Supplementary Online Content

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Supplement 3. eAppendix
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This supplementary material has been provided by the authors to give readers additional information about their work.

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ONLINE SUPPLEMENT #3 TO THE ARTICLE:

Effect of C-reactive-protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial

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eAppendix 1: Immunosuppression as an exclusion criterion

Patients who were deemed severely immunosuppressed in the two weeks before screening were not eligible for inclusion. Fixed criteria for severe immunosuppression were the following:

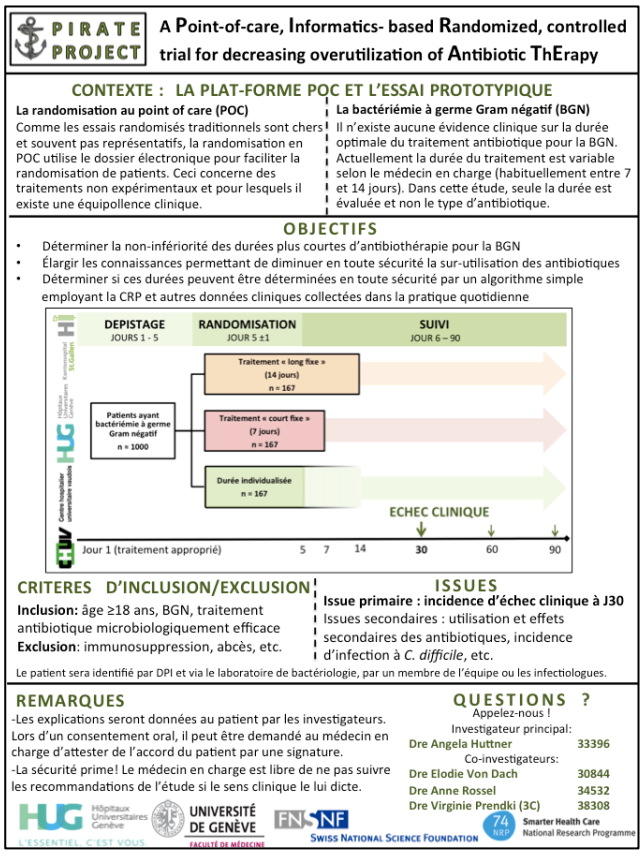
- HIV infection with CD4 cell count ≤500/µl
- Hematopoietic stem-cell transplantation in the first month after transplantation and at any time before engraftment
- Neutropenia in the 48 hours prior to randomization
- Receipt of high-dose steroids [>40 mg prednisone or its equivalent] daily for > 2 weeks) in the two weeks prior to randomization

Other immunosuppressive factors, such as high-dose immunosuppressant therapy, were taken into account by including investigators on a case-by-case basis.

eAppendix 2: Double blinding between randomization and therapy discontinuation

The purpose of this blind was, above all, to protect against any potential change in physician behavior and management. For example, a physician with a bias toward 14 days of therapy, once aware that his or her patient was randomized to only 7 days, might have ordered additional imaging on day 6 to rule out some kind of occult abscess—and thus reassure him or herself.

Each site's investigator team kept at least one person unblinded. This person was responsible for randomizing included patients and for contacting the investigator or patient and/or his or her doctor on the morning of the day the antibiotic therapy was to be discontinued. For patients in the CRP group, this meant following CRP and temperature trends closely. In order to keep the blind, all patients' physicians were encouraged and reminded to obtain regular CRP levels, whatever their patients' actual duration assignment.



Before the trial launched, information sessions were held for physicians and nurses of all participating hospitals. The strategy of discontinuation in the CRP group was described only qualitatively: staff were informed only that a "simple algorithm using the CRP and other routinely collected clinical data" would be applied (see study flyer, right). The specifics of the algorithm (75% reduction from peak CRP) were not disclosed so that physicians would not be able to determine for themselves when the discontinuation date would be.

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eAppendix 3: Rationale for the algorithm for C-reactive-protein-guided antibiotic discontinuation

The rationale for the individualized algorithm's specific use of a 75% reduction in peak C-reactive protein (CRP) values is based on a randomized clinical trial of patients in intensive-care units with severe sepsis or septic shock with or without bacteremia.[1] That study demonstrated that an even more restrictive algorithm (antibiotic discontinuation once the CRP decreased by ≥ 50% if peak CRP was ≥ 100 mg/l or once CRP was less than 25 mg/l if peak CRP was < 100 mg/l) was safe and effective to reduce antibiotic use. This study additionally used a 7-day maximum duration of antibiotic therapy for non-bacteremic patients, while bacteremic patients received at least 7 day of antibiotics.[1] Our individualized algorithm is slightly adapted in analogy to procalcitonin-based algorithms, which have been successfully tested in several randomized clinical trials (RCT) and used ≥ 80% decreases of procalcitonin to discontinue antibiotic therapy.[2-6] Our slight modifications take into account the slower decrease of CRP values compared to procalcitonin after resolution of an infection[5,7] and incorporate an additional safety margin compared to the study by Oliveira et al., which treated bacteremic patients differentially.[1] Of note, if the CRP value did not decreased by 75% by day 14, the marker was no longer used to guide the duration of therapy. In these cases, the duration was determined by clinical judgment, per usual practice.

eAppendix 4: Total days of antibiotic therapy (DOT)

The outcome of total days of antibiotic therapy (DOT) in the 90-day study period included all antibiotics taken from day 1 (the first day of microbiologically efficacious antibiotic therapy) to day 90. By definition, if a patient received two different antibiotics on one day, the patient was considered to have two DOT on this day.

eAppendix 5: Laboratory methods

Blood culturing

Blood cultures and CRP values were processed by the three sites' laboratories, which follow the same procedures. Blood cultures are routinely drawn for temperatures ≥38.0˚C. For each blood culture set, the combination of one BD BACTEC™ Plus Aerobic medium and one BD BACTEC™ Plus Anaerobic medium are inoculated by 8-10ml of whole blood. Inoculated bottles are immediately placed in the BD BACTEC™ FX. Individual blood culture bottles are removed from the automated blood culture system when growth is detected and direct examination with gram and acridine-orange staining is performed on an aspirate, with inoculation of solid culture media (Columbia agar, Columbia CNA agar, Chocolate agar**,** MacConkey agar, and CDC anaerobe agar). The remaining material is incubated in traditional incubators for 7 days before being inactivated. For CRP determination, whole blood is collected in heparin tubes and centrifuged; serum CRP is measured via immunoturbidimetry.

Diagnosis of *Clostridioides difficile* infection

At all sites, testing for *C. difficile* infection was done only in the presence of clinical symptoms supporting the diagnosis. Per routine in Geneva and Lausanne, a single stool sample is collected for detection of toxin by polymerase chain reaction (PCR); if this is positive, the laboratories perform an enzyme immunoassay (EIA) for toxins A and B on the same sample. If this second test is positive, the diagnosis is considered probable. In St. Gallen, samples are tested by combined EIA for both glutamate dehydrogenase and toxins A/B. If both assays are positive, a diagnosis of *C. difficile* is confirmed. If only one is positive, a nucleic acid amplification test (NAAT) is performed; a diagnosis of *C. difficile* is confirmed if the NAAT is positive. If both EIAs for GDH and toxin A/B are negative, a diagnosis of *C. difficile* is considered unlikely.

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eAppendix 6: P values for non-inferiority

Two-samples proportion tests are used. They rely on the z-statistic, which test the absence of difference

$z = (P_{int} – P_{ctrl})/SE$

where SE is the standard error. To include the non-inferiority margin into the calculation, the z-statistic needs to be modified to

$z = (P_{int} – P_{ctrl} – \delta)/SE$

where δ is the non-inferiority margin.

The following R code is used for the computations of the non-inferiority p-values.

```
int.f <- 4 # failure in intervention
ctrl.f <- 9 # failure in control
int.s <- 160 # success in intervention
ctrl.s <- 154 # success in control
n.int <- int.f + int.s # number of observations (patients) in intervention
n.ctrl <- ctrl.f + ctrl.s # number of observations (patients) in control

p.int <- int.f / n.int # proportion of failure in intervention arm
p.ctrl <- ctrl.f / n.ctrl # proportion of failure in control arm

ni.margin <- 0.1 # non-inferiority margin
# diff in proportion (int - ctrl)
p.int - p.ctrl

# upper bound of one-sided 97.5% confidence interval
(p.int-p.ctrl) + qnorm(1-0.025)*sqrt( p.int*(1-p.int)/n.int + p.ctrl*(1-p.ctrl)/n.ctrl)

# z-statistic for non-inferiority
p.pool <- ( int.f + ctrl.f ) / ( n.int + n.ctrl ) # proportion of failure overall
se <- sqrt( ( p.pool * ( 1 - p.pool ) ) * ( 1/n.int + 1/n.ctrl ) ) # pooled se
z <- ( p.int - p.ctrl - ni.margin ) / se # subtract margin for non-inferiority p-value

# p-value for non-inferiority
pnorm(z)
```


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Results

Table S1. Baseline demographic and clinical characteristics in the per-protocol population.

	CRP-guided N=130	**7 days** N=141	**14 days** N=143
Female sex (%)	77 (59)	90 (64)	80 (56)
Male sex (%)	53 (41)	51 (36)	63 (44)
Median age (IQR)	79 (71-86)	80 (70-87)	79 (64-85)
Ethnicity (%)			
- Caucasian	126 (97.6)	134 (95)	134 (94)
- Asian	1 (1)	3 (2)	2 (1)
- Hispanic	1 (1)	2 (1)	4 (3)
- African	1 (1)	2 (1)	1 (1)
Median body mass index (IQR)	26 (23-31)	26 (23-30)	26 (24-29)
Median estimated glomerular filtration rate, ml/min/1.73 m^2 (IQR)	51 (38-72)	51 (32-70)	56 (38-74)
Median Charlson comorbidity index* (IQR)	1 (0-2)	1 (0-2)	1 (0-2)
Diabetes mellitus (%)	30 (23)	31 (22)	33 (23)
Presence of removable urethral catheter (%)	14 (11)	6 (4)	19 (13)
Presence of foreign-body material (%)	32 (25)	30 (21)	26 (18)
- Implanted urinary device** (%)	4 (3)	3 (2)	5 (4)
- Artificial joint (%)	4 (3)	5 (4)	9 (6)
- Endovascular device (%)	3 (2)	2 (1)	0 (0)
- Artificial valve (%)	3 (2)	2 (1)	0 (0)
- Other (%)	18 (14)	19 (13)	13 (9)
Source of bacteremia			
- Urinary (%)	98 (75)	91 (65)	102 (71)
- Abdominal (%)	22 (17)	29 (21)	17 (12)
- Pulmonary (%)	5 (4)	13 (9)	13 (9)
- Endovascular device (%)	1 (1)	4 (3)	5 (3)
- Wound (%)	0 (0)	2 (1)	2 (1)
- Unknown (%)	5 (4)	2 (1)	4 (3)
Bacteremia acquisition			
- Community-acquired (%)	85 (65)	90 (64)	84 (59)
- Nosocomial (%)	33 (25)	37 (26)	39 (27)
- Healthcare-associated (%)	12 (9)	14 (10)	20 (14)
Median qSOFA score (IQR)	1 (0-2)	1 (0-2)	1 (0-1)

*Full range was 0-9 for the CRP-guided group, 0-7 for the 7-day group, and 0-8 for the 14-day group with higher values indicating greater number or degree of underlying comorbidities

**Suprapubic catheter (n=6), J-tube ("pigtail") catheter (n=2), nephrostomy tube (n=3), ileal conduit (n=1).

[+] Bacteremias were characterized as nosocomial if the first positive blood culture was drawn ≥48 hours after admission; healthcare-associated if drawn in the first 48 hours of hospitalization in a patient transferred from another healthcare facility, receiving chronic dialysis, or diagnosed with metastatic cancer;[18] and community-acquired if none of these conditions were met.

[§]Full range was 0-3 in all groups with higher values indicating higher severity of acute illness. The qSOFA score was developed for early identification of patients at high risk for poor outcome with an infection. The patient receives one point for each of the following: low blood pressure (systolic blood pressure ≤100 mmHg), high respiratory rate (≥22 breaths/minute), or altered mentation (Glasgow coma scale score ≤14). A score of ≥2 is associated with a higher risk of death or prolonged ICU stay.[19]

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Table S2. Clinical outcomes in the per-protocol population.

The primary outcome was clinical response through day 30; clinical response through days 60 and 90 were secondary outcomes.

	CRP-guided N=130	**7 days (fixed)** N=141	**14 days (fixed)** N=143	**% Difference**	
				CRP-guided vs 14 days	7 days vs 14 days
				1-sided 97.5%CI; *P*°	1-sided 97.5%CI, *P*°
Clinical response through day 30					
Clinical success (%)	**127 (97.7)**	**133 (94.3)**	**137 (95.8)**		
Clinical failure (%)	**3 (2.3)**	**8 (5.7)**	**6 (4.2)**		
Recurrent bacteremia (%)	0 (0)	1 (13) [§]	2 (33)		
Suppurative local complication (%)	0 (0)	2 (25) [§]	0 (0)	**-1.9 (-infinity, 2.3); <.001**	**1.5 (-infinity, 6.5); <.001**
Distal complication (%)	0 (0)	0 (0)	0 (0)		
Targeted therapy restart (%)	2 (66.7)	3 (38)	2 (33)		
All-cause mortality* (%)	1 (33.3)	3 (38)	2 (33)		
Clinical response through day 60					
Clinical success (%)	**116 (94.3)**	**119 (90.2)**	**131 (93.6)**		
Clinical failure (%)	**7 (5.7)**	**13 (9.8)**	**9 (6.4)**		
Recurrent bacteremia (%)	0 (0)	1 (77) [§]	2 (22)		
Suppurative local complication (%)	0 (0)	2 (15) [§]	0 (0)	-0.7 (-infinity, 5.0); <.001	3.4 (-infinity, 9.9); .023
Distal complication (%)	0 (0)	0 (0)	0 (0)		
Targeted therapy restart (%)	6 (86)	8 (62)	5 (56)		
All-cause mortality* (%)	1 (14)	3 (23)	2 (22)		
Clinical response through day 90					
Clinical success (%)	**107 (93.0)**	**114 (89.8)**	**124 (90.5)**		
Clinical failure (%)	**8 (7.0)**	**13 (10.2)**	**13 (9.5)**		
Recurrent bacteremia (%)	0 (0)	1 (77) [§]	2 (15)		
Suppurative local complication (%)	0 (0)	2 (15) [§]	0 (0)	-2.5 (-infinity, 4.2); <.001	0.7 (-infinity, 7.9); .006
Distal complication (%)	0 (0)	0 (0)	0 (0)		
Targeted therapy restart (%)	7 (88)	8 (62)	9 (70)		
All-cause mortality* (%)	1 (12)	3 (23)	2 (15)		

*Through day 30. [§]One patient had both recurrent bacteremia and a suppurative local complication by day 30.
°*P* value for non-inferiority (see Supplement).

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Table S3. Protocol deviations by study group and reasons for non-adherence to treatment duration assignment, primary analysis set.

	CRP-guided n=169	**7 days** n=169	**14 days** n=165
Number excluded from per-protocol population (%)	**39 (23)**	**28 (17)**	**22 (13)**
Lost to follow-up by day 30 (%)	5 (13)	3 (11)	2 (9)
Protocol deviation (%):	**34 (87)**	**25 (89)**	**20 (91)**
Antibiotic duration exceeded protocol-designated duration (%)	**13 (38)**	**24 (96)**	**7 (35)**
- Reason: - Unintentional (logistic difficulty or communication error) (%) - Physician overrode duration assignment, complication suspected (%) - Physician overrode duration assignment in absence of complication (%) - Patient's wish, outpatient physician agreed (%)	 9 (69) 1 (8) 3 (23) 0 (0)	 13 (54) 1 (4) 10 (42) 0 (0)	 4 (57) 1 (14) 1 (14) 1 (14)
- Modality: - CRP decreased by 75% but therapy continued (%) - CRP did not decrease by 75% and therapy continued >14 days (%)	 10 (77) 3 (23)	 NA NA	 NA NA
Antibiotic duration was shorter than protocol-designated duration (%)	**9 (26)**	**1 (4)**	**13 (65)**
- Reason: - Unintentional (logistic or communicative error) (%) - Physician overrode duration assignment, evidence of side effect (%) - Physician overrode duration assignment in absence of side effect (%) - Patient's wish (%)	 0 (0) 7 (78) 1 (11) 1 (11)	 0 (0) 0 (0) 0 (0) 1 (100)	 9 (69) 1 (8) 1 (8) 2 (15)
- Modality: - Duration was <5 days (%) - Therapy discontinued although CRP had not decreased by 75% (%) - Antibiotic discontinued despite fever in the preceding 48h (%)	 0 (0) 8 (89) 1 (11)	 1 (100) NA NA	 0 (0) NA NA
Insufficient CRP data* (%)	**12 (35)**	NA	NA
- Physician prescribed 7 (±1) days (%) - Physician prescribed 10 (±1) days (%) - Physician prescribed 14 (±) days (%)	8 (67) 2 (17) 2 (17)	NA	NA

*No discernible peak value was obtained, or no follow-up value documenting a 75% reduction from peak was obtained.

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Table S4. Baseline characteristics and outcomes of patients receiving antibiotic therapy durations longer than the per-protocol assignment.

	CRP-guided group		7-day group		14-day group	
	Per-protocol n=130	Received ≥3 days more n=13	Per-protocol n=141	Received ≥10 days n=24	Per-protocol n=143	Received ≥17 days n=7
Baseline characteristics						
Female sex (%)	77 (59)	12 (92)	90 (64)	13 (54)	80 (56)	4 (57)
Male sex (%)	53 (41)	1 (8)	51 (36)	11 (46)	63 (44)	3 (43)
Median age (IQR)	79 (71-86)	76 (61-83)	80 (70-87)	74 (67-82)	79 (64-85)	83 (70-90)
Median body mass index (IQR)	26 (23-31)	28 (21-30)	26 (23-30)	25 (24-30)	26 (24-29)	20 (18-21)
Median estimated glomerular filtration rate at inclusion, ml/min/1.73 m^2 (IQR)	51 (37-72)	44 (18-59)	51 (32-70)	58 (43-79)	56 (38-74)	52 (33-98)
Median Charlson comorbidity index (IQR)	1 (0-2)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)	2 (1-6)
Diabetes mellitus (%)	30 (23)	5 (38)	31 (22)	1 (4)	33 (23)	0 (0)
Presence of removable urethral catheter (%)	14 (11)	1 (8)	6 (4)	1 (4)	19 (13)	1 (14)
Presence of implanted foreign-body material (%)	32 (25)	2 (15)	30 (21)	5 (20)	26 (18)	2 (29)
-Artificial joint (%)	4 (3)	0 (0)	3 (2)	0 (0)	5 (4)	1 (14)
-Implanted urinary-tract device (%)	4 (3)	0 (0)	5 (4)	0 (0)	9 (6)	0 (0)
-Endovascular device (%)	3 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
-Artificial valve (%)	3 (2)	1 (8)	2 (1)	0 (0)	0 (0)	0 (0)
-Other (%)	18 (14)	1 (8)	19 (13)	5 (20)	13 (9)	1 (14)
Source of bacteremia						
-Urinary (%)	98 (75)	8 (62)	91 (65)	13 (54)	102 (71)	3 (43)
-Abdominal (%)	22 (17)	3 (23)	29 (21)	8 (33)	17 (12)	2 (29)
-Pulmonary (%)	5 (4)	0 (0)	13 (9)	1 (4)	13 (9)	2 (29)
-Endovascular device (%)	1 (1)	0 (0)	4 (3)	0 (0)	5 (3)	0 (0)
-Wound (%)	0 (0)	0 (0)	2 (1)	1 (4)	2 (1)	0 (0)
-Unknown (%)	5 (4)	2 (15)	2 (1)	2 (8)	4 (3)	0 (0)
Bacteremia acquisition						
-Community-acquired[+] (%)	85 (65)	10 (77)	90 (64)	14 (58)	84 (59)	4 (57)
-Nosocomial (%)	33 (25)	1 (8)	37 (26)	8 (33)	39 (27)	3 (42)
-Healthcare-associated (%)	12 (9)	2 (15)	14 (10)	2 (8)	20 (14)	0 (0)
Median qSOFA score (IQR)	1 (0-2)	1 (1-2)	1 (0-2)	1 (0-1)	1 (0-1)	1 (0-3)
Clinical outcomes						
Day 30 clinical success (%)	127 (97.7)	13 (100)	133 (94.3)	21 (87.5)	137 (95.8)	6 (85.7)
Day 30 clinical failure (%)	3 (2.3)	0 (0)	8 (5.7)	3 (12.5)	6 (4.2)	1 (14.3)
Day 60 clinical success (%)	116 (94.3)	13 (100)	119 (90.2)	21 (87.5)	131 (93.6)	4 (80.0)*
Day 60 clinical failure (%)	7 (5.7)	0 (0)	13 (9.8)	3 (12.5)	9 (6.4)	1 (20.0)*
Day 90 clinical success (%)	107 (93.0)	13 (100)	114 (89.8)	21 (87.5)	124 (90.5)	3 (75.0)*
Day 90 clinical failure (%)	8 (7.0)	0 (0)	13 (10.2)	3 (12.5)	13 (9.5)	1 (25.0)*

*In this group of seven patients, two were lost to follow-up by day 60, and a third patient by day 90.

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Table S5A. Patients and clinical failure in the CRP-guided group by days of antibiotic therapy received.

Antibiotic duration, days	Patients, n		Clinical failure through day 30, n	
	Primary analysis N=169 (%)	Per-protocol N=130 (%)	Primary analysis	Per-protocol
5	14 (8)	13 (10)	0	0
6	29 (17)	26 (20)	2	2
7	42 (25)	35 (27)	1	1
8	23 (14)	17 (13)	0	0
9	9 (5)	5 (4)	0	0
10	22 (13)	20 (15)	0	0
11	4 (2)	3 (2)	1	0
12	2 (1)	1 (1)	0	0
13	6 (4)	4 (3)	0	0
14	10 (6)	4 (3)	0	0
15	4 (2)	2 (2)	0	0
16	2 (1)	0 (0)	0	0
17	1 (1)	0 (0)	0	0
18-27	*0 (0)*	*0 (0)*	*0*	*0*
28*	1 (1)	0 (0)	0	0

* The patient in the CRP group receiving 28 days of antibiotics was diagnosed with multiple renal abscesses the day after randomization.

Table S5B. C-reactive protein kinetics by study group.

	CRP-guided N=169	**7 days** N=169	**14 days** N=165
Median peak CRP concentration, mg/l (IQR)	171 (112-251)	164 (104-246)	154 (104-250)
Peak CRP, median study day* (IQR)	1 (0-2)	1 (0-2)	1 (0-2)
75% reduction from peak within 3 days (%)	36 (21)	38 (23)	54 (32)
50% reduction from peak within 3 days (%)	91 (53)	94 (56)	94 (57)

*Day 1 was the day that microbiologically efficacious antibiotic therapy was begun, thus day 0 was the day before.

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Table S6. All-cause mortality by treatment group at all study time points (primary analysis population).

	CRP-guided n=169	**7 days** n=169	**14 days** n=165	***P* value*** CRP-guided vs 14 days	***P* value*** 7 days vs 14 days
Mortality through day 30 (%) *Missing (%)*	2 (1.2) *5 (3.0)*	6 (3.7) *3 (1.8)*	4 (2.4) *2 (1.2)*	.45	.75
Mortality through day 60 (%) *Missing (%)*	7 (4.4) *9 (5.3)*	11 (6.9) *7 (4.1)*	8 (4.9) *3 (1.8)*	1.0	.64
Mortality through day 90 (%) *Missing (%)*	13 (8.4) *15 (8.9)*	14 (8.9) *10 (5.9)*	9 (5.6) *7 (4.2)*	.38	.39

*Two-sided alpha, Fisher exact test

Table S7. Sensitivity analyses for the primary outcome with best-worst-case and worst-best-case scenarios.

Table S7A shows the "best-worst" case, in which it is assumed that all participants lost to follow-up in the CRP-guided and 7-day groups have had clinical success, and that all those with missing outcomes in the 14-day arm have experienced clinical failure. Table S7B shows the "worst-best" case, in which it is assumed that all participants lost to follow-up in the CRP-guided and 7-day groups have experienced clinical failure, and that all those with missing outcomes in the 14-day group have experienced clinical success.

Table S7A: Best-worse case sensitivity analysis for clinical response through day 30					
	CRP-guided N=169	**7 days (fixed)** N=169	**14 days (fixed)** N=165	**% Difference**	
				CRP-guided vs 14 days	7 days vs 14 days
				1-sided 97.5%CI; *P*	1-sided 97.5%CI; *P*
Clinical success (%)	165 (97.6)	158 (93.5)	154 (93.3)	-4.3 (-infinity, 0.1); <.001	-0.2 (-infinity, 5.2); <.001
Clinical failure (%)	4 (2.4)	11 (6.5)	11 (6.7)		
Table S7B: Worst-best case sensitivity analysis for clinical response through day 30					
	CRP-guided N=169	**7 days (fixed)** N=169	**14 days (fixed)** N=165	**% Difference**	
				CRP-guided vs 14 days	7 days vs 14 days
				1-sided 97.5%CI; *P*	1-sided 97.5%CI; *P*
Clinical success (%)	160 (95.0)	155 (91.7)	156 (94.5)	-0.5 (-infinity, 4.7); <.001	2.8 (-infinity, 8.2); .005
Clinical failure (%)	9 (5.3)	14 (8.3)	9 (5.5)		

°*P* value for non-inferiority (see Supplement).

Table S8. Mixed-effects modeling results.

Odds ratios are for failure by day 30 according to treatment duration, with study site as a random intercept (site effect estimate 0.18 [97.5% CI 0.002-15.80]).

	Odds ratio	**97.5%CI**
CRP-guided versus 14-day group	0.43	0.19-1.68
7-day versus 14-day group	1.22	0.43-3.44

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Table S9. Bivariable logistic regression models for clinical failure at day 30.

	Odds ratio	95% CI	*P* value
Age			
- <70 years	0.11	0.01 - 0.81	.03
- 70-79 years	1.98	0.84 - 4.65	.12
- 80-89 years	1.34	0.58 - 3.09	.49
- >90 years	1.29	0.43 - 3.89	.65
Male sex	0.92	0.40 - 2.15	.85
Site of infection			
- Urinary site	0.50	0.22 - 1.14	.10
- Abdominal	0.67	0.20 - 2.31	.53
- Pulmonary	4.87	1.80 - 13.17	.002
Type of acquisition			
- Community-acquired	1.03	0.44 - 2.40	.95
- Nosocomial	1.35	0.56 - 3.22	.50
- Health-care associated	0.35	0.05 - 2.64	.31
Presence of foreign-body material	3.28	1.42 - 7.55	.005
qSOFA score			
- 0	1.13	0.50 - 2.58	.77
- 1	0.59	0.22 - 1.61	.31
- 2	1.11	0.40 - 3.04	.85
- 3	1.82	0.52 - 6.42	.35
Charlson comorbidity index			
- <1	0.65	0.26 - 1.60	.35
- 1-2	1.03	0.45 - 2.37	.94
- > 2	1.62	0.65 - 4.02	.30
Study site			
- Geneva	0.44	0.18 - 1.08	.07
- Lausanne	1.52	0.65 - 3.55	.34
- St. Gallen	1.65	0.69 - 3.96	.26
Pathogen			
- *Escherichia coli*	0.28	0.12 - 0.63	.002
- *Klebsiella* spp.	2.55	1.05 - 6.16	.04
- *Proteus* spp.	3.80	1.03 - 13.98	.05
Delay in appropriate therapy*			
- 1 day	1.74	0.49 - 6.15	.39
- 2 days	1.00	NA	NA
- ≥3 days	1.16	0.15 - 9.15	.89
Empiric cephalosporin therapy	1.41	0.52 - 3.86	.50
Empiric carbapenem therapy	0.96	0.28 - 3.30	.94
Empiric penicillin-based therapy			
- Amoxicillin-clavulanate	1.64	0.59 - 4.53	NA
- Piperacillin-tazobactam	3.54	1.49 - 8.41	.004
Fluoroquinone therapy	0.48	0.18 - 1.32	.16
Co-trimoxazole therapy	0.70	0.23 - 2.10	.53
Intravenous-to-oral switch	0.594	0.26 - 1.36	.22

*Beginning at presentation, due to resistance.

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Table S10A. Multivariable logistic regression model for clinical failure at day 30.
This model includes variables as pre-specified in the statistical analysis plan.

	Odds ratio	95% CI	*P* value
Age - <70 years	0.10	0.01 – 0.79	.03
Female sex	0.60	0.23 - 1.54	.29
Charlson index >2	1.24	0.46 - 3.35	.67
qSOFA score=3	1.26	0.32 – 5.00	.74
Site of infection - Pulmonary	3.88	1.27 - 11.83	.02
Presence of foreign-body material	2.82	1.15 - 6.92	.02
Pathogen - *Klebsiella* spp.	2.22	0.85 - 5.83	.11
Empiric therapy with piperacillin-tazobactam	2.44	0.94 – 6.32	.07

Hosmer-Lemeshow chi^2 = 2.33, *P*=.94.

Table S10B. *Post-hoc* multivariable logistic regression model for clinical failure at day 30.
This model was constructed *post-hoc* with fewer variables introduced, in order to avoid over-fitting given the relatively small number of failure events.

	Odds ratio	95% CI	*P* value
Age - <70 years	0.10	0.01- 0.79	.03
Site of infection - Pulmonary	3.78	1.26 - 11.32	.02
Presence of foreign-body material	2.61	1.09 - 6.24	.03
Pathogen - *Klebsiella* spp.	2.20	0.85 - 5.67	.10
Empiric therapy with piperacillin-tazobactam	2.41	0.95 – 6.10	.06

Hosmer-Lemeshow chi^2 = 2.47, *P*=.78

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Table S11. Adverse events considered possibly, probably or certainly related to study antibiotic(s).

Adverse event	**CRP-guided group** n=169	**7-day group** n=169	**14-day group** n=165
Missing by day 30, n	*5*	*3*	*2*
C. difficile infection (%)	7 (4.3)	2 (1.2)	4 (2.4)
Diarrhea (%)	2 (1.2)	2 (1.2)	1 (0.6)
Rash (%)	0 (0)	1 (0.6)	1 (0.6)
Pruritis (%)	1 (0.6)	0 (0)	0 (0)
Glossitis (%)	0 (0)	0 (0)	1 (0.6)
Thrush (%)	0 (0)	1 (0.6)	1 (0.6)
Tongue discoloration (%)	0 (0)	1 (0.6)	0 (0)
Abdominal pain/cramping (%)	1 (0.6)	0 (0)	0 (0)
Catheter infection (%)	0 (0)	1 (0.6)	0 (0)
Elevated creatinine (%)	0 (0)	0 (0)	1 (0.6)
Headache (%)	0 (0)	0 (0)	1 (0.6)
Fever (%)	1 (0.6)	0 (0)	0 (0)
QT prolongation (%)	0 (0)	0 (0)	1 (0.6)
Total (%)	**12 (7.3)**	**8 (4.8)**	**11 (6.7)**

Table S12. Serious adverse events considered possibly, probably or certainly related to study antibiotic(s).

Serious adverse event	**CRP-guided group** n=169	**7-day group** n=169	**14-day group** n=165
Missing by day 90, n	*15*	*10*	*7*
Hospitalization for *C. difficile* infection (%)	1 (0.6)	1 (0.6)	1 (0.6)
Hospitalization for abdominal pain (%)	0 (0)	1 (0.6)	0 (0)
Hospitalization for headache (%)	0 (0)	0 (0)	1 (0.6)
Death* (%)	0 (0)	1 (0.6)	0 (0)
Total (%)	**1 (0.6)**	**3 (1.8)**	**2 (1.2)**

*Cause unknown, occurred shortly after discontinuing antibiotic therapy. All cultures negative.

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