Author's response to reviews

Title: Evaluation of Ertapenem Use with Impact Assessment on Extended-spectrum Beta-lactamases (ESBL) Production and Gram-negative Resistance

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Author's response to reviews: see over
Dear Sir/Mdm,

Re: Manuscript reference no. (2079100816101609)

Please find attached a revised version of our manuscript “Evaluation of Ertapenem Use with Impact Assessment on Extended-spectrum Beta-lactamases (ESBL) Production and Gram-negative Resistance”, which we would like to resubmit for publication in BMC Infectious Diseases.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

Revisions in the text are shown in blue. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Infectious Diseases.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of Reviewer #1

1. Abstract

The methodology described in the abstract is not clear; also there is an abbreviation of NARSS that only the text got to know that it is for Antimicrobial Resistance Surveillance Network Singapore. The results do not mention the impact on the production of ESBL.

Response: We apologized for the use of an unfamiliar abbreviation. The full name of NARSS has been included in the abstract as requested. To clarify, we have stated the impact on the production of ESBL in the result in our abstract, as “Overall, the increasing trend of ertapenem consumption correlated with 1) increasing incidence-densities of cephalosporin-resistant E. coli at zero time lag” and hence, that is concluded as “Increasing Ertapenem consumption did not result in a decreasing trend of ESBL producing Enterobacteriaceae”. The impact is analysed as an epidemiological impact in result which is translated to the stated conclusion as above. In the context of Singapore, ceftriaxone is utilized to test for resistance to cephalosporins.

Reference:


2. Methodology

The use of ertapenem was considered appropriate if the indication and dose were filled. However, in the results there is a description of 35% of cases due to bacteremia and we know that efficacy of ertapenem in cases of bacteremia is limited. Please clarify whether the cases were classified as primary or secondary bacteremia.

Response: 33.8% of cases were due to bacteremia. Out of 306 cases that were due to bacteremia, 134 cases were due to primary bacteremia while 172 cases were due to secondary bacteremia with known sources (Page 10). We have considered the use of ertapenem in primary bacteremia as inappropriate as the reviewer has rightly pointed out that the efficacy of ertapenem in cases of bacteremia is limited. This has been added as highlighted text (page 7).
ESBL production was detected only based on resistance to cephalosporins 3rd generation? There was no confirmation by phenotypic tests? Please clarify.

Response: Screening for ESBL production was done with an indicator cephalosporin in our lab, before confirmation with double-disk diffusion method. This has been clarified as highlighted text in our methodology (page 6-7).

3. Results
There are two figures numbered as number 1. Figure 2 shows the types of microorganisms isolated during the study where we noted the presence of grampositive coci. For it is a study focused solely on gram negative considering the hypothesis drawn from this figure, the gram-positive cocci. Again we note that production of ESBL was considered only by resistance to cephalosporins 3rd generation including Pseudomonas aeruginosa and Acinetobacter species. We consider that this is not an appropriate methodology for detection of resistance mechanism. Again I doubt if the cases of bacteremia may be considered like appropriate use. There is a need to check if the cases of bacteremia were primary or secondary.

Response: The figure number has been amended for Figure 2, and we apologize for this oversight. We have also omitted the non-Enterobacteriaceae from the figure, as suggested by the reviewer. On the points of detection of ESBLs and cases of types of bacteremia, please see the explanation above.

102 cases had new infections, of these how many were bacteremia? Please clarify. The same applies to cases of readmission within 30 days (how many were bacteremia?) Does ertapenem used for this indication may have failed?

Response: New infections were defined as infections, of different pathogens, that were absent prior to ertapenem therapy. This definition is included in page 7 as highlighted text.

“Out of the 102 cases with new infections, 8 and 4 were primary and secondary bacteremia respectively” has been added in page 11-12, highlighted, for clarification. Ertapenem has not been used to treat these new infections.

When evaluating the efficacy of ertapenem, treatment failure was observed in 57 cases, where 14 cases were bacteremia (page 11). “Out of the 14 cases of bacteremia, 8 and 6 cases were primary and secondary bacteremia respectively” has been added in page 11, highlighted, for clarification. “Seventy-three (36 primary and 37 secondary) out of 306 cases with bacteremia were readmitted within 30 days” has been added in page 11, highlighted.
There are a discrepancy between the numbers in the text and described in Table 4 related mortality. Which is correct? 98 (10.7%) or 110 (12.1%)? Please fix.

Response: The correct 30-day mortality rate is 10.7% (n = 97), as indicated in the text. The numbers in Table 4 has been amended (page 27). We apologize for the oversight.

The duration of therapy with ertapenem is not described in the results.

Response: It was included in Table 2, where median duration of ertapenem therapy is 8 days (range of 1 – 75 days). This has been included, highlighted, in the results, as suggested (page 10).

4. Discussion
The discussion is in agreement with the findings and conclusion as well. However they can be changed according to the results of bacteremia.

Response: A paragraph (highlighted) has been added into the discussion regarding efficacy of ertapenem in bacteremia, as mentioned above (page 15).

Reference:

Lee NY, Huang WH, Tsui KC, Hsueh PR, Ko WC. Carbapenem Therapy for Bacteremia Due to Extended-spectrum Beta-lactamase-producing Escherichia coli or Klebsiella pneumonia. Diagnostic Microbiology & Infectious Disease 2011;70(1):150-3


Responses to the comments of Reviewer #2

Major Compulsory Revisions

1. There are too many main objectives in this study and two of them cannot be
properly assessed. Because of its retrospective design, the study cannot evaluate correctly ertapenem efficacy and tolerance. And since it is monocentric and the definition of “appropriateness” can be criticized, evaluation of the appropriateness of the ertapenem use is of limited interest.

In fact, the main interest of this paper is the evaluation of the impact of ertapenem use on local bacterial epidemiology, since there are a large number of patients treated in a single center. Thus results and discussion must focus on this point, and other elements should be cited as minor data.

Response: While we agree with the reviewer that the main interest of this paper is to look at the impact of ertapenem use on local bacterial epidemiology on a macroscopic level, by including a drug use evaluation of appropriateness of ertapenem, we are able to evaluate ertapenem use and development of gram-negative bacterial resistance at patient-level. This gives a microscopic viewpoint that has not been included in previously published studies (refer to references below). Even though time series analysis may identify trends, it does not establish causation; which can be examined by including patient-specific data.

For example, in this study, fifty cases (5.5%) had cultures growing *Pseudomonas aeruginosa* within 30 days from initiation of ertapenem therapy (Table 5) with 25 cases growing carbapenem-resistant *Pseudomonas aeruginosa*. This is similar to the observation that increasing ertapenem consumption correlates with increasing incidence of carbapenem-resistant *Pseudomonas aeruginosa* over 3 years. This was also observed for *Acinetobacter baumannii*, where 20 out of 27 cases were carbapenem-resistant.

Therefore, we decided to still include the evaluation of ertapenem appropriateness and clinical outcomes, but briefly describe the results for this, and include more information on ertapenem impact on gram-negative resistance in SGH, such as DDD and incidence of gram-negative resistance as suggested below.

Reference:


Minor Essential Revisions

Introduction

1. Must be shortened and should focus on reasons for which ertapenem use could impact on bacterial ecology in general, and in the specific case of Singapur Hospital.

Response: The first part of the introduction, which focuses on the process of introduction of ertapenem into the hospital formulary, has been summarized. More details have been included in the introduction on how general carbapenem use (including ertapenem) can bring about acquired resistance (page 4-5).

Methodology

2. A three years study could be considered as too short to evaluate the real impact of ertapenem use on local bacterial epidemiology.

Response: Our study duration to assess the impact of ertapenem use on local bacterial epidemiology was 4.5 years (Jan 2006 till Jun 2010). It is true that even a 4.5 years study can be considered as too short to evaluate the real impact of ertapenem use on local bacterial epidemiology, as ideally more than 5 years study duration should be employed for epidemiological impact study. However, we did observe significant trends with increasing ertapenem consumption and increasing ESBL E. coli at zero lag. Increasing ertapenem use did not result in decreasing trend of ESBL E. coli. Ertapenem use did not affect ESBL Klebsiella spp, which was already trending downwards, before the increase in ertapenem consumption. In addition, we also observe increasing trends of ertapenem resistant E.coli and Klebsiella spp. with increasing ertapenem consumption. We also observe an increasing trend of carbapenem resistant Pseudomonas aeruginosa with increasing ertapenem consumption (page 13 and table 6).
Gram-negative resistance usually develops rapidly, and therefore 4.5 years may be sufficient to evaluate impact of ertapenem on gram-negative bacterial resistance. Nevertheless, the study duration of 4.5 years has been included as a limitation (page 19).

3. The definition of appropriateness can be criticized (to my mind, CNS infection and urinary tract colonization should be excluded, and penicillin allergy cannot justify by itself ertapenem use in case of enterobacteriaceae infection).

Response: We agree that CNS infection and urinary tract colonization are not appropriate indications for ertapenem use. The above reviewer’s comment seems to arise from the misleading nature of Table 1. We apologize for that. Table 1 merely described the types of infections for which ertapenem was used in the study patients, and these infections may or may not be appropriate for ertapenem use. This has been clarified in the text in page 9. We have also changed the heading for Table 1 and the text beneath the table. Also, it was urinary tract infections (diagnosed by Infectious Disease Physicians) that were depicted in Table 1, and not urinary tract colonization.

As this is a drug-use evaluation in Singapore General Hospital, appropriateness of ertapenem use is defined according to the antibiotic guidelines in our local institution. We have included ertapenem use for patients with penicillin allergy as appropriate if there is very limited treatment options left, like, in the case of causative pathogens that were resistant to fluoroquinolones, co-trimoxazole, and aztreonam, but susceptible to carbapenems.

There was only 1 case of CNS infection in the patients included, whereby ertapenem was initiated based on culture-directed ESBL Klebsiella brain abscess, where therapy was then escalated to meropenem for another 6 weeks. This was deemed as inappropriate use, as ertapenem has poor CNS penetration and is not recommended as 1st-line for ESBL CNS infections. There is only one paper investigating the use of ertapenem in meningitis in rabbits, where a dose of ertapenem given at 60mg/kg (equivalent to 1g in humans) was observed to have effective CSF sterilization.

Reference:


4. Please precise ertapenem dose adjustment according to renal function
Response: Ertapenem is usually dosed at 1g once daily, and according to company recommendations, dose is to be reduced to 500mg once daily for patients with creatinine clearance less than 30ml/min. This has been added into the methodology of the paper, as indicated by tracked changes (page 7).

5. Statistical analysis: no demographic data with univariate analysis appear in the results.

Response: The median age and length of stay of the patients were included in the first paragraph of the results (page 9). Figure 1 includes the percentage of patients with common co-morbidities such as diabetes and hypertension. Other demographics were not included as we feel that it does not have a great impact on the main objectives of this paper.

6. In addition to the correlation statistical analysis, it would be interesting, and even necessary, to give the DDD of the antibiotics cited, and the incidence rate reported by NARSS (references 15 to 21) since they are not easily searchable.

Response: Antibiotic utilization data for ertapenem has been included under the results section, as well as the antibiotic utilization data for anti-pseudomonal carbapenems, ciprofloxacin, ceftriaxone and cefepime, that showed a more significant change after introduction of ertapenem into the SGH formulary). Incidence density of significant changes in gram-negative resistant bacteria has also been added under the results section (page 12-14).

7. Table 5: legend is not appropriate since it describes “carbapenem-resistant microorganism” whereas ESBL enterobacteriaceae also appear in the table.

Response: Thank you for pointing this out, We have changed the title of Table 5 to “Microorganisms Isolated within 30 Days from the Start Date of Ertapenem Therapy” to reflect the actual intent of Table 5.