Author's response to reviews

Title: Clinical and microbiological characteristics of bloodstream infections due to AmpC beta-lactamase producing Enterobacteriaceae: An active surveillance cohort in a large centralized Canadian region.

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Author's response to reviews: see over
Philippa Harris  
Executive Editor, *BMC Infectious Diseases*  

October 16, 2014  

Dear Dr. Harris;  

**Re: Clinical and microbiological characteristics of bloodstream infections due to AmpC beta-lactamase producing Enterobacteriaceae: An active surveillance cohort in a large centralized Canadian region.**  

Thank you for your thoughtful reviews of our manuscript and the opportunity to resubmit a revised version for consideration of publication in *BMC Infectious Diseases*. We feel that the revised manuscript is an improved report, which addresses the Reviewers comments. Please find below an itemized list of detailed responses to each of the Reviewers comments. Within this itemized list, we cite each comment verbatim in bold type followed by our response.  

We hope that you will find this version suitable for publication in *BMC Infectious Diseases*, and look forward to your response.  

Vikas P. Chaubey  
Johann D. D. Pitout  
Bruce Dalton  
Daniel B. Gregson  
Terry Ross  
Kevin B. Laupland
Reviewer: Yasufumi Matsumura

Major Compulsory Revisions

1. The study design. The authors stated that this study investigated characteristics of AmpC-producing Enterobacteriaceae. All of the potential chromosomally encoded AmpC-positive organism and plasmid-mediated AmpC-producers that lack chromosomal AmpC were included in the study. Chromosomally encoded AmpC-positive Enterobacteriaceae do not always produce AmpC. For example, one study reported the production of AmpC was 38% in Enterobacter, 15% in Serratia, and 1% in Citrobacter (CID 2013;57:781). Others may have inducible AmpC but some isolates may not produce AmpC. Thus, to justify study design, 1) inclusion of only (phenotypically) confirmed or presumptive AmpC producers, or 2) inclusion of all Enterobacteriaceae and analyze according to AmpC-production seems to be appropriate.

We appreciate and agree with the Reviewer’s comments. We designed this study to answer this question in the clinical context. In general, clinicians obtain susceptibility results from the microbiology laboratory and tailor their antibiotic choices according to these susceptibility results. To prevent physicians from using β-lactam antibiotics in the treatment of these infections our laboratory does not report susceptibility of AE organisms to β-lactam antibiotics. Although cautious, this practice is not evidence based. Clinical and Laboratory Standards Institute (CLSI) recommends reporting β-lactams susceptibilities of these organisms, with a footnote suggesting that resistance may develop during therapy. Clinicians are generally uncertain if they should use β-lactam antibiotics, particularly for severe infections. In the clinical context it is impractical due to time and financial constraints to test each such isolate for the presence of the AmpC gene and/or inducibility of these genes. As such our study attempted to answer this question from a feasibility perspective. The isolates that were presumed to contain chromosomally mediated AmpC β-lactamases were not tested for inducibility or the presence of the AmpC gene and as such we are not able to do the analysis as the reviewer has requested.

2. Severity of illness strongly affects mortality of bacteremia. Although the authors acknowledge this problem, this is a serious limitation in the mortality analysis, the main analysis of this study.

We agree with the Reviewer on this point.
3. Line 196 and Table 2. Choice of antibiotics for treatment should be presented in detail. Not only comparison between piperacillin-tazobactam and oxyimino-cephalosporins, but also Group I and Group II or non-beta-lactam antibiotics is important to elucidate effects of adequate therapy of a specific drug.

4. Line 94. Study objective included effects of empiric and definitive treatment on mortality. However, details of definitive therapy were not shown in Results and Table 2. Most of patients were treated with non-beta-lactam definitive therapy, which is characteristic in this study and seems interesting to analyze.

Number 3 and number 4 are answered together. We have included one new table (Tables 3). This tables outline the details of empiric, first adequate and definitive therapy respectively. The manuscript has been modified to reference this table outlining details of therapy.

5. Line 293. A conclusion of avoiding oxyimino-cephalosporin for previous treatment history seems not suitable, because this study did not analyze risk factors.

This line has been removed.

Minor Essential Revisions
Page 162. (n=54, 9). What is 9?

Thank you for pointing out this typo. This has been removed.

6. Table 1. Please include cepefime, cefotaxime, or ceftadizime susceptibility and outcomes.

Cefepime susceptibility was not routinely performed on all isolates and therefore is not included in the revised table. Ceftazidime susceptibility has now been included.
Reviewer: Zeina Kanafani

Major Compulsory Revisions:
1- In the Introduction, the significance of the problem is not well stated. It would be important to make reference to studies from Canada regarding the prevalence and impact of AE.

Thanks you for this commentary. Our study has focused on AmpC producing Enterobacteriaceae that are chromosomally mediated. A very small number of isolates (30 E. Coli, 1 K. pneumonia, 2 S. enterica) were plasmid mediated of a total 458 episodes. There is no Canadian literature looking at optimal therapy of severe infections caused by AmpC producing Enterobacteriaceae that are chromosomally mediated.

2- The Results section (particularly the Outcomes subsection) is not very clear to the reader and is confusing. I suggest to either delete some of the details or to summarize them in a table format.

Thank you for pointing this out. We have restructured the Results section. We hope you will find this acceptable.

Minor Essential Revisions:

1- The authors found that Enterobacter is the most common AE causing BSI. This is not consistent with major literature reviews showing E. coli and Klebsiella spp to be more common. It would be important to comment on this discrepancy.

Our study has focused on AmpC producing Enterobacteriaceae that are chromosomally mediated. We agree with the reviewer that the literature comments on E. coli and Klebsiella spp. being the most important AE organisms in the literature. The literature has however focused on plasmid mediated AE and there is a paucity of literature focusing on chromosomally mediated AE.

In addition some institutions have described remarkably high rates of resistance in E. coli and K. pneumonia as a result of clonal spread of plasmids. Although present in our institution the rates of plasmid-mediated resistance by AmpC-beta lactamases has been stably low.