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Title	Pathogens and antimicrobial susceptibility patterns in Canadian critically ill patients with bloodstream infections: a descriptive study
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Reviewer 1	Dr. Jane Buxton
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General comments (author response in bold)	*Implications for policy/practice:* *1. One described benefit of reporting on local routine clinical isolate testing data was more timely information about resistance. It would therefore be of interest to know the expected difference in timeliness between reports from the proposed process versus the CANWARD process (how long does the CANWARD process take?* **We are unable to define the exact duration of time required for microbiological surveillance networks such as CANWARD to determine prevailing antimicrobial susceptibility patterns, but the process will by definition be more protracted than using readily available clinical microbiology results, because of the need to gather, transport and process biologic specimens. Although there may be similar time delays in establishing a network based on routinely available data, once established, such a network would be able to much more quickly generate serial updates. We have clarified this notion in the introduction section (page 3, paragraph 3).** *2. A proposal made in this manuscript is to expand data sharing between Canadian ICUs, but it is not clear how data sharing would help guide local empiric antimicrobial management in ICUs.* **Data sharing would facilitate comparison between ICUs which is important for benchmarking, and identifying where local ICUs are doing well with management and areas where they could improve.** *3. Another stated benefit of utilizing routine diagnostic data to create databases, versus a process such as CANWARD, is the potential to link "detailed clinical and outcome data" to these databases. However, this was not demonstrated. It would be helpful to know what clinical data they may want to collect for linking and how this may impact practice.* **Linking to patient characteristics (age, sex, comorbidities, source of infection, etc.) and outcomes (length of hospitalization, mortality, etc) could identify which pathogens affect which sub-populations, and which pathogens have more severe consequences and require prompt attention.** *Method:* *4. Please describe variables collected for example:* *a. Mean age was reported in results but not clear when age determined - at time of symptom onset, on admission to ICU, on taking of sample presumable age was normally distributed as mean presented- was distribution of age assessed to determine if mean was appropriate?* **Age was abstracted from patient records and was based on age at admission (either to hospital or ICU, whichever came first).** **The distribution of age followed a normal distribution with a slight left-skew; the median of 62 years was very similar to the reported mean of 60 years, and so we felt it was appropriate to report the mean.** *b. Results also mention co-morbidities - how and who determined the presence of co-morbidity?* **Similarly, co-morbidities were abstracted from patient records, and were therefore assessed for and recorded at admission by on site research co-ordinators.** *5. Only one episode of bacteremia per patient was included in the study: how was the episode to include chosen – first or last?* **The first episode was chosen; repeat episodes of bloodstream infection in the index hospital admission for patients already enrolled were excluded.**

6. Patients with a single positive culture with a common contaminant were excluded. Unclear if excluded if cultured a common contaminant in addition to a known pathogen. What are the potential biases will this decision introduce?

We excluded patients with cultures that only yielded a common contaminant in a single culture. We did not exclude patients with cultures that yielded both a pathogen and a contaminant. This distinction is now clarified in the methods section (page 4, paragraph 1).

7. What were sample sizes (up to max 100 but exact #s or range each); we do know one hospital had small #s and was excluded from some analyses.

The sample size of patients included from each ICU is provided in the table below. One hospital site contributed only 5 patients – this site was excluded in any analyses comparing sites. For the remaining 13 sites, more than half (n=7) contributed the maximum of 100 patients to the study population; the remaining contributed a range of 38 to 99 patients. We have added the following to the methods section: "Seven ICU sites contributed the maximum number of patients to the cohort, five contributed >80 patients, and two contributed 5 and 38 patients respectively." (Page 4, paragraph 1).

ICU	N
1	99
2	82
3	5
4	100
5	100
6	85
7	100
8	94
9	99
10	100
11	100
12	100
13	38
14	100
Total	1,202

8. What is time duration of retrospective analysis at each site? States backwards from Dec 2013- how far back did they go? This may be important to know since resistance patterns are affected by time.

In the table below, the distribution of patients by admission year is shown below. More than 80% of the study population was accrued in the three most recent years (2011, 2012, and 2013). We have also added a statement to indicate this in the methods.

Year	Number of patients
2002	5
2003	3
2004	8
2005	7
2006	16
2007	14
2008	32

2009	33
2010	109
2011	239
2012	645
2013	91

9. Time periods suggest within 48 hours and more than 48 hours. Where are patients classified if the blood culture was obtained exactly 48 hours after hospital admission or 48 hours after ICU admission?

Only the date (not time) of hospital admission was collected (in contrast to ICU admission and first blood culture for which both date and time was collected). As a result, we could only determine the time between hospital admission and blood culture in days. 47 patients had an infection diagnosed on a blood culture obtained 2 days (48 hours) after hospital admission, and were classified as community-acquired.

We have updated the wording in our methods section to reflect this (i.e. The setting of acquisition for the bloodstream infection was classified as community-acquired if it was diagnosed on a blood culture obtained within *or equal to* 48 hours of hospital admission…). (page 4, last paragraph).

Results:
10. Please define the APACHE II score – what is score out of and are higher or lower #s better i.e. help the reader to interpret a mean score of 29 SD=9.

Each patient's baseline Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated within 24 hours of ICU admission. APACHE II is a measure of severity of disease that is based on initial values of 12 routine physiologic measurements, age, and previous health status. Scores range from 0 to 71, with higher scores indicating more severe disease. We have added a short description of the measure to our "*Data collection and measures"* **section of the methods (page 4 last paragraph).**

11. Under patient descriptions, are the numbers and percentages consistently referring to numbers of patients, or are they sometimes referring to numbers of microbial isolates.

In the section 'patient description' both the numbers and percentages refer to numbers of patients, not to number of isolates. We have now clarified this in the Statistical Analysis section (final paragraph of methods).

12. Did mortality vary by mono versus polymicrobial infection? Did mortality vary by community versus hospital versus ICU acquired?

Mortality rates were similar for patients with monomicrobial infection (406/1025 or 39.6%) compared to polymicrobial infection (73/177 or 41.2%) (X^2=0.168, P value=0.682).

Mortality rates did, however, vary significantly by acquisition setting. Rates were highest for patients who acquired their infection in hospital (110/208 or 52.9%) and ICU (163/364 or 44.8%) and lowest for patients with community-acquired infection (206/630 or 32.7%) (*X*2=31.877, P value<0.001).

We have added these findings to our Results section (first paragraph).

13. How did different comorbidities and previous antibiotic use correlate with different infections, susceptibility, HRMOs, and mortality?

Our study team abstracted information on more than 30 comorbid conditions, making it challenging to present all of this data in one manuscript. If the Editor or Reviewer is interested in certain specific conditions, we are happy to conduct additional analyses.

	Interpretation *14. It is important to know the range in timeframes from which data was analysed between different sites in order to know if it is appropriate to pool the data from all ICU sites.* **The majority of data derived from the three most recent years (see above), and so we felt it was appropriate to pool the data for this proof-of-principle study. Future use of this methodology in Canada, could include serial updated analyses restricted to narrower time frames (see final paragraph of discussion).** *15. What are the potential consequences/biases of excluding patients with deep seated infections and those who grew a single positive culture with a common contaminant?* **The exclusion of those with a single positive culture with a common contaminant should not introduce bias, because we did not exclude cultures that yielded both a pathogen and a common contaminant.** **The exclusion of deep seated infections means that the dataset is biased (slightly) towards pathogens which are less likely to cause deep seated infections, and so could, for example, underestimate the proportion of bloodstream infections that are due to *Staphylococcus aureus*.** *Figures/Tables:* *16. Figure one is difficult to see and difficult to interpret especially if printed/viewed in black and white and the key is just a horizontal list.* **We have changed Figure 1 to grayscale.** *17. Figure two: is the dot the mean?* **In Figure 2, the red dots represent the overall prevalence of a pathogen for all ICUs combined, while the arrows represent the range in proportion of the particular pathogen across ICU sites. This is described in the figure title – we welcome editorial suggestions to make this clearer.** *18. Figure three: Assuming that the ICU sites are consistently numbered, it seems that site 8 is an outlier. Can/should this be explained?* **The ICU sites are consistently numbered, but it does not appear to us that site 8 is an outlier. The error bars are wider, and overlap those of the other ICU sites.**
Reviewer 2	**Ibrahim MomenKhan**
Institution	Clinical Assistant Professor of Medicine St. Clare's Hospital, St. John's NL
General comments (author response in bold)	*1. On page 5, first paragraph, is that 24 hour period as it seems?* **Thank you for catching this omission. We have added the word "hour" to the following sentence: "Only one episode of bacteremia was included per patient, but all organisms isolated in blood culture sets over the first 24 hour period from the index blood culture were considered to be contributors to the index bacteremia." (Methods paragraph 1).** *2. The term HRMO, although based on modified version of de Smet definitions, but is relative particularly for non enterobacteriacea where 3 Antimicrobials resistances seem too many to be required to meet the definition, when the rate of CRNE is quite high (Carbenem resistance non enterobacteriacea is almost 20% as shown on Table 2.); relative to only 4 isolates of CRE. One may like to see in the HRMO definition those CRNE to be more prominent probably by adding a category of CRNE (? Instead of Carbenem resistant Acinetobacter).* **There are no consistent global definitions of highly resistant micro-organisms, but we have selected the de Smet definition for two reasons. First, it is a broad definition of relevant pathogens (whereas most North American definitions are limited to MRSA, VRE, ESBL and CREs. Second, it has been used widely in studies of antimicrobial resistance in intensive care units.** *3. Again on the HRMO definition for Acinetobacter, ceftazidime would not be clinically relevant to be used in Acinetobacter bacteremic critical ICU patient particularly*

	that cephalosporins in general are not reliable particularly due to AmpC gene prevalence. **There was only one patient who had *Acinetobacter* spp resistant to at least two of fluoroquinolones, aminoglycosides or ceftazidime. The patient was in fact resistant to all three, and so, in our study, there were no patients with *Acinetobacter* spp infection that met the HRMO definition on the basis of resistance to ceftazidime.** *4. The "Non enterobacteriacea" referred to in the article are Gram Negative bacteria? This would be important to specify although seem clear.* **Yes, they are. We have added this as a footnote to Table 2**. *5. The 5 commonest pathogens did not include enterococcus sp. (11% as shown on Table 1) and yeast (6.6%, unless excluded by replacing "pathogens" by "bacteria") in results nor in interpretation.* **In Table 1, pathogens have been grouped by related species (spp); in the text of the results we provide the five most common pathogens, ungrouped, to provide additional information to the reader. We have added wording in the text and table heading to clarify that we grouped the organisms by species in the figure title and in the description of the results.** *6. We would like to thanks authors for documenting the limitation of selective testing of isolates causing potential under- or overestimation of resistance. An important example here is from Table 2, Carbepenem susceptibility among non enterobacteriacea (80.9%) vs. FQ (84.4%) which may be underestimated as only 54% tested vs. 76%, respectively.* **We agree that incomplete testing of isolates is a potential trade-off of using this approach for antimicrobial resistance surveillance. We have emphasized this limitation in the discussion section (see limitations in penultimate paragraph). We also agree with reviewer #2 that it is essential to report not only the % susceptibility, but also the % tested, and so we have provided this information in table 2.**