

00608223

Conclusion: Major revision

Scientific Quality: Grade
C (Good)

Language Quality: Grade
A (Priority publishing)

The title reflects the main subject of the manuscript and the abstract and key words summarize/reflect the work described in the manuscript. In general the manuscript is coherently organized and presented, and language appropriate. A STROBE checklist is not uploaded as supporting file, but the features required by STROBE have mostly been included. The introduction adequately describes the background to the study regarding VAP, and some of the background on cancer patients in the ICU.

It would have been good to see some additional epidemiology about these patients in the ICU setting - are they more commonly being admitted to ICU now compared to the past? What features might be dictating any changes? I ask this mainly because only half of the patients were thought to be in remission, with others having progressive disease - many ICU worldwide would not accept patients with progressive cancers for such invasive treatments at MV.

Response: The characteristics of the patients admitted to the ICU during the study period have not changed in recent years. The ICU admission policies in our hospital include the admission of patients in complete remission, but also in relapse or progression, as long as they have an expectation of survival > 3 months, an adequate functional state, and if they are in the first or second line of treatment, depending on the type of cancer and clinical stage. Discussion page 12, 2nd. paragraph.

This would help the authors contextualize their cohort with the rest of the world. The manuscript describes methods in adequate detail, this being a retrospective cohort

study largely using routine data, however there are some improvements which could be made, mainly on the statistical approach.

In this area the methods are not wholly consistent with the reporting of results, which requires clarification - for example the methods state "Variables with p values of <0.5 in the univariate analysis were included in the multivariate analysis", however in the table in which the multivariate results are shown there are many factors which appear to have $p < 0.5$ in the univariate that were not in the multivariate model.

This was a mistake, the p values in univariate analysis included in multivariate analysis were <0.3. It was corrected in statistical analysis. Page 8.

Why was logistic regression chosen over Cox regression and was there any assessment of collinearity in the data?

Logistic regression was chosen because we focus on outcome, more than the time of VAP presentation.

Why was multivariate analysis only reported for mortality and not for development of VAP in its full form? The methods say it was done and there is some reporting in the text but I was not clear which factors went into the model.

It was not included because we only found that ICU length was the only risk factor associated. We included the table 3 with VAP vs. non-VAP uni- and multivariate analysis. Page 22.

Ethics was approved, in that a certificate was uploaded to the journal, but this is not stated in the actual manuscript - this should be added to the methods.

It was included. The study was approved by the INCAN Institutional Review Board (REF/INCAN/CI/0922/2019).

The results largely concur with prior work in the field of general ICU patients indicating factors which may predispose to VAP and to mortality after an ICU stay. The organisms observed in the VAP patients were also fairly typical. The novel factor in this study was looking at cancer patients - I would be interested if cancer status (progressive or not) was a risk factor for VAP or death, and whether any treatment limitations were put in place (eg not for haemofiltration, not for CPR) in those with progressive disease.

We included data comparing recent diagnosis, complete and partial remission vs. cancer progression or relapse in table 3, and did not find a relationship to present or not VAP. Therapeutic limitations in these patients are individualized according to the criteria of the medical oncologist in conjunction with the intensivist.

Reporting of VAP multivariate work could be better too as listed above. Tables are sufficient and appropriately illustrative of the paper contents. SI units were used. In the discussion the manuscript interprets the findings appropriately, but I felt the novelty of the cancer cohort was not enough - however to do this and really discuss the impact of cancer on ICU admission the team would need to analyze more around the cancer angles as described above. The limitations section is very brief and could be expanded.

		<p><i>The discussion regarding cancer was expanded. Page 11, 12.</i></p> <p><i>Limitations were also expanded. Page 15.</i></p> <p>Referencing in the discussion was reasonable.</p>
03342506	<p>Conclusion: Minor revision</p> <p>Scientific Quality: Grade C (Good)</p> <p>Language Quality: Grade B (Minor language polishing)</p>	<p>Authors present a single center retrospective observational study from a cancer referral center looking at ventilator associated pneumonia in patients with cancer and impact of multi drug-resistant bacteria. The study is overall well presented and of some interest to clinicians and researchers in the field. The following issues should be addressed prior to considering the manuscript for publication:</p> <p>One of the primary findings is the association of LOS and VAP . This finding needs some explanation. Is this LOS BEFORE VAP? Otherwise, the reason for association would be explained by "effect-cause" bias (VAP causing increased LOS, rather than viceversa), The same comment is related to hospital LOS and duration of ventilation. Please clarify. <i>This explanation related with effect-cause bias was included in the discussion page 12, 3rd paragraph.</i></p> <p>Please consider specific suggestion for each section below: ABSTRACT Methods: Page 2 Line 17-18 needs to be rephrased "They were classified as those who developed or not VAP" to "they were classified as those who developed VAP versus those who did not". <i>It was rephrased, abstract, page 3.</i></p>

Page 2 Line 19: "The presence of MDRB was recorded" is redundant as authors have mentioned this in the preceding sentence.

The sentence was omitted.

"Outcome at 60-day was assessed" what were the assessed outcomes (primary & secondary)?

Clinical evolution at 60-day was assessed. It was changed. Abstract, page 3.

Conclusion: "This study highlights the high percentage of Gram-negative bacteria, which allows the initiation of empiric antibiotic coverage for these pathogens." This adds no new knowledge to the current literature available regarding microbiology of ventilator associated pneumonia. Lopez-Ferraz, C., et al. (2014). "Impact of microbial ecology on accuracy of surveillance cultures to predict multidrug resistant microorganisms causing ventilator-associated pneumonia." J Infect 69(4): 333-340. Thakuria, B., et al. (2013). "Profile of infective microorganisms causing ventilator-associated pneumonia: A clinical study from resource limited intensive care unit." J Anaesthesiol Clin Pharmacol 29(3): 361-366.

We partially agree, since although previous studies have been published with the profile of MDR bacteria in patients with VAP in the ICU, this study shows different results (example when compared to Thakuria and cols). We included this reference. discussion, page 13).

However, the main difference is that our study is focused on cancer patients, who although they have an additional factor of comorbidity and immunosuppression, don't therefore present more frequently VAP episodes, or a higher frequency of MDRB.

“There was no impact on mortality related to MDRB.” This study does not have enough power due to limitations of small sample size to establish this statement as a conclusion. The authors could potentially rephrase the statement as “In this single centered retrospective observational study, MRDB VAP was not directly linked to increased mortality at 60 days”.

We change the statement in the conclusions. Page 4.

MAIN MANUSCRIPT Material and Methods: Page 5 Line 4: “Diagnosis of VAP”, authors should provide details on how they defined VAP for this study or provide a reference for standard diagnosis of VAP. Different than “pneumonia” present at the time of admission.

Definition was added in methods, page 6-7.

Page 5 Line 5: “XRD” acronym is used for the first time without previously explaining it. *XDR acronym was included. Page 6.*

Authors should also clearly state what were the primary and secondary outcomes. *These outcomes were added. Page 7.*

Results: Page 6 line 12: " 736 patients were admitted to the ICU: 245 patients required MV for less than 48 h and 128 did not require intubation; 263 patients were included" Adding $245+128+263 = 636$, authors should explain this discrepancy.

It was a typo: 345 patients required MV for less than 48 h and 128 did not require intubation; 263 were included: $345 + 128 + 263: 736$. It was corrected, results page 8.

In the results section authors described that 38 patients had pneumonia as the primary diagnosis requiring mechanical ventilation and 32 patients had developed VAP. How did the investigators differentiate progression of pneumonia from development of new ventilator associated pneumonia is unclear in the manuscript.

In those 38 patients who were admitted to the ICU with pre-existing pneumonia, the clinical worsening, and/or the appearance of new clinical data compatible with pneumonia criteria were considered to be redefined as VAP. It was included in definition, page 7.

Page 7 Line 25 : Risk factors for VAP Authors do not provide any information about the immunocompromised state of the patient such as active chemotherapy, use of steroids etc.

This was expanded in the results page 9, and Table 3 was added, where the comparative analysis is made between patients who develop vs. those who don't, a VAP

Discussion Page 8 Line 28: "An important finding in this study was that patients with VAP more frequently received broad-spectrum antibiotics (particularly cephalosporins, Tazobactam/Piperacillin, carbapenems, and Vancomycin)." This is expected, since this subset of patients was critically ill and required empiric antibiotics.

It is explained later in that same paragraph, because it is part of the empirical treatment, however, it is a finding that was very clear, which is why we consider it important to highlight it. Page 12, 13.

They are understandably at a higher risk for longer intubation and length of stay in ICU. *These were also clarified as potential bias in the discussion. Page 12.*

Further correlation with immunocompromised state (active chemotherapy and/or steroids) needs to be taken into account.

This were added in table 3 and included in discussion, page 13.

Also correlation with degree of illness SOFA and charlson comorbidity index is not discussed.

"The median of Charlson Comorbidity Index was 3 for the whole group, that corresponds to one-year mortality rate of 52%. SOFA index was less than 10 in all patients, without differences between VAP vs. non-VAP, that indicates between one or two organ failures, and a mortality percentage between 10 and 25%". This sentence was included in discussion, page 12.

The median duration of mechanical ventilation is quite long with subsequent high mortality related to primary disease. It would be interesting to explain the palliative care and end of life care practices in your institution.

CONCLUSION Page 10 Line 28: "It is important to highlight that the MDRB bacteria had no clinical impact in this group of patients." This study does not have enough power due to limitations of small sample size to establish this statement as a conclusion.

It was changed as same as the conclusion in the abstract. "In this retrospective, single center, observational study, MDRB VAP was not directly linked to increased mortality at 60 days".Page 15.

TABLES Table 1: Instead of presenting clinical and demographic characteristics of all patients with mechanical ventilation during the study. Authors should consider presenting a table comparing the group of patients that developed ventilator associated pneumonia versus group of patients that did not developed ventilator associated pneumonia (VAP) to see if the groups were appropriately matched and important differences between the groups. Same comments for Table 2.

Both tables were changed comparing patients with and without VAP.

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Conclusion: Accept
(General priority)

Scientific Quality: Grade

First, Original aspects: This study highlights the high percentage of Gram-negative bacteria, which allows the initiation of empiric antibiotic coverage for these pathogens. Second, this study demonstrate of empiric antibiotic coverage no impact on mortality

C (Good)

Language Quality: Grade

B (Minor language
polishing)

related to MDRB. Third, the limitation of the study: the results are referral in only one center in Mexico City.