Impact of Vancomycin-Resistance on Mortality in Neutropenic Patients with Enterococcal Bloodstream Infection: a retrospective study

Thank you for the opportunity to review this manuscript

This retrospective study describes the outcomes of neutropaenic patients with enterococcal bacteraemia at a single centre. Several papers have demonstrated an increased mortality with VRE bacteraemia however the patient cohorts in previous studies are often heterogenous. Therefore attributing mortality to VRE bacteraemia is challenging. This study aims to describe and compare the mortality between VRE and VSE bacteraemia in patients with neutropaenic fever in the setting of chemotherapy or SCT for haematological diseases.

This manuscript overlaps with the study by Vydra et al, which prospectively examined the incidence of enterococcal BSI in 752 patients undergoing allogenic stem cell transplantation.

The conclusion of the paper is erroneous: the 30 day mortality was OR 1.38 (95% CI 1.08,1.17, p=0.059) and the authors have concluded vancomycin resistance itself is not associated with mortality. This is an incorrect assumption. The authors noted in the manuscript that the study was underpowered to detect a difference therefore it is unclear whether there truly is no difference in mortality or the study size was too small. The authors should amend their concluding statement.

Background:

“Whether vancomycin resistance increases mortality among patients with enterococcal BSI is a major problem because such a trend could affect the empirical therapeutic approach…”

Empirical therapy should be guided by the incidence of isolated organisms and should aim to cover (a) the most frequently identified pathogen and (b) common (but less frequently isolated) organisms associated with significant patient morbidity and mortality. It should not be guided by mortality alone. The study justification is that VRE is an increasingly common isolate, about which current
knowledge regarding risk factors, impact and mortality is conflicting. I would suggest the authors rephrase this sentence for clarity.

Methods:

There were a number of methodological issues identified that need further attention / explanation:

The authors need to expand on the process of data collection and data source. Was it obtained from a prospectively collected database or retrospective chart review? This is an important point to assist in assessment and interpretation of the results.

The authors have excluded neutropaenic patients with enterococcal BSI if they had not received chemotherapy or SCT. The authors should justify why they excluded these patients? How many patients were excluded? Did it affect the overall analysis?

The authors need to include in the analysis important factors such as prior exposure to antibiotics, gastrointestinal disease etc in table 1 and for table 3, septic shock, ICU admission, hemodialysis etc.

The definition of ‘separate episode’ of bacteraemia is at odds with other published studies where the conventional definition of new episode of bacteraemia is 7 days. The authors should explain why this definition was selected. In addition, how many patients fitting the conventional definition of separate episodes were excluded from this current study?

The authors used the SAPS II (predominantly used for patients admitted to ICU): this predictive score uses measures such as urine output and PaO2 – given this was a retrospective chart review and only 23 patients required ICU admission, how did the authors calculate this score and how complete was the data? If patients had missing data were they excluded, or was that parameter scored as ‘normal’?

Similarly with the Charlson’s Comorbidity Index, was underlying haematological malignancy included in the calculated score (given all patients had haematological malignancy) or was it excluded to examine for the impact of other comorbidities, given the type of haematological malignancy was examined separately?

Given the minimum value in both the VRE and VSE group is 0, I suspect the authors have adjusted CCI but this is not clear.

The authors included ICU care in their analysis. It is not clear whether this was ICU care before or after enterococcal BSI.

The authors discuss the empiric therapy for neutropaenia at their centre referring to glycopeptides. Is teicoplanin (which is active against some types of VRE) part of the empiric therapy, or are the authors referring to vancomycin?

The authors introduce the hospital policy for screening and isolation of VRE at
their centre in the discussion: this should be included in the methodology. Define and reference ASBMT guidelines.

In addition, the statistical methods should be expanded upon including the selection of factors to include in the multivariate Cox proportional hazards model (including forward or backward elimination). Given the small numbers (only 21 events) inclusion of a large number of variables in the multivariate model is problematic and may lead to over-fitting of the model (rule of 10).

Results:

The authors comment that of the 24 VRS BSI patients, rectal swabs were performed in 20 however, it suggests that only 9 patients had swabs prior to BSI: the authors should also include data on how many patients with VSE BSI were colonized and how many patients in the haematology unit.

The authors state that a monthly review of incidence rates of enterococcal BSIs showed no outbreaks. This is a crude means of assessment. Were molecular tests performed to exclude any epidemiological link between cases?

The authors state that the median interval from the onset of febrile episode to administration of adequate antibiotics was 1.4 days in the VSE group and 2.8 days from the VRE group. The authors had previously defined delayed antibiotic therapy from the time of blood culture attainment. Whilst one may presume that the onset of fever coincided with the drawing of blood cultures, it is best to keep a consistent definition.

Discussion:

“Our results suggest that current antibiotic strategy of adding glycopeptides in febrile neutropenic patients with presumptive bacteremia caused by Gram-positive organisms is sufficient, and that administration of anti-VRE therapy empirically or pre-emptively before obtaining the final microbiology results may not be necessary.”

The authors need to be cautious in their interpretation of the association (or lack of association) in crude mortality and VRE BSI given the small numbers, particularly as the chi2 p value of 0.059. Indeed, the authors have highlighted that the study was under-powered to detect a difference. I suggest the authors amend this statement: it is too strong a statement to make on the basis of this study (See comments in the abstract and background).

Authors thought the results suggest that administration of anti-VRE therapy empirically or pre-emptively before obtaining the final microbiology results may not be necessary. However, it can be interpreted otherwise. Early institution of anti-VRE therapy may improve the outcomes of VRE BSI: this current study is not adequate to evaluate the usefulness of empiric or preemptive anti-VRE therapy.
I would avoid phrases such as “favorable outcomes in the VRE BSI group” – there was a 17% 7-day and 27.3% crude mortality rate in this group.

Delayed administration of antibiotic therapy should not be assessed as a risk factor for the development of enterococcal BSI as it occurring after the episode of bacteraemia. However, it is reasonable to examine the impact of this variable on mortality.

**Tables:**
1. the authors have not provided a p value for the types of haematological malignancy, treatment or enterococcal species from the chi2 test.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests