Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram-negative Bacteremia: a Non-inferiority Randomized Controlled Trial

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Summary:

Shortening antibiotic duration is important for antimicrobial stewardship.

This randomized controlled trial showed non-inferiority of 7 days compared to 14 days of covering antibiotics for patients with uncomplicated Gram-negative bacteremia.

Seven days of antibiotics are sufficient for uncomplicated Gram-negative bacteremia.

This study has been presented as oral presentation at the ECCMID annual conference, Madrid, Spain, 21-24 April 2018.

Abstract

Background: Gram-negative bacteremia is a major cause of morbidity and mortality in hospitalized patients. Data to guide the duration of antibiotic therapy are limited.

Methods: Randomized, multicenter, open-label, non-inferiority trial. Inpatients with Gram-negative bacteremia, afebrile and hemodynamically stable for at least 48 hours, were randomized to receive 7 (intervention) or 14 days (control) of covering antibiotic therapy. Patients with uncontrolled focus of infection were excluded. The primary outcome at 90 days was a composite of all-cause mortality; relapse, suppurative or distant complications; and re-admission or extended hospitalization (>14 days). The non-inferiority margin was set at 10%.

Results: We included 604 patients (306 intervention, 298 control) between January 2013 and August 2017 in three centers in Israel and Italy. The source of the infection was urinary in 411/604 (68%); causative pathogens were mainly Enterobacteriaceae (543/604, 90%). A 7-day difference in the median duration of covering antibiotics was achieved. The primary outcome occurred in 140/306 (45.8%) patients in the 7 days group versus 144/298 (48.3%) in the 14 days group (risk difference [RD] -2.6%, 95% confidence interval [CI] -10.5% to 5.3%). No significant differences were observed in all other outcomes and adverse events, except for a shorter time to return to baseline functional status in the short therapy arm.

Conclusions: In patients hospitalized with Gram-negative bacteremia achieving clinical stability before day 7, an antibiotic course of 7 days was non-inferior to 14 days. Reducing antibiotic treatment for uncomplicated Gram-negative bacteremia to 7 days is an important antibiotic stewardship intervention.

(ClinicalTrials.gov number, NCT01737320)

Keywords: Duration; bacteremia; Gram-negative; antibiotics

Introduction

Shortening the duration of antibiotic therapy is an important strategy for reducing unnecessary antibiotic use in the hospital setting, where antibiotic pressure is the most intense. [1] Shorter courses of antibiotics may reduce drug related adverse events, duration of hospitalization, emergence of antibacterial resistance and superinfections, including fungal and *Clostridium difficile* infection. [2]

Several randomized controlled trials (RCTs) demonstrated no significant difference between short and long antibiotic courses in the treatment of mainly Gram-negative infections such as pyelonephritis, [3] and complicated intra-abdominal infections. [4-5] However, patients with bacteremia were rarely enrolled in these trials. A meta-analysis of mostly non-randomized studies demonstrated no significant difference in the outcome of 155 patients with bloodstream infections treated with short versus long antibiotic courses. [6] A recent pilot RCT randomized 115 critically-ill patients with Gram-negative bacteremia to 7 vs. 14 days of antibiotics, but reported only on feasibility and patients' characteristics. [7]

Gram-negative bacteremia is frequent with pyelonephritis, occurring in 10% to 60% of patients [8] and intra-abdominal infections (<10% to 75% of patients depending on the type of infection) and represents the more severe end of the spectrum of illness. [9] The lack of data on the appropriate treatment duration for this subset of patient leads to uncertainty, usually resolved by prolonged treatment durations. [10] Current guidelines recommend a wide range of antibiotic treatment duration between 7 to 14 days. [11]

Given the limited evidence available to guide the duration of antibiotic therapy in Gram-negative bacteremia this randomized trial was designed to test the hypothesis that short-course (7 days)

antibiotic therapy for Gram-negative bacteremia in hospitalized patients is non-inferior to a long-course (14 days).

Methods

Study design

Open-label/ analyst-blinded non-inferiority, 1:1 parallel group, randomized-controlled trial conducted between 1 Jan 2013 to 31 Aug 2017 in two academic centers in Israel and between 1 Nov 2015 to 31 Aug 2017 in one academic center in Italy, with follow-up completed in November 2017. The study was approved by the local ethics board of each participating center.

Participants

We included hospitalized adult patients with aerobic Gram-negative bacteremia at day 7 of covering antibiotic therapy, if hemodynamically stable and afebrile for at least 48 hours. Patients achieving clinical stability and planned for discharge before day 7 could be recruited before discharge.. Patients with urinary tract; intra-abdominal; respiratory tract; central venous catheter (CVC); skin and soft tissue or unknown source of bacteremia were eligible for inclusion whether infection was community or hospital acquired. Patients with other sources of infection; uncontrolled focus of infection; polymicrobial growth; specific pathogens (Brucella, Salmonella); and immunosuppression (neutropenia at time of randomization, HIV, recent allogeneic stem-cell transplantation) were excluded. A complete list of the inclusion and exclusion criteria is provided in Supplement 1. All participants (or an authorized proxy) provided written informed consent before randomization.

Randomization and Treatment

Patients were randomly assigned to short course (7 days) or long course (14 days) antibiotic therapy, counting from the first day of covering antibiotics, whether empirical or directed. Covering antibiotic therapy was defined as that matching the in-vitro susceptibility of the Gram-negative in blood. Empirical treatment was defined as that given before reporting of pathogen

identification and susceptibility, while directed treatment was tailored to the final microbiological results. The type of empirical and directed antibiotic treatments was chosen by the treating physicians. The decision on timing of switch to oral antibiotic therapy as well as time of discharge was also left to the discretion of the treating physician.

Randomization was performed using computer-generated list of random numbers in a 1:1 ratio, without blocking or stratification and was concealed using sealed opaque envelopes prepared centrally and opened consecutively after patient recruitment in each site. Blinding was not performed due to practical limitations.

Outcomes

The primary outcome at 90 days from randomization was a composite of all-cause mortality; clinical failure, including either relapse of the bacteremia, local suppurative complications or distant complications; and re-admission or extended hospital stay (>14 days). Re-admission was defined as any hospitalization occurring after discharge in both groups; hospital stay was defined as extended for any patient who continued hospitalization after day 14. Secondary outcomes included individual components of the primary outcome; development of new clinically or microbiologically-documented infection by 90 days; functional capacity at day 30 and time to return to baseline activity by day 90; total hospital days among survivors and among all patients by 90 days; total antibiotic days by 90 days and duration of appropriate antibiotic treatment for the Gram-negative bacteremias; development of resistance defined as secondary clinical isolates resistant to one or more of the antibiotics used to treat the index Gram-negative bacteremia; and adverse events, including *Clostridium difficile* infection. Detailed definitions of the outcomes are provided in Supplement 1. Outcome data following discharge were collected through telephone

interviews at day 30 and 90 after randomization, supplemented by access to national or regional healthcare databases.

Statistical analysis

We aimed to include 600 patients for a primary outcome event of 35% in the control and intervention groups. Originally, we planned to enroll 400 patients and assess all-cause mortality; clinical failure (as currently defined) and development of new clinically or microbiologically-documented infection as primary outcome. Safety monitoring was conducted by an independent monitoring committee following completion of the follow-up of every 150 patients. After the second safety monitoring, the committee remarked on a lower than expected outcome event rate. We re-considered the patient-relevant outcomes among the bacteremia survivors achieving rapid clinical cure, defined the final composite primary outcome and increased the target sample size to 600 patients. The study was designed to have 80% power with a 10% α-risk to exclude the non-inferiority of short to long antibiotic therapy with a 10% non-inferiority margin. A 10% non-inferiority margin was chosen based on FDA's recommendation for trials assessing drugs for complicated UTIs, [12] considering this clinically-acceptable for the population and outcome assessed in our trial; and the ecological gain of reducing antibiotic use.

The primary analysis was performed by intention to treat including all patients randomized. We planned a per protocol analysis for the primary outcome, including patients treated with appropriate antibiotics for the allocated treatment duration +/- 2 days (i.e., 5-9 days versus 12-16 days). Pre-specified subgroups for analyses of the primary outcome included patients receiving covering (appropriate) vs. non-covering (inappropriate) empirical antibiotics, patients with urinary tract infection (UTI) or other source of the bacteremia and patients with Gram-negative

bacteremia caused by multidrug-resistant (MDR) Gram-negative bacteria vs. non-MDR bacteria. Definitions of multidrug resistance are provided in Supplement 1.

Outcome variables were compared using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. Results are reported using risk difference and 95% confidence intervals, calculated using the Wald method. Analyses were performed with SPSS software, version 24.

Role of the Funding source: The study was investigator-initiated and with no external funding and is registered at ClinicalTrials.gov (NCT01737320)

Results

Of 4807 patients with Gram-negative bacteremia surviving to day 7, 2169 potentially-eligible patients were assessed and 604 patients were included (306 in the short duration arm and 298 in the long duration arm) between 1 Jan 2013 to 31 Aug 2017 (Figure 1). Ninety-day follow-up for the primary outcome was completed for all patients. Overall, baseline characteristics of included patients were balanced between study arms (Table 1). The main source of bacteremia was the urinary tract (411/604, 68%) and the main pathogens were Enterobacteriaceae (543/604, 89.9%). Characteristics of the antibiotics prescribed were also balanced between groups, including type of antibiotics and way of administration (intra-venous/oral); (Supplementary Table 1, Supplement 1).

The primary composite outcome of mortality, clinical failure, readmissions or extended hospitalization at 90 days occurred in 140 of 306 patients in the short duration group (45.8%) compared with 144 of 298 in the long duration group (48.3%) (Risk difference [RD] -2.6%, 95% confidence interval [CI], -10.5% to 5.3%), establishing non-inferiority. In a stratified analysis by the study centers, weighted by inverse variance, results were similar, RD -2.7% (95% CI -10.7% to 5.2%). No significant differences between study groups were demonstrated for any of the individual primary outcome components (Table 2), including 90-day all-cause mortality, with 36 (11.8%) deaths in the short duration group and 32 (10.7) deaths in the long group (RD 1.0%, 95% CI -4% to 6.1%).

Overall 556 patients (92%) received the protocol-specified duration +/- 2 days and were included in the per protocol analysis. For the per-protocol population the composite primary outcome occurred in 128/280 (45.7%) patients in the short duration group compared with 132/276 (47.8%) in the long duration group (RD -2.1%, 95% CI -10.4% to 6.2%).

The primary outcome in pre-specified subgroups is shown in Figure 2. No significant difference between study arms was documented for all predefined subgroups. Non-inferiority criteria were met in all subgroups, except for the subgroups that were small: patients receiving inappropriate empirical antibiotic treatment and those with bacteremia caused by a MDR pathogen.

In a post-hoc analysis, there was no mortality difference between groups at 14 and 28 days; no complications or relapses were observed between 7 and 14 days. No significant difference between study groups was demonstrated for most of the secondary outcomes, including development of new clinically or microbiologically documented infections in 70 (22.9%) of patients in the short vs. 68 (22.8%) patients in the long treatment group (RD 0.06 %, 95% CI -6.6 to 6.8%;) and development of resistance observed overall in 62 (10.3%) of patients (RD 1.0%, 95% CI -3.7% to 5.9%). Total days in hospital were also similar between study arms (Table 2). Time to return to baseline activity within 90 days was significantly shorter in the short duration arm (median 2 weeks (IQR 0-8.3) vs 3 (1-12 weeks)). Duration of appropriate covering antibiotic treatment for the index bacteremia was compatible with assignment (median 7.0 days, IQR 7.0-8.0 vs median 14.0 days, IQR 14.0-14.0 in the 14 days arm). Total antibiotic days from culture collection to 90 days from randomization were significantly fewer in the short duration arm (median 10 days, IQR 9-18 vs median 16 days, IQR 15-22 in the 14 days arm), Table 2.

Adverse events, including acute kidney injury, liver function test abnormalities, rash and diarrhea were reported with no significant differences between study groups. (Table 2)

Clostridium difficile infection was documented in 4 patients overall.

Discussion

In this randomized controlled trial including hospitalized patients with Gram-negative bacteremia, hemodynamically stable by day 7, we found 7 days of antibiotic therapy to be non-inferior to 14 days in terms of mortality, clinical failure, readmissions and prolonged hospitalization. A difference in the median antibiotic treatment duration of 7 days between treatment groups was maintained until day 90. Duration of hospitalization, rates of superinfections, development of resistance and adverse events were not significantly different between 7 and 14 days. Subgroup analysis demonstrated no significant difference between 7 and 14 days groups for the composite primary outcome in patients with UTI, patients receiving inappropriate empirical therapy and patients with MDR pathogen (mostly ESBL). Adherence to the allocated regimen was good, with 556 patients (92%) receiving the preplanned allocated duration +/- 2 days. No significant difference in the composite primary outcome was demonstrated between study arms in the per protocol population.

Limited data are available to support the optimal duration of antibiotic therapy for Gram-negative bacteremia. Few retrospective, propensity score-matched cohort studies have addressed this issue in recent years, showing conflicting results. Chotiprasitsakul et al. compared 6–10 days vs 11–16 days for the treatment of Enterobacteriaceae bloodstream infections and showed no difference in 30-day mortality or relapse between treatment groups with a trend towards less emergence of resistance in the 6-10 days treatment group. [13] Park et al. conducted a similar study in children and demonstrated no difference in 30-day mortality or relapse and a trend towards higher risk of candidemia with treatment duration of above 10 days. [14] Similar results were also demonstrated in patients with *E.coli* bacteremia. [15] In contrast, Nelson et al. found higher rates of treatment failure using less than 10 days of antibiotics for Gram-negative bacteremia in adults,

including the subgroup of patients with UTI. [16-17] This study assessed death or infection relapse after discharge among patients with Gram-negative bacteremia who were discharged alive after the bacteremia and without an extended hospitalization. Excluding extended hospitalization and readmissions from our primary outcome results in an outcome defined similarly to the one reported by Nelson et al. (death, relapse or bloodstream-related complication), but in our RCT there was no significant difference between groups: 57/306 (18.6%) with short therapy vs. 45/298 (15.1%) with long therapy (RD 3.53% (95% CI -2.48 to 9.49). In an ongoing similar trial conducted in ICUs (BALANCE), [18] the aim is to show non-inferiority with respect to 90-day survival with a non-inferiority margin of 4%; our trial nearly achieves this aim as well (RD for 90-day mortality -1.03%, 95% -6.06 to 4.01%). Judging by the high adherence to the study protocol in our trial and in a report of a pilot study preceding the BALANCE ICU trial, [9] short treatment is acceptable to both physicians and patients.

Functional decline is well described following sepsis, although few data addressing predictors of return to baseline capacity are available. It is probably the most significant adverse consequence among elderly survivors of sepsis. [19] In the current study a more rapid return to baseline activity was documented for the short duration antibiotic arm. This occurred despite the lack of superiority of other outcomes. Functional capacity was assessed as the patient's subjective assessment of her/ his performance relative to the baseline before the bacteremia. The perception of illness while taking antibiotics might have biased this outcome is favor of the short treatment. However, we believe this bias reflects a true advantage to short treatment with respect to patients' perception of wellbeing and functional performance. Adverse events that were not captured might have occurred, explaining this difference.

Shortening antibiotic treatment is expected to result in less adverse events, mainly antibiotic-associated diarrhea and *Clostridium difficile* infections. The finding of fewer antibiotic days during the three months following randomization in the short duration arm was not reflected in these outcomes in our trial. This could possibly be explained by low rates of *Clostridium difficile* infection and other adverse events in our patients. The main spur for shortening antibiotic treatment duration is the basic assumption that shorter duration will reduce resistance selection and development. In our trial, this was assessed through monitoring of secondary infections caused by bacteria resistant to the antibiotics used for the index bacteremia and we did not detect an advantage to the shorter treatment. This could have occurred since we did not monitor for ESBLs or other resistant bacteria uniformly in both groups and since we did not perform surveillance sampling for colonization by such bacteria. However, the timescale of development and spread of resistance are not compatible with that of a randomized controlled trial. These outcomes should be assessed on a longer time scale within a setting (hospital, unit) in which antibiotic treatment duration is shortened as a policy.

Strengths and limitations

Our study is the first randomized controlled trial assessing antibiotic duration in Gram-negative bacteremia. Strengths of the trial, in addition to its design, are the non-restrictive inclusion criteria allowing a representative cohort of eligible patients, including a large population of elderly patients (404/604, 66.9% ≥65 years) and immunocompromised patients (150/604, 24.8%. mainly solid organ transplanted patients and patients treated for malignancy). However, this trial's cohort is not comparable to other bacteremia cohorts, since it starts from 7-day survivors of Gram-negative bacteremia achieving hemodynamic stability for at least 48 hours before day 7 with no uncontrolled source of infection. Its results are valid for these patients. Our primary

outcome is composed of the outcomes relevant to early survivors of bacteremia, namely long-term survival, without complications and discharged from hospital. Among secondary outcomes, we considered all those later suggested for the Desirability of Outcome Ranking and Response Adjusted for Duration of Antibiotic Risk ((DOOR/ RADAR), including functional capacity and exposure to antibiotics. [20]

Limitations include the dominance of Enterobacteriaceae as the offending pathogens (~90%), which limits the applicability of the results for Gram-negative non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* We could not show the impact of reducing antibiotic use on resistance. The potential of shorter antibiotic courses to shorten the length of hospital stay was not fully realized in our trial, since patients in the long duration arm could complete therapy as outpatients using highly-absorbable antibiotics, such as quinolones. Including of re-admissions and extended hospitalization in the primary outcome, might have favored non-inferiority.

In summary, among hospitalized patients with Gram-negative bacteremia, hemodynamically stable and afebrile for at least 48 hours without an ongoing focus of infection, 7 days of antibiotic therapy were non-inferior to 14 days. Seven days of antibiotic therapy had the advantage of fewer cumulative antibiotic days within 3 months and more rapid regain of baseline functional capacity.

Contributors: MP, DY, CM, AT, FK, NER and LL conceived of and designed the study. MP, DY, NER, BP, AT, TB, FK, EF, CV, AS, and LL wrote the protocol and developed the database. MP, DY, TS, BP, NER, EF, RB, AN, NGZ, AS, YD, EM, HAZ, JB, DA, EG, YE and CM recruited patients and did sampling. AT, TB, FK, AS and CV collected data. MP, DY, CM and LL analyzed or interpreted data. All authors contributed to the writing or critical revision of the final manuscript.

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Declaration of interests: We declare no competing interests.

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Table 1: Baseline characteristics of included patients

Variable	**Short arm (7 days)** **N=306 patients**	**Long arm (14 days)** **N=298 patients**
Patient characteristics		
Age	71 (61.8-81)	71 (61-80)
Gender – female	156 (51.0)	163 (54.7)
Center		
Rambam Hospital , Israel	133 (43.5)	118 (39.6)
Beilinson Hospital, Israel	131 (42.8)	143 (48.0)
Hospital of Modena, Italy	42 (13.7)	37(12.4)
Charlson comorbidity score	2 (1-3)	2 (1-4)
Malignancy		
None	222 (72.5)	223 (74.8)
Solid	64 (20.9)	58 (19.5)
Hematological	20 (6.5)	17 (5.7)
Immunosuppression [a]		
Any	69 (22.5)	81 (27.2)
Solid organ transplantation	25 (8.2)	26 (8.7)
Stem cell transplantation	2 (0.7)	3 (1.0)
Functional capacity		
Independent	186 (61.1)	189 (63.4)
Needs assistance in ADL	53 (17.3)	44 (14.8)

Dependent in ADL	40 (13.1)	51 (17.1)
Bedridden	26 (8.5)	14 (4.7)
Devices at baseline		
Urinary device [b]	61 (19.9)	72 (24.2)
Central venous catheter	22 (7.2)	19 (6.4)
Endotracheal tube	8 (2.6)	8 (2.7)
Prosthetic valve/ intracardiac implantable device	14 (4.6)	13 (4.4)
Infection characteristics		
Hospital acquired infection	81 (26.5)	95 (31.9)
Presentation of infection		
SOFA score at presentation	2 (1-3)	2 (1-3)
Leukocytes at presentation (cells/microliter)	10.6 (7.4-15.4), 306 patients	11.3 (7.8-15.2), 297 patients
Creatinine at presentation (mg/dL)	1.2 (0.9-1.7), 304 patients	1.3 (0.8-1.8), 297 patients
Albumin at presentation (g/dL)	3.3 (2.7-3.8), 195 patients	3.3 (2.9-3.8), 197 patients
SOFA score at	1 (0-2)	1 (0-2)

randomization		
Systolic blood pressure at randomization (mmHg)	128.0 (115.0-144.3)	126.0 (110.0-140.0)
Temperature at randomization (Celsius degrees)	36.8 (36.6-37.1), (304 patients)	36.8 (36.6-37.0), 298 patients
Appropriate empirical therapy administered within 48 hours	260 (85.0)	242 (81.2)
Bacteria type [c]		
E. Coli	186 (60.8)	194 (65.1)
Klebsiella spp.	47 (15.3)	33 (11.1)
Other Enterobacteriaceae	40 (13.1)	43 (14.4)
Acinetobacter spp.	2 (0.7)	4 (1.3)
Pseudomonas spp.	28 (9.2)	20 (6.7)
Other	3 (1)	4 (1.3)
MDR Gram-negative bacteremia [d]	58 (18.9)	51 (17.1)
Source of bacteremia		
Urinary tract	212 (69.3)	199 (66.8)

Primary bacteremia	23 (7.5)	28 (9.4)
Abdominal	37 (12.1)	34 (11.4)
Respiratory	14 (4.6)	10 (3.4)
Central venous catheter	15 (4.9)	23 (7.7)
Skin and soft tissue	5 (1.6)	4 (1.3)

Continuous data are presented in median (interquartile range); categorical data are presented in number (percentage)

ADL – activities of daily living; MDR – multidrug resistance; ESBL – extended spectrum beta-lactamase

[a] Immunosuppression –any immunosuppressive drugs, including prednisone >=20mg/d or equivalent.

[b] Urinary device – including urinary catheter (58/298 long arm, 42/306 short arm) and nephrostomy tubes or double J catheters (14/298 long arm, 19/306 short arm).

[c] Sixteen patients with bloodstream infection with Enterobacteriaceae had a polymicrobial infection (7 patients in the short duration arm and 9 patients in the long duration arm had 7 and 11 isolates respectively). Of these 16 patients, 11 had another Enterobacteriaceae as a co-pathogen, and 5 had a different Gram negative pathogen as the co-pathogen (3 *Aeromonas* spp. – , 2 short arm, one long arm; 2 *Pseudomonas spp*. – 1 in each arm). Other Gram-negative bacteria included: long duration arm: 1 *Stenotrophomonas maltophilia*, 1 *Chryseobacterium meningosepticum, 1 Haemophilus influenza, 1 Aeromonas* spp.; short duration arm: 1 *Stenotrophomonas maltophilia*, 1 other non-fermenter, 1 *Aeromonas* spp.

[d] MDR pathogens: ESBL - 56/273 (20.5%) Enterobacteriaceae in the short arm versus 49/270 Enterobacteriaceae (18.1%) in the long arm. MDR non fermenters – *one Pseudomonas aeruginosa* and one *Acinetobacter baumannii* in the short arm (2/33 non-fermenters, 6.1%) versus one *Pseudomonas aeruginosa* and one Chryseoba*cterium meningosepticum* in the long arm (2/28 non-fermenters, 7.1%). For definitions of ESBL and MDR see Supplement 1.

Table 2: Outcomes

Outcome	**Short arm (7 days) N=306 patients**	**Long arm (14 days) N=298 patients**	**Risk difference (95% confidence interval)**	**P-value**
Primary outcome	140 (45.8)	144 (48.3)	-2.6 (-10.5 to 5.3)	0.527
90 day all-cause mortality	36 (11.8)	32 (10.7)	1.0 (-4.0 to 6.1)	0.702
Readmissions	119 (38.9)	127 (42.6)	-3.7 (-11.5 to 4.1)	0.363
Extended hospitalization beyond 14 days	15 (4.9)	19 (6.4)	-1.5 (-5.1 to 2.2)	0.483
Distant complications	2 (0.7)	1 (0.3)	-	1.0
Relapse of bacteremia	8 (2.6)	8 (2.7)	-0.07 (-2.6 to 2.5)	0.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (-1.4 to 5.1)	0.257
14-day mortality	7 (2.3%)	4 (1.3%)	0.95 (-1.42 to 3.44)	0.288
28-day mortality	15 (4.9%)	13 (4.4%)	0.54 (-2.98 to 4.06)	0.753
New clinically or microbiologically documented infection	70 (22.9)	68 (22.8)	0.06 (-6.6 to 6.8)	0.987
Functional capacity needs assistance/dependent in ADL or bedridden at 30	150 (51.4) (292 patients)	163 (57.2) (285 patients)	-5.8 (-13.9 to 2.3)	0.031

days				
Resistance development	33 (10.8)	29 (9.7)	1 (-3.7 to 5.9)	0.690
Time to return to baseline activity in weeks (90 days)	2 (0-8.3) (218 patients)	3 (1-12) (222 patients)	**0.010**	
Total hospital days (90 days from randomization) - survivors	3 (1-9) (270 patients alive at day 90)	3.5 (1-10) (266 patients alive at day 90)	0.923	
Total hospital days (90 days from randomization) – all	4 (1-10)	4 (1-12)	0.603	
Duration of appropriate antibiotic therapy for bacteremia	7 (7.0-8.0)	14.0 (14.0-14.0)	**<0.001**	
Total antibiotic days from culture collection to day 90 post randomization	10.0 (9.0-18.0) (270 patients alive at day 90)	16.0 (15.0-22.0) (266 patients alive at day 90)	**<0.001**	
Adverse events				
Acute kidney injury	14 (4.6)	12 (4.0)	0.5 (-2.7 to 3.8)	0.842
Liver function abnormalities	16 (5.2)	20 (6.7)	-1.5 (-5.3 to 2.3)	0.494
Diarrhea during hospital	17 (5.6%)	23 (7.7)	-2.2 (-6.1 to 1.8)	0.285

stay				
Diarrhea until day 90 [a]	49 (16%)	54 (18.1%)	- 2.1 (-8.1 to 3.9)	0.491
Rash	2 (0.7)	4 (1.4)	0.445	
Clostridium difficile infection	3 (1.0)	1 (0.3)	0.322	

[a] Diarrhea – defined as >=3 episodes per day for at least two days

Figure Legends:

Figure 1: Trial flow

*All patients with Gram-negative bacteremia during the study period, surviving to day 7 and not discharged before recruitment

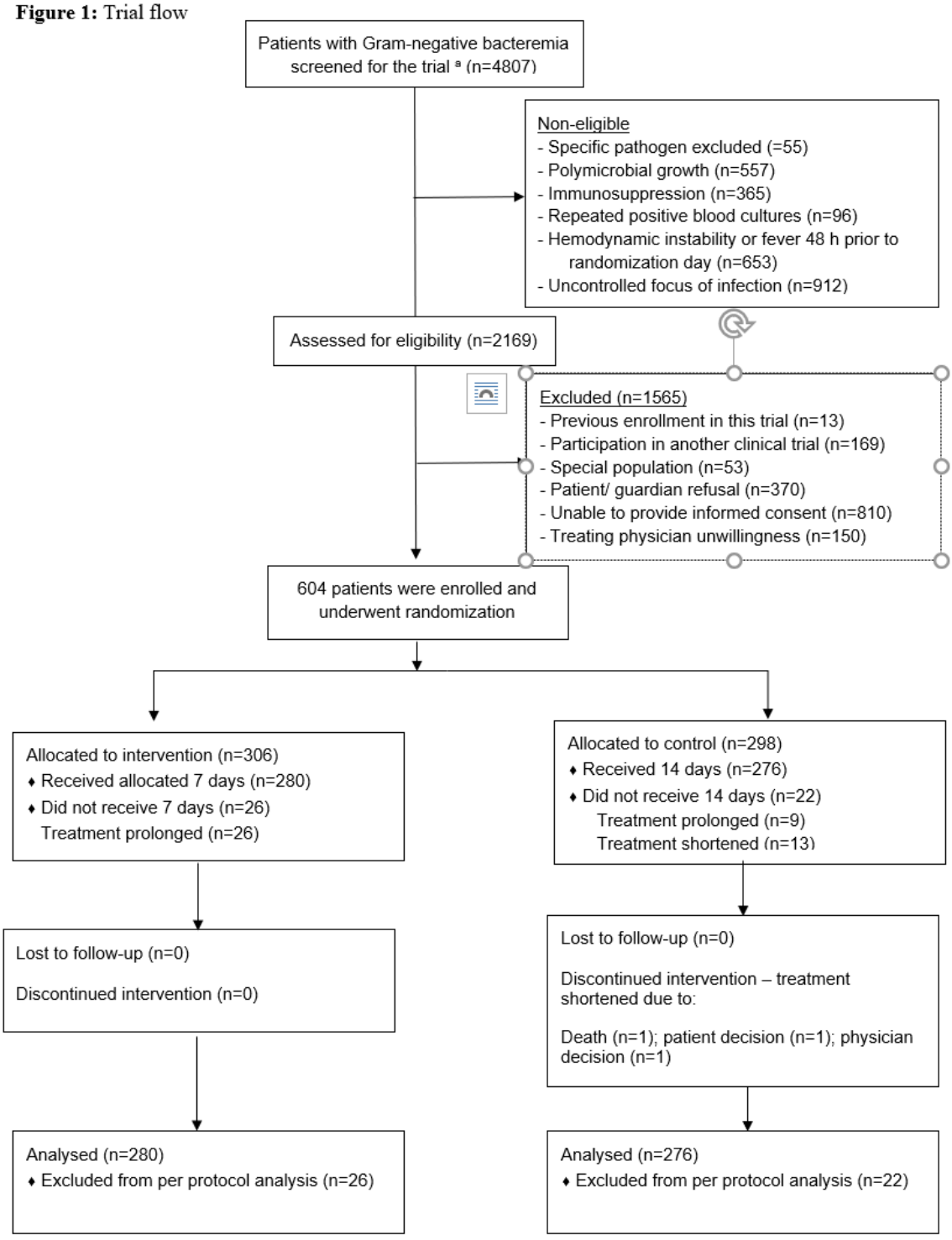
Figure 2: Primary outcome according to patient subgroups

UTI: urinary tract infection

Empirical antibiotic treatment – covering antibiotics to the specific pathogen according to susceptibility pattern administered within 48 hours

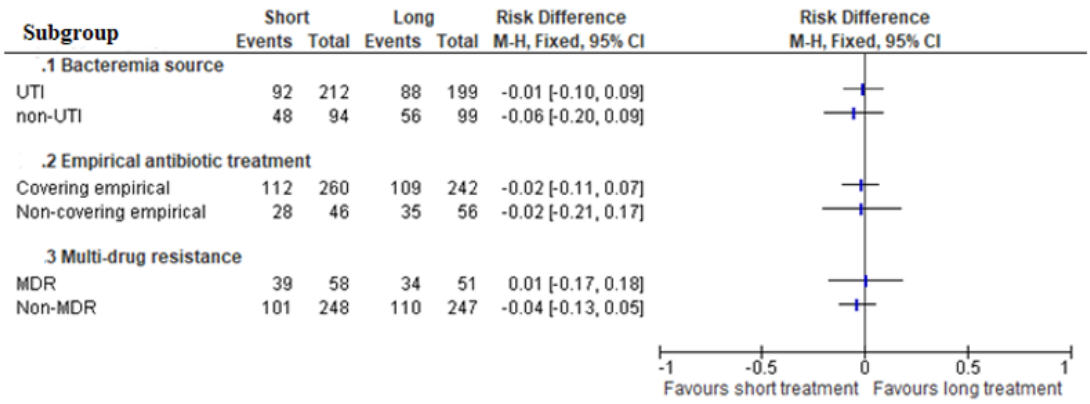
MDR: Multidrug resistance. This subgroup includes 105 patients with an ESBL Ebterobacteriaceae and 4 additional patients with another MDR bacteria (2 *Pseudomonas aeruginosa,* one *Acinetobacter baumannii* and one*Chryseobacterium meningosepticum).*

Figure 1: Trial flow



[a] All patients with Gram-negative bacteremia during the study period, surviving to day 7 and not discharged before recruitment

Figure 2: Primary outcome according to patient subgroups



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