Reviewer's report

Title: 7 versus 14 days of Antibiotic Treatment for Critically Ill Patients with Bloodstream Infection: A Pilot Randomized Clinical Trial

Version: 0 Date: 26 Nov 2017

Reviewer: Felipe Castañeda

Reviewer's report:

Dear Authors.

This is an interesting article about a Randomized Clinical Trial (RCT) comparing 7 days versus (vs) 14 days antibiotic treatment for critically ill patients with bloodstream infections. After its review the following comments have been raised up.

ABSTRACT. It would interesting if the authors could comment quite more extensively the "Background" subsection. In addition, in the "Methods" subsection, it would be correct if the authors could define better the RCT: it was an open RCT, it was a single, Double or Triple blinded RCT? Or it was a double dummy RCT? In addition, please precise better the inclusion-exclusion criteria. And please mention briefly the Primary - Secondary objectives and outcomes. Please describe briefly, in this section, the interventions done during the study (antibiotics used, doses used, and posology). Regarding the "Results" subsection, the fact about the "recruiting rate" should be better explained because it is alligned with the primary feasibility outcome. Please explain better the "adherence results" because when reading them are quite confusing. Please comment to some extent the " Conclusion" subsection: it is considered that, if the principal outcomes are feasibility and adherence to treatment, then the achievement/not achievement of these outcomes should be better commented in the Conclusion Section. And if a "90 days survival" concept is mentioned in the Conclusion "subsection", this same concept should be defined in the "methods" subsection as a primary-secondary objective or outcome.

BACKGROUND.

The authors comment that "both antibiotic use and antibiotic resistant organisms are high in the in the Intensive Care Unit (ICU) where critically ill patients are vulnerable to bacterial infections and antibiotic complications". It would be interesting if the authors could comment to some extent, this clinical information (commenting about its epidemiology, the principal antibiotics used in the ICU, their principal indications in the ICU, the principal resistant-microorganisms, the main antibiotics to whom bacteria have developed resistance, the principal mechanisms of resistance, etc). Additionally, the authors comment that RCTs have established that "shorter
duration treatments are sufficient for a wide of bacterial infections, including some infections in critically ill patients”. It would be correct if the authors could comment, to some extent, these RCTs, these shorter regims, the addressed infections (in non critically ill patients and critically ill patients), and the evaluated antibiotics (as pooled data). The authors also comment, that through a literature systematic review, they identified studies of other bacterial infections where pooled data showed similar clinical outcomes when giving short term antibiotic treatment versus long term antibiotic treatments. It would correct if the author could comment also, and to some extent, this information too (type of infections, antibiotics used, interventions done (short and long treatments), main results (already explained but commenting them quite longer) safety aspects etc) commenting them as pooled data. All these information could describe better the actual “state of the art” of this important medical field (bloodstream infections) giving a complete view of what it is done and what has to be done. And it would give a better support to the rationale of this RCT explaining why it is important to carry out this study.

PRIMARY AND SECONDARY OBJECTIVES. Please explain the Primary and Secondary Objectives that were defined for the Randomized Clinical Trial.

METHODS.

General Study Design. Please define better the Clinical Trial. Opened?, Single Blinded ?, Double Blinded?, Triple Blinded? Double dummy ? Superiority ?, Non inferiority ? (Already commented). Please explain better why one of the aims of this RCT is to inform the results of a non - inferiority CT ?. Is this study that one non inferiority CT ? In addition please explain the relationship between this RCT and the BALANCE Clinical Trial (CT). If this CT is non randomized and is the BALANCE CT please include it in its definition. Additionally please explain why did the authors decided an experimental design (CT) for the evaluation of the feasibility of a project and the adherence to a treatment?. This is so, because an observational - analytical study (cohort study) could possibly demonstrate, better than a CT, these objectives (feasibility and adherence).

Study Setting. If the authors consider so, a brief description of the study setting could be done. It considered that it is enough with mentioning that the CT was carried out in 11 centers (sites) in 10 cities across 5 Canadian provinces. And in the annexes to include a list with all the participant Intensive Care Units (ICU´s) and Hospitals (with their respective city and province).

Patient Selection Criteria.

It is considered that this section should be reorganized: divided in two sections with defined the Inclusion Criteria and the defined Exclusion Criteria.
Inclusion Criteria. Please define better the Inclusion Criteria: Accepted Minimum and Maximum Patient Ages, Gender, Pregnancy State (did the authors consider to do a pregnancy test to all those eligible female patients before including them in the CT?). Do patients with other chronic infections (High Blood Pressure, Diabetes, Hypercholesterolemia, Ischemic Cardiomyopathy, Atrial Fibrillation, COPD, Asthma, etc) and having a concomitant bloodstream infection were considered eligible patients? Non Risk Factor Patients with acute infections (community acquired pneumonia, Gastrointestinal Infections, Central Nervous System (CNS) Infections, Dermatologic Infections, etc) and with concomitant Bloodstream Infections were eligible to participate in the CT? Please define better all these aspects. Please define what do the authors consider as a Bloodstream Infection (principal clinical criteria) to be eligible for inclusion in the CT. How many positive blood cultures were considered to be needed for the inclusion of patients? Please specify the protocol followed for the correct extraction of blood for the blood culture in order to avoid false positive results? (risk of ibas).

Exclusion Criteria please define if patients taking immunosuppresant medications (ciclosprine, azathoiprine, mophetil mycophenolate, etc), HIV patients, HCV patients, Lung, Breast, Prostate, Cancer Patients, receiving chemotherapy - hormonetherapy or not, (all of them susceptible for the acquisition of severe infections) were excluded from participaron in the CT. Please explain why patients having cultures with Coagulase negtive Staphylococi, Corynebacterium, Staphylococcus aureus and fungal organisms were excluded form the CT. It could be because habitually the treatment for all these infections last for more than 14 days? Please explain better these aspects and if patients with medication (antibiotic) allergy were considered to be excluded.

Intervention: 7 versus 14 days of Adequate Antimicrobial Treatment. According to the article, the clinical team was alouded to select the most suitable antimicrobial treatment based on their criteria. Please explain if this criterira was supported by appropriate and recognized International Clinical Guidelines - Protocols for the Treatment of Bacteremia in the ICU setting. If so, please refer those Clinical Guidelines - Protocols used for the selection of the antibiotic treatments by the Clinical Teams in this CT. In addition please comment if the selection of the most appropriate antimicrobial treatment were guided by the realization of Antibiograms and please describe better what do the authors consider as "in vitro" activity. Plase explain better the methodology followed for the selection of the treatment duration: does this shouldn´t be established undergoing the randomization and the allocation (concealed or not) rather than calendar days?

INFORMED CONSENT SIGNATURE AND RANDOMIZATION. Please describe the procedures for the explanation of the CT to patients /relatives (in case of patients with severa illness) and the informed consnt signature. In addition please explain better the procedures for the randomization and the allocation concealment of the elegible patients to the experimental interventions of the CT. When revising it, it is not completely comprehensible. As commented before, does the allocation was open, single, double, triple, blindeed ? Was there was a double dummy or not ? It is not completely understood why the mantaining ot the allocation concealment until the end of day no. 7 could avoid selection bias. Habitually the selection bias
are avoided with the rigorous application of correct inclusion and exclusion criteria. Please explain better. In addition, it is recommend to the authors to place this section before the Methodology section.

PRIMARY AND SECONDARY FEASIBILITY OUTCOMES.

It would be correct if the authors could creat a section with the Primary- Secondary Objectives and Outcomes. Regarding the Primary Feasibility Outcomes please explain what do the authors consider as "adherence to treatment"; who has to comply this "adherence to treatment"? The patients?, The Clinical Team?, The investigators?. Additionally, please explain why Adherence to Treatment and Recruitment Rates were established as a primary feasible outcome in a RCT. For the purposes of the study, it is considered that probably an analytical - observational study (cohort study) would be a more suitable study design rather than a RCT (already commented). Please explain better why the authors decided to include a 90 days mortality outcome only if the treatments were going to last 7 and 14 days?. Which are the facts that are going to be evaluated after day No. 14 and before día No. 90? Is this outcome going to receive an appropriate analysis (Kaplan-meier analysis? Log-rank analysis) ? Do the other secondary outcomes mentioned in the text belong to this CT and are going to be analyzed within the present study?. Or they are part of the future CT which the authors are willing to do? If they belong to the second CT, it is considered that they can be removed. Does the Antibotic free days is a secondary outcome of this CT or it belongs to the "larger CT"? If it corresponds to the "larger CT" it is considered that it could be also removed. If no, please explain better the Clinical Rationale for the inclusion of an outcome, with the characteristics of this one, in the CT?

MECHANISTIC SUBSTUDIES.

It is considered that this section could be removed from the text. Evnthough it is a substudy derived from the first one, It is about a different CT rather than the actual one.

STATISTICAL ANALYSIS.

According to the text, a main descriptive analysis was performed. It si considered that this type of analysis was selected according to the type of included outcomes (Cualitative Outcomes). And because, as the authors comment, a pilot- RCT whith no efficacy neither safety endpoints is not suitable to undergo a proper Clincial Investigation Statistical Analysis. Completely agree. However, didn’t the authors consider to use a more appropriate cualitative statistical test for RCTs (Chi-square test for example)? In the other hand, and regarding to the 90 day mortality outcome, what type of statistical analysis is going to undergo this outcome? : a Kaplan Meier Analysis, a Log Rank analysis, or another survival analysis? This is because this outcome (eventhough of being cualitative) is a mortality outcome and must be analyzed following a
mortality analysis but not a merely descriptive analysis. Please explain better. It is considered that designing a correct Satistical Analysis will really avoid over-interpreting the results of the trial rather than than avoiding the underpower of the results in the Clinical Endpoints. Finally does the analysis was an "intention to treat" or a "per protocol" analysis ?.

SAMPLE SIZE CALCULATION.

After reading the sample size calculation it is assumed that because this is a RCT with no clinical comparative objectives neither outcomes (efficacy or safety), a classical RCT sample size calculation was not done. Therefore this is why the authors do not mention the "alpha error" used, the "beta error" used, neither the magnitude nor the proportion of the expected differences between interventions, neither the expected precision. Given this, the authors do not describe if the test used for this sample size calculation was one sided or two sided. It is considered that this should be reflected in the text of the study with a brief explanation. in addition the authors should explain if in the Sample Size calculation they included the proportion of losses.

RESULTS

Screened, Eligible and Randomized Patients. A complete descriptive exposition of the patients Clinical characteristics has been done. Please explain better why do the authors consider as "lack of consent by the ICU physician". Does the consent was given by the treatment MD but no by the patient ? Please explain in what consists the Substitute Decision Maker (SDM). In line No. 3 please change the word "me" by the word "met". Nothing else to add.

Patient, Infection and Pathogen Characteristics. A descriptive exposition of the facts has been done. it would be advisable if the authors could include in the text the main patients comorbidities to make more homogenous and contrastable the information of this section.

Treatement Characteristics, Recruitment Rate and Adherence to Treatment Protocol. A descriptive exposition of the major finding results has been done. However it is recommended to make a more complete results description in the text in order to be alligned with the information included in the Tables. Do the adherence treatment comply the established expectatives established by the authors ???. In addition it would be advisable if the authors could separate the Adherence to Treatment Results between the 7 days regimen and the 14 days regimen. this would be more alligned and coherent with principal aims, purposes, objectives and outcomes of the study. And separating them in two different tables. This would be more clarity to the results obtained.
Clinical Outcomes. A descriptive analysis was done. Please explain the treatment underwent by patients with relapsed infection. In addition please explain better the 14-day free antibiotic period and its significance in the results of the trial. Please include what do they mean with "wide variability" and "bimodal distribution". And please explain if the authors consider the overall mortality rate obtained as a high or low result in concordance to the expectatives of the trial regarding this fact. The safety aspects are described. Please comment if the authors consider them as positive or negative results? Do they support the good pharmacologic profile of the used antibiotics and the well conduction of the interventions? Do they give support (from a safety aspect) the realization of a wider CT? Please explain.

Mechanistic Substudies. It is considered that they could commented elsewhere. Because these results are part of another study which is not these one. And because the measurement of the procalcitonin levels ,in the included patients and derived from the interventions, are not defined as primary and secondary objectives neither outcomes.

Discussion. The discussion is alligned with the findings of the trial. The authors comment their results and analyze them adequately when commenting strenghts and weaknesses. Although interesting and promising, the pro-calcitonin results should be commented elsewhere because it is part of other substudy rather than this CT. And their use in the Clinical context of this study (bloodstream infections) has not been currently validated. In addition, the discussion should be more focused with the findings of this CT rather than with the Clinical Research purposes of the BALANCE study.

Conclusion. The conclusion is alligned with purposes and objectives of the Trial.

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Please indicate how interesting you found the manuscript:
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All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

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Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

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