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Title	Emerging resistance among Escherichia coli strains in bloodstream infections in Toronto, Canada, 2006–2017: a retrospective cohort study
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Reviewer 1	Romain Basmaci
Institution	Hopital Universitaire Robert Debre, Paris, France
General comments (author response in bold)	Authors chose to include one isolate per species, per patient and per year (p4, lines 24-25). How did authors select the isolate, i.e. which isolate did authors select if the same patient had experienced non-ESBL and ESBL-producing Enterobacteriaceae during the same year? Similarly, did authors include twice a patient having an ESBL positive blood culture on December 31, 2007 and on January 1, 2008, for example? Please, clarify inclusion criteria. **We chose to include one isolate per species, per patient, per year following standard Clinical Laboratory Standards Institute (CLSI) recommendations (M39-A4 Vol. 34 No. 2 Analysis and Presentation of Cumultative Antimicrobial Susceptibility Test Data; Approved Guideline 4th Edition, CLSI, Wayne, Pennsylvania) as described in our response to comment 4 above. This includes choosing the first isolate per patient per year regardless of susceptibility results. This also includes choosing one isolate per patient per year which theoretically could include a patient on Dec 31 of one year and the same patient on Jan 1 of the following year. While we find the reviewer's suggestion an interesting perspective, we would prefer utilizing established methods allow for better comparisons between antibiograms developed in other laboratories.** Authors did not specify the p value used to define a significant difference (p6, lines 1-7), thus they stated that the "upward trend of K. pneumonia (…) failed to achieve statistically significance (p=0.04…)" (p7, lines 6-8). Please clarify. **We thank the reviewer for pointing out this error. We regret this error and have defined in the methods what our statistically significant cut-off value was for the study (see page 6 lines 3-4) and have corrected the error (page 6 lines 3-5).** Authors observed a high rate of ESBL producing Enterobacteriaceae and concluded "ceftriaxone may not be an appropriate empiric choice for treatment of suspect E. coli bacteremia" (p8, line 28-30). Although they noiced "a significant increase in aminoglycoside susceptibility in ESBL" (p8, lines 30-31), authors did not state whether they results have led to change their practices, and which antibiotics they recommend in such clinical situations. **We were purposely not prescriptive in our suggestions given that we believe local data should inform individual choices of empiric treatment and that the patient's clinical status should also be taken into consideration along with antimicrobial stewardship input. We have added a statement to this effect in the manuscript (see page 8 line 30 and page 9 lines 1-2). We have moved the reference to the change in aminoglycoside susceptibility to page 8 lines 19-22 to better reflect the intent of this statement which suggests a possible novel strain of ESBL having been introduced into the population in more recent years. This finding currently would not impact empiric choice given that the overall aminoglycoside susceptibility amongst all E. coli was not significantly impacted.** Minor comments: -P6, lines 17-18: Please add the total number of included isolates as well as the percentage of each species involved in Enterobacteriaceae bacteremia **We have added in the total number of included isolates as well as the percentage of each species on page 6 lines 14-15.** -P7, lines 23-25, please specify that these results were obtained with the 2016 data (as specified in Table 3) **We have included that data reflect data from 2016 on page 7 line 19.** Typographical comments -Please write the genus and species in italics (title of Figure 1, references) -Figure 2 is difficult to read in black and white printing **The E. coli in the title of Figure 1 has been italicized as have the organisms in the references. To improved readability of Figure 2 in black and white printing, we have changed the shapes associated with each line to make it easier to differentiate.**
Reviewer 2	Gabriel López-Velázquez
Institution	Instituto Nacional de Pediatria, Medicina Experimental, Ciudad de México, Mexico
General comments (author response in bold)	No comments
Reviewer 3	M. Angarone
Institution	Division of Infectious Disease, Northwestern University Feinberg School of Medicine, Chicago, Ill.
General comments (author response in bold)	One comment I have is that on Page 11, Line 6-8: the sentence states that the upward trend in ESBL K. pneuomiae was not statistically significant, however the p=0.04. Is this not significant? **We thank the reviewer for pointing out this error. We regret this error and have defined in the methods what our statistically significant cut-off value was for the study (see page 6 lines 3-4) and have corrected the error (page 6 lines 3-5).**