PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomized controlled trial
AUTHORS	Foucrier, Arnaud; Roquilly, Antoine; Bachelet, Delphine; Martin-Loeches, Ignacio; Bougle, Adrien; Timsit, Jean-François; Montravers, Philippe; Zahar, Jean-Ralph; Eloy, Philippine; Weiss, Emmanuel

VERSION 1 – REVIEW

REVIEWER	Huttner, Benedikt D. World Health Organization
REVIEW RETURNED	13-Jul-2022

GENERAL COMMENTS	GENERAL COMMENT FOR THE AUTHORS: This interesting study protocol describes a multicenter non-inferiority RCT of two different strategies for the duration of antibiotic treatment in patients with microbiologically confirmed VAP. Adult patients with a first episode of VAP hospitalized in 24 French ICUs will be randomized 1:1 stratified by center for a standard duration of 7 days or individualized duration based on standardized daily clinical assessment. The primary endpoint is a composite endpoint of day 28 all-cause mortality, treatment failure or a new episode of microbiologically confirmed VAP within 28 days, Strengths of this manuscript include: • Trials on the optimal duration of treatment and potential for individualization are important • The protocol is well written and the methodology is sound Weaknesses of this manuscript include: • The evidence for the assumption that reduction of antibiotic duration has an impact on antibiotic resistance is relatively weak. In addition to the rectal swabs for MDRO colonization /acquisition it would have been good to associate some microbiome / resistome analysis. SPECIFIC COMMENTS: ABSTRACT: Minor comment: “pragmatic prospective national multicenter, phase III, non-inferiority, comparative randomized” since any randomized trial is prospective, I would suggest deleting this word.

	INTRODUCTION: Minor comment: “Reduction of use of antibiotics is a major point in the war” With a real war going on in Europe I would suggest to avoid the bellicose terminology. Minor comment: “More surprisingly, the CPIS (Clinical Pulmonary Infection Score) was ranked 6th while it is no longer considered a determinant for initiating antibiotic treatment » Please add more information regarding CPIS and why this is “more surprising”. METHODS: Major comment: Please define duration of treatment exactly. Is 7 days = 7 calendar days or 7x24 hours? Major comment: “Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as usual care. » Is there any attempt to assess the impact of the different strategies on the resistome and microbiome? Rectal swabbing for MDRO will probably not significantly add to the question whether shorter treatment has an impact on resistance (isolation of MDRO will depend a lot on the presence or absence of certain MDRO in the ICU; furthermore, a cluster-randomized design would probably be needed). The evidence that shorter treatment duration is associated with less resistance is still rather limited and a trial like this one offers a unique opportunity to assess this in more detail. Major comment: Please describe the implementation of the intervention (based on clinical assessment) in detail (training of prescribers etc.) Minor comment: What is the reason for excluding VAP superinfection after viral infection (This still unfortunately risks representing a large patient population and reducing antibiotic exposure in these patients would be an important contribution to antibiotic stewardship). Minor comment: Some information about the standard empiric therapy for VAP in French ICUs would be useful. Minor comment: “computer-generated randomization scheme of various-sized blocks » randomly permutated block sizes? Minor comment: The role (if any) of PCT guided treatment duration should be commented on. Minor comment: “Assuming that 25% of the patients will encountered all-cause mortality” Isn’t that a bit high especially since VAP by non-fermenters is also excluded. Is this based on data from the participating ICUs? Minor comment: “The non-inferiority margin of 10% was chosen as the largest difference that may be potentially clinically acceptable » That is a bit debatable since mortality is part of the composite outcome. 10% is a commonly used margin and makes the study feasible but I would argue that a difference of e.g. 9% would probably not be acceptable for physicians and patients, especially also given the scarce evidence the reducing treatment duration from 7 days to shorter periods actually has an impact on resistance (hence the importance of studying resistance outcomes).

REVIEWER	Miranda-Novales, Guadalupe Mexican Social Security Institute, Analysis and Synthesis of Evidence Research Unit
REVIEW RETURNED	07-Oct-2022

GENERAL COMMENTS	This study protocol will provide relevant results that will optimize the use of antibiotics in one of the main healthcare-associated infections in the ICUs. I have only one comment on the sample size calculation. In the sample size justification (page 15) the investigators are assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm (reference 19), and, established that 590 subjects (295 per 308 arm) are needed to establish non-inferiority with the absolute difference of death, treatment failure or occurrence of new episode of VAP doesn't exceed 10% (non-inferiority margin). In the next sentence, they mentioned that absolute rate of treatment failure / new episode of VAP without treatment cannot be estimated. Therefore, the sample size calculation seems to be calculated with only one of the three outcomes. The section is not clear. Also, the non-inferiority margin of 10% chosen as the largest difference that may be potentially clinically acceptable may not be "acceptable" for the three main outcomes separately. Please clarify this section and preferably add more references to support the calculation. Minor comments: along the document (figures included) there are several typographic errors that need to be corrected.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Benedikt D. Huttner, World Health Organization
Comments to the Author:

GENERAL COMMENT FOR THE AUTHORS:

This interesting study protocol describes a multicenter non-inferiority RCT of two different strategies for the duration of antibiotic treatment in patients with microbiologically confirmed VAP. Adult patients with a first episode of VAP hospitalized in 24 French ICUs will be randomized 1:1 stratified by center for a standard duration of 7 days or individualized duration based on standardized daily clinical assessment. The primary endpoint is a composite endpoint of day 28 all-cause mortality, treatment failure or a new episode of microbiologically confirmed VAP within 28 days,

Strengths of this manuscript include:

- Trials on the optimal duration of treatment and potential for individualization are important
- The protocol is well written and the methodology is sound

Weaknesses of this manuscript include:

- The evidence for the assumption that reduction of antibiotic duration has an impact on antibiotic resistance is relatively weak. In addition to the rectal swabs for MDRO colonization /acquisition it

would have been good to associate some microbiome / resistome analysis.

SPECIFIC COMMENTS:

ABSTRACT:

Minor comment: “pragmatic prospective national multicenter, phase III, non-inferiority, comparative randomized” since any randomized trial is prospective, I would suggest deleting this word.

We thank the reviewer for this remark. We delete this word.

INTRODUCTION:

Minor comment: “Reduction of use of antibiotics is a major point in the war” With a real war going on in Europe I would suggest to avoid the bellicose terminology.

We thank the reviewer for this remark. We changed the term war to “control” (Line 2, Page 5)

Minor comment: “More surprisingly, the CPIS (Clinical Pulmonary Infection Score) was ranked 6th while it is no longer considered a determinant for initiating antibiotic treatment » Please add more information regarding CPIS and why this is “more surprising”.

We thank the reviewer for this comment.

The CPIS as described by Pugin et al.[1] included six variables: (1) body temperature, (2) blood leukocyte count and number of band forms, (3) character of tracheal secretions (purulent or not) and quantity of tracheal aspirates, (4) microscopic examination (Gram stain) and semi- quantitative culture results of the bronchial secretions, (5) arterial oxygen tension/inspiratory fraction of oxygen (PaO2/FiO2), and (6) chest X-ray. Although it is no longer the consensus for the diagnosis of VAP, this score is still widely used. In this sense, the analysis of the evolution of its components could also have been useful to describe clinical cure over time. In this respect, it seems surprising that experts have not formally retained it as a tool to describe improvement. This is nevertheless consistent with the literature, which lists very few favourable studies in this sense. To avoid any confusion, we have deleted the sentence mentioning the CPIS because it was finally not included in the protocol (Line 5, page 6)

METHODS:

Major comment: Please define duration of treatment exactly. Is 7 days = 7 calendar days or 7x24 hours?

For duration, one day is considered as a full 24h treatment. 7days is 7 times consecutive 24hours. This was specified in the revised manuscript (Line 9, page 7)

Major comment: “Rectal swabbing for collection of data on colonization or acquisition of Multidrug Resistant (MDR) bacteria will be performed at ICU admission and weekly until ICU discharge as part as usual care. » Is there any attempt to assess the impact of the different strategies on the resistome and microbiome?

We thank the reviewer for this question. The protocol does not aim to collect material for analysis in terms of resistome and/or microbiome. Only species identification and determination of antibiotic susceptibility testing (to characterize presence of MDR as defined). It was impossible to obtain funding to include these analyses. However, an ancillary study is currently discussed (see below)

Rectal swabbing for MDRO will probably not significantly add to the question whether shorter treatment has an impact on resistance (isolation of MDRO will depend a lot on the presence or absence of certain MDRO in the ICU; furthermore, a cluster-randomized design would probably be needed). The evidence that shorter treatment duration is associated with less resistance is still rather limited and a trial like this one offers a unique opportunity to assess this in more detail.

We thank the reviewer for this suggestion.

We plan to set up a biocollection of rectal samples in pilot centers. Additional funding is being considered for more precise analyses of microbiome/resistome during an ancillary study. In addition, the microbiological profile of subsequent infections (ie. ocurring after the first episode of VAP) will be analyzed.

Major comment: Please describe the implementation of the intervention (based on clinical assessment) in detail (training of prescribers etc.)
In experimental group, after 3 times full 24h of appropriate antibiotic treatment, investigators are encouraged to evaluate clinical cure according 4 items: aspect and quantity of tracheal secretions, body temperature, oxygenation and arterial pressure.
From day 3 and each subsequent day, the investigator collects the most favorable parameter of each item from the previous 24 hours, by following the STOP algorithm. During this evaluation period, when at least 3 criteria are met, the protocol states that antibiotics should be stopped. In order to facilitate the collection of daily clinical information, a collection sheet (attached at the end of this response) is provided. In case of questioning by the investigators on the reality of the clinical cure according to the established criteria, a phone hotline will be available for the investigators
Minor comment: What is the reason for excluding VAP superinfection after viral infection (This still unfortunately risks representing a large patient population and reducing antibiotic exposure in these patients would be an important contribution to antibiotic stewardship).
We thank the reviewer for raising this important point showing that our protocol was not entirely clear. We decided to exclude VAP superinfection occurring in the context of viral VAP and not after viral VAP, meaning that the inclusion of bacterial VAP occurring after appropriately treated viral VAP can be included. We chose not to include bacterial VAP complicating viral pneumonia to avoid confounding factors that may be due to the cure of viral pneumonia. (See Line3, page 11)
Minor comment: Some information about the standard empiric therapy for VAP in French ICUs would be useful.
The current French recommendations on the use of empirical antibiotic therapy are described in the table below. We give these guidelines as an indication for all participating centres. Nevertheless, the choice of empirical treatment is left to the discretion of physicians. The choice is mainly made by considering the bacterial ecology of the participating ICUs, as strongly recommended.
French guidelines for empiric antibiotic therapy for ventilator associated pneumonia[2]

Situations	**Therapeutic agent**
<u>Early VAP</u> ≤ 5th day after admission absence of - septic shock - risk factor* of MDR	amoxillin+clavulanic acid OR 3rd cephalosporin
<u>Early VAP</u> ≤ 5th day after admission AND - septic shock - absence of risk factor *of MDR	amoxillicin+clavulanic acid OR 3rd cephalosporin AND aminosid
<u>Delayed VAP</u> > 5th day of admission Or other risk factor* non-fermenting GNB$^{\circ}$	ceftazidim OR cefepim OR piperacillin+tazobactam (in absence of known carriage of MDR) OR imipenem or meropenem (if known carriage of MDR) AND Amikacin or ciprofloxacin
Risk factor$^{\#}$ of SAMR$^{\bullet}$	Vancomycin OR linezolid

*Prior intravenous antibiotic use within 90 day, Septic shock at time of VAP, ARDS preceding pneumonia, five or more days of hospitalization prior to the occurrence of VAP, acute renal replacement therapy prior to VAP onset.° GNB : Gram Negative Bacilli• SAMR : Staphyococcus aureus methicillin-resistant # if local prevalence of SAMR is elevated, recent colonization to SAMR, chronic cutaneous lesion, chronic dialysis

Minor comment: "computer-generated randomization scheme of various-sized blocks » randomly permutated block sizes?

Random block sizes proportional to the number of groups will be generated using a pre-specified maximum blindly from the investigators. Permuted block technique will be used to assign treatment within the various-sized blocks.
This was specified in the revised manuscript (Line 24-25, page 11 and Line 1-2, page 12).

Minor comment: The role (if any) of PCT guided treatment duration should be commented on.
In a pragmatic approach, only clinical criteria are evaluated as key elements of clinical cure. Paraclinic informations (radiological and/or biological), although collected prospectively, are not included in the decision algorithm and its interpretation will be left to the discretion of the investigators. Regarding PCT guided treatment, the data are not all concordant for the relevance of its systematic use to monitoring treatment of VAP. The European recommendations are therefore unfavorable in this indication. The medico-economic dimension of its systematic use must also be weighed against the potential reduction in antibiotic therapy.
Minor comment: "Assuming that 25% of the patients will encountered all-cause mortality" Isn't that a bit high especially since VAP by non-fermenters is also excluded. Is this based on data from the participating ICUs?
In our manuscript, the text reads "Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm…". In other words, the proportion of 25% refers to the whole composite endpoint. The primary endpoint is composite. When a patient meets one or more of the three events (all-cause mortality, treatment failure, occurrence of a new episode of VAP) that compose it, the endpoint is met.
The estimate of the 25% proportion of occurrence of the primary endpoint is based on data from the international literature and not from the participating centers.
In the ASPECT study (Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia)[3], all-cause mortality ranged from 24% (experimental group) to 25.3% (control group). Pneumonia due to *P. aeruginosa* (Non-Fermenting Gram Negative Bacilli) accounted for 25.4% and 18.5% of all events, respectively. Pneumonia due to P. aeruginosa (Non-fermenting Negative Gram Bacilli) accounted for 25.4% and 18.5% of all events, respectively. Furthermore, in the iDiapason study[4], which included 186 patients randomized in 2 groups (15 days of treatment versus 8 days of treatment), 30-day mortality was 12.3% and 15.9% respectively, suggesting that episodes of *P .aeruginosa*-related VAP (PA-VAP) do not result in excess mortality compared with other organisms. In this study, the primary endpoint (all-cause mortality or recurrence of PA-VAP at day 90) was reached in 25,5% and 35,2%, respectively. This difference was not statistically significant.
Therefore, we consider that the hypothesis that the primary endpoint will occur in approximately 25% of cases is consistent with currently published data

Minor comment: “The non-inferiority margin of 10% was chosen as the largest difference that may be potentially clinically acceptable » That is a bit debatable since mortality is part of the composite outcome. 10% is a commonly used margin and makes the study feasible but I would argue that a difference of e.g. 9% would probably not be acceptable for physicians and patients, especially also given the scarce evidence the reducing treatment duration from 7 days to shorter periods actually has an impact on resistance (hence the importance of studying resistance outcomes).

We thank the reviewer for this comment.

We chose the non-inferiority margin of 10% taking into account the methodological data applied to the RCT dedicated to VAP. In a systematic review[5], nine trials (33%) used a non-inferiority design with non-inferiority margins (i.e., absolute percentage difference in the primary outcome acceptable for non-inferiority to be established) mentioned in eight of them (20%, 15% and 10% in three studies, four studies, and one study, respectively).

According European medicine Agency[6], “Clinical outcome documented at a Test-of-Cure visit timed from randomisation so that it occurs within a window of approximately 7-14 days after the last possible day of treatment would be an acceptable primary endpoint. The secondary endpoints should include all-cause mortality (e.g. deaths that occur up to day 28 post-randomisation) and the proportions of patients that are discharged from hospital within a pre-specified post-randomisation follow-up period. The suggested non-inferiority margin should not exceed -12.5% in studies confined to VAP or HAP or including both HAP and VAP patients. ». In this recommendation, the margin of 12,5% do not include mortality.

We agree that it is difficult to determine non-inferiority margins in a trial using a composite primary endpoint.

However, the ASPECT was, for instance designed to show non-inferiority for the primary endpoint in the intention-to-treat population, with a 10% non-inferiority margin to achieve 90% power at a one-sided significance level of 0,025 (based on regulatory agency guidance)[7], and assuming a 28-day all-cause mortality rate of 20% in both groups.

We also specify that each component of the primary endpoint will be analysed independently in secondary endpoint.

Regarding impact on resistance, focus will be made on impact on global antibiotic free days at day 28 and its correlation with resistance acquisition (not only relationship between expected decreased reduction of given antibiotic therapy for VAP and resistance acquisition)

Reviewer: 2

Dr. Guadalupe Miranda-Novales, Mexican Social Security Institute

Comments to the Author:

This study protocol will provide relevant results that will optimize the use of antibiotics in one of the main healthcare-associated infections in the ICUs.

I have only one comment on the sample size calculation.

In the sample size justification (page 15) the investigators are assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm (reference 19), and, established that 590 subjects (295 per 308 arm) are needed to establish non-inferiority with the absolute difference of death, treatment failure or occurrence of new episode of VAP doesn’t exceed 10% (non-inferiority margin).

In the next sentence, they mentioned that absolute rate of treatment failure / new episode of VAP without treatment cannot be estimated. Therefore, the sample size calculation seems to be calculated with only one of the three outcomes.

The section is not clear. Also, the non-inferiority margin of 10% chosen as the largest difference that may be potentially clinically acceptable may not be “acceptable” for the three main outcomes separately.

Please clarify this section and preferably add more references to support the calculation.
We agree that the argumentation using estimations of outcomes without any treatment was not clear enough. In our manuscript, the text reads “Assuming that 25% of the patients will encountered all-cause mortality, treatment failure or occurrence of new episode of VAP before day 28 in the control arm…”. In other words, the proportion of 25% refers to the whole composite endpoint and the sample size calculation was calculated taking into account the whole composite endpoint.
Based on our answer to the last Reviewer 1 minor comment, we proposed a new explanation for the choice of the 10% non-inferiority margin. This was modified in the revised manuscript (Line 4-12, page 16).

Minor comments: along the document (figures included) there are several typographic errors that need to be corrected.
We thank the reviewer for this comment and we have made every effort to correct them.

Reviewer: 1
Competing interests of Reviewer: None

Reviewer: 2
Competing interests of Reviewer: I declare that I have no known competing financial interests or personal relationships that could have appeared to influence this review.

References

1. Pugin J, Auckenthaler R, Mili N, and al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis. 1991 May;143(5 Pt 1):1121-9. doi: 10.1164/ajrccm/143.5_Pt_1.1121. PMID: 2024824

2. Leone M, Bouadma L, Bouhemad B and al. Hospital-acquired pneumonia in ICU. Anaesth Crit Care Pain Med. 2018 Feb;37(1):83-98.doi:10.1016/j.accpm.2017.11.006. Epub 2017 Nov 15. PMID: 29155054.

3. Kollef MH, Nováček M, Kivistik, Ü. and al. Ceftolozane–tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial, The *Lancet Infectious Diseases* **19**, 12 (2019). https://doi.org/10.1016/S1473-3099(19)30403-7

4. Bouglé A, Tuffet S, Federici L, and al ; iDIAPASON Trial Investigators. Comparison of 8 versus 15 days of antibiotic therapy for Pseudomonas aeruginosa ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial. Intensive Care Med. 2022 Jul;48(7):841-849. doi: 10.1007/s00134-022-06690-5. Epub 2022 May 13. Erratum in: Intensive Care Med. 2022 Jun 21;: PMID: 35552788

5. Weiss, E., Essaied, W., Adrie, C. *et al.* Treatment of severe hospital-acquired and ventilator-associated pneumonia: a systematic review of inclusion and judgment criteria used in randomized controlled trials. *Crit Care* **21**, 162 (2017). https://doi.org/10.1186/s13054-017-1755-5

6. https://www.ema.europa.eu/en/documents/scientific-guideline/addendum-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections_en.pdf

7. US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research.Guidance for industry. Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia: developing drugs for treatment. Silver Spring, MD: Center for Drug Evaluation and Research, 2014.

VERSION 2 – REVIEW

REVIEWER	Miranda-Novales, Guadalupe Mexican Social Security Institute, Analysis and Synthesis of Evidence Research Unit
REVIEW RETURNED	28-Nov-2022

GENERAL COMMENTS	Authors have proper addressed all the comments

VERSION 2 – AUTHOR RESPONSE

Dr. Guadalupe Miranda-Novales, Mexican Social Security Institute Comments to the Author:

Authors have proper addressed all the comments

We thank the reviewer for response