PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	MULTICENTRE RANDOMISED CONTROLLED TRIAL TO INVESTIGATE USEFULNESS OF THE RAPID DIAGNOSTIC βLACTA™ TEST PERFORMED DIRECTLY ON BACTERIAL CELL PELLETS FROM RESPIRATORY, URINARY OR BLOOD SAMPLES FOR THE EARLY DE-ESCALATION OF CARBAPENEMS IN SEPTIC INTENSIVE CARE UNIT PATIENTS: THE BLUE-CARBA PROTOCOL
AUTHORS	Garnier, Marc; Gallah, Salah; Vimont, Sophie; Benzerara, Yahia; Labbe, Vincent; Constant, Anne-Laure; Siami, Shidasp; Guerot, Emmanuel; Compain, Fabrice; Mainardi, Jean-Luc; Montil, Mélissa; Quesnel, Christophe

VERSION 1 – REVIEW

REVIEWER	Dr Assaf MIZRAHI Groupe hospitalier Paris Saint Joseph, Clinical Microbiology
REVIEW RETURNED	18-Jun-2018

GENERAL COMMENTS	The protocol for this multi-center randomised controlled open-label non-inferiority clinical trial is well written and concerns a topical issue. The results of this study will help in the rapid descaling of carbapenems as well as the democratization of the use of the βlacta test in current practice.

REVIEWER	Dr. Theodoros Karampatakis MD,PhD Hippokration General Hospital, Thessaloniki, Greece
REVIEW RETURNED	10-Jul-2018

GENERAL COMMENTS	GENERAL COMMENTS Garnier et al. present their proposal on a protocol in which 30 French centers will participate. The protocol aims on examining if a rapid diagnostic test (βLACTA test, Bio-Rad, CA, USA) is equally confident with the reference strategy of the antibiogram results on 48-72h in de-escalation therapy. The authors will implement an open label randomized control trial (RCT) to provide an answer to their question. In terms of research of medical methodology performing a double-blinded or blinded RCT would not be that feasible so I firmly believe that an open label RCT is fine. However, it is important the experts of the final committee and the statisticians will be masked to the group assignment. The authors have clearly presented their PICO question, defining their Population, Intervention, Comparator and Outcomes. The authors also clearly describe their primary and secondary outcomes. In addition, the randomization process descries in the Methods' section using a safe randomization web-based system is satisfying.

	The effectiveness of de-escalation of antimicrobials is a controversial issue. It is commonly used to prevent over-consumption of broad-spectrum antimicrobials which can lead to increased antimicrobial resistance through selective pressure. On the other hand it could potentially impair the effectiveness in several infections. The problem is that there are obviously not many RCTs answering the question and most data come from observational studies. However, a systematic review and meta-analysis, which are placed on the top of evidence based medicine, by Ohji et al. 2016 reveals that despite the poor quality of existing studies de-escalation appeared safe. As a consequence I firmly believe that de-escalation could potentially diminish antimicrobial resistance and the authors' protocol in trying to implement it as fast as possible seems safe and promising. I would also recommend the authors to change the word 'antibiotics' to 'antimicrobials' throughout the text. I have only some minor comments to express and I really would like to congratulate the investigators for the design of the protocol. Abstract Minor comments: Introduction Lines 15-22: Please rephrase the sentence to provide a clearer meaning. Methods and analysis Better change to 'outcomes' than 'endpoints' throughout the whole paragraph. In addition, as the proposal regards a future protocol please use simple future tense throughout the paragraph. Introduction Background rationale Minor comments: Page 5: Lines 17-19: 'Beta-lactam antibiotics……Human health'. Please rephrase the sentence Line 27: 'hospital sector'……better 'hospital setting' Lines 40-42: 'reference to treat'……better 'the antimicrobial of choice to treat'…. Page 6: Lines 21-25: It is not actually only the wide use of antibiotics which has led to the emergence of ESBLs. Also the cross transmission of these strains due to inadequate implementation of infection control measures is a risk factor which should be added in the Introduction section. Page 7: Line 22: 'protector'…..rather 'protective' Methods and analysis The methods section is fine. Page 10: Lines 17-19: 'they will present risk factors for infection'…..better 'they will present increased risk for infection'…. Discussion The discussion section is fine. All the contents of the protocol are also fine.

REVIEWER	André Scherag Jena University Hospital, Institute of Medical Statistics, Computer and Data Sciences and Center for Sepsis Control and Care, Germany
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	"MULTICENTRE RANDOMISED CONTROLLED TRIAL TO INVESTIGATE THE USEFULNESS OF THE RAPID DIAGNOSTIC βLACTA™ TEST PERFORMED DIRECTLY ON BACTERIAL CELL PELLETS FROM RESPIRATORY, URINARY OR BLOOD SAMPLES FOR THE EARLY DE-ESCALATION OF CARBAPENEMS IN SEPTIC INTENSIVE CARE UNIT PATIENTS: THE BLUE-CARBA PROTOCOL" is a study protocol for a multicenter, randomized, controlled trial (RCT) focusing on non-inferiority of two different diagnostic strategies for intensive care unit (ICU) patients treated empirically with carbapenems . This is an important topic; more well designed RCTs are required in this field. As this is an ongoing study, very little can be changed at this point. Nevertheless, I would like to highlight several methodological challenges that the authors should consider. The authors work with a composite endpoint and they should invest into carefully analyzing the assumptions related to this criticized concept (there is a lot of new methodology for addressing this). While 90 day mortality may not be an issue, the documentation of infection recurrence (at the same site and of the same pathogen) in a non-blinded study can be affected by an observational bias. The authors should ensure that the patients are similarly observed for both arms by a blinded observer (until day 90 after randomization and not limited to the ICU setting as may patients will not stay 90 days at the ICU). My main concern, however, is related to the sample size calculation. Please provide the references for your proposed 45% control rate expectation. More importantly, what is the (statistical and clinical) justification for the proposed non-inferiority margin of 10% (in terms of an absolute risk reduction!). This is a rather big effect which will be hard to justify (here I refer (e.g.) to the EMA guidance on the choice of such margins) in a publication of the results. Finally, the authors should describe who others can access the data sets after study completion and publication. Minor: Please change "participants" to "patients" throughout

VERSION 1 – AUTHOR RESPONSE

REVIEWER: 1

We thank Dr Mizrahi for his comments.

REVIEWER: 2

We thank Dr Karampatakis for his comments.

GENERAL COMMENTS I would also recommend the authors to change the word ‘antibiotics’ to ‘antimicrobials’ throughout the text.

This correction was made in all the manuscript.

Abstract

Introduction: Lines 15-22: Please rephrase the sentence to provide a clearer meaning.

The final sentence of the introduction in the abstract has been modified as follows: “The objective of this work conducted in the Intensive Care Unit is to determine whether an early de-escalation of empirical carbapenems guided by the result of the LACTA™ test is not inferior to the reference strategy of de-escalating carbapenems after the antibiogram result has been rendered.”

Methods and analysis: Better change to ‘outcomes’ than ‘endpoints’ throughout the whole paragraph. In addition, as the proposal regards a future protocol please use simple future tense throughout the paragraph.

“Endpoint(s)” has been changed to “Outcome(s)”. The future was used throughout the paragraph of the revised version of the abstract.

Introduction

Lines 17-19: ‘Beta-lactam antibiotics……Human health’. Please rephrase the sentence.

&

Lines 21-25: It is not actually only the wide use of antibiotics which has led to the emergence of ESBLs. Also the cross transmission of these strains due to inadequate implementation of infection control measures is a risk factor which should be added in the Introduction section.

The beginning of the introduction was rephrased to clarify the rationale, according to the comments of the Reviewer, as follows: “The rise of multi-drug-resistant (MDR) pathogens, particularly of MDR Gram-Negative Bacilli (GNB), presents a grave public health challenge. The wide use of antimicrobials in human and animal medicine resulted in an intensive selective pressure that is considered to have been a major driving force towards antimicrobial resistance [1]. Beta-lactam antimicrobials are the most commonly prescribed antimicrobial class in human medicine. They represented 71.7% of the total systemic antimicrobial consumption in France and 61.4% in Europe in 2016 [2]. This wide use of beta-lactam antimicrobials led to selection of Extended-Spectrum Beta-Lactamase-producing *Enterobacteriaceae* (ESBL-E), whose spread have been exacerbated by inadequate implementation of infection control measures.”

Line 27: ‘hospital sector’……better ‘hospital setting’

Corrected.

Lines 40-42: ‘reference to treat’……better ‘the antimicrobial of choice to treat’….

Corrected.

Line 22: ‘protector’…..rather ‘protective’.

Corrected.

Methods and analysis

Page 10: Lines 17-19: ‘they will present risk factors for infection’…..better ‘they will present increased risk for infection’….

Corrected.

REVIEWER: 3

We thank Dr SCHERAG for his comments.

As this is an ongoing study, very little can be changed at this point. Nevertheless, I would like to highlight several methodological challenges that the authors should consider.

As pointed out by the reviewer, no significant changes in methodology can be made at this stage. Nevertheless, we have considered with attention all the methodological issues highlighted by the Reviewer and provided answers just below.

The authors work with a composite endpoint and they should invest into carefully analyzing the assumptions related to this criticized concept (there is a lot of new methodology for addressing this).

We thank the reviewer for its comment and suggestions. Statistical analysis plan of the protocol will be amended to add sensitivity analysis of individual components of the endpoint (death and recurrence) and considering the primary endpoint as a censored endpoint to allow potential sensitivity analysis using Finkelstein-Schoenfeld approach.

While 90 day mortality may not be an issue, the documentation of infection recurrence (at the same site and of the same pathogen) in a non-blinded study can be affected by an observational bias. The authors should ensure that the patients are similarly observed for both arms by a blinded observer (until day 90 after randomization and not limited to the ICU setting as may patients will not stay 90 days at the ICU).

As mentioned in the manuscript, in order to limit any potential observation bias due to the non-blinded design of the study, the definite diagnosis of recurrence will be confirmed or denied *a posteriori* by 3 independent experts in the field of infectious diseases and critical care medicine, blinded to the

allocation group, composing the endpoint adjudication committee. In addition to the experts of the endpoint adjudication committee, the statisticians will be masked to the group assignment.

Concerning the period of time during which a recurrence of infection may be observed, we chose to limit the observation period to the ICU stay (within the limit of 90 days) for 2 main reasons:

- Extending the follow-up period to 90 days including the post-ICU period seemed complicated because it would have required continuous data collection in the hospital wards, in the rehabilitation centre and possibly at home. In this context, ensuring reliable follow-up and diagnosis of infection recurrence seemed impossible. On the contrary, collection of infection recurrence during the ICU stay should allow all recurrences to be collected.
- Considering ICU patients, significant recurrence implies an extension of ICU stay or re-admission to the ICU. Thus, such recurrences will be diagnosed considering an observation limited to ICU stay. We will probably miss minor recurrences occurring outside the ICU but we chose to consider recurrence with a level of severity quite similar to the first infection leading to inclusion.

Such a strategy (i.e. limiting recurrence or superinfection collection to the ICU stay) was previously adopted by several past (*see for instance "De-escalation of Empirical Antimicrobial Therapy Study in Severe Sepsis » - Leone et al. Intensive Care Med 2014, PMID25091790*) or ongoing (*see for instance Impact of the Duration of Antibiotics on Clinical Events in Patients With Pseudomonas Aeruginosa Ventilator-associated Pneumonia (iDIAPASON) - NCT02634411*) randomized controlled trials.

My main concern, however, is related to the sample size calculation. Please provide the references for your proposed 45% control rate expectation.

The 45% control rate was calculated as the sum of mortality and infection recurrence rates, considering pneumonia as this site of infection is expected to represent approximately 70-75% of the infections leading to inclusion. Along these lines, previous studies reported mortality rates between 35% and 50% for severe pneumonia requiring ICU admission (PMID: 24158167, 24026297, 30118377); and incidence of recurrence between 2% and 27% (PMID: 22743372, 18461027). It can be noted that incidence of recurrence for urinary tract infections (UTI) and bloodstream infections (BSI) (PMID: 15375106, 25131028) is quite similar. Finally, as mortality for BSI, and above all for UTI, has been reported lower than rates for pneumonia, we chose the lower limit of the interval, leading to an expected control rate of 35% (death) + 10% (recurrence) = 45%.

These references, and the calculation made to obtain the 45% control rate expectation, are already available in the discussion (bottom of page 19).

More importantly, what is the (statistical and clinical) justification for the proposed non-inferiority margin of 10% (in terms of an absolute risk reduction!). This is a rather big effect which will be hard to justify (here I refer (e.g.) to the EMA guidance on the choice of such margins) in a publication of the results.

The choice of the non-inferiority margin has been an issue, especially due to the composite nature of the outcome. In our estimation of the control rate, the contribution of recurrence is about 20% of the

endpoint but it could be higher, leading to consider a margin of 10% acceptable. Furthermore, the margin has been approved by the methodologists and clinician experts of the French national drug safety agency (ANSM).

Finally, the authors should describe who others can access the data sets after study completion and publication.

As mentioned in the manuscript, “only the sponsor and the statisticians will have access to the final data set” (page 14).

Minor: Please change "participants" to "patients" throughout

Corrected.

VERSION 2 – REVIEW

REVIEWER	Dr. Theodoros Karampatakis MD, PhD Medical Microbiologist Hippokration General Hospital
REVIEW RETURNED	14-Oct-2018

GENERAL COMMENTS	All my minor comments have now been addressed and I am really satisfied by the corrections that will further improve the protocol's quality. I really wish all investigators good luck in the execution of their project.

REVIEWER	Prof. Dr. André Scherag Institute of Medical Statistics, Computer and Data Sciences (IMSID), Jena University Hospital, Jena, Germany
REVIEW RETURNED	10-Oct-2018

GENERAL COMMENTS	I thank the authors for adressing my concerns. I still think that the non-inferiority margin is too larger and that this may be questionned when the study is to be published. Finally, my comment on access to the data set intended to question how and if other can access the patient-level (pseudonymized) data for other purposes after the primary publication. The intention is to support data sharing and cooperation and I would love to see that the authors also support this idea.

VERSION 2 – AUTHOR RESPONSE

We thank the Editor-in-Chief, the Associate Editor and reviewers for their comments on our manuscript. Please find below our answers to these comments.

REVIEWER: 2

We thank Dr Karampatakis for his comments.

REVIEWER: 3

We thank Dr Scherag for his comments.

I still think that the non-inferiority margin is too larger and that this may be questionned when the study is to be published.

As pointed out by the reviewer, no significant changes in methodology can be made at this stage but we will consider with attention this methodological issue. In particular, we will take attention on the relative weight of incidence of death and recurrence of infection in the main composite outcome criterion, and will discuss the choice of such a non-inferiority margin when the study will be published.

Finally, my comment on access to the data set intended to question how and if other can access the patient-level (pseudonymized) data for other purposes after the primary publication. The intention is to support data sharing and cooperation and I would love to see that the authors also support this idea.

We fully support data sharing and cooperation. Thus, we added in the “Dissemination policy” section of the manuscript the following sentence: “According to data-sharing policy, patient-level data that support the findings of this study will be available from the authors upon reasonable request and with permission of the sponsor (Clinical Research and Development Department of Assistance Publique - Hôpitaux de Paris, AP-HP, France), owner of the data.”