ORIGINAL ARTICLE

Cefazolin for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

The *Staphylococcus aureus* Network Adaptive Platform (SNAP) Trial Group

ABSTRACT

BACKGROUND

Staphylococcus aureus bacteremia is associated with high mortality. Whether cefazolin or an antistaphylococcal penicillin should be preferred for the treatment of methicillin-susceptible *S. aureus* bacteremia is unclear.

METHODS

In an ongoing international Bayesian adaptive platform trial, we conducted an open-label, randomized comparison of cefazolin with an antistaphylococcal penicillin (flucloxacillin or cloxacillin) in adult patients with penicillin-resistant, methicillin-susceptible *S. aureus* bacteremia. The primary outcome, which was evaluated with a hierarchical Bayesian logistic-regression model, was death from any cause within 90 days after enrollment in the platform. We assessed the posterior probability of the noninferiority of cefazolin to flucloxacillin or cloxacillin (with the criterion for noninferiority prespecified as an adjusted odds ratio of <1.2, which approximates an absolute difference in mortality of <2.5 percentage points if mortality in the antistaphylococcal-penicillin group is 15%), as well as the posterior probability of superiority (with the criterion of an adjusted odds ratio of <1.0). Secondary safety outcomes included the development of acute kidney injury within 14 days.

RESULTS

This domain of the ongoing trial was conducted between February 17, 2022, and August 7, 2024, by which time the criterion for noninferiority had been met. Mortality at 90 days among adults who could be evaluated was 15.0% (97 deaths among 645 patients) in the cefazolin group and 17.0% (109 deaths among 642 patients) in the antistaphylococcal-penicillin group (adjusted odds ratio, 0.81; 95% credible interval, 0.59 to 1.12; probability of noninferiority, 99.2%; probability of superiority, 89.8%). Acute kidney injury occurred in 92 of 660 patients (13.9%) in the cefazolin group, as compared with 127 of 648 (19.6%) in the antistaphylococcal-penicillin group (adjusted odds ratio, 0.67; 95% credible interval, 0.50 to 0.89; probability of superiority, 99.7%).

CONCLUSIONS

In patients with methicillin-susceptible *S. aureus* bacteremia, cefazolin was noninferior to flucloxacillin or cloxacillin with respect to 90-day mortality and was associated with a lower incidence of acute kidney injury. (Funded by the National Health and Medical Research Council and others; SNAP ClinicalTrials.gov number, NCT05137119.)

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Staphylococcus aureus bacteremia is a leading cause of bacteria-related death worldwide,[1] with more than one in four affected patients dying within 90 days.[2] Although there are accepted best practices in the management of *S. aureus* bacteremia,[3] the preferred antibiotic for the treatment of methicillin-susceptible *S. aureus* bacteremia is unclear.[4] Expert opinion from endocarditis guidelines[5,6] favors the antistaphylococcal penicillins (e.g., nafcillin, oxacillin, cloxacillin, or flucloxacillin) over cefazolin[5] owing to theoretical concerns about the cefazolin inoculum effect, an in vitro destruction of cefazolin by beta-lactamases, which may be relevant in high-burden infections.[7,8] However, meta-analyses of observational studies suggest that cefazolin may be superior to antistaphylococcal penicillins for 30-day mortality (odds ratio, 0.73; 95% confidence interval [CI], 0.62 to 0.85),[9] with a more favorable adverse-event profile.

Given that observational analyses may be subject to multiple biases,[10] a randomized clinical trial is the most reliable way to inform disease management. We launched the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial in 2022 to answer multiple questions related to the treatment of patients with *S. aureus* bacteremia.[11] Within the SNAP trial, we evaluated the efficacy and safety of cefazolin for the treatment of methicillin-susceptible *S. aureus* bacteremia.

METHODS

TRIAL DESIGN AND OVERSIGHT

We used a Bayesian adaptive platform to conduct a pragmatic, open-label, randomized, noninferiority comparison of cefazolin with an antistaphylococcal penicillin (cloxacillin or flucloxacillin, depending on the country) at 91 sites in eight countries (Australia, Canada, Israel, the Netherlands, New Zealand, Singapore, South Africa, and the United Kingdom) (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The SNAP trial comprises a series of investigator-initiated, international trials.[11] The platform features a master protocol (available at NEJM.org) and an integrated statistical framework,[12] with domain-specific appendixes that contain nested questions. Health care consumers were involved in the trial design through participation in focus groups and representation on steering committees.

Each domain of the platform[11] addresses a question about the management of *S. aureus* bacteremia with a comparison of at least two interventions (e.g., treatment with backbone antibiotics, adjunctive clindamycin therapy,[13] or early switching to oral treatment[14]) (see the Supplementary Appendix). The backbone domain is further divided into silos (mutually exclusive subgroups) on the basis of the susceptibility of *S. aureus* to antibiotics: penicillin-susceptible *S. aureus*; methicillin-susceptible, penicillin-resistant *S. aureus*; and methicillin-resistant *S. aureus*. Here, we report results for methicillin-susceptible *S. aureus* in the antibiotic backbone domain of the SNAP trial.

Ethics and regulatory approval were obtained at each participating site. Written or oral informed consent, in accordance with regional regulations, was obtained from all the patients, their surrogates, or both. The trial was designed by the investigators through international working groups. International coordination was provided by the University of Melbourne under the direction of a global trial steering committee.[11] Within each participating region, trial coordination and monitoring were provided by an academic institution that was responsible for ensuring that the trial was conducted in accordance with regional laws.

Data were analyzed by a dedicated analytic team of investigators. Five authors (see the Supplementary Appendix) vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial was supported by funding organizations and academic sponsors in multiple countries (see the Supplementary Appendix), who had no role in the design or conduct of the trial, the analysis of the data, or the reporting of the results. The domain-specific appendix and the statistical analysis plan are available with the master protocol,[11] and the statistical methods[12] are described in the Supplementary Appendix.

PATIENTS

We enrolled hospitalized patients with *S. aureus* bacteremia in the platform within 72 hours after the collection of the blood sample for the index blood culture (the first culture positive for *S. aureus*). The analyses described here involved adults at least 18 years of age. The pediatric trial is ongoing. Details of the platform and domain eligibility criteria are provided in the Supplementary Appendix.

Notable criteria for exclusion from the platform were enrollment more than 72 hours after collection of the first positive blood sample, the presence of polymicrobial bacteremia, or limitations on active treatment (such as in the case of patients receiving only end-of-life care, with no active antibiotic therapy). Key domain-specific exclusion criteria were an active history of allergy to penicillin or cefazolin, current treatment with maintenance dialysis, or ongoing treatment with other systemic antibacterial agents with activity against *S. aureus*. In addition, because the cefazolin inoculum effect is dependent on the production of penicillinase, we included only patients with bacteremia due to penicillin-resistant, methicillin-susceptible *S. aureus* to avoid bias toward noninferiority of cefazolin. Susceptibility to methicillin and to penicillin was determined locally with the use of automated testing methods, phenotypic disk diffusion,[15], or molecular testing for the *mecA* and *blaZ* genes or with a combination of these methods (see the Supplementary Appendix).

RANDOMIZATION AND ASSIGNMENT

All the patients underwent randomization in a 1:1 ratio within the methicillin-susceptible *S. aureus* silo at platform entry. Simple randomization without stratification was performed with a Web-based interactive randomization system (Spiral Software). As soon as patients were confirmed to be eligible for the methicillin-susceptible *S. aureus* silo of the backbone domain, their assignment to receive cefazolin or to receive flucloxacillin or cloxacillin was revealed to the trial staff and the treating clinical teams.

INTERVENTIONS

The recommended dose was 2 g of cefazolin administered intravenously every 8 hours (or every 6 hours for critical illness or endocarditis), 2 g of flucloxacillin administered intravenously every 6 hours (or every 4 hours for critical illness or endocarditis), or 2 g of cloxacillin administered intravenously every 4 hours, with dose adjustments according to renal function (see the Supplementary Appendix). Postenrollment administration of additional antibiotics was discouraged, unless patients were also assigned to a treatment group in the trial domain for adjunctive antibiotics.[13]

Consultation with specialists in infectious diseases was advised. The protocol recommended that the assigned antibiotic be continued for the entire duration of intravenous antibiotic treatment, with a minimum duration of antibiotic treatment of 14 days for uncomplicated bacteremia and 28 to 42 days for complicated bacteremia.[16] Subsequent randomization to the domain evaluating early switching to oral treatment[14] was permitted for eligible participants at 7 days for uncomplicated bacteremia and 14 days for complicated bacteremia. Apart from the antistaphylococcal antibiotics used, clinical management was left to the discretion of the treating clinician.

OUTCOMES

The primary outcome for the platform and domain was death from any cause within 90 days after platform entry. Secondary platform outcomes included death from any cause within 14, 28, and 42 days; microbiologic treatment failure and diagnosis of new foci of infection between days 15 and 90; and *Clostridioides difficile* infection within 90 days. Secondary domain-specific safety outcomes included acute kidney injury, defined as an absolute increase in the creatinine level of at least 26.5 μmol per liter (0.3 mg per deciliter) within 5 days or a relative increase of at least 50% from baseline within the first 14 days; initiation of renal-replacement therapy; and acute liver injury. Detailed definitions of these outcomes are provided in the Supplementary Appendix.

ADVERSE EVENTS

In addition to assessing the prespecified safety outcomes, site investigators were asked to conform to regional requirements regarding the reporting of adverse events. At a minimum, they were to record serious adverse reactions, which were defined as any serious adverse event that was thought to be possibly, probably, or definitely related to the trial drug or trial procedures. Whether an adverse event was related to the trial drug or trial procedures was determined by site investigators and subsequently confirmed by central review.

STATISTICAL ANALYSIS

For each estimand, trial populations were defined on the basis of the randomized treatment assignment, regardless of the receipt of treatment, according to the intention-to-treat principle. The primary outcome was also analyzed in

a population defined according to adherence to the protocol (see the Supplementary Appendix).

The scheduled and final analyses were performed by an independent analytic team that was separate from the trial team and whose members were aware of treatment-group assignments. For these analyses, we used a minimally informative prior probability distribution for all model parameters. The analyses are described in the statistical appendix included with the Supplementary Appendix.

The adjusted odds ratio for the primary outcome was calculated with a hierarchical Bayesian logistic-regression model. This model incorporated data from all the patients in the platform to adjust for age, country, temporal epoch (epochs were defined as contiguous 26-week periods counted from the start of the domain), and eligibility and treatment assignment in other platform domains. Details of the model fitting and diagnostics are provided in the Supplementary Appendix. The treatment effect that pertained to cefazolin as compared with flucloxacillin or cloxacillin was calculated exclusively with data from patients included in the randomized comparison in this silo (Fig. 1), with prespecified information sharing from the 87 pediatric patients enrolled in this silo (for whom the trial is ongoing).

The probability of noninferiority (with the criterion for noninferiority prespecified as an adjusted odds ratio of <1.2, which approximates an absolute difference in mortality of less than 2.5 percentage points if mortality in the antistaphylococcal-penicillin group was 15%) and the probability of superiority (with the criterion of an adjusted odds ratio of <1.0) were estimated. The primary analysis of the primary outcome was a complete-case analysis that excluded patients with missing 90-day mortality data. Post hoc analyses included analyses in which all the patients with missing 90-day mortality data were assumed to have survived and in which all such patients were assumed to have died.

Binary secondary outcomes were analyzed similarly. We planned a time-to-event analysis with a Bayesian–Weibull proportional-hazards model; however, the assumptions of this model were not satisfied, and so unadjusted Kaplan–Meier curves are presented. Prespecified subgroup analyses for the primary outcome were stratified according to the presence or absence of endocarditis and the presence or absence of suspected or proven central nervous system infection. During peer review, a post hoc subgroup analysis was conducted with stratification according to the time from the collection of the blood sample for the index blood culture to enrollment (<48 hours vs. 48 to 72 hours).

Because analyses were conducted in a Bayesian framework, we report the means of the posterior distributions of treatment effects with 95% credible intervals and, as appropriate, associated posterior probabilities. No P values were calculated, and no adjustment for multiple analyses was prespecified. Therefore, for the secondary estimands, with the exclusion of safety outcomes, the 95% credible intervals should not be used to draw definitive conclusions.

With the perpetually adaptive Bayesian platform, simulations were conducted to optimize trial operating characteristics, such as the number and timing of interim analyses and decision rule thresholds, and the maximum sample size was set at 6000 patients.[12] We planned and conducted scheduled analyses after every 500 platform patients reached day 90 of follow-up, with prespecified rules for stopping at each analysis for each domain.[12] For the methicillin-susceptible *S. aureus* silo of the antibiotic backbone domain, if the posterior probability of noninferiority of cefazolin was greater than 99% in adults, the independent data and safety monitoring committee could recommend stopping recruitment. If the posterior probability of superiority in adults was less than 1%, the data and safety monitoring committee could recommend stopping for futility. If no threshold was met, recruitment was to continue unless the data and safety monitoring committee had substantial safety concerns, which were not prespecified. For the noninferiority comparison involving methicillin-susceptible *S. aureus*, simulations indicated an approximate frequentist type I error of 2%.

On June 21, 2024, at the fourth planned interim analysis, the data and safety monitoring committee requested that recruitment be paused in the methicillin-susceptible *S. aureus* silo because of a safety signal involving acute kidney injury. Subsequently, on August 5, 2024, the committee recommended closing the methicillin-susceptible *S. aureus* silo because the statistical trigger for noninferiority had been met and the safety signal persisted. On August 7, 2024, without additional knowledge of trial outcomes, the trial steering committee accepted the recommendation.

RESULTS

TRIAL POPULATION

Patients in the methicillin-susceptible *S. aureus* silo in the antibiotic backbone domain were enrolled between February 17, 2022, and June 21, 2024, with the last patient reaching 90 days of follow-up on September 19, 2024. Of 8546 patients screened as of June 21, 2024, a total of 2602 adults (30.4%) were enrolled in the platform and underwent one or more randomizations (Fig. S1 in the Supplementary Appendix). Of those, 1757 (67.5%) had methicillin-susceptible *S. aureus*, and 1341 underwent randomization in the methicillin-susceptible *S. aureus* silo (671 were assigned to receive cefazolin, and 670 to receive flucloxacillin or cloxacillin) (Fig. 1). Of these patients, 54 (4.0%) were lost to follow-up or were withdrawn, with the remaining 1287 patients included in the analysis of the primary

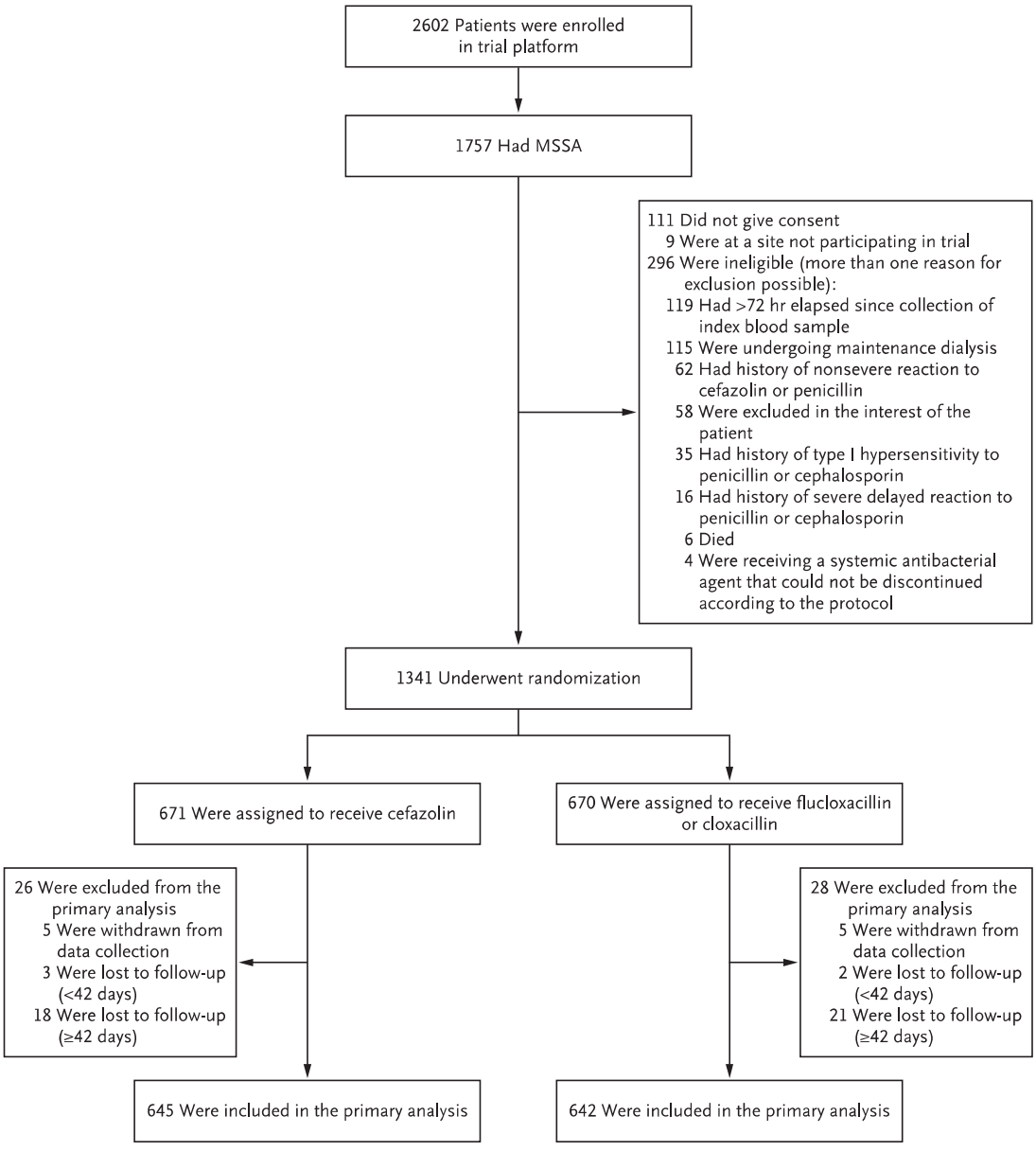

Figure 1. Enrollment, Randomization, and Follow-up.

Patients could choose to withdraw from the trial and ongoing data collection at any time. In each group, five patients who had undergone randomization were withdrawn from data collection according to the decision of the patient, surrogate, treating clinical team, or trial investigators. MSSA denotes methicillin-susceptible *Staphyloccocus aureus*.

outcome. Recruitment to the SNAP trial is ongoing, and to maintain trial integrity, the results for the pediatric patients, the methicillin-resistant *S. aureus* silo, and the other domains remain blinded.

Baseline characteristics are presented according to treatment assignment in Table 1. The median age of the patients was 66 years (interquartile range, 53 to 76), and 421 (31.4%) were women; these characteristics are representative of a typical cohort with *S. aureus* bacteremia (Tables S1, S2, and S3). The most common site of infection was osteoarticular (32.1%) (Table 2). Antibiotics received before randomization are listed in Table S4. At enrollment, 488 patients (36.4%) were receiving cefazolin and 665 (49.6%) were receiving flucloxacillin or cloxacillin, with similar numbers in the two treatment groups. For more than 99% of the patients in this trial, consultation with a specialist in infectious diseases occurred. The duration of administration of intravenous antibiotics and of oral antibiotics was similar in the two treatment groups (Table S5).

PRIMARY OUTCOME

Of 645 patients in the cefazolin group who could be evaluated, 97 (15.0%) died within 90 days, as compared with 109 of 642 patients (17.0%) in the antistaphylococcal-penicillin group who could be evaluated (adjusted odds ratio, 0.81; 95% credible interval, 0.59 to 1.12). These results correspond to a posterior probability of noninferiority of 99.2% and a posterior probability of superiority of 89.8% (Table 3 and Fig. S2). Among the 4.0% of patients with missing primary-outcome data, the baseline characteristics were similar to those with complete data, apart from a younger age and a history of injection drug use in both treatment groups (Table S6). The results of the complementary analyses that accounted for missing outcomes were congruent with those of the primary analysis, with posterior probabilities of noninferiority that exceeded 99%. A further post hoc sensitivity analysis with the use of a broader prior probability distribution yielded results similar to those of the primary analysis (Table S7). The results of the post hoc subgroup analysis with stratification according to the time from the collection of the blood sample for the index blood culture to enrollment are shown in Table S8.

SECONDARY OUTCOMES

Secondary outcomes are presented in Table 3. At every time point before day 90, cefazolin had a probability of noninferiority for mortality that exceeded 98.8% and a probability of superiority that exceeded 94.1%. Unadjusted Kaplan–Meier plots for mortality are provided in Figure S3.

Patients who received cefazolin had a lower incidence of acute kidney injury than those who received flucloxacillin or cloxacillin (92 of 660 [13.9%] vs. 127 of 648 [19.6%]; adjusted odds ratio, 0.67; 95% credible interval, 0.50 to 0.89; probability of superiority, 99.7%). The posterior probability of a lower risk of initiation of renal-replacement therapy within 90 days with cefazolin than with flucloxacillin or cloxacillin was 94.6% (Table 3 and Fig. S4). The staging of acute kidney injury is presented in the Table S9.

ANALYSES OF PROTOCOL-ADHERENT AND PRESPECIFIED SUBGROUPS

The analysis of the protocol-adherent population showed a 95.4% probability of cefazolin being noninferior to flucloxacillin or cloxacillin (Table 3). Among patients with endocarditis, death occurred in 8 of 51 (15.7%) in the cefazolin group and in 13 of 53 (24.5%) in the group receiving flucloxacillin or cloxacillin (adjusted odds ratio, 0.54; 95% credible interval, 0.20 to 1.43; probability of noninferiority, 94.4%; probability of superiority, 88.9%). Only 7 patients had a central nervous system infection, which precluded meaningful comparison.

REPORTED ADVERSE EVENTS

Serious adverse reactions related to the trial drugs are summarized in Table 3 and Table S10. Overall, cefazolin was associated with substantially lower odds of a serious adverse reaction being reported than flucloxacillin or cloxacillin (adjusted odds ratio, 0.41; 95% credible interval, 0.21 to 0.77), as well as substantially lower odds of treatment discontinuation due to an adverse event (adjusted odds ratio, 0.21; 95% credible interval, 0.11 to 0.38).

DISCUSSION

In this pragmatic, randomized clinical trial involving adults with methicillin-susceptible *S. aureus* bacteremia, cefazolin was noninferior to flucloxacillin or cloxacillin for the primary outcome of

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cefazolin (N = 671)	Flucloxacillin or Cloxacillin (N = 670)
Demographic characteristics		
Median age (IQR) — yr	66 (53–76)	66 (52–77)
Female sex — no. (%)	215 (32.0)	206 (30.7)
Median weight (IQR) — kg	82.0 (69.0–96.8)	80.0 (68.0–95.0)
Coexisting conditions — no. (%)		
Diabetes mellitus	231 (34.4)	217 (32.4)
Chronic kidney disease†	96 (14.3)	93 (13.9)
Cirrhosis	34 (5.1)	30 (4.5)
Cancer leading to any surgical or medical therapy within past 12 mo‡	95 (14.2)	76 (11.3)
Dementia	23 (3.4)	32 (4.8)
Iatrogenic immunosuppression§	105 (15.6)	84 (12.5)
Implanted intravascular prosthesis or endovascular device¶	64 (9.5)	58 (8.7)
Previous infective endocarditis	11 (1.6)	10 (1.5)
Underlying cardiac abnormality conferring predisposition to endocarditis‖	50 (7.5)	42 (6.3)
Injection drug use within past 6 mo	31 (4.6)	52 (7.8)
Limitations to care**	80 (11.9)	84 (12.5)
Prognostic factors		
Median time to index blood culture positivity (IQR) — hr	15.7 (12.0–21.0)	15.3 (12.0–20.7)
Median time from index blood culture to entry in trial platform (IQR) — hr	52.3 (43.5–65.5)	50.9 (42.3–64.7)
Median time from index blood culture to entry in silo (IQR) — hr	62.2 (50.2–67.9)	61.1 (50.0–67.5)
Inpatient in intensive care unit at time of recruitment — no. (%)	74 (11.0)	72 (10.7)
Median Pitt bacteremia score (IQR)††	0 (0–1)	0 (0–1)
Median C-reactive protein level (IQR) — mg/liter	192.0 (113.5–266.5)	203.1 (122–283.8)

* Data are shown for the intention-to-treat population, which includes all the patients who underwent randomization and were enrolled in the methicillin-susceptible *Staphylococcus aureus* silo of the antibiotic backbone domain. IQR denotes interquartile range.

† Chronic kidney disease was defined as an estimated glomerular filtration rate below 50 ml per minute per 1.73 m^2 of body-surface area. Four patients (0.3%) were undergoing hemodialysis or peritoneal dialysis (which were deviations from the protocol) at baseline. However, they were included in the intention-to-treat population.

‡ Numbers do not include patients with nonmelanoma skin cancers.

§ Iatrogenic immunosuppression was defined as having received an immunosuppressive agent (prednisone at a dose of >0.5 mg per kilogram of body weight per day or the equivalent for more than 14 days, cyclosporine, tacrolimus, sirolimus, azathioprine, leflunomide, mycophenolate, cyclosporine, methotrexate, a monoclonal antibody such as infliximab, chemotherapy for cancer, or any other immunosuppressive agent with similar effects) within the past 3 months, having undergone bone marrow transplantation within the past 3 months, or having a diagnosis of acquired immunodeficiency syndrome (AIDS).

¶ Numbers do not include patients with central catheters, whether temporary or tunneled.

‖ Numbers do not include patients with an implanted intravascular prosthesis or endovascular device.

** Limitations to care included active orders or advance care directives limiting resuscitation efforts and intensive care admission.

†† The Pitt bacteremia score is a measure of the severity of acute illness; scores range from 0 to 14, with higher scores indicating greater severity.

death from any cause within 90 days. Cefazolin was also associated with a lower risk of acute kidney injury, a lower risk of initiation of renal-replacement therapy, and a lower risk of treatment discontinuation due to adverse events. The data suggest that treatment with cefazolin led to

Table 2. Foci of Infection.*

Focus or Type of Infection	Cefazolin (N=671)	Flucloxacillin or Cloxacillin (N=670)
	number of patients (percent)	
Osteoarticular infection	220 (32.8)	210 (31.3)
Septic arthritis or extra-axial osteomyelitis	167 (24.9)	151 (22.5)
Vertebral osteomyelitis, septic discitis, or both	61 (9.1)	59 (8.8)
Epidural abscess	45 (6.7)	49 (7.3)
Orthopedic hardware–associated infection	34 (5.1)	31 (4.6)
Skin and soft-tissue infection	177 (26.4)	204 (30.4)
Isolated skin and soft-tissue infection	127 (18.9)	136 (20.3)
Intravascular catheter–associated infection	103 (15.4)	102 (15.2)
Isolated intravascular catheter–associated infection	91 (13.6)	91 (13.6)
Primary bacteremia, with no other focus identified	81 (12.1)	80 (11.9)
Endocarditis	55 (8.2)	57 (8.5)
Native-valve infection on the left side	35 (5.2)	33 (4.9)
Native-valve infection on the right side	13 (1.9)	19 (2.8)
Prosthetic-valve infection	13 (1.9)	9 (1.3)
Pleuropulmonary infection	40 (6.0)	42 (6.3)
Other deep focus	27 (4.0)	37 (5.5)
Genitourinary infection	24 (3.6)	22 (3.3)
Native vascular or vascular-graft infection	15 (2.2)	16 (2.4)
Unspecified	14 (2.1)	13 (1.9)
Infection associated with cardiac device or other implantable nonorthopedic device	12 (1.8)	16 (2.4)
Central nervous system infection	5 (0.7)	2 (0.3)

* Patients may have had more than one focus of infection, unless isolated skin and soft-tissue infection or isolated catheter-associated infection is specified.

lower mortality than treatment with flucloxacillin or cloxacillin, with an estimated probability of superiority of cefazolin of 94% to 99% at days 14, 28, and 42; the probability of superiority remained approximately 90% by day 90.

The adjusted odds ratio for 90-day mortality of 0.81 (credible interval, 0.59 to 1.12) for cefazolin as compared with flucloxacillin or cloxacillin is similar to pooled estimates from observational studies of an overall odds ratio of 0.73 for cefazolin as compared with the antistaphylococcal penicillins and 0.31 to 0.92 for cefazolin as compared with individual drugs within the class.[9] Although patients with *S. aureus* bacteremia are at direct risk for acute kidney injury owing to acute illness,[17] the potential nephrotoxic effects of the antistaphylococcal penicillins have been recognized since the 1960s.[18] We used flucloxacillin and cloxacillin in this trial, but other antistaphylococcal penicillins have similar antibacterial activity and similar chemical structures[19]; according to observational data, the risk of nephrotoxic effects or of treatment discontinuation due to adverse events with flucloxacillin or cloxacillin is similar to that with other antistaphylococcal pencillins that have been compared with cefazolin.[9] Therefore, the findings in this trial with regard to mortality and nephrotoxic effects may apply to antistaphylococcal penicillins other than flucloxacillin or cloxacillin.

Cefazolin has some potential disadvantages as compared with flucloxacillin or cloxacillin, including higher drug-acquisition costs than flucloxacillin or cloxacillin in some markets and a potentially broader antimicrobial spectrum. However, these concerns are balanced by its longer half-life,

Table 3. Primary and Secondary Outcomes.

Outcome	Cefazolin (N=671)	Flucloxacillin or Cloxacillin (N=670)	Odds Ratio (95% Credible Interval)*	Probability of Noninferiority†	Probability of Superiority†
	number/total number (percent)			*percent*	
Primary outcome					
Death from any cause within 90 days					
Primary analysis	97/645 (15.0)	109/642 (17.0)	0.81 (0.59–1.12)	99.2	89.8
Analysis with all patients with missing data assumed to be dead	123/671 (18.3)	137/670 (20.4)	0.83 (0.63–1.10)	99.6	90.7
Analysis with all patients with missing data assumed to be alive	97/671 (14.5)	109/670 (16.3)	0.81 (0.59–1.11)	99.3	90.5
Analysis of protocol-adherent population	81/589 (13.8)	73/520 (14.0)	0.88 (0.61–1.26)	95.4	76.0
Secondary outcomes					
Acute kidney injury within 14 days‡	92/660 (13.9)	127/648 (19.6)	0.67 (0.50–0.89)	>99.9	99.7
Acute liver injury within 14 days§	75/574 (13.1)	78/562 (13.9)	0.96 (0.68–1.35)	90.0	59.7
Any serious adverse reaction related to trial drug	12/671 (1.8)	33/670 (4.9)	0.41 (0.21–0.77)	99.9	99.8
Death by day 14	25/667 (3.7)	37/665 (5.6)	0.67 (0.39–1.11)	NR	NR
Death by day 28	47/665 (7.1)	70/665 (10.5)	0.61 (0.41–0.91)	NR	NR
Death by day 42	63/663 (9.5)	86/662 (13.0)	0.66 (0.46–0.94)	NR	NR
Change of antibiotic due to perceived inefficacy	14/671 (2.1)	16/670 (2.4)	1.05 (0.51–2.10)	NR	NR
Microbiologic treatment failure after day 14	18/587 (3.1)	12/566 (2.1)	1.41 (0.71–2.78)	NR	NR
Diagnosis of new foci of infection after day 14	28/623 (4.5)	30/609 (4.9)	0.87 (0.53–1.45)	NR	NR
Change of antibiotic due to adverse event	11/671 (1.6)	61/670 (9.1)	0.21 (0.11–0.38)	NR	NR
Initiation of renal-replacement therapy within 90 days	17/668 (2.5)	27/657 (4.1)	0.61 (0.33–1.11)	NR	NR
Ongoing renal-replacement therapy at 90 days	4/662 (0.6)	3/643 (0.5)	1.00 (0.31–3.16)	NR	NR
Clostridioides difficile infection¶	14/664 (2.1)	10/661 (1.5)	1.28 (0.60–2.66)	NR	NR
Intravenous catheter complication leading to removal‖	22/668 (3.3)	33/665 (5.0)	0.68 (0.39–1.16)	NR	NR

* Shown are the median adjusted odds ratios. The 95% credible intervals do not include adjustment for multiplicity.
† The posterior probability of the noninferiority or superiority of cefazolin to flucloxacillin or cloxacillin is shown. Posterior probabilities are not reported (NR) for secondary outcomes, with the exception of safety outcomes.
‡ Acute kidney injury was defined by an absolute increase in the creatinine level of at least 26.5 μmol per liter (0.3 mg per deciliter) within 5 days or a relative increase of at least 50% from baseline within the first 14 days.
§ Acute liver injury was defined by an increase in the alanine aminotransferase or γ-glutamyltransferase level above 2.5 times the upper limit of the normal range.
¶ Patients were considered to have *C. difficile* infection if they had symptoms of the infection, tested positive for *C. difficile*, and received treatment for the infection.
‖ Removal of an intravenous catheter due to complication was considered to be an outcome event if it occurred while a patient was receiving the assigned treatment.

more favorable side-effect profile, and possible superiority to flucloxacillin or cloxacillin.

The trial has limitations. For reasons of practicality and feasibility, we used an open-label design; however, the primary outcome, death from any cause within 90 days, was objective, and the criteria for a decision to stop the trial were based on prespecified statistical rules. We had limited control over physician decisions after randomization. In the presence of persistent bacteremia or other clinical factors, some physicians might have performed more diagnostic testing than others, changed or added antibiotics, or performed more aggressive source control. We did not collect and therefore cannot present these data. We do not believe that postrandomization care would

have differed owing to knowledge of the assigned treatment group, but this uncertainty is a limitation of the open-label design. In addition, variability of practices across sites may have introduced heterogeneity. A change from the assigned treatment to a different therapy due to clinician-perceived treatment failure occurred in less than 2.5% of patients, and the results of the analysis of the protocol-adherent population were consistent with those of the primary analysis.

We have not yet tested isolates for the presence of the cefazolin inoculum effect; a report on the microbiologic subgroup is planned when testing of all the isolates has been performed at central reference laboratories. In the interim, concerns about the clinical relevance of the cefazolin inoculum effect[7] should be substantially allayed by the narrow noninferiority margin and the finding that the estimated treatment effect in patients with infective endocarditis was similar to that in the overall population. We performed a complete-case analysis for the primary outcome (which excluded the 4.0% of patients with missing data), as well as complementary analyses in which all the patients with missing primary-outcome data were assumed to be alive or in which all such patients were assumed to be dead, which yielded results nearly identical to those of the primary analysis.

In this pragmatic, international, open-label trial, treatment with cefazolin was noninferior to treatment with flucloxacillin or cloxacillin with respect to 90-day all-cause mortality among adults with methicillin-susceptible *S. aureus* bacteremia. Cefazolin was associated with fewer serious adverse events, in particular, a lower incidence of acute kidney injury.

The views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.

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