PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis
AUTHORS	Shamsrizi, Parichehr; Gladstone, Beryl Primrose; Carrara, Elena; Luise, Dora; Cona, Andrea; Bovo, Chiara; Tacconelli, Evelina

VERSION 1 – REVIEW

REVIEWER	Jason Burnham Washington University in St. Louis School of Medicine, USA Dr. Burnham reports that he is supported by the NIH-National Center for Advancing Translational Sciences (NCATS), components of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research (grant no. UL1 TR002345, subaward KL2 TR002346). Reviews content are solely the responsibility of the reviewers and do not necessarily represent the official view of NCATS or NIH.
REVIEW RETURNED	20-Mar-2019

GENERAL COMMENTS	Overall, an important study, with results that are consistent with what one would expect for ESBL infections - that they confer increased risk of death/prolonged hospital stay. Minor comments: A general editing comment - Enterobacteriaceae should be italicized Link to study protocol gave error message and I was unable to access it. Major comments: Authors should update the search through present, as there have been several studies in this area in the last 6 months. In addition, searching only PubMed may miss important studies. Other databases should be considered - Ovid Medline, Embase, Scopus, the Cochrane Library, clinicaltrials.gov to name a few. In addition, search strategy needs to be more robust - no synonyms were considered during record retrieval (or if they were, are inadequately described). Assistance from a librarian trained in search methodologies would significantly improve the quality of the search and the manuscript. Synonym examples (not exhaustive) follow: mortality - 'death', ESBL - 'extended spectrum beta lactamase', length of hospitalisation' - length of stay, hospital length of stay, length of hospitalization. Exclusion of non-English studies may also miss important data.

	General comment - I think that readers would find it helpful to also have results presented in two groups: 1) adult studies, 2) pediatric studies

REVIEWER	Lavillegrand Jean-Rémi MD/Maury Eric MD PhD CHU Hôpital Saint-Antoine, Assistance Publique des Hôpitaux de Paris, France Université Pierre-Marie Curie, Paris VI, France
REVIEW RETURNED	04-Apr-2019

GENERAL COMMENTS	Review of the manuscript entitled « Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis » by Shamsrizi et al. ESBL producing enterobacteria related infections are on the rise and promotes intense research since they induce an increase in carbapenem use and put in perspective the dread of carbapenem resistant species which could be elicited by unrestrained carbapenem use. This topic is therefore of interest ant the authors are right when they wonder whether ESBL producing bacteria are responsible of increased mortality and/or length of stay. Shamsrizi and colleagues performed a systematic review focused on the comparison of the mortality of ESBLs infections with integration of specific roles of confounders. This is an impressive work on a very hot topic and a major healthcare problem with a actualization of 2 previous systematics reviews published in 2007 and 2012 with an addition of fifty more studies. The conclusion reported by the authors are similar : infections caused by ESBLs bacteria have a worse prognosis than infection caused by bacterias non producing ESBL. This a well-written study and the authors should be congratulated for their commitment in producing such an extensive review. The multiple analysis computed suggest that ESBL producing bacteria's related infection are associated with a worse prognosis than infection caused by bacteria not producing theses enzymes. These conclusions should however be examined with caution and the relationship evidenced by all these calculations could be an association rather that a causal relation. There are also some issues which deserve discussion/clarification. The herein reported study analyzed data from 1960 to 2018 and therefore included historical ESBL (SHV and TEM) described during the 1980's for which infected patients were hospitalized patients with surgical history and long stay in ICU and more recent enzymes (CTMX family) which are often observed in the community setting. The authors considered this point in assessing the RR on different period "The RR increased over time from 1.56 (95% CI: 1.15-2.11; p=0.004) in 1991-1999 to 1.74 (95% CI: 1.50-2.01; p<0.001) in 2000-2009, and it was stable in 2010- 2018 (1.72, 95% CI: 1.39-2.13; p<0.001). One could therefore have expected a less important impact on mortality associated with the more recent strains involving more frequently the community and less severely ill patients. The authors do not discuss this point. Infections caused by ESBL producing bacteria are difficult to compared to infections caused by strains not producing these enzymes because patients included in these case control study are not similar in term of underlying status (age, comorbidity, immunodepression status, associated medications…) and infection (severity that could be assessed by the Pitt score or the SOFA

	score,) time course of infection, size of inoculum, duration of bacteremia but also by the site of infection. As a matter of fact, urinary tract infections (UTIs) are associated with a less pejorative prognosis than pneumonia or peritonitis caused by the same pathogens. It is unfortunate that site of infection has not been considered in the review. Furthermore, antibiotic therapy is major determinant of prognosis and the authors tried to assess the effect of appropriate therapy. However the reported effect is a little bit surprising. “The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26-1.90; p<0.001). Should we therefore understand that appropriate therapy is associated with a worse prognosis? The authors should have discussed this point. Appropriateness of antibiotic therapy can be defined as appropriate empirical therapy or as definite therapy (whatever initial therapy was) and can be defined as a single component active against the responsible pathogen whatever the dose administered. Having received a single dose of an efficient treatment is not similar to have received multiple doses. These issues should have been discussed. Another one important issue associating all these parameters is patients with UTI receiving inappropriate empirical antibiotic therapy and who have nevertheless a favorable outcome due to the fact that the concentrations of antibiotic reached in the urinary tract is very high and is therefore active against the pathogen involved in the infection. The increased mortality observed in infections due ESBL producing bacterias even when antibiotic therapy is appropriate suggests a different virulence of the strains (which has not been described) or to a different underlying status of the patient (which is a plausible explanation). Last, even if considered as a rough criterion, mortality is probably not the most accurate criteria to compare the course of infection. D28 mortality could be not close enough to infection course. The assessment of improvement or its absence after 7 days is probably a relevant parameter The other parameter which was explored in length of stay or ICU LOS. This a frequently used marker of severity even not perfect. It should be emphasized that in some European countries, patients with infection and or colonization by ESBL producing bacterias are cohorted in single bedroom and this issue is in part responsible for a prolongation of ICU stay.

REVIEWER	Olli Saarela University of Toronto, Canada
REVIEW RETURNED	07-Aug-2019

GENERAL COMMENTS	Summary: The authors report a systematic review and meta-analysis of the effect of ESBL producing bacterial infection on all-cause mortality, attributable mortality and length of hospital stay compared to non-ESBL infections. 84 relevant studies were identified, with pooled results from random effect meta-analysis reported for overall effect and various subgroup effects. Substantial heterogeneity was observed, but ESBL producing infection was found to be associated with higher mortality and longer hospital stay. I have listed some comments/questions below, mainly concerning reporting of the statistical analyses. Major comments:

	1. It was not clear to this reviewer how the effects across various subgroups of effect modifiers were compared. It seems that p-values were reported for the within-subgroup effects, but I did not see p-values for the between-subgroup comparisons of effects. These could be obtained from meta-regression. 2. Did the authors consider multivariable meta-regression? It might be relevant to test for residual heterogeneity after the most important effect modifiers have been accounted for. 3. The between-study effect modifiers were referred to as confounders in the manuscript; I believe within-study confounding is a separate issue from between-study effect modification, and the former cannot be controlled in an aggregate data meta-analysis. I suggest clarifying the terminology used. 4. In addition to I^2 statistics, were p-values calculated for the presence of heterogeneity to support the statement that significant heterogeneity was observed? Minor comments: 1. p. 4, l. 57-: Are there quotes missing here? 2. p. 5, l. 22: This refers to trials; if I understood correctly, the studies here were not trials. 3. p. 6, l. 19: Are all the p-values reported in the manuscript Bonferroni-corrected? How many tests were accounted for in the correction? 4. It was not obvious how Figure 2 and Supplemental Figure 1 are different; some content seems to be duplicated.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 comments	Authors' response
A general editing comment - Enterobacteriaceae should be italicized	The Enterobacteriaceae has been italicized all over in the manuscript.
Link to study protocol gave error message and I was unable to access it.	We thank the reviewer for noticing it. The text for the link had a typo and has been corrected (page 6, line 21).
Authors should update the search through present, as there have been several studies in this area in the last 6 months. In addition, searching only PubMed may miss important studies. Other databases should be considered - Ovid Medline, Embase, Scopus, the Cochrane Library, clinicaltrials.gov to name a few. In addition, search strategy needs to be more robust - no synonyms were considered during record retrieval (or if they were, are inadequately described). Assistance from a librarian trained in search methodologies would significantly improve the quality of the search and the manuscript. Synonym examples (not exhaustive) follow: mortality - 'death', ESBL - 'extended spectrum beta lactamase', length of hospitalisation' - length of stay, hospital length of stay, length of hospitalization.	We agree with the reviewer that the search could have been updated and improved by adding other databases. Unfortunately, the project funded by the DZIF (German Center for Infectious Diseases) has been completed in December 2019. The paper has been submitted in March, but we received the review comments only in August. Being more than 6 months from the end of the projects we cannot provide the necessary personnel for the update. This issue has been added in the limitations section of the manuscript. As for a second database we trust that adding Ovid Medline, Scopus, the Cochrane Library, and clinicaltrials.gov, due to the type of PICO questions and the studies we found limited to observational studies, we could assume, also based on previous systematic reviews on this topic from the research group (cite some in parenthesis) that the addition would be marginal. For the same reason given above we are not, unfortunately, in a position to stat a new search. This limitation has been

	added to the relevant section (page 10, line 23) As for the search term, the search was developed by expert librarian and the words provided in the manuscript were only a summary of what applied. This has been clarified in the revised version of the manuscript (page 4, line 31) and the full search has now been included in the supplementary materials.
Exclusion of non-English studies may also miss important data	We agree with the reviewer. Actually, the sentence included in the methodology section is wrong, since search 'was not' limited to English studies. We correct this mistake in the revised version of the manuscript (page 5, line 7). Out of 84 studies, we found only one Chinese study which has been deleted due to the exclusion criteria of the protocol.
General comment - I think that readers would find it helpful to also have results presented in two groups: 1) adult studies, 2) pediatric studies	We agree with the reviewer on the importance of stratifying by age groups. Figure 2 and online supplementary figure S1 present data on all cause mortality for adult and pediatric population (page 7, line 24)

Reviewer #2 comments	**Authors' response**
This topic is therefore of interest ant the authors are right when they wonder whether ESBL producing bacteria are responsible of increased mortality and/or length of stay. Shamsrizi and colleagues performed a systematic review focused on the comparison of the mortality of ESBLs infections with integration of specific roles of confounders. This is an impressive work on a very hot topic and a major healthcare problem with a actualization of 2 previous systematics reviews published in 2007 and 2012 with an addition of fifty more studies. The conclusion reported by the authors are similar : infections caused by ESBLs bacteria have a worse prognosis than infection caused by bacterias non producing ESBL. This a well-written study and the authors should be congratulated for their commitment in producing such an extensive review. The multiple analysis computed suggest that ESBL producing bacteria's related infection are associated with a worse prognosis than infection caused by bacteria not producing theses enzymes. These conclusions should however be examined with caution and the relationship evidenced by all these calculations could be an association rather that a causal relation.	We thank the reviewer for the appreciation of our work.
The herein reported study analyzed data from 1960 to 2018 and therefore included historical ESBL (SHV and TEM) described during the 1980's for which infected patients were hospitalized patients with surgical history and long stay in ICU and more recent enzymes (CTMX family) which are often observed in the community setting. The authors considered this point in assessing the RR on different period "The RR increased over time from 1.56 (95% CI: 1.15-2.11; p=0.004) in 1991-1999 to 1.74 (95% CI: 1.50-2.01; p<0.001) in 2000-2009, and it was stable in 2010- 2018 (1.72, 95% CI: 1.39-2.13; p<0.001). One could therefore have expected a less important impact on mortality associated with the more recent strains involving more frequently the community and less severely ill patients. The authors do not discuss this point.	We agree with the reviewer that both resistance mechanisms and place of infection acquisition can have an impact on disease severity. However, studies are usually including a mixed patients' population and very few report patients' outcome stratified by genotypic resistance, making subgroup analysis difficult to perform.

Infections caused by ESBL producing bacteria are difficult to compared to infections caused by strains not producing these enzymes because patients included in these case control study are not similar in term of underlying status (age, comorbidity, immunodepression status, associated medications…) and infection (severity that could be assessed by the Pitt score or the SOFA score,) time course of infection, size of inoculum, duration of bacteremia but also by the site of infection. As a matter of fact, urinary tract infections (UTIs) are associated with a less pejorative prognosis than pneumonia or peritonitis caused by the same pathogens. It is unfortunate that site of infection has not been considered in the review.	We do agree with the reviewer's comment. Source of infections was included in the variables for the subgroup analysis. Due to limitations in data reported in the included studies, we could perform the subgroup analysis only by invasive versus non-invasive infections. This has been now clarified at page 6, line 6.
Furthermore, antibiotic therapy is major determinant of prognosis and the authors tried to assess the effect of appropriate therapy. However the reported effect is a little bit surprising. "The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; p<0.001) than in those that did not (RR=1.55; 95% CI 1.26-1.90; p<0.001). Should we therefore understand that appropriate therapy is associated with a worse prognosis? The authors should have discussed this point. Appropriateness of antibiotic therapy can be defined as appropriate empirical therapy or as definite therapy (whatever initial therapy was) and can be defined as a single component active against the responsible pathogen whatever the dose administered. Having received a single dose of an efficient treatment is not similar to have received multiple doses. These issues should have been discussed.	The sentence refers to the fact that the RR is higher in studies who adjusted their results by appropriateness of therapy. The lack of consideration of appropriateness of therapy in the studies evaluating of mortality seems to underestimate the risk of ESBL production on mortality. This has been clarified in the revised version of the manuscript (page 9, line 31).
Another one important issue associating all these parameters is patients with UTI receiving inappropriate empirical antibiotic therapy and who have nevertheless a favorable outcome due to the fact that the concentrations of antibiotic reached in the urinary tract is very high and is therefore active against the pathogen involved in the infection.	We agree with the reviewer. The point has been added to the discussion of results (page 10, line 9).
The increased mortality observed in infections due ESBL producing bacterias even when antibiotic therapy is appropriate suggests a different virulence of the strains (which has not been described) or to a different underlying status of the patient (which is a plausible explanation). Last, even if considered as a rough criterion, mortality is probably not the most accurate criteria to compare the course of infection. D28 mortality could be not close enough to infection course. The assessment of improvement or its absence after 7 days is probably a relevant parameter The other parameter which was explored in length of stay or ICU LOS. This a frequently used marker of severity even not perfect. It should be emphasized that in some European countries, patients with infection and or colonization by ESBL producing bacterias are cohorted in single bedroom and this issue is in part responsible for a prolongation of ICU stay.	We agree with the reviewer and we believe our systematic review could contribute to the discussion on the limitation of current evidence for the estimation of mortality due to antibiotic-resistant infections. The importance of considering the source of infections, in particular for the UTIs, has been added to the discussion (page 10, line 8). We agree with the reviewer that ICU stay is not a perfect outcome, since it is influenced by many concurrent factors (mainly underlying comorbidities). However, we are not aware of studies proving that isolation of ESBLs' carriers is an

	independent factor for a prolonged ICU-stay.

Reviewer #3 comments	Authors' response
The authors report a systematic review and meta-analysis of the effect of ESBL producing bacterial infection on all-cause mortality, attributable mortality and length of hospital stay compared to non-ESBL infections. 84 relevant studies were identified, with pooled results from random effect meta-analysis reported for overall effect and various subgroup effects. Substantial heterogeneity was observed, but ESBL producing infection was found to be associated with higher mortality and longer hospital stay. I have listed some comments/questions below, mainly concerning reporting of the statistical analyses.	We thank the reviewer for the valuable inputs.
It was not clear to this reviewer how the effects across various subgroups of effect modifiers were compared. It seems that p-values were reported for the within-subgroup effects, but I did not see p-values for the between-subgroup comparisons of effects. These could be obtained from meta-regression.	We clarified the methodology in the revised version of the manuscript (page 6, line 9). The reviewer has correctly understood the methodology. The p-values for the between-subgroup comparisons of effects have been added (page 7, line 17 and page 8, line 3).
Did the authors consider multivariable meta-regression? It might be relevant to test for residual heterogeneity after the most important effect modifiers have been accounted for.	A multivariable meta-regression was not carried out due to the small number of studies in each subclass, limiting the possibility of undertaking such an analysis.
The between-study effect modifiers were referred to as confounders in the manuscript; I believe within-study confounding is a separate issue from between-study effect modification, and the former cannot be controlled in an aggregate data meta-analysis. I suggest clarifying the terminology used.	We agree that effect-modifier is a better terminology. We replaced the word 'confounder' with 'effect modifier' where appropriate.
In addition to I^2 statistics, were p-values calculated for the presence of heterogeneity to support the statement that significant heterogeneity was observed?	The p-values were calculated to test the presence of heterogeneity and presented behind the I-squared value wherever it is reported.
p. 4, l. 57-: Are there quotes missing here?	The search terms have been provided as a supplementary table and the sentence has been corrected to include it (page 4, line 31).
p. 5, l. 22: This refers to trials; if I understood correctly, the studies here were not trials.	Thanks, it has been corrected.
p. 6, l. 19: Are all the p-values reported in the manuscript Bonferroni-corrected? How many tests were accounted for in the correction?	The P-values referring to the effect estimate in each subgroup does not have Bonferroni-corrections. The significance testing comparing subgroups done using meta-regression took into account Bonferroni corrected threshold value (16 subgroups tested =

	0.05/16=0.003125). The sentence in the methods has been clarified (page 6, line 11).
It was not obvious how Figure 2 and Supplemental Figure 1 are different; some content seems to be duplicated.	The two figures reported data on all-cause mortality. Figure 1, which includes additional subgroups, has been moved among the supplemental figures.

VERSION 2 – REVIEW

REVIEWER	Jason Burnham Washington University in St. Louis School of Medicine, USA Assistant Professor of Medicine
REVIEW RETURNED	21-Sep-2019

GENERAL COMMENTS	Authors have addressed my comments to the best of their ability. While being unable to include other databases is unfortunate, they have noted this limitation in the discussion and certainly funding limitations is well understood

REVIEWER	Jean Rémi Lavillegrand /. Eric Maury Intensive Care Unit Hôpital Saint-Antoine AP-HP Paris France
REVIEW RETURNED	09-Oct-2019

GENERAL COMMENTS	We read with interest and thank Shamsrizi and colleagues for their revised manuscript work and for the attention paid on our comments. However, we have still a major concern focused on the definition of non-invasive infections vs invasive infections. Did it rely on bacteremia presence or not (i.e. blood culture positive?). It's well known than the presence of positive blood cultures is not related to the mortality especially for pneumonia urosepsis and for septic shock (2). Conversely intravascular infection is of greater severity. Invasive infection is defined by the presence of infection and presence of organisms in a normally sterile site (blood CSFS articular fluid). Separating for instance, bacteremic urinary tract infection from non bacteremic urinary tract infections is to our opinion non relevant. It would be more relevant to analyze mortality according to the source of infection and exclude or separately analyze urinary tract infection (with or without associated bacteremia) to finally compare ESBL UTI vs non ESBL UTI and ESBL non UTI vs non ESBL non UTI. Moreover, it's also important to discuss the possible role of ESBL infection on patients with more severe or numerous comorbidities. Finally the increasing incidence of community ESBL, and this could be a part of the explanation of the difference of mortality.

REVIEWER	Olli Saarela University of Toronto, Canada
REVIEW RETURNED	12-Oct-2019

GENERAL COMMENTS	No further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2 comments	Authors' response
We read with interest and thank Shamsrizi and colleagues for their revised manuscript work and for the attention paid on our comments.	We thank the reviewer for this comment
We have still a major concern focused on the definition of non-invasive infections vs invasive infections. Did it rely on bacteremia presence or not (i.e. blood culture positive?). It's well known than the presence of positive blood cultures is not related to the mortality especially for pneumonia urosepsis and for septic shock (2). Conversely intravascular infection is of greater severity. Invasive infection is defined by the presence of infection and presence of organisms in a normally sterile site (blood CSFS articular fluid). Separating for instance, bacteremic urinary tract infection from non bacteremic urinary tract infections is to our opinion non relevant. It would be more relevant to analyze mortality according to the source of infection and exclude or separately analyze urinary tract infection (with or without associated bacteremia) to finally compare ESBL UTI vs non ESBL UTI and ESBL non UTI vs non ESBL non UTI.	Invasive infections were defined as infections causing a systemic inflammatory response syndrome (sepsis) and requiring hospitalization and treatment, opposed to non-invasive infections that are mainly localized infections (i.e. UTI, superficial surgical site infections). The most of the studies reported data on BSIs, therefore the term 'invasive' has been now replaced with BSI in order not to generate confusion. The studies addressing only localized infections have been defined as 'non-invasive' infections (i.e. not only non bacteremic patients, but also localized sign and symptoms). We tried to clarify better this aspect in the revised version of the manuscript (page 6, line 5). As already suggested by the reviewer, we presented additional forest plots underlining how the impact of ESBL production changes according to the infection source (supplementary figures 5 and 6). We added a sentence in the results referring to this aspect (page 8, line 5). We understand the concern of the reviewer regarding the difference between bacteremia, sepsis and localized infections (such as non-bacteremic-UTIs). However, observational studies generally report data on cohorts of bacteremic patients without clarifying the outcome of individual patients according to the infections' source. To answer this specific question, we would need individual patient data and a different study design, such as network meta-analysis. We added this aspect as a further limitation of the study (page 11, line 9).
Moreover, it's also important to discuss the possible role of ESBL infection on patients with more severe or numerous comorbidities.	We agree with the reviewer that comorbidities act as relevant confounders when assessing the outcome of ESBL infections. As underlined in the discussion part, a high heterogeneity among reporting of patients' characteristics made impossible to perform further subgroup analysis. For this purpose, we could only use categorical variables, such as settings (ICU, surgical, haematological wards) or study population (such as diabetics, burns) as proxies for underlying comorbidities. This has been clarified in the discussion in the limitations section. (page 11, line 1-5).
Finally the increasing incidence of community	We agree with the reviewer that the increasing

ESBL, and this could be a part of the explanation of the difference of mortality.	incidence of community ESBL might influence overall mortality estimates. However, the place of infection acquisition could not be studied in our meta-analysis due to the lack of reporting of data. Despite the increasing incidence of community-acquired infections, our subgroup analysis by 'study-year' did not show any modification over the years. This might be due to the contemporary increased of patients' age and comorbidities. A sentence on this point has been added to the discussion (page 10, line 13).

VERSION 3 – REVIEW

REVIEWER	Jean Rémi Lavillegrand /. Eric Maury Intensive Care Unit Hôpital Saint-Antoine Assistance Publique-Hôpitaux de Paris Paris, France
REVIEW RETURNED	05-Dec-2019

GENERAL COMMENTS	the relevance of data should be mitigated in the discussion by the fact that bacteremic infection is not more severe than non bacteremic infection and finally that mixing bacteremic and non bacteremic infections will result in non homogeneous groups of infections limiting the relevance of conclusions this is mandatory

VERSION 3 – AUTHOR RESPONSE

Reviewer #2 comments	Authors' response
The relevance of data should be mitigated in the discussion by the fact that bacteremic infection is not more severe than non bacteremic infection and finally that mixing bacteremic and non bacteremic infections will result in non homogeneous groups of infections limiting the relevance of conclusions this is mandatory	We thank the editor and the reviewers for their thoughtful consideration of our manuscript. Following the reviewer's suggestion, we mitigated our conclusions and highlighted the limitations of the analysis, especially in respect to the bacteremic/non-bacteremic issue (page 11, line 2). It is true that non-bacteremic patients can have severe infections (i. e. VAP). However, when performing systematic review, authors have to compromise with pre-defined categories and accept what is reported in original studies. Studies on AMR infections are often observational and the enrollment process starts from positive blood cultures, since they are the easiest 'true infections' available for data collection'. Thus, bacteremic patients are usually the most represented population and non-bacteremic infections are very rarely reported, thus limiting the validity of results for this specific patients' population. As we stated in the conclusions of our manuscript, meta-analysis with single patients data and a more homogeneous reporting of relevant key-variables are needed to improve the quality of the evidence on this topic