients who were clinically cured does not help the reader. If the authors do not wish to compare the use of carbapenems to AAE, then this recommendation can be ignored,
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		however direct comparisons between the two treatment modalities should also be avoided in the body of the manuscript. Ans: Table 1 and Table 2 have now been removed from the revised manuscript. But we have kept the lines 137-155 as these lines are required to describe about the patients. Demographic characteristic and comorbidities. We do not wish to compare the use of carbapenem to AAE. Pg 6, Ln 40: The title states that this study was performed in ICU patients but the results state that almost a quarter of the patients were from ward floors. Please reconcile. Ans: Corrections have now been done. Pg 9 Ln 182: treatment duration seems short, especially since this study is focused in ICU patients, many of which have pneumonia (per IDSA guidelines, pseudomonas and acinetobacter pneumonia is treated
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		for 14 days). Is this because EDTA should not be administered for >5 days secondary to toxicity? Discussion Authors should include a brief review of prior studies that have been performed utilizing ceftriaxone/sulbactam/EDTA - A Combination Strategy of Ceftriaxone, Sulbactam and Disodium Edetate for the Treatment of Multi-Drug Resistant (MDR) Septicaemia: A Retrospective, Observational Study in Indian Tertiary Care Hospital. J Clin Diagn Res. 2015 Nov;9(11):FC29-32. - Bhatia P. Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: a new way to spare carbapenems. <i>Res J Infect Dis.</i> 2015; 3:2. http://dx.doi.org/10.7243/2052-5958-3-2 Ans: As in this combination EDTA is used in very less quantity, hence, there is lesser chance of toxicity. I agreed
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		with the IDSA guidelines but the patients were got cured in such a less treatment duration. We have included both of the suggested references in our revised manuscript. Pg 10 Ln 218: this may be the case in India, but not worldwide. In the US, the most common causes of carbapenem resistance are carbapenem efflux pumps and loss of porin channels. Ans:This line has now been reworded in the revised manuscript. Pg 10 Ln 221-223: with these types of resistance, this EDTA combination therapy would not be affected – please state this limitation. Ans:This has now been stated in the revised manuscript. Pg 11 Ln 239-240: Please explain the statement “significantly high percentage of...false in vitro susceptibility results”? How do the
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		authors know this? Could the failure rates just be due to failure of the drug or progression of infection despite adequate treatment? Ans: This section has now been eliminated from the revised manuscript. Pg 11, Ln 249: again, would use softer wording with regards to “superiority” – would change to “treatment success with AAE in the setting of meropenem failure”. Ans: as suggested by reviewer, the word superiority has now been changed into treatment success with AAE. Conclusion Pg 12 274-277: multiple conclusions are drawn that cannot be extrapolated from the study results alone. Ans: These lines have now been revised/deleted. Pg 12 Ln 278: agree with this conclusion and would recommend
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		making this a bigger focus of the manuscript Ans: Has now been done. Pg 13, Ln 284: Need data to support this. Change in carbapenem susceptibility is not presented in the manuscript. Ans: This line has been deleted as we are not providing any additional data in conclusion part. Recommend omitting Table 3 and instead adding %s and Group names to the boxes in Figure 1. Ans: Table 3 has now been omitted from the revised manuscript. Due to shortage of space in figure 1, % S has been mentioned in the text. Tables 5-8 seem unnecessary given the fact that isolated pathogens and group breakdown are provided in Figure 1 and Table 4. Ans: Tables 5-8, have been
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		removed from the revised manuscript.
<u>Optional/General</u> comments	Many general spelling and grammatical errors should be corrected. Figure 1 is difficult to read as is (many lines of text are cut off).	