PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Targeted simplification versus antipseudomonal broad-spectrum beta-lactams in patients with bloodstream infections due to Enterobacteriaceae (SIMPLIFY): a study protocol for a multicenter, open-label, phase III randomized, controlled, non-inferiority clinical trial
AUTHORS	López-Cortés, Luis Eduardo; Rosso-Fernández, Clara; Núñez-Núñez, María; Lavín-Alconero, Lucía; Bravo-Ferrer, José; Barriga, Ángel; Delgado, Mercedes; Lupión, Carmen; Retamar, Pilar; Rodriguez-Baño, Jesús

VERSION 1 - REVIEW

REVIEWER	Benedikt Huttner Geneva University Hospitals, Switzerland
REVIEW RETURNED	23-Dec-2016

GENERAL COMMENTS	GENERAL COMMENT: This interesting study protocol concerns a multicenter randomized controlled trial aiming to demonstrate that “de-escalation” of antimicrobial therapy in patients with bloodstream infections caused by Enterobacteriaceae. Strengths of this protocol include: • The protocol is overall well reported • The study seems overall well designed Weaknesses of this protocol include: • Some sections could be more detailed and / or would merit some discussion • The lack of a more thorough assessment of the impact of de-escalation on antimicrobial resistance (P. aeruginosa, intestinal microbiota) is a weak point of the study (In my opinion the real question is not whether de-escalation is safe – I think that the “prior” for safety is overall very high; but whether it has an impact on antimicrobial resistance). SPECIFIC COMMENTS: ABSTRACT: Major comment: The primary outcome should be specified in the abstract as well as the non-inferiority margin chosen for the study. Minor comment: Not sure this study qualifies as phase III trial (I would have categorized as phase IV. INTRODUCTION:

	Minor comment: “This imposes strong selection pressure, particularly on Pseudomonas aeruginosa isolates.” Since this is stressed so much in the introduction and seems to be the rationale behind the study, it seems strange that it is not assessed in more detail. METHODS: Major comment: I am not sure I understand the choice of the primary outcome “clinical cure, 3-5 days after the end of antibiotic treatment. Major comment: “in a subgroup of patients, the rate of intestinal colonization by ESBL, AmpC- and carbapenemase-producing Enterobacteriaceae will also be assessed by rectal swab.” The whole premise of de-escalation in this study is that sparing of anti-psuedomonal agnets will have a positive impact on the ecology of Pseudomonas. It is therefore difficult to understand why the resistance of Pseudomonas is not assessed. Major comment: The setting of the study could be described in more detail Major comment: The choice of the 10% non-inferiority margin should be justified. Minor comment: Why did the authors chose not to stratify randomization also by center. This should be justified. Minor comment: The number of agents available for de-escalation seems rather large. It is understandable in a pragmatic trial, but it limits the interpretability. Minor comment: Although often use the term “modified ITTP” is misleading, rather it is one kind of “per protocol” analysis”proposed in the protocol (the other kind is the “clinical evaluable population”). Minor comment: “The principal investigator will assess the primary outcome (clinical cure) in the clinically evaluable population (CEP) at TO”.”recovered on two occasions by the external blinded investigator:” It should be made clearer if the “principal investigator” and the “external blinded investigator” are the same person (It seems like they are but using different terms creates unnecessary confusion). Minor comment: “Special consideration will be given in the multivariate analysis to the center of origin of the study sample.” Wouldn’t stratified randomization by centre not have been preferable. Minor comment: “Switching to oral therapy is allowed from the sixth day of treatment” This seems very conservative. If we include oral switch in the definition of “de-esclation” (which may be debatable; but certainly is an intervention with benefit for the patient), this should occur earlier if possible. Minor comment: “A Cox regression analysis of mortality at 5-7, 14, 30 and 60 days will be performed on the mITTP.” Not sure I understand, shouldn’t one Cox regression analysis with day-specific mortality data over 60 days be performed? DISUCSSION: Minor comment: “(4) there is some doubt about the real effectiveness of certain drugs against isolates producing specific mechanisms of resistance, such as ESBL.” But this study is not designed to answer that question.

REVIEWER	Majdi Al-Hasan University of South Carolina School of Medicine
REVIEW RETURNED	24-Jan-2017

GENERAL COMMENTS	I sincerely thank all the investigators of this protocol for carrying out a study that has huge benefit for both patients and the scientific community. We highly welcome the first ever randomized clinical trial on de-escalation of antimicrobial therapy in patients with bloodstream infections (BSI) due to Enterobacteriaceae. I have few comments regarding this protocol. - Exclusion of patients with life expectancy <30 days is logical, but seems subjective. Do the investigators plan to use an objective assessment of predicted survival following BSI, such as the bloodstream infection mortality risk score (BSIMRS) or at least an acute severity of illness score such as SOFA, etc.? - It makes a lot of sense to randomize based on urinary vs. non-urinary source of BSI since this is a predictor of both survival and shorter hospital length of stay. Would it be useful to randomize by age given its potential impact on outcomes as well? - Why cefazolin was not considered an option in the experimental group? It is a relatively narrow spectrum beta-lactam that is frequently used in clinical practice to treat BSI due to susceptible Enterobacteriaceae. - The authors state that all study drugs are officially approved for BSI without providing appropriate citations. - I am not aware of studies demonstrating the effectiveness of trimethoprim-sulfamethoxazole (a bacteriostatic agent) in the treatment of BSI due to Enterobacteriaceae, especially this early in the course of therapy (within 3 days of BSI). For this reason, I have strong reservations for ranking this agent as a second option in the experimental group. I am worried many providers will consider this a deviation from the standard of care for treatment of this condition, which may negatively impact the implications of study results. I suggest moving trimethoprim-sulfamethoxazole to either just before or after ciprofloxacin. - I understand the rationale in the current protocol for allowing patients to be switched to the same oral agent, if possible. However, this will create another layer of analysis (and confounding) that may overshadow the intended aim of this study, that is examining the efficacy and safety of de-escalation. As per the current protocol, the majority of patients in the control group will receive oral ciprofloxacin. However, there will be more heterogeneity of oral agents used in the experimental group. This will make interpretation of study results very complex in multiple ways. First, a recent study has demonstrated that effectiveness of oral agents for treatment of Enterobacteriaceae BSI varies based on bioavailability (Kutob LF, et al. IJAA 2016). So if recurrent infections were more common in the experimental than the control group, it would be difficult to tell from current design whether this is due to de-escalation from antipseudomonal beta-lactams to narrower spectrum intravenous agents or due to use of oral agents with lower bioavailability than ciprofloxacin. On the other hand, if adverse events (C. difficile infections, etc.) were more frequent in the control than experimental group, it would also be difficult to know whether this is due to continuation of broad-spectrum intravenous agents or higher proportion of patients receiving oral ciprofloxacin. This may either confuse the readers or allow some to interpret the study results based on their own opinions regardless of offered explanations by the authors in the manuscript. Since this is the first clinical trial on

	de-escalation of antimicrobial therapy in Enterobacteriaceae BSI, I suggest keeping it simple and neutralizing the oral therapy component by offering the same oral regimens to both groups. I suggest making ciprofloxacin the preferred oral agent in both groups, followed by oral trimethoprim-sulfamethoxazole, then oral beta-lactams, if the first 2 options were not possible due to either in vitro resistance or patient factors such as allergy or drug interactions, etc. This will minimize the impact of oral regimens on the trial and will allow everyone to make the same conclusion regarding the efficacy and safety of de-escalation from anti-psedomonal beta-lactams to narrower spectrum antimicrobial agents. - Finally, according to current protocol, it will be up to the treating physician to decide total treatment duration with a wide range of 7-14 days based on IDSA guidelines for treatment of catheter-associated BSI (which will contribute to only a small proportion of Enterobacteriaceae BSI, but may not be applicable to other sources of BSI). How will the authors account for this wide variability in treatment duration that may potentially affect both recurrence rates and adverse events? This is another question that has not been studied in a clinical trial design yet in this patient population. I suggest narrowing the range of treatment duration to 10-14 days to minimize the impact of this variable on study results. If 10 days of therapy are recommended to treat otitis media based on recent clinical trial results (Hoberman A, et al. NEJM 2016), it does not make any sense to treat BSI for a shorter duration than 10 days.

VERSION 1 – AUTHOR RESPONSE

Reviewer :1

Reviewer Name: Benedikt Huttner
Institution and Country: Geneva University Hospitals, Switzerland
Please state any competing interests: None declared

Please leave your comments for the authors below

GENERAL COMMENT:

This interesting study protocol concerns a multicenter randomized controlled trial aiming to demonstrate that “de-escalation” of antimicrobial therapy in patients with bloodstream infections caused by Enterobacteriaceae.

Strengths of this protocol include:

• The protocol is overall well reported
• The study seems overall well designed

Weaknesses of this protocol include:

• Some sections could be more detailed and / or would merit some discussion
• The lack of a more thorough assessment of the impact of de-escalation on antimicrobial resistance (P. aeruginosa, intestinal microbiota) is a weak point of the study (In my opinion the real question is not whether de-escalation is safe – I think that the “prior” for safety is overall very high; but whether it has an impact on antimicrobial resistance).

RESPONE: The trial was designed to assess the non-inferiority of de-escalation in terms of clinical efficacy, since this is the more important barrier to de-escalate for many doctors because of the lack of high level evidence, as explain in the Introduction section. The ecological impact on antimicrobial resistance is one of the secondary outcomes of the study, but to assess that as a primary outcome the sample size would have need to be much higher (which was not feasible according to the available funding) to consider the different epidemiological situations at each site, etc.

SPECIFIC COMMENTS:

ABSTRACT:
Major comment: The primary outcome should be specified in the abstract as well as the non-inferiority margin chosen for the study.
RESPONSE: We have included it in lines 43 and 47, respectively.

Minor comment: Not sure this study qualifies as phase III trial (I would have categorized as phase IV.
RESPONSE: The study was submitted to the Spanish Regulatory Agency and approved based on the definition of phase III study (according to Spanish regulations, Royal Decree 223/2004-1090/2015) as studies for which the fundamental objectives are to evaluate the efficacy and safety of an experimental treatment trying to reproduce the usual conditions of use and considering the therapeutic alternatives available in the indication studied. The experimental intervention to be demonstrated is the de-escalation as a treatment strategy and not for each drug used itself.

INTRODUCTION:
Minor comment: “This imposes strong selection pressure, particularly on Pseudomonas aeruginosa isolates.” Since this is stressed so much in the introduction and seems to be the rationale behind the study, it seems strange that it is not assessed in more detail.

RESPONSE: We stress about this because all the antibiotics included in the control arm are antipseudomonal beta-lactams. As stated in a response to another comment below, assessment of colonisation by carbapenem- or pipireacillin-resistant P. aeruginosa is included as a secondary outcome.

METHODS:
Major comment: I am not sure I understand the choice of the primary outcome “clinical cure, 3-5 days after the end of antibiotic treatment.
RESPONSE: The duration of therapy was stated as 7-14 days (with an exception considered in the protocol). Therefore, the test of cure will be performed 3-5 days after the end of therapy. Death during treatment, change of antibiotic therapy due to clinical failure, or need to prolong the treatment will be considered as failures. We have included it in line 261.

Major comment: “in a subgroup of patients, the rate of intestinal colonization by ESBL, AmpC- and carbapenemase-producing Enterobacteriaceae will also be assessed by rectal swab.” The whole premise of de-escalation in this study is that sparing of anti-psuedomonal agents will have a positive impact on the ecology of Pseudomonas. It is therefore difficult to understand why the resistance of Pseudomonas is not assessed.
RESPONSE: The reviewer is right, and actually we had included an incorrect statement. We have included the correct in line 269 and 308 as follows: “To do this, samples will be taken by rectal swab from the patients of both treatment arms on the day of randomization, the day when treatment finish, the day of test of cure, and visit of day 30. The presence of P. aeruginosa resistant to carbapenemase or piperacillin / tazobactam, Stenotrophomonas spp., multiresistant A. baumannii and enterobacteria producing ESBL, carbapenemase and chromosomal AmpC (hyperproduction) or plasmid will be

sought."

Major comment: The setting of the study could be described in more detail.
RESPONSE: we added a commentary about how many of the participant hospitals are Universitary ones in lines 131.

Major comment: The choice of the 10% non-inferiority margin should be justified.
RESPONSE: There is no previous clinical trials on de-escalation using "clinical cure" as primary outcome. A 10% non-inferiority margin has been used in recent trials in complicated urinary tract infections (Wagenlehner et al, Clin Infect Dis 2016) or complicated intraabdominal infections (Solomkin et al, Clin Infect Dis 2015). We added that in the text in line 346.

Minor comment: Why did the authors chose not to stratify randomization also by center. This should be justified.
RESPONSE: The reason is to guarantee an appropriate allocation concealment. Because the study is open, stratification by site might prevent the inclusion of some high risk patients if there is a suspicion that the patient would be allocated to the de-escalation arm. We added that in the text.

Minor comment: The number of agents available for de-escalation seems rather large. It is understandable in a pragmatic trial, but it limits the interpretability.
RESPONSE: We agree with the reviewer but the trials was designed to represent clinical practice, in which the antibiotic to use is selected based on the susceptibility results. We are not comparing one drug vs another but one strategy vs another. Therefore, we were careful to provide a rule based on the susceptibility data and including drugs with proven efficacy. We do think this is a strength of the study.

Minor comment: Although often use the term "modified ITTP" is misleading, rather it is one kind of "per protocol" analysis" proposed in the protocol (the other kind is the "clinical evaluable population").
RESPONSE: Patients receiving one dose of the drugs in trials are usually termed as modified intention-to-treat population. We think a per-protocol analysis would only include patients with a much longer exposure to the drugs (e.g., 5 days). Anyway, if the Editor thinks otherwise we may change the name of the populations to avoid any confusion.

Minor comment: "The principal investigator will assess the primary outcome (clinical cure) in the clinically evaluable population (CEP) at TO"."recovered on two occasions by the external blinded investigator:" It should be made clearer if the "principal investigator" and the "external blinded investigator" are the same person (It seems like they are but using different terms creates unnecessary confusion).
RESPONSE: We agree with the reviewer. With the presented methodology, the principal investigator could not be blinded, so the variable "clinical cure" will be reviewed for other persons. We have changed the text (line 326) as follows: "The local principal investigator in the centre where the patient was included will assess the primary outcome (clinical cure) in the clinically evaluable population (CEP) at TOC. Due to the intrinsic characteristics of the primary outcome (soft outcome) and the study methodology (non-blinded), this evaluation done will be reviewed later on the basis of clinical data recovered on two occasions by an external blinded investigator: firstly, during the interim analysis to monitor safety; secondly before the complete cleaning and closure of the eCRF".

Minor comment: "Special consideration will be given in the multivariate analysis to the center of origin of the study sample." Wouldn't stratified randomization by centre not have been preferable.
RESPONSE: Please see our response to the previous comment about the randomisation process. Because randomisation will not be stratified by site, the site effect must be controlled in the analysis.

Minor comment: “Switching to oral therapy is allowed from the sixth day of treatment” This seems very conservative. If we include oral switch in the definition of “de-escalation” (which may be debatable; but certainly is an intervention with benefit for the patient), this should occur earlier if possible.
RESPONSE: We are afraid this was not clearly expressed in the paper. Switch to oral therapy is allowed after 3 days of therapy once the patient is randomised. We will include patients who need a minimum exposure to the IV drugs to really assess the efficacy. We clarify it in the text.

Minor comment: “A Cox regression analysis of mortality at 5-7, 14, 30 and 60 days will be performed on the mITTP.” Not sure I understand, shouldn’t one Cox regression analysis with day-specific mortality data over 60 days be performed?
RESPONSE: The reviewer is right. We modified that.

DISCUSSION:
Minor comment: “(4) there is some doubt about the real effectiveness of certain drugs against isolates producing specific mechanisms of resistance, such as ESBL.” But this study is not designed to answer that question.

RESPONSE: We agree. We deleted the reference to ESBLs.

Reviewer: 2
Reviewer Name: Majdi Al-Hasan
Institution and Country: University of South Carolina School of Medicine
Please state any competing interests: None

Please leave your comments for the authors below

I sincerely thank all the investigators of this protocol for carrying out a study that has huge benefit for both patients and the scientific community. We highly welcome the first ever randomized clinical trial on de-escalation of antimicrobial therapy in patients with bloodstream infections (BSI) due to Enterobacteriaceae. I have few comments regarding this protocol.

- Exclusion of patients with life expectancy <30 days is logical, but seems subjective. Do the investigators plan to use an objective assessment of predicted survival following BSI, such as the bloodstream infection mortality risk score (BSIMRS) or at least an acute severity of illness score such as SOFA, etc.?

RESPONSE: We agree with the reviewer. We decided not to specify an objective assessment of life expectancy as this is the usual practice in trials, and because all the cases will be evaluated by experienced physicians treating patients with bacteraemia.

- It makes a lot of sense to randomize based on urinary vs. non-urinary source of BSI since this is a predictor of both survival and shorter hospital length of stay. Would it be useful to randomize by age given its potential impact on outcomes as well?

RESPONSE: We agree with the reviewer that age is a predictor of outcome. There are many other well-known variables that have impact on the prognosis of patients with bacteraemia. However, it is recommended to keep randomisation as less stratified as possible to avoid problems in the allocation concealment in an open trial. We expect that randomisation will allocate patients with similar age in the two study arms, but if not, the effect of age will be controlled in the analysis.

- Why cefazolin was not considered an option in the experimental group? It is a relatively narrow

spectrum beta-lactam that is frequently used in clinical practice to treat BSI due to susceptible Enterobacteriaceae.
RESPONSE: The reviewer is right. Unfortunately, susceptibility to cefazolin is not routinely reported in many participating centres for Enterobacteriaceae, which made it impossible to include in this pragmatic trial.

- The authors state that all study drugs are officially approved for BSI without providing appropriate citations.
RESPONSE: The reviewer is right – actually the drugs are not approved for BSI but for the specific infections (UTI, intraabdomnal, etc), causing BSI or not. We modified the sentence to specify that the drugs are recommended for BSI, and provided the references (Cisneros-Herreros JM, et al. Enferm Infecc Microbiol Clin 2007).

- I am not aware of studies demonstrating the effectiveness of trimethoprim-sulfamethoxazole (a bacteriostatic agent) in the treatment of BSI due to Enterobacteriaceae, especially this early in the course of therapy (within 3 days of BSI). For this reason, I have strong reservations for ranking this agent as a second option in the experimental group. I am worried many providers will consider this a deviation from the standard of care for treatment of this condition, which may negatively impact the implications of study results. I suggest moving trimethoprim-sulfamethoxazole to either just before or after ciprofloxacin.
RESPONSE: As we precise in the protocol, the use of trimethoprim-sulfamethoxazole is only recommended for urinary tract infections without abscess. Although trimethoprim-sulfamethoxazole is an basteriostatic agent, there are several studies and recommendations supporting the use of this drug in UTI including pyelonephritis (Talan DA, et al. JAMA 2000; 283:1583–1590. McCarty J, et al. Am J Med 1999; 106:292–9. Harding GK, et al. Ann Intern Med 1991; 114:713–719. Talan DA, et al. Clin Infect Dis 2008; 47:1150–8). The fact that the ITU has presented with bacteremia has not been associated with poor prognosis.

- I understand the rationale in the current protocol for allowing patients to be switched to the same oral agent, if possible. However, this will create another layer of analysis (and confounding) that may overshadow the intended aim of this study that is examining the efficacy and safety of de-escalation. As per the current protocol, the majority of patients in the control group will receive oral ciprofloxacin. However, there will be more heterogeneity of oral agents used in the experimental group. This will make interpretation of study results very complex in multiple ways.
RESPONSE: We agree with the reviewer and that will be taken into account in the analysis. We wanted/needed the trial to be as similar as possible to clinical practice both to make it feasible and applicable. Because we are comparing strategies and not specific drugs, we do think the design is appropriate to answer the research question.

First, a recent study has demonstrated that effectiveness of oral agents for treatment of Enterobacteriaceae BSI varies based on bioavailability (Kutob LF, et al. IJAA 2016). So if recurrent infections were more common in the experimental than the control group, it would be difficult to tell from current design whether this is due to de-escalation from antipseudomonal beta-lactams to narrower spectrum intravenous agents or due to use of oral agents with lower bioavailability than ciprofloxacin.
RESPONSE: We agree with the reviewer. This is the reason why we choose only antibiotics with an oral bioavailability higher than 60%. Although some of them has a lower oral bioavailability than quinolones, all have proven to be good choices in sequential treatment. Anyway, oral treatment is only allowed after some days of intravenous treatment, so that the most important effect of antibiotic therapy will have been obtained and therefore we think the safety of switch to oral therapy will be as expected.

On the other hand, if adverse events (C. difficile infections, etc.) were more frequent in the control than experimental group, it would also be difficult to know whether this is due to continuation of broad-spectrum intravenous agents or higher proportion of patients receiving oral ciprofloxacin. This may either confuse the readers or allow some to interpret the study results based on their own opinions regardless of offered explanations by the authors in the manuscript. Since this is the first clinical trial on de-escalation of antimicrobial therapy in Enterobacteriaceae BSI, I suggest keeping it simple and neutralizing the oral therapy component by offering the same oral regimens to both groups. I suggest making ciprofloxacin the preferred oral agent in both groups, followed by oral trimethoprim-sulfamethoxazole, then oral beta-lactams, if the first 2 options were not possible due to either in vitro resistance or patient factors such as allergy or drug interactions, etc. This will minimize the impact of oral regimens on the trial and will allow everyone to make the same conclusion regarding the efficacy and safety of de-escalation from anti-pseudomonal beta-lactams to narrower spectrum antimicrobial agents.
RESPONSE: We thank the comment and agree that this may be a controversial decision. Since the Spanish Medicines Agency (AEMPS) already approved the study protocol, such a modification would not be possible at this stage. In fact we had considered the option provided by the reviewer but after considering pros and cons of both possibilities we decided to use the same drug used intravenously whenever possible in the de-escalation arm.

- Finally, according to current protocol, it will be up to the treating physician to decide total treatment duration with a wide range of 7-14 days based on IDSA guidelines for treatment of catheter-associated BSI (which will contribute to only a small proportion of Enterobacteriaceae BSI, but may not be applicable to other sources of BSI). How will the authors account for this wide variability in treatment duration that may potentially affect both recurrence rates and adverse events?.
RESPONSE: This is an important point. There are no well stablished recommendations about the duration of therapy in BSI due to Enterobacteriaceae BSI, and this may depend on the source. We chose a range of 7 to 14 days according to urinary tract, healthcare-associated pneumonia, and catheter-related infections guidelines. It is a usual practice in randomised trials that the duration of therapy is decided within a range of days by the investigator. We did not want to request a fix duration of therapy because the clinical situations will be diverse as a reflection of real clinical practice.

This is another question that has not been studied in a clinical trial design yet in this patient population. I suggest narrowing the range of treatment duration to 10-14 days to minimize the impact of this variable on study results. If 10 days of therapy are recommended to treat otitis media based on recent clinical trial results (Hoberman A, et al. NEJM 2016), it does not make any sense to treat BSI for a shorter duration than 10 days.
RESPONSE: For some infections shorter duration of therapy is already recommended, irrespective of whether there is bacteraemia or not. This is the case of complicated UTI, healthcare-associated pneumonia, complicated intraabominal infections or catheter-related infections. However, we agree that several patients might need longer duration of treatment and therefore provided the option to prolong it until 14 days. We therefore think that the proposed duration of therapy is appropriate.

VERSION 2 – REVIEW

REVIEWER	Benedikt Huttner Geneva University Hospitals, Switzerland
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	The authors have adresses all major comments raised during the initial review and I have no further comments.

REVIEWER	Majdi Al-Hasan

	University of South Carolina School of Medicine
REVIEW RETURNED	08-Mar-2017

GENERAL COMMENTS	I thank the authors for responding to all pervious comments. I have no additional suggestions at this time.