ORIGINAL ARTICLE

Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections

The BALANCE Investigators, for the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network

ABSTRACT

BACKGROUND

Bloodstream infections are associated with substantial morbidity and mortality. Early, appropriate antibiotic therapy is important, but the duration of treatment is uncertain.

METHODS

In a multicenter, noninferiority trial, we randomly assigned hospitalized patients (including patients in the intensive care unit [ICU]) who had bloodstream infection to receive antibiotic treatment for 7 days or 14 days. Antibiotic selection, dosing, and route were at the discretion of the treating team. We excluded patients with severe immunosuppression, foci requiring prolonged treatment, single cultures with possible contaminants, or cultures yielding *Staphylococcus aureus*. The primary outcome was death from any cause by 90 days after diagnosis of the bloodstream infection, with a noninferiority margin of 4 percentage points.

RESULTS

Across 74 hospitals in seven countries, 3608 patients underwent randomization and were included in the intention-to-treat analysis; 1814 patients were assigned to 7 days of antibiotic treatment, and 1794 to 14 days. At enrollment, 55.0% of patients were in the ICU and 45.0% were on hospital wards. Infections were acquired in the community (75.4%), hospital wards (13.4%) and ICUs (11.2%). Bacteremia most commonly originated from the urinary tract (42.2%), abdomen (18.8%), lung (13.0%), vascular catheters (6.3%), and skin or soft tissue (5.2%). By 90 days, 261 patients (14.5%) receiving antibiotics for 7 days had died and 286 patients (16.1%) receiving antibiotics for 14 days had died (difference, −1.6 percentage points [95.7% confidence interval {CI}, −4.0 to 0.8]), which showed the noninferiority of the shorter treatment duration. Patients were treated for longer than the assigned duration in 23.1% of the patients in the 7-day group and in 10.7% of the patients in the 14-day group. A per-protocol analysis also showed noninferiority (difference, −2.0 percentage points [95% CI, −4.5 to 0.6]). These findings were generally consistent across secondary clinical outcomes and across prespecified subgroups defined according to patient, pathogen, and syndrome characteristics.

CONCLUSIONS

Among hospitalized patients with bloodstream infection, antibiotic treatment for 7 days was noninferior to treatment for 14 days. (Funded by the Canadian Institutes of Health Research and others; BALANCE ClinicalTrials.gov number, NCT03005145.)

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CME

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Bloodstream infections are common and can be lethal, with more than 600,000 cases and an estimated 90,000 related deaths occurring per year in North America alone and 2.9 million deaths per year worldwide.[1,2] Bloodstream infections originate from a variety of infectious foci and collectively rank among the top seven causes of death.[1] Early and appropriate antibiotic therapy improves survival,[3] but the duration of treatment is understudied.

Traditionally, short-course antibiotic treatment has aroused concerns that insufficient durations could result in clinical failure, relapsing infection, and selection of resistance in the culprit pathogen.[4] The harms of excessive duration of treatment include avoidable adverse events,[5] *Clostridioides difficile* infection,[6] development of resistance among nontarget bacteria, and excess costs.

Randomized clinical trials have documented the noninferiority of shorter durations of treatment (7 days or less) as compared with longer durations for bacterial infections, including community-acquired and hospital-acquired pneumonia,[7,8] uncomplicated intraabdominal infection,[9] pyelonephritis,[10] and cellulitis.[11] However, there are limitations to generalizing the results of previous trials because many of them excluded patients with accompanying bacteremia,[12] have focused on uncomplicated bacteremia, or have been of modest size and unable to detect or exclude clinically important effects.[13-15]

In the absence of evidence to guide clinical practice, recommendations regarding treatment duration for patients with bloodstream infection are variable,[16-18] with median durations of 14 days or longer for patients with critical illness.[19] Therefore, we conducted the Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE) randomized clinical trial to test 7 days of antibiotic treatment as compared with 14 days of treatment in patients with bloodstream infection. We hypothesized that 7 days of treatment would be noninferior to 14 days of treatment with respect to mortality and would confer benefits including decreases in antimicrobial exposure, complications, and resistance.

METHODS

TRIAL DESIGN, SETTING, AND OVERSIGHT

BALANCE was an investigator-initiated, multicenter, open-label, randomized, controlled, noninferiority trial assessing 7 days of antibiotic treatment as compared with 14 days of antibiotic treatment in hospitalized patients with bloodstream infection. We conducted the trial at 74 hospital sites in seven countries (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The full protocol was published previously[20] and is available at NEJM.org. The BALANCE trial was overseen by a steering committee and an independent data and safety monitoring committee, with interim analyses planned when one sixth, one third, and two thirds of the targeted number of patients had been enrolled. The trial was approved by the institutional review board at each participating site. We obtained informed consent from patients or agreement from their substitute decision makers before enrollment. The trial was conceived by the corresponding authors with input from the steering committee, the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network. The first draft of the manuscript was written by the corresponding authors with input thereafter by the steering committee and then all the other authors. All the authors approved the submission of the manuscript. Data were collected by the investigators and research coordinators at all participating sites (see the Supplementary Appendix). The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PATIENTS AND ELIGIBILITY CRITERIA

Patients were eligible for enrollment if they were admitted to a participating hospital at the time a blood culture was reported as positive with a pathogenic bacterium. We excluded patients who had been previously enrolled in the trial, were severely immunocompromised (i.e., had neutropenia or were receiving immunosuppressive treatment after solid-organ transplantation or hematopoietic stem-cell transplantation), had prosthetic heart valves or endovascular grafts, had a documented or suspected infectious syndrome for which prolonged treatment was necessary (e.g., endocarditis, osteomyelitis, septic arthritis, undrained abscess, or unremoved prosthetic-associated in-

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fection), had a positive culture with a common contaminant (such as coagulase-negative staphylococci), had *Staphylococcus aureus* or *S. lugdunensis* bacteremia, bacteremia from rare organisms that required prolonged receipt of treatment, or fungemia. A full list of inclusion and exclusion criteria is provided in Table S2.

RANDOMIZATION AND INTERVENTIONS

We used Web-based randomization, with variable block sizes, stratified according to hospital site and admission to the intensive care unit (ICU) or hospital ward. Participants were randomly assigned, in a 1:1 ratio, to receive a shorter duration (7 days) or a longer duration (14 days) of adequate antibiotic treatment. Adequate was defined as antibiotic therapy to which the organism was susceptible according to local laboratory reports; daily assessments for adherence were conducted, and reasons for nonadherence were recorded. Selection of specific antibiotics, doses, frequency, and route of delivery was at the discretion of treating clinicians. The diversity of pathogens, underlying infections, and treatments for bloodstream infection rendered placebo controls infeasible, but we aimed to minimize bias by concealing group assignments until day 7 of adequate treatment.

OUTCOME MEASURES

The primary outcome was death from any cause by 90 days after diagnosis of the bloodstream infection, which was defined by the date of the positive index blood culture. The secondary outcomes included death in the hospital, death in the ICU among the patients enrolled in the ICU or admitted to the ICU after the diagnosis of a bloodstream infection, relapse of bacteremia with the same organism that had caused the original infection, allergy to the antibiotic and adverse events, *C. difficile* infection in the hospital, secondary infection or colonization with antimicrobial-resistant organisms in the hospital, length of stay in the ICU and number of ICU-free days, length of stay in the hospital and number of hospital-free days, duration of invasive mechanical ventilation and number of ventilation-free days, number of antibiotic-free days, and duration of vasopressor use and number of vasopressor-free days. Antibiotic-free days, mechanical ventilation–free days, and ICU-free days were calculated as the number of days alive and not receiving that treatment in the time period from the day that the index blood culture was obtained to 28 days; vasopressor-free days were calculated from the day that the index blood culture was obtained to 14 days. Patients who died before day 28 (or before day 14 for the calculation of vasopressor-free days) were reported as having zero treatment-free days. Antimicrobial-resistant organisms were defined on the basis of a positive routine culture yielding a highly resistant microbial organism as defined by the Dutch nosocomial infection surveillance guidelines.[21] This broad definition includes methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase–producing Enterobacterales, carbapenem-resistant gram-negative bacilli, and multidrug-resistant gram-negative bacilli (with the definition of multidrug resistance differing according to Enterobacterales and non-Enterobacterales species).[21] We also conducted a sensitivity analysis limited to isolation of these organisms from only sterile site specimens. The outcome adjudication of antimicrobial-resistant organisms and the analyses of all outcomes were blinded to group assignment.

STATISTICAL ANALYSIS

We calculated that a target sample size of 3626, which was based on anticipated baseline 90-day mortality of 22%[19] and a noninferiority margin of no more than 4 percentage points, would give the trial 80% power, at a one-sided alpha level of 2.5%, accounting for a maximum of 5% loss to follow-up and for early stopping rules for three interim analyses.[20] Many trials in which death was the primary outcome, including several prominent infectious disease trials,[8,22] used a noninferiority margin of 10 percentage points,[23] but we considered a lower noninferiority margin to be desirable. When the trial was initially launched, only patients admitted to the ICU were included,[24] but after a successful parallel pilot trial involving patients on the wards was conducted (October 2016 through December 2018),[25] the BALANCE trial was extended to include all hospitalized patients with bloodstream infection.

The primary analysis evaluated whether 7 days of antibiotic treatment was noninferior to 14 days of treatment with respect to death by 90 days after diagnosis, as determined by whether the 95.7% two-sided confidence interval excluded an absolute between-group difference of 4 percentage points.

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Table 1. Characteristics of the Patients, Infections, and Pathogens at Baseline (Primary Intention-to-Treat Analysis).*

Characteristic	Overall (N=3608)	7-Day Group (N=1814)	14-Day Group (N=1794)
Male sex — no. (%)	1922 (53.3)	974 (53.7)	948 (52.8)
Median age (IQR) — yr	70 (59–80)	70 (58–80)	70 (59–80)
Median SOFA score on day 0 (IQR)†	4 (2–8)	4 (2–8)	5 (2–8)
Enrolled in ICU — no. (%)	1986 (55.0)	997 (55.0)	989 (55.1)
Enrolled in hospital ward — no. (%)	1622 (45.0)	817 (45.0)	805 (44.9)
Receiving mechanical ventilation — no. (%)	766 (21.2)	374 (20.6)	392 (21.9)
Coexisting conditions — no. (%)			
Diabetes mellitus	1148 (31.8)	596 (32.9)	552 (30.8)
Solid-organ cancer	782 (21.7)	400 (22.1)	382 (21.3)
Obesity	655 (18.2)	331 (18.2)	324 (18.1)
Arrhythmia	540 (15.0)	264 (14.6)	276 (15.4)
Glucocorticoid use or immunosuppression‡	440 (12.2)	230 (12.7)	210 (11.7)
Chronic obstructive pulmonary disease	393 (10.9)	198 (10.9)	195 (10.9)
Renal insufficiency	425 (11.8)	217 (12.0)	208 (11.6)
Coronary artery disease	393 (10.9)	193 (10.6)	200 (11.1)
Congestive heart failure	386 (10.7)	205 (11.3)	181 (10.1)
Liver disease	227 (6.3)	117 (6.4)	110 (6.1)
Peripheral vascular disease	223 (6.2)	107 (5.9)	116 (6.5)
Dialysis dependency	127 (3.5)	60 (3.3)	67 (3.7)
Leukemia or lymphoma	101 (2.8)	49 (2.7)	52 (2.9)
Median Clinical Frailty Scale score (IQR)§	4 (3–5)	4 (3–5)	4 (3–5)
Any use of procedures to control the source of infection — no. (%)¶	1621 (44.9)	795 (43.8)	826 (46.1)
Source of acquisition of bacteremia — no. (%)			
Community	2722 (75.4)	1380 (76.1)	1342 (74.8)
Hospital ward	483 (13.4)	231 (12.7)	252 (14.0)
ICU	403 (11.2)	203 (11.2)	200 (11.1)
Source of bacteremia — no. (%)			
Urinary tract	1523 (42.2)	757 (41.7)	766 (42.7)
Intraabdominal or hepatobiliary	679 (18.8)	337 (18.6)	342 (19.1)
Lung	469 (13.0)	229 (12.6)	240 (13.4)
Vascular catheter	229 (6.3)	116 (6.4)	113 (6.3)
Skin, soft tissue, or both	187 (5.2)	104 (5.7)	83 (4.6)
Other	67 (1.9)	37 (2.0)	30 (1.7)
Undefined or unknown	454 (12.6)	234 (12.9)	220 (12.3)
Most commonly isolated pathogens in blood cultures — no. (%)‖			
Escherichia coli	1582 (43.8)	805 (44.4)	777 (43.3)
Klebsiella species	552 (15.3)	273 (15.0)	279 (15.6)
Enterococcus species	250 (6.9)	119 (6.6)	131 (7.3)
Coagulase-negative staphylococci	174 (4.8)	81 (4.5)	93 (5.2)
Pseudomonas species	170 (4.7)	80 (4.4)	90 (5.0)

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Table 1. (Continued.)

Characteristic	Overall (N=3608)	7-Day Group (N=1814)	14-Day Group (N=1794)
Streptococcus pneumoniae	164 (4.5)	86 (4.7)	78 (4.3)
Enterobacter species	157 (4.4)	80 (4.4)	77 (4.3)
Proteus species	133 (3.7)	58 (3.2)	75 (4.2)
Serratia species	86 (2.4)	38 (2.1)	48 (2.7)
S. pyogenes	74 (2.1)	39 (2.1)	35 (2.0)
S. agalactiae	75 (2.1)	40 (2.2)	35 (2.0)
Number and type of organisms — no. (%)			
Monomicrobial, gram-negative	2562 (71.0)	1299 (71.6)	1263 (70.4)
Monomicrobial, gram-positive	625 (17.3)	323 (17.8)	302 (16.8)
Polymicrobial	421 (11.7)	192 (10.6)	229 (12.8)

* ICU denotes intensive care unit and IQR interquartile range.
† Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating more severe organ failure.
‡ Immunosuppression included chemotherapy and prednisone or equivalent glucocorticoid use of more than 15 mg per day.
§ Scores on the Clinical Frailty Scale range from 1 to 9, with higher scores indicating greater frailty.
¶ One patient in the 14-day group was missing source-control data.
‖ See the Supplementary Appendix for the full list of organisms.

The 95.7% confidence interval reflects the exact alpha spending incurred in the interim analyses. The statistical analysis was conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines[26] and in accordance with our protocol[20] and publicly available statistical analysis plan, which were published before we knew the trial results. The primary analysis was performed in accordance with the intention-to-treat principle, but we also conducted a per-protocol analysis, which limited the analysis to patients receiving treatment within 2 days of their assigned duration (i.e., 2 days less to 2 days more than the assigned duration),[27] and a modified intention-to-treat analysis, which excluded patients who died before day 7 of treatment (i.e., before divergence in the treatment-duration assignment).[28] Adherence to the treatment-duration assignment was defined as receipt of adequate antibiotics for 7±2 days in the shorter duration group and for 14±2 days in the longer duration group. Prespecified subgroup analyses were based on the underlying infectious source of the bloodstream infection (vascular catheter, lung, urinary tract, abdomen, skin and soft tissue, other identified source, or unknown source); ICU or non-ICU enrollment; community or hospital acquisition of infection; gram-positive, gram-negative, or polymicrobial infections; the Acute Physiology and Chronic Health Evaluation (APACHE) II score (<25 vs. ≥25; range, 0 to 71, with higher scores indicating an increased risk of death); the Clinical Frailty Scale score (<5 vs. ≥5; range, 1 to 9, with higher scores indicating greater frailty); and vasopressor use on the day that the index blood culture was obtained.

Secondary binary outcomes such as death at other time points, infection or colonization with an antimicrobial-resistant organism, *C. difficile* infection, and adverse events were evaluated as risk differences with 95% confidence intervals. Continuous secondary outcomes, such as ventilation duration, vasopressor duration, and numbers of antibiotic-free days, ICU-free days, hospital-free days, and vasopressor-free days were compared with the use of medians estimated by quantile regression. Effect estimates are represented by the difference in medians with corresponding 95% confidence intervals. Because no correction for multiple comparisons was made in the analyses of secondary outcomes, confidence intervals are reported instead of P values; however, confidence intervals should not be used in place of hypothesis testing, and the results should be considered to be exploratory.

In a prespecified secondary analysis, we planned a generalized linear mixed model to account for

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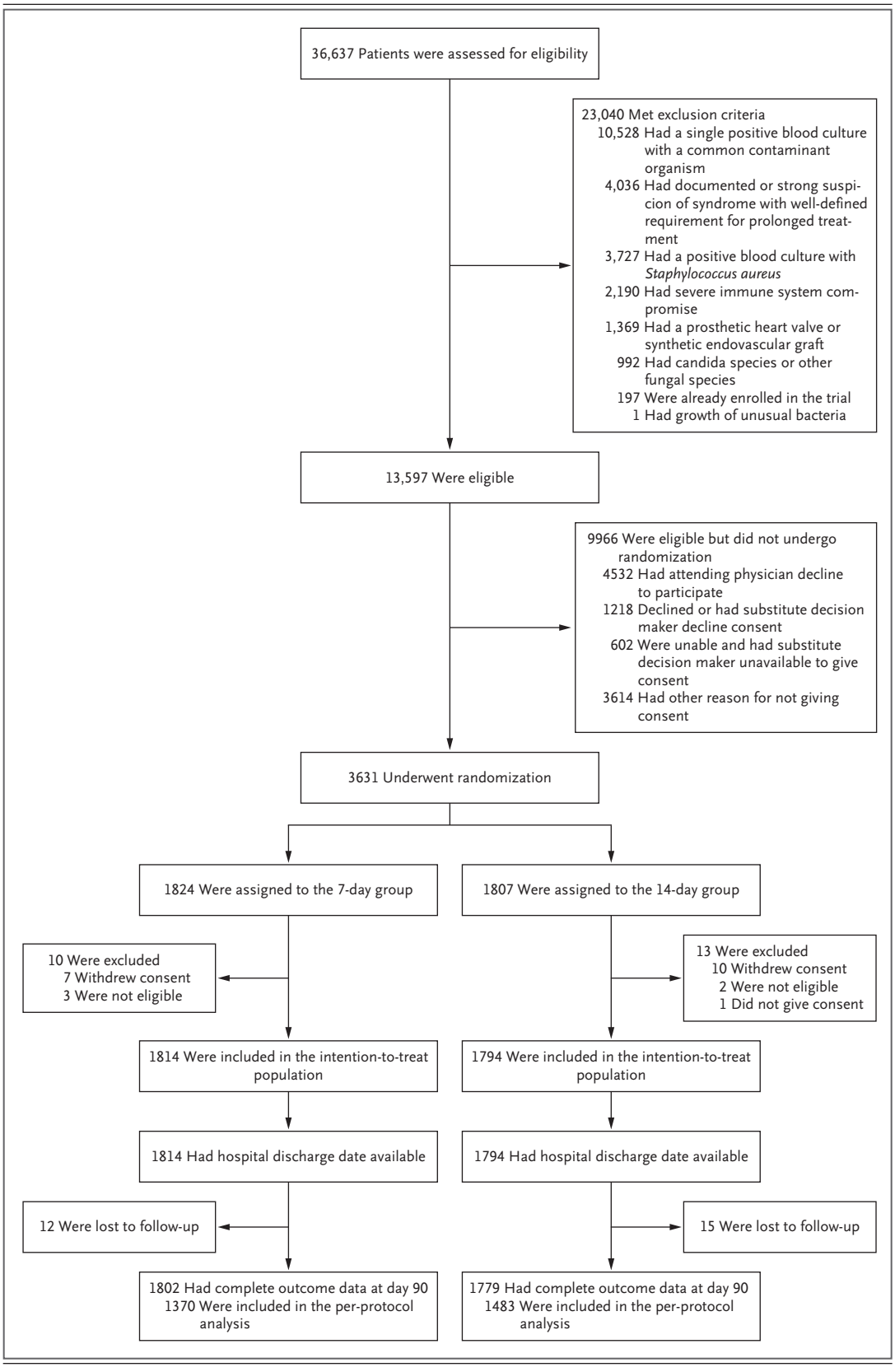

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Figure 1 (facing page). Eligibility, Randomization, and Outcomes.

The per-protocol analysis was limited to patients who received treatment within 2 days of their assigned duration (i.e., 2 days less to 2 days more than the assigned duration).

clustering by center (and specifying ICU or ward within each center) of enrollment. We performed a meta-analysis of our trial results with other published randomized trials comparing mortality in patients receiving antibiotic treatment for 7 days as compared with 14 days for nonneonatal bloodstream infections, using random effects, and inverse variance weighting.

RESULTS

PATIENTS

The first patient in the BALANCE pilot trial was enrolled on October 17, 2014, and the last patient was enrolled on May 5, 2023. Among 36,637 patients with positive blood cultures at participating sites, 13,597 patients (37.1%) met eligibility criteria to enroll in the trial, and 3631 of these patients (26.7%) were enrolled (Fig. 1). The intention-to-treat groups included 3608 patients: 1814 patients randomly assigned to 7 days and 1794 patients to 14 days of antibiotic treatment. The characteristics of the patients, pathogens, syndromes, and treatments were similar in the two groups (Table 1 and Tables S3, S4A, and S4B). The median age of the patients was 70 years (interquartile range, 59 to 80). A total of 1922 patients (53.3%) were men, and 1986 (55.0%) were in the ICU at the time of enrollment. The bloodstream infections were classified as community-onset in 2722 patients (75.4%), hospital ward–acquired in 483 patients (13.4%), and ICU-acquired in 403 patients (11.2%). The most common underlying source of infection was the urinary tract (1523 patients [42.2%]), followed by intraabdominal or hepatobiliary system (679 patients [18.8%]), the lung (469 patients [13.0%]), a vascular catheter (229 patients [6.3%]), and the skin or soft tissues (187 patients [5.2%]). Various organisms were responsible for the bloodstream infections, including 2562 monomicrobial gram-negative bacteria (71.0%), 625 monomicrobial gram-positive bacteria (17.3%), and 421 polymicrobial organisms (11.7%) (Table 1, Table S3, and Table S4C).

PRIMARY OUTCOME

Results for the primary outcome were available for 1802 patients (99.3%) in the 7-day group and for 1779 patients (99.2%) in the 14-day group; 27 patients (0.7%) were lost to follow-up (Fig. 1). Death by 90 days (the primary outcome) occurred in 261 patients (14.5%) in the 7-day group and in 286 patients (16.1%) in the 14-day group. In the primary intention-to-treat analysis, 7 days of treatment was noninferior to 14 days of treatment (difference, –1.6 percentage points [95.7% confidence interval {CI}, –4.0 to 0.8]) (Table 2 and Fig. 2). Nonadherence to the protocol (i.e., receipt of antibiotics for a longer or shorter duration than the assigned number of days ±2 days) occurred in 23.9% of the patients in the 7-day group, including 0.8% who received antibiotics for a shorter duration and 23.1% who received antibiotics for a longer duration; nonadherence occurred in 16.5% of the patients in the 14-day group, including 5.8% who received antibiotics for a shorter duration and 10.7% who received antibiotics for a longer duration. The median duration of antibiotic treatment in the 7-day group was 8 days (interquartile range, 7 to 11), and the median duration in the 14-day group was 14 days (interquartile range, 14 to 15). The per-protocol analysis showed that 7 days of treatment remained noninferior to 14 days of treatment (difference, –2.0 percentage points [95% CI, –4.5 to 0.6]). Noninferiority was preserved in the modified intention-to-treat analysis that excluded patients who died before day 7 of treatment (difference, –1.6 percentage points [95% CI, –3.9 to 0.7]).

SECONDARY OUTCOMES

The difference between the 7-day group and the 14-day group regarding death in the ICU was –0.6 percentage points (95% CI, –3.2 to 1.9); the difference regarding death in the hospital was –1.0 percentage points (95% CI, –2.9 to 0.9); and the difference regarding bacteremia relapse was 0.4 percentage points (95% CI, –0.6 to 1.4). Other secondary clinical outcomes, including measures of length of stay, vasopressor use, and mechanical ventilation use, were similar in the two groups (Table 2 and Table S5). The median number of antibiotic-free days by day 28 was higher among the patients assigned to 7 days of treatment than among the patients assigned to 14 days (19 days [interquartile range, 11 to 21] vs. 14 days [interquartile range, 11 to 14]). Percentages of patients

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Table 2. Primary and Secondary Outcomes.

Outcome	7-Day Group (N = 1814)	14-Day Group (N = 1794)	Difference (95% CI)*
			percentage points
Primary outcome, death from any cause by 90 days — no./total no. (%)			
Primary analysis, intention-to-treat population	261/1802 (14.5)	286/1779 (16.1)	−1.6 (−4.0 to 0.8)
Secondary analysis, per-protocol population	178/1370 (13.0)	222/1483 (15.0)	−2.0 (−4.5 to 0.6)
Modified intention-to-treat analysis, survival ≥7 days	247/1788 (13.8)	272/1765 (15.4)	−1.6 (−3.9 to 0.7)
Secondary outcomes			
Death in hospital — no. (%)†	168 (9.3)	184 (10.3)	−1.0 (−2.9 to 0.9)
Death in ICU — no./total no. (%)‡	91/1014 (9.0)	97/1008 (9.6)	−0.6 (−3.2 to 1.9)
Median no. of days in hospital (IQR)	10 (6–21)	11 (6–22)	−1 (−1.5 to −0.5)
Median no. of hospital-free days by day 28 (IQR)	17 (0–21)	15 (0–21)	2 (0.8 to 3.2)
Median no. of days in ICU (IQR)§	5 (3–11)	5 (3–11)	0 (−0.4 to 0.4)
Median no. of days of vasopressor use (IQR) ¶	3 (2–5)	3 (2–4)	0
Median no. of days of mechanical ventilation (IQR)‖	6 (3–14)	5 (2–12)	1 (−0.6 to 2.6)
Relapse of bacteremia — no. (%)	47 (2.6)	39 (2.2)	0.4 (−0.6 to 1.4)
Median no. of antibiotic-free days by day 28 (IQR)**	19 (11–21)	14 (11–14)	5 (4.6 to 5.4)
Antimicrobial-related adverse outcomes — no. (%)			
Allergy	14 (0.8)	19 (1.1)	−0.3 (−0.9 to 0.3)
Anaphylaxis	1 (0.1)	1 (0.1)	0 (−0.2 to 0.2)
Acute kidney injury	15 (0.8)	17 (0.9)	−0.1 (−0.7 to 0.5)
Acute hepatitis	2 (0.1)	4 (0.2)	−0.1 (−0.4 to 0.2)
Clostridioides difficile infection — no. (%)	31 (1.7)	35 (2.0)	−0.2 (−1.1 to 0.6)
Secondary infection or colonization with antibiotic-resistant organisms — no. (%)	173 (9.5)	152 (8.5)	1.1 (−0.8 to 2.9)
Secondary infection or colonization with antibiotic-resistant organisms in sterile culture — no. (%)	20 (1.1)	24 (1.3)	−0.2 (−1 to 0.5)

* Differences are expressed as absolute risk differences or, for variables shown as medians, as median differences. A 95.7% confidence interval is shown for the primary analysis (accounting for alpha spending in interim analyses), and 95% confidence intervals are shown for the per-protocol analysis, the modified intention-to-treat analysis, and the secondary outcomes. The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity. The 95% confidence intervals for the median differences were estimated with the use of quantile regression.

† One patient in the 7-day group is still in the hospital.

‡ Deaths in the ICU include patients who were enrolled in the ICU or were admitted to the ICU after the diagnosis of a bloodstream infection.

§ The length of stay in the ICU was evaluated in patients who were enrolled in the ICU or were admitted to the ICU after the diagnosis of a bloodstream infection.

¶ Included are data for the patients who received vasopressors at any time after enrollment (722 patients in the 7-day group and 743 patients in the 14-day group).

‖ Included are the data for patients who received mechanical ventilation (469 patients in the 7-day group and 488 patients in the 14-day group).

** Data regarding antibiotic-free days are missing for 2 patients in the 14-day group.

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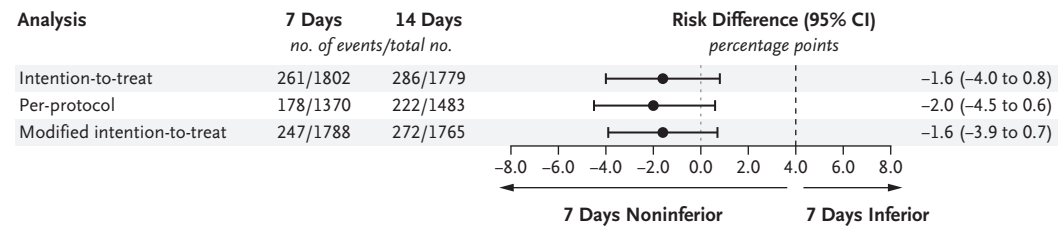

Figure 2. Primary Outcome According to Analysis.

Shown are the differences between the groups in the primary outcome — death from any cause by 90 days after the date of diagnosis of a bloodstream infection — in the intention-to-treat, per-protocol, and modified intention-to-treat analyses. The modified intention-to-treat analysis excluded patients who died before day 7 of treatment (i.e., before divergence in the treatment-duration assignment). A 95.7% confidence interval is shown for the intention-to-treat analysis (accounting for alpha spending in interim analyses), and 95% confidence intervals are shown for the other two analyses. The widths of the confidence intervals have not been adjusted for multiplicity. The dashed line indicates the noninferiority margin of 4 percentage points.

with antimicrobial-related adverse outcomes, *C. difficile* infections, and secondary infection or colonization with antibiotic-resistant organisms were similar in the two groups (Table 2).

SUBGROUP AND SECONDARY ANALYSES

Prespecified subgroup analyses stratified according to the underlying source of infection generally showed that treating bacteremia with 7 days of antibiotics as compared with 14 days of antibiotics led to noninferior results with respect to death by 90 days (Fig. 3). However, confidence intervals were wide around the estimate of the treatment effect on death in a number of subgroups.

The secondary analysis accounting for clustering by center (and specifying ICU vs. hospital ward within each center) with the use of a generalized linear mixed model yielded results that were consistent with the results of the primary analysis. Details are provided in the Supplementary Appendix.

DISCUSSION

Among more than 3600 hospitalized patients who had bloodstream infections from various pathogens and underlying infectious syndromes, 7 days of antibiotic treatment was noninferior to 14 days of treatment with respect to death from any cause by 90 days (the primary outcome). Noninferiority of 7 days of treatment was established across the intention-to-treat, modified intention-to-treat, and per-protocol analyses and was consistent across a range of secondary clinical outcomes, as well as multiple prespecified subgroups defined according to patient, pathogen, and syndrome characteristics.

Since recruitment for the BALANCE trial began, three well-conducted, smaller, randomized, clinical trials have compared 7 days and 14 days of treatment in patients with bloodstream infection.[13-15] All three trials showed noninferiority of the shorter, 7-day, duration of treatment, but they enrolled fewer patients (604 patients in the first trial,[13] 503 patients in the second trial,[14] and 248 patients in the third trial[15]), and therefore used larger noninferiority margins (10 percentage points), composite outcomes, or both. The sample size and much smaller noninferiority margin (4 percentage points) in the BALANCE trial provide a stronger inference about the noninferiority of a 7-day treatment strategy (see Fig. S1 for a meta-analysis). These previous trials either excluded patients who were treated in the ICU or enrolled very few patients in the ICU and in some cases required patients' conditions to be improving before enrollment; thus, the BALANCE trial extends the evidence for shorter treatment duration to critically ill patients. More than half the patients were in the ICU when bacteremia was diagnosed, and this large subgroup had similar and noninferior results with respect to death by 90 days in the 7-day and 14-day groups. We found no apparent differences in treatment

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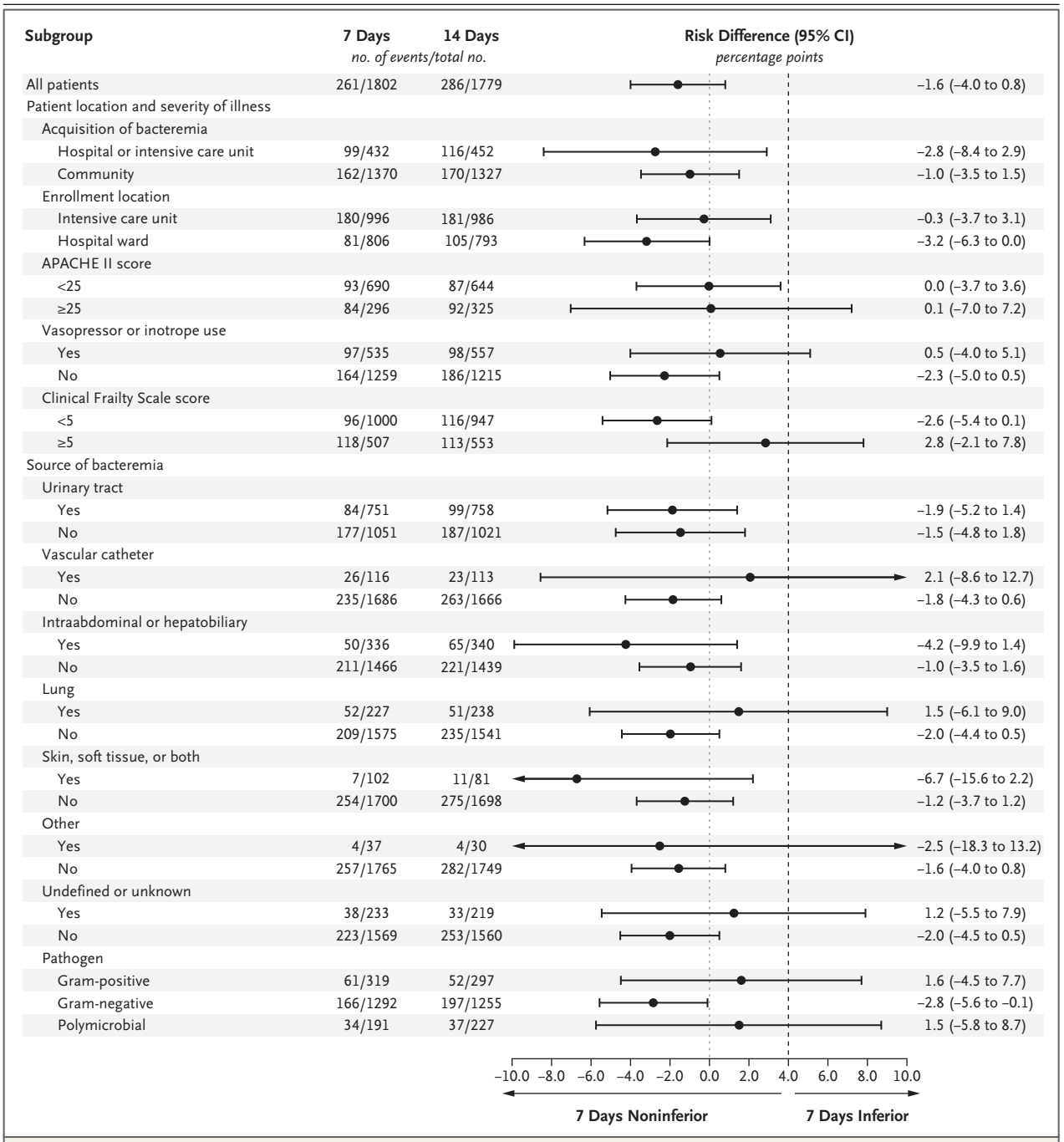

Figure 3. Primary Outcome According to Subgroup.

A 95.7% confidence interval (accounting for alpha spending in interim analyses) is shown for the overall population (the primary analysis), and 95% confidence intervals are shown for the subgroups. The widths of the confidence intervals have not been adjusted for multiplicity. The dashed line at 4 percentage points indicates the noninferiority margin. The Acute Physiology and Chronic Health Evaluation (APACHE) II score ranges from 0 to 71, with higher scores indicating an increased risk of death; the Clinical Frailty Scale score ranges from 1 to 9, with higher scores indicating greater frailty.

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effect among patients with differing severity of illness according to the APACHE II score. The three previous trials were also focused only on gram-negative bloodstream infections, and the BALANCE trial extends findings to other pathogens.

We hypothesized that a shorter duration of antibiotic treatment would lead to fewer antimicrobial-related adverse outcomes, fewer episodes of *C. difficile* infection, and less infection or colonization with antibiotic-resistant organisms. *C. difficile* infections and infection or colonization with antimicrobial-resistant organisms were infrequent events in our trial. Late *C. difficile* infections could have been missed if patients were treated in the ambulatory setting or readmitted to other facilities. Our approach to measuring antimicrobial-resistant organisms relied on routinely collected specimens rather than active surveillance. Accordingly, confidence intervals around the estimates of the treatment effect were wide, and our data do not preclude the possibility of clinically important differences in these outcomes attributable to shorter or longer durations of antibiotic treatment.

Nonadherence is particularly important in a noninferiority trial because it can contribute to bias toward the finding of noninferiority. There was some nonadherence to treatment-duration assignment in this pragmatic trial — antibiotics were stopped after a median of 8 days in the 7-day group and after a median of 14 days in the 14-day group. Other trials of fixed (shorter vs. longer) duration of antibiotic treatments in critically ill patients have also shown nonadherence[8]; yet, adherence rates seen in fixed-duration comparisons have been much lower than those in randomized clinical trials of biomarker-guided treatment durations.[29] Some nonadherence to assigned treatment duration is also to be expected in a trial of severe bacterial infections and among acutely ill patients, given that clinicians may continue treatment in some patients with persistent sepsis or shock or prescribe prolonged antibiotics for a new secondary hospital-acquired infection. However, the results of our intention-to-treat, per-protocol, and modified intention-to-treat analyses show that an initial plan to use a shortened duration of treatment was noninferior to a strategy of committing all patients to 14 days of treatment.

This trial is limited by the lack of placebo controls. However, both the BALANCE pilot trial and the main randomized, controlled trial included a wide variety of pathogens and a diverse range of antibiotic treatment regimens, which precluded the preparation of universal placebos for this global trial. To mitigate this challenge, we used an objective primary outcome, death from any cause by 90 days, and we prolonged the concealment of group assignment to day 7. A noninferiority trial can never prove that outcomes are identical in the two groups, but in comparison with existing trials of bloodstream and other severe bacterial infections, our sample size was much larger and our 4-percentage-point noninferiority margin was much smaller, which lowered the risk of missing a signal for harm.[13,14,22,23,30,31]

This trial was underpowered to assess whether prolonged treatment conferred a potential benefit in some of the smaller subgroups of patients. Our results do not apply to syndromes or pathogens excluded from the trial, such as *S. aureus*, the second most common global cause of bloodstream infections,[32] which has unique virulence factors that enable it to adhere to host tissues and cause metastatic infection. Observational data regarding such infections suggest a higher relapse rate with a shorter duration of treatment.

The BALANCE trial showed that a clinician-driven, 7-day antibiotic treatment strategy was noninferior to a 14-day strategy among hospitalized patients with bloodstream infections from a wide range of pathogens and underlying foci of infection. Adopting a 7-day treatment strategy requires no new expensive medications or technologies, could lead to large savings in drug-acquisition costs,[33] and has the potential to generate downstream benefits in selection of antimicrobial resistance at an individual and population level. Although 7 days of treatment was noninferior to 14 days of treatment, further research is needed to test individualized and potentially shorter treatment durations, so that each patient receives just as long a course as is needed and to balance the benefits and possible harms of antibiotic treatment more fully.

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