

Peer Review File

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Reviewer A comments

Comment 1: Abstract: It's structured and well-constructed.

Reply 1: No action required

Comment 2: Introduction: Rationale is well-described, and objectives are specified. Authors should again, at line 63, add that the review is a narrative review.

Reply 2: Thank you for raising this, narrative review has been added as suggested.

Changes in the text: Word narrative added on page 2, line 63

Comment 3: Methods: Since is a narrative review, authors can be succinct when specifying searching distractors. But perhaps they should add if they followed a general search or focused exclusively on reviews, meta-analyses, RCTs and observational studies. Nor do they specify whether the selection of studies carried out in the Intensive Care Unit was done manually or through some other search criteria. I think they could extend a little more in this part.

Reply 3: Thank you for your comments and the opportunity to explain the search method in more detail. We have expanded this section to include details regarding search of intensive care related articles and why studies used were selected.

Changes in the text: page 3, lines 67-71.

Method section now reads 'PubMed was searched for reviews, meta-analyses, randomised control trials (RCTs) and observational studies with the terms 'antibiotic de-escalation' and 'antimicrobial de-escalation' both with and without '+ intensive care', and 'antimicrobial stewardship', including articles up to November 2021. Publications with ADE-related outcomes were included. Bibliographies of relevant papers were also reviewed, and applicable articles hand-picked.'

Comment 4: Discussion: Well-conducted, they chase specific topics of the key findings and explain potential limitations, bias or interpretation of the results.

Reply 4: Thank you for your comments, no action required.

Comment 5: Figure 1: Part of the text is cut, upper phrases. The figure should be corrected.

Reply 5: Thank you for highlighting this. Have text wrapped the diagram and the whole entity should now be "fixed" on the initial document so when converted to PDF it should not change. Have also made the text slightly smaller to ensure it fits.

Changes in the text: See figure 1 – attached separately.

Comment 6: Table 1: Tables tend to be self-explanatory. Authors should explain acronyms below the table, regardless those acronyms had been previously explained in the manuscript (MRD, ADE, LOS, CAP).

Reply 6: Acronyms used in table 1 are all now explained below the table.

Changes in the text: See table 1, attached separately.

Reviewer B comments

Comment 1: I suggest that the authors measure the risk of bias of each study, for example by applying the tool of the Cochrane group. This information would be very useful to understand the strength of the evidence supporting the conclusions of the review.

Reply 1: Thank you for your recommendation, which we agree would be a useful addition and help discern the strength of evidence. After discussion and with the time available to us we felt this fell beyond the remit of a narrative review. We have made attempt to discuss potential bias and limitations of studies in the text as highlighted by reviewer A in comment 4.

Comment 2: It would be interesting to add information on the main characteristics of the studies selected for the conclusions, such as: 1) Author and year of publication; 2) Study design: RCTs, non-RCTs, or controlled before and after studies; which could be added in a table in the supplementary material.

Reply 2: We have added a table in supplementary material which includes the studies that have an outcome related to ADE. It describes the first author, type of study, year of publication and impact of ADE on the particular outcome in question by section.

Changes in the text: Supplementary material attached separately. Study characteristics (study type, author and year) also added in text to final conclusion, please see page 11, lines 336-337 and line 340.

Comment 3: Has the study been registered in an international database of review studies?

Reply 3: Thank you for raising this but no, we have not done this with it being a narrative review.

Comment 4: Studies on febrile neutropenia have mainly been conducted in onco-hematological patients during their stay on the hospital ward. Therefore, what is the reason for including febrile neutropenia in this study focused on ICU patients? I suggest excluding this part of the information from the present study.

Reply 4: Thank you for highlighting this. On review, we agree that it is not specific to the question/area covered by this review and have removed this part.

Changes in the text: Text deleted page 7, lines 216-218.

Comment 5: Due to the weakness of the reviewed studies, I suggest adding in the conclusions that well-designed studies are needed to understand the benefits and risks of de-escalation of antimicrobial therapy in ICU patients.

Reply 5: Thank you for this important comment. We have added a sentence to this effect.

Changes in the text: 'Well-designed studies are needed to understand the benefits and risks of de-escalation of antimicrobial therapy in ICU patients.' Added page 11, lines 348-349.