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STUDY PROTOCOL

A Randomized, Open-Label, Non-inferiority Clinical Trial Assessing 7 Versus 14 Days of Antimicrobial Therapy for Severe Multidrug-Resistant Gram-Negative Bacterial Infections: The OPTIMISE Trial Protocol

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ABSTRACT

Introduction: Shorter courses of antimicrobials have been shown to be non-inferior to longer, "traditional" duration of therapies, including for some severe healthcare-associated infections, with a few exceptions. However, evidence is lacking regarding shorter regimes against severe infections by multidrug-resistant Gram-negative bacteria (MDR-GNB), which are often caused by distinct strains and commonly treated with second-line antimicrobials. In the duratiOn of theraPy in severe infecTIons by MultIdrug-reSistant gram-nEgative bacteria (OPTIMISE) trial, we aim to assess the non-inferiority of 7-day versus 14-day antimicrobial therapy in critically ill patients with severe infections caused by MDR-GNB.

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Methods: This is a randomized, multicenter, open-label, parallel controlled trial to assess the non-inferiority of 7-day versus 14-day of adequate antimicrobial therapy for intensive care unit (ICU)-acquired severe infections by MDR-GNB. Adult patients with severe infections by MDR-GNB initiated after 48 h of ICU admission are screened for eligibility. Patients are eligible if they proved to be hemodynamically stable and without fever for at least 48 h on the 7th day of adequate antimicrobial therapy. After consenting, patients are 1:1 randomized to discontinue antimicrobial therapy on the 7th (± 1) day or to continue for a total of 14th (± 1) days.
Planned Outcomes: The primary outcome is treatment failure, defined as death or relapse of infection within 28 days after randomization. Non-inferiority will be achieved if the upper edge of the two-tailed 95% confidence interval of the difference between the clinical failure rate in the 7-day and the 14-day group is not higher than 10%.
Conclusion: The OPTIMISE trial is the first randomized controlled trial specifically designed to assess the duration of antimicrobial therapy in patients with severe infections by MDR-GNB.
Trial Registration: ClinicalTrials.gov, NCT05210387. Registered on 27 January 2022. Seven Versus 14 Days of Antibiotic Therapy for Multidrug-resistant Gram-negative Bacilli Infections (OPTIMISE).

Keywords: Gram-negative bacilli; Antimicrobial therapy; Antimicrobial resistance; Enterobacterales; *Klebsiella pneumoniae*; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*

Key Summary Points

There is a lack of studies addressing shorter regimes against severe infections by multidrug-resistant Gram-negative bacteria (MDR-GNB).

The duratiOn of theraPy in severe infecTIons by MultIdrug-reSistant gram-nEgative bacteria (OPTIMISE) trial aims to assess the non-inferiority of 7-day versus 14-day antimicrobial therapy in critically ill patients with severe infections caused by MDR-GNB.

Patients are eligible if they proved to be hemodynamically stable and without fever for at least 48 h on the 7th day of adequate antimicrobial therapy.

The primary outcome is treatment failure, defined as death or relapse of infection within 28 days after randomization.

INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the leading public health threats of the twenty-first century [1–4]. This is a particular problem in healthcare-associated infections (HCAI) by Gram-negative bacteria (GNB), which are resistant to first- and last-line beta-lactams generally used to treat these infections [1, 4]. In 2017, the World Health Organization (WHO) published a list of priority multidrug-resistant (MDR) pathogens for research and development

of new antimicrobials [1]. Carbapenem-resistant Enterobacterales, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, along with third-generation cephalosporin-resistant Enterobacterales have been listed as critical priority pathogens [1]. Indeed, infections by these carbapenem-resistant GNB challenge effective antimicrobial therapy and have been associated with increased mortality [5–9].

Although the recent launching of new antimicrobial agents, namely the new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol, have attenuated dreaded therapeutic scenarios associated with AMR, and have been recommended as the first options for treating serious infections caused by these organisms, they are not active against all carbapenem-resistant organisms and the access to these new compounds is still limited in low- and middle-income countries, where HCAI and AMR is an even more severe problem [4, 10–12]. Therefore, there is still a long way to go to maximize antimicrobial therapeutic options and improve strategies to better use old and new drugs for HCAI for these difficult-to-treat pathogens.

Aiming to decrease unnecessary antimicrobial exposure, which may contribute to further escalation of AMR, as well to reduce antimicrobial-associated adverse effects, in the last 20 years, there have been several randomized clinical trials evaluating shorter-duration treatment regimes in comparison with more "traditional" time of antibiotic therapies [13–15]. With few exceptions, most trials have shown that shorter treatment durations (depending on the infection, 5–8 days) are usually non-inferior to longer, more "conventional" times of treatment (14–21 days) [13–15].

Despite the promising results of the trials, there are still some gaps that may impair a broader implementation of shorter-duration treatment strategies in HCAIs, particularly in more severely ill patients with multidrug-resistant Gram-negative bacteria (MDR-GNB) infections. More studies are still needed in critically ill patients, particularly those with sepsis [16]. Furthermore, there is ongoing controversy whether in ventilator-associated pneumonia, a severe infection that commonly affects critically ill patients [17, 18], certain microorganisms, such as *P. aeruginosa*, may require longer, more "traditional" courses of antimicrobial therapy [19, 20]. Finally, difficult-to-treat MDR-GNB are still underrepresented in most of these studies, impairing a wider implementation of this strategy in clinical practice [21]. Notably, recent guidelines were unable to provide recommendations for the duration of therapy for severe MDR-GNB because of the absence of studies addressing this issue [22, 23].

The combination of severe infections and MDR-GNB may be a case against shorter-duration therapies. First, because severe infections—particularly those associated with sepsis—may be associated with higher bacterial inoculum, they increase target organ damage, which may affect the pharmacokinetics of antimicrobials, and immune dysfunction, which may impair pathogen clearance [16]. Second, infections by MDR-GNB more commonly affect or immunocompromised patients or those with more comorbidities [21]. Finally, although novel antimicrobials may change this landscape [22, 23], several MDR-GNB are still treated with less potent second-line antimicrobials, such as polymyxins, aminoglycosides, and tigecycline [22, 23], for which a longer duration might be necessary.

On the other hand, there are many compelling potential benefits of shortening treatment of MDR-GNB in patients who present a favorable clinical response in the first days of therapy. First, it could avoid unnecessary exposure to novel agents, hampering the emergence of resistance to these new drugs. Second, it could reduce the incidence of adverse effects commonly associated with these second-line agents, notably the high rates of acute kidney injury (AKI) associated with polymyxins and aminoglycosides [24, 25], but also *Clostridioides difficile* infections, for which there is evidence that even a single day of antibiotic use may increase their incidence [26]. In addition, an overall reduction in selective pressure might potentially decrease the incidence of new infections by other MDR pathogens. Finally, avoiding unnecessary antimicrobials may decrease the length of use of intravascular catheters, potentially reducing catheter-

associated bloodstream infections, and it ultimately may lead to lower lengths of hospitalization, resulting in clinical and economic benefits [27].

Therefore, in this open-label, randomized clinical trial, we address the duratiOn of theraPy in severe infecTIons by MultIdrug-reSistant gram-nEgative bacteria (OPTIMISE). Our main objective is to assess the non-inferiority of 7-day antibiotic therapy compared to 14-day therapy in the treatment of intensive care unit (ICU) patients with severe infections caused by MDR-GNB who presented clinical stability on the 7th day of antimicrobial therapy.

METHODS

Study Design

This is a randomized, open-label trial, with parallel groups and 1:1 allocation ratio to assess the non-inferiority of 7 versus 14 days of antimicrobial therapy for severe infections by ICU-acquired MDR-GNB in patients who are hemodynamically stable and afebrile on the 7th day of treatment. The study intervention consists of suspending antimicrobial therapy on the 7th day in participants allocated to the intervention group versus maintaining antimicrobial therapy until the 14th day in the control group.

The study protocol and amendments have been approved by the research ethics committee (institutional review board, IRB) of the coordinating center (Hospital Moinhos de Vento), as well as IRBs from all other participant sites (Supplementary Material).

Study Setting

Participants have been recruited at ICUs of Brazilian hospitals participating in the IMPACTO MR platform [28] since 27 January 2022. In December 2022, additional centers, outside the IMPACTO MR platform, were included as participants sites, affording a total of 36 centers in October 2023, in order to increase recruitment rate. The recruitment period is expected to close on 20 December 2023.

Eligibility Criteria

Participants are eligible for the study if they are at least 18 years of age; provide written informed consent; have been admitted to the ICU for at least 48 h at the onset of infection; have a severe infection caused by an MDR-GNB; are hemodynamically stable and afebrile for at least 48 h on day 7 $\pm$ 1 of appropriate antibiotic therapy since the onset of infection (defined as the day on which the culture that yielded the growth of the isolate was collected); and the patients' care team consents to inclusion of participant in the trial. The European Committee for Antimicrobial Susceptibility Testing (EUCAST) [29] criteria were used for interpreting antimicrobial susceptibility tests, except for ampicillin-sulbactam and *A. baumannii*, when Clinical Laboratory Standard Institute (CLSI) [30] breakpoint was used. Definitions of infection and infection sites were adapted from the criteria of the Brazilian Health Regulatory Agency [31] (Supplementary Material). A full description of eligibility criteria definitions is found in Table 1.

They are excluded if one or more of the following conditions are present: (i) Participation in other experimental trials involving antimicrobial therapy; (ii) Primary site of infection that requires longer therapy (such as endocarditis, necrotizing fasciitis, osteomyelitis, abdominal abscess, central nervous system infections, empyema, periprosthetic infections; see full description in the Supplementary Material; any other infection sites are considered eligible); (iii) Immunosuppression (see definitions in the Supplementary Material); (iv) Growth of the same bacteria under study in blood culture samples collected in the 48 h prior to randomization (if cultures requested by the care team); (v) Concomitant uncontrolled infection by another GNB (regardless of susceptibility profile); (vi) Prior participation in this trial; (vii) Known pregnancy; (viii) Patient on palliative care only for whom initiation of antimicrobials, if necessary, or hemodynamic support measures (e.g., initiation or uptitration of vasopressors) has already been decided against.

Table 1 Essential definitions of eligibility criteria of the OPTIMISE trial

Term	Definition
Severe Infection	Bloodstream infection; or
	Pneumonia (with or without mechanical ventilation); or
	Infection at any other site[a] if sepsis or septic shock is also present[b]
Multidrug-resistant Gram-negative bacteria (MDR-GNB)	Enterobacterales:
	In vitro resistance to ceftriaxone and cefepime
	or
	In vitro resistance to carbapenems
	Pseudomonas aeruginosa:
	In vitro resistance to ceftazidime, cefepime, and/or carbapenems
	Acinetobacter baumannii complex:
	In vitro susceptibility to carbapenems, provided they are not susceptible to other beta-lactams (if tested and interpreted according to CLSI) or to ampicillin/sulbactam (if tested and interpreted according to CLSI). If the microbiology laboratory does not carry out susceptibility testing for other beta-lactams and for ampicillin/sulbactam, the organism will be considered resistant to these antimicrobials
	or
	In vitro resistance to carbapenems
Hemodynamic stability	Maintenance of mean arterial pressure $\geq$ 60 mmHg without the need for vasopressors or fluid resuscitation in patients not on mechanical ventilation, not on sedatives, and not requiring dialysis
	In case of patients who are mechanically ventilated, requiring renal replacement therapy, and/or in need of sedation, due to the hypotensive effects of many of these drugs, low-dose norepinephrine ($<$ 0.1 mcg/kg/min) is allowed, provided the dose remained stable in the 48 h preceding randomization
Fever	Axillary temperature $\geq$ 37.8 °C

Table 1 continued

Term	Definition
Appropriate antimicrobial therapy	Use of at least one antimicrobial to which the MDR-GNB isolate exhibits in vitro susceptibility, which has been initiated within 7 days of culture collection
	Prior use of other antimicrobials to which the isolated pathogen lacks in vitro susceptibility is not considered appropriate treatment and should not count as treatment time
	In the case of ceftazidime/avibactam, in the absence of specific susceptibility testing, Enterobacterales isolates in which phenotypic or genotypic testing indicates the presence of a class A carbapenemase will be considered susceptible
	Tigecycline is accepted as appropriate treatment for the purposes of this study if the isolated pathogen has a minimum inhibitory concentration $\leq$ 1 mg/L and the treated patient received tigecycline at a dose of 100 mg every 12 h [31–34]
	If antimicrobial therapy is switched from an antimicrobial to which the pathogen is susceptible in vitro to another antimicrobial to which it is also susceptible in vitro, there is no need to restart the "appropriate treatment" time counting
	Dose adequacy is not included in the definition of appropriate treatment, but it will be evaluated as a covariate. In the case of polymicrobial infections, for antimicrobial treatment to be considered appropriate, it must include at least one antibiotic to which each of the isolated bacteria shows in vitro susceptibility

CLSI Clinical Laboratory Standards Institute

[a]Infection and infection site are defined according to the criteria of the Brazilian Health Regulatory Agency (Supplementary Material)

[b]Sepsis and septic shock are defined according to SEPSIS-3 criteria [36]

Intervention

The study intervention is the discontinuation of antibiotic therapy for the infection that prompted the participant's enrollment in the trial. In the intervention group, antimicrobials prescribed for the MDR-GNB infection should be discontinued on day 7 of therapy (a variation of $\pm$ 1 day is acceptable for per protocol analysis). The control group consists of patients whose antimicrobial therapy prescribed for the MDR-GNB infection should be continued until day 14 ($\pm$ 1 day) of therapy.

If the participant is discharged before day 28, the coordinating center will contact the participant by telephone. This evaluation can be carried out with a 7-day window (i.e., up to day 35 of follow-up). The calls will be made by investigators from the coordinating center and will be recorded.

After randomization, patients are discontinued only if consent is withdrawn. Adherence to the proposed intervention is assessed through the patient's medical prescription. There are no other care or therapeutic interventions prohibited by this protocol. If the patient develops new signs and symptoms of active bacterial infection after randomization and (according to group allocation) discontinuation of therapy, regardless of whether this is new infection or a relapse of the infection that prompted enrollment in the trial, there is no restriction whatsoever on resumption or initiation of further antimicrobial therapy at the discretion of the

care team. The protocol does not plan to discontinue patients because of the adverse effects of antimicrobial therapy, especially in the 14-day group, since this is the time considered standard for treatment. However, decisions regarding maintenance or interruption are made by the medical assistance team and all these participants will be subject to intention-to-treat analysis.

Outcomes

The primary outcome is treatment failure within 28 days of randomization, defined as death or reinfection with the same bacteria at any site. Reinfection is defined as growth of the same pathogen with the same susceptibility profile to the antimicrobials of interest (i.e., the same GNB species with the same antimicrobial resistance profile of interest), at any site of infection, in addition to meeting the diagnostic criteria of the Brazilian Health Regulatory Agency (ANVISA) [31] (see definitions in the Supplementary Material).

Secondary outcomes, which are also assessed within 28 days of participant randomization, are the following: (a) days alive and free from hospitalization; (b) days alive and free of antimicrobial therapy; (c) incidence of infections with other MDR-GNB and other bacteria; (d) length of ICU stay (assessed in survivors at 28 days); (e) acute kidney injury [32]; (f) cumulative incidence of all-cause diarrhea; (g) cumulative incidence of confirmed *C. difficile* infection; (h) cumulative incidence of other antimicrobial-related adverse events (hepatotoxicity; ALT > 250 U/L, AST > 200 U/L, and/or total bilirubin > 1.5 mg/dL), neutropenia (neutrophils < 1000 cells/mm^3), and thrombocytopenia (platelets < 100,000 cells/mm^3); and (i) cumulative incidence of hemodynamic instability lasting > 6 h (within 14 days of randomization).

The component of primary outcome, relapse of the infection, will be adjudicated by two independent infectious diseases physicians, who will be blinded to the intervention. They will receive the specific medical records and laboratory and radiological examination results which have been used to fulfill the criteria for infection. If the physicians' adjudications do not agree, a third infectious diseases specialist will review the case.

Participant Timeline

Screening, evaluation for eligibility and follow-up is detailed in Fig. 1. Each participant will be voluntarily invited to participate in the study and must provide their consent by signing an informed consent form (ICF)—see the ICF in the Supplementary Material. If the participant is unable to provide consent, the invitation will

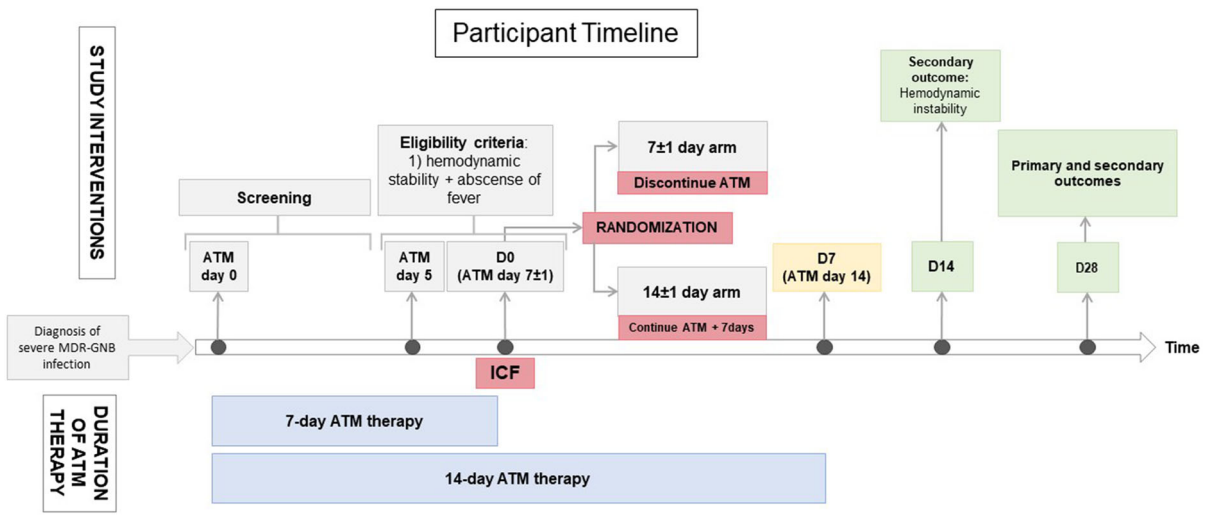

Fig. 1 Participant timeline. *ATM* antimicrobial, *D* day of the study, *ICF* informed consent form

be made to their legal guardian or proxy. The consent can be obtained between the 5th and 8th day of antimicrobial treatment once they are identified as eligible for the study.

Assignment of Interventions

The randomized patient allocation sequence was created using the R studio program [33] by a statistician, respecting an individual randomization in blocks of 2 and 4, in a 1:1 ratio and stratified by sites and by risk for mortality due to infection (high versus low risk). For the purposes of this study, urinary tract infections and central line-associated bloodstream infections are defined as low risk. All other infections are considered high risk. Randomization is performed by the investigator of each participating hospital through the REDCap data collection platform ensuring concealment of the randomization list.

This is an open-label randomized clinical trial and, as such, investigators and patients are not blinded to group allocation. However, outcomes will be assessed by a blinded evaluation committee.

Data Collection

The information will be recorded on electronic Case Report Forms (eCRFs) using REDCap. After randomization, information will be evaluated daily regarding development of hemodynamic instability, clinical variables (antimicrobials administered, diarrhea, urinary output), adverse events related to antimicrobial therapy, and laboratory variables (new cultures, creatinine) (Table S1 in the Supplementary Material).

All staff members involved in data collection will receive training in utilizing the REDCap tool, as well as training in Good Clinical Practice guidelines. Quality assessment and consent forms and eCRFs will be checked by the coordinator center monitors.

Data Management

Several procedures have been adopted to ensure data quality and protocol standardization. These procedures include (i) Online training with all investigators; (ii) A detailed investigator brochure describing each step of the protocol; (iii) Contacting participating centers to review the protocol and offer new training sessions; (iv) Real-time data assessment by a team of investigators from the coordinating center; and (v) Monthly reports on patient screening, recruitment, and randomization.

No patient data will be disclosed to the study or data management teams. In the eCRFs, patients and sites are identified by numbers. Data from printed medical records are kept confidential (stored in locked files) by all participating sites. The identity of all patients will be anonymized in all interim and final reports.

Considering the profile of patients who will be included in the research and the 28-day follow-up period, it is unlikely that these participants will be lost to follow-up. However, participants who are discharged and with whom the research team is unable to make contact will be considered as "missing".

Sample Size

The sample size was calculated considering a clinical failure of 30% in both groups, a randomization ratio of 1:1, a non-inferiority margin of 10%, an alpha of 0.05, and a beta of 0.20. A total of 520 participants will be needed. The sample size will be monitored throughout the study, through interim analyses, for adjustment if necessary.

Data Analysis

All statistical analyses will be performed in R. A non-inferiority analysis of the 7-day course of treatment compared to the conventional 14-day course of treatment will be performed. The primary analysis will be conducted by intention to treat. Secondarily, a per protocol analysis will also be performed. Non-inferiority will be achieved if the upper edge of the two-tailed 95% confidence interval (CI) of the difference between the failure rate in the intervention group and the control group is not higher than 10%.

A superiority analysis will also be performed for the secondary outcomes, as the shorter duration of antimicrobial therapy is expected to yield a lower incidence of toxicity, reduce length of hospital stay and use of antimicrobials, and reduce the incidence of superinfections, such as *C. difficile*-associated diarrhea. For this purpose, chi-square or Fisher's exact test will be used for categorical outcomes and Student's *t* test for independent samples or non-parametric tests for continuous outcomes, depending on the nature of the variable (see full description of statistical analysis for secondary outcomes in the Supplementary Material). All tests will be two-tailed and a $p \leq 0.05$ will be considered statistically significant.

Six subgroups analysis are defined for the primary outcome, considering the variables infecting bacteria (Enterobacterales, *A. baumannii*, or *P. aeruginosa*); susceptibility profile (resistant vs. susceptible to carbapenems); criteria defining infection severity (SOFA score ≥ 2 [sepsis or septic shock] [34], bloodstream infection, or pneumonia); empirical therapy (appropriate vs. initially inappropriate); antimicrobial therapy (monotherapy vs. combination therapy); risk of infection (low risk vs. high risk).

Missing Data

We anticipate minimal missing values for outcomes, given that the study procedures involve both training of site research staff and independent remote data monitoring by the study coordinator. Nevertheless, the coordinating center will contact site investigators to retrieve any missing data values. Analyses for primary and secondary outcomes will be based on participants for whom outcome data are available, i.e., available case analysis.

Statistical Interim Analysis and Stopping Guidance

A statistical interim analysis is planned when 25% (130 participants), 50% (260 participants), and 75% (390 participants) are recruited. In these analyses, the safety of the study participants will be evaluated on the basis of data related to the primary outcome "clinical failure", the components of the main outcome separately (death and relapse of infection), and the secondary outcome "new hemodynamic instability in the first 14 days of study follow-up". We defined as a stopping rule a statistical significance with $p < 0.001$ (Peto's rule) in any of these analyses. The interim analysis will be carried out by an external committee (data monitoring and safety board, DMSB) composed of three independent members (one infectious diseases specialist, one statistician, and one specialist in clinical research bioethics) and it will provide guidance on how to proceed with the study, and may guide the interruption of the study if the level of significance described above is found in the analyzed variables, or if the committee decides that the study should be interrupted for other reasons, such as the high rate of serious adverse events.

The Brazilian Ministry of Health will be notified of the DMSB decision and, if any change is identified as necessary, such as a change in the sample size or interruption of the study, it will be involved in these discussions. In addition, at each interim analysis, the sample size will be reassessed for possible readjustment if the overall event rates are different from those initially estimated. As this is a non-inferiority study, there is no provision for early stoppage due to superiority of the treatment of interest, and no theoretical rationale to support this hypothesis.

Adverse Events

Severe adverse events (SAE) must be reported to the coordinating center within 24 h of becoming aware of the event. The principal investigator at each participating center will be responsible for informing the Research Ethics Committees of any SAE, as required by local regulations.

This study will not test any experimental medication or treatment other than the standard of care already implemented by the participating hospitals. The sole intervention of the study concerns the duration of antibiotic therapy. Therefore, the expected risk is recurrence of

infection, which could lead to sepsis or death. However, as previously described, the medical team is free to resume or initiate treatment in case of recurrence or new infection.

Protocol Amendments

The second to fourth versions of the protocol amendments were done before the initiation of the study. The major amendments to the protocol are presented in Table S2 in the Supplementary Material.

STRENGTHS AND LIMITATIONS

Recommendations of antimicrobial therapy duration for severe HCAIs have been mostly based on expert opinion rather than on solid evidenced-based data. There have been few completed studies addressing the effectiveness of shorter durations in severe HCAIs, all of them in ventilator-associated pneumonia [35–37]. In two, there was no MDG-GNB included [35, 36], while in the other there was no description of the susceptibility profile [37]. There were also two randomized clinical trials comparing duration of therapy for GNB bloodstream infections [38, 39]. However, one included both community-acquired and HCAIs, excluded non-fermentative-GNB, and did not report the number of MDR isolates [39]; while in the other study, less than 20% were considered MDR-GNB [38], using a less restrictive WHO definition when defining critical priority pathogens [1, 38]. Therefore, none of the currently published trials has been designed to assess MDR-GNB infections, which have limited therapeutic options, often with less reliable agents [1]. OPTIMISE is the first randomized clinical trial specifically designed to evaluate the non-inferiority of shorter durations in two scarcely investigated conditions, i.e., severe infections caused by WHO critical priority MDR-GNB.

Unlike most previous studies addressing 7–8 versus 14–15 days of therapy, in which randomization happens soon after the infection diagnosis, before any clinical indication of improvement, and ultimately is interrupted at day 7–8 regardless of the patient's clinical status, in the OPTIMISE trial, eligible patients are those with severe infections, who have been treated with appropriate antimicrobials for at least 7 ± 1 days and present clinical signs of improvement for at least 48 h. In addition, to protect patients from a potential early interruption when the clinical condition might indicate a poor response in the first 7 days of treatment, we believe it better represents clinical practice, in which clinicians consider stopping antimicrobial therapy after some consistent evidence that the patients have improved their clinical condition and additional therapy may not be necessary. Finally, in previous trials, the events accounting for the outcomes may occur before day 7 of therapy, i.e., when groups have not yet become differentiated in relation to the intervention. The design of OPTIMISE is similar to that used in the trial by Yahav et al. [38], addressing duration of therapy for GNB bloodstream infection.

Another strength of this trial is that randomization has been stratified for important factors that might affect the outcome. The stratification by site diminishes the effect that local protocols and other differences in patients' care provided at each hospital may have on the outcomes of interest. We also stratified by risk of infection (high vs. low risk) so that infections of lower severity, potentially associated with lower bacterial inoculum and/or ease control with device removal, would be homogeneously distributed between the two groups.

The major limitation of this trial is its open design. As previously commented [20], the treating physician could tend to seek a new infection diagnosis in patients without antimicrobial therapy, in this case in the 7-day therapy group. Since relapse of the infection is part of the composite outcome, it could imply more clinical failures in the 7-day group, simply because of asymmetric (longer) time exposure to develop relapse compared to the 14-day group. To mitigate this issue, two independent and blinded infectious diseases physicians are adjudicating any reported relapses of infection.

Another limitation of the study is the definition of adequate antimicrobial treatment since this concept only takes into account in vitro susceptibility to the antimicrobial and

does not consider the class of the antimicrobial. For example, polymyxins and aminoglycosides are no longer recommended therapy for carbapenem-resistant Enterobacterales [22, 23], but they are still used in some resource-limited centers. Currently, neither has a breakpoint that could be recommended for monotherapy [29, 40]; nonetheless, assuming that the patient infected by a MDR-GNB with a susceptible result for any of these antimicrobials received any of them in monotherapy and presents the eligibility criteria of clinical stability, it is considered as adequate. It does not mean that the investigators recommend any of these agents in monotherapy for severe infections, but since it has been demonstrated that it might have acted positively in a given case, it is assumed that it was appropriate. No antimicrobial with in vitro results showing resistance may be considered as adequate. In addition, doses are also not considered in the evaluation of appropriateness of therapy, with the exception of tigecycline, where an adapted breakpoint considering the minimal inhibitory concentration and dose was considered in this evaluation, based on data from previous studies [41–44].

Ethics

This study has been conducted in accordance with the Brazilian and international regulations set forth in the following documents: Declaration of Helsinki; Brazilian National Health Council Resolution CNS 466/2012 and related Brazilian Ministry of Health publications; and1996 ICH Harmonized Tripartite Guideline for Good Clinical Practice.

The study protocol and amendments have been approved by the research ethics committee (IRB) of the coordinating center (Hospital Moinhos de Vento), as well as IRBs from all other participant sites.

Each patient or legal representative is asked to sign an ICF consenting to participate in the study. The ICF (see Supplementary Material) can be administered between day 5 and day 8 of antimicrobial treatment.

Dissemination Plans

The principal investigator and co-investigators that fulfill the authorship criteria (see Supplementary Material) will prepare a manuscript that will be submitted for publication in an international peer-reviewed journal that is made available free of charge, so that the information can be accessible to all interested parties in the matter, such as health professionals located in the centers where the study is being carried out. The results will also be made available to the Ministry of Health of Brazil and disseminated in international scientific conferences and events in the area.

CONCLUSIONS

The OPTIMISE trial is the first randomized clinical trial specifically designed to assess the optimal duration of antimicrobial therapy in patients with severe infections by MDR-GNB. We expect to demonstrate that 7-day therapy is not inferior to 14-day therapy, in patients who present signs of clinical stability on the seventh day of appropriate antimicrobial therapy, and might be superior in reducing length of ICU, decreasing the use of antimicrobials and the incidence of adverse events.

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Author Contribution. Beatriz Arns and Alexandre P. Zavascki conceived of the study; Beatriz Arns, Guilhermo Prates Sesin and Alexandre P. Zavascki wrote the first draft of the first manuscript; Beatriz Arns, Jaqueline Driemeyer C. Horvath, Guilhermo Prates Sesin, Crepin Aziz Jose Oluwafoumi Agani, Tiago Marcon dos Santos, Liliane Spencer Bittencourt Brochier, Alexandre Biasi Cavalcanti, Bruno Martins Tomazini, Adriano Jose Pereira, Viviane Cordeiro Veiga, Giovana Marssola Nascimento, Andre C. Kalil and Alexandre P. Zavascki made significant contributions to the final study design; Gabriela Soares Rech and Bruna Silveira

da Rosa provided statistical help; Alexandre Biasi Cavalcanti, Bruno Martins Tomazini, Adriano Jose Pereira, Viviane Cordeiro Veiga, Giovana Marssola Nascimento, and Andre C. Kalil provided critical review of the manuscript for important intellectual content. All authors contributed and agreed with the content and conclusions of this manuscript.

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Data Availability. The anonymous stored data will be available on reasonable request after all analyzes are done.

Declarations

Conflict of Interest. All authors confirm that they have no conflicts of interest to declare. Alexandre P. Zavascki is a research fellow of the National Council for Scientific and Technological Development (CNPq), Ministry of Science and Technology, Brazil.

Ethical Approval. This study has been conducted in accordance with the Brazilian and international regulations set forth in the following documents: Declaration of Helsinki; Brazilian National Health Council Resolution CNS 466/2012 and related Brazilian Ministry of Health publications; and 1996 ICH Harmonized Tripartite Guideline for Good Clinical Practice. The study protocol and amendments have been approved by the research ethics committee (IRB) of the coordinating center (Hospital Moinhos de Vento), as well as IRBs from all other participant sites.

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