Supplementary Online Content

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

eTable 1: Primary and Secondary Outcomes Adjusted for Baseline Stratification Variables of Study Site and Hemodialysis

	No./Total No. (%)		Risk difference, % (95% CI)	*P* value
	Combination	Standard		
Primary Outcome[a,b]				
Primary analysis	59/170 (35%)	68/175 (39%)	-3.8 (-13.7-6.1)	0.45
Per protocol	47/144 (33%)	68/175 (39%)	-5.6 (-15.9-4.8)	0.29
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8%)	13/174 (7%)	-0.1 (-5.4-5.2)	0.98
Day 42	25/170 (15%)	19/174 (11%)	3.4 (-3.1-9.9)	0.30
Day 90	35/170 (21%)	28/174 (16%)	4.1 (-3.5-11.7)	0.29
Persistent bacteremia				
Day 2	50/167 (30%)	61/173 (35%)	-5.1 (-15.0-4.8)	0.31
Day 5	19/166 (11%)	35/172 (20%)	-8.6 (-16.3--0.9)	0.03
Microbiological relapse[a]	14/169 (8%)	18/175 (10%)	-2.1 (-8.3-4.0)	0.49
Microbiological treatment failure[a]	16/170 (9%)	17/175 (10%)	-0.3 (-6.4-5.9)	0.93
Acute Kidney Injury (AKI)[e]	34/145 (23%)	9/145 (6%)	17.6 (9.3-25.9)	<0.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		0.69

a. The primary outcome was a composite of mortality at Day 90, persistent bacteremia at Day 5, microbiological relapse (a positive blood culture for methicillin-resistant *Staphylococcus aureus* [MRSA] at least 72 hours after a preceding negative culture), and microbiological treatment failure (a positive sterile site culture for MRSA at least 14 days after randomization).
b. The primary analysis population consisted of all participants with data available for the primary endpoint and were analysed according to the treatment allocation, regardless of treatment received. The per-protocol population was defined as (1) for the combination group: received at least 75% of study β-lactam doses; (2) for the standard treatment group: received ≤1 defined daily dose of study β-lactam; (3) for both groups: data available for the primary endpoint.
c. Results for secondary outcomes are reported for the primary analysis population.
d. One patient did not have mortality data available, but did meet the criteria for persistent bacteremia and so met the primary composite endpoint.
e. Participants on dialysis at randomisation are excluded from the acute kidney injury (AKI) outcome. AKI was defined as at least stage 1 modified RIFLE criteria (1.5-fold increase in the serum creatinine) at any time within the first 7 days or new need for renal replacement at any time from days 1 to 90.

eTable 2: Sensitivity Analyses for the Primary Outcomes, Unadjusted and Adjusted for Baseline Stratification Variables of Study Site and Hemodialysis

	No./Total No. (%)		Unadjusted		Adjusted	
	Combination	Standard	Risk difference, % (95% CI)	*P* value	Risk difference, % (95% CI)	*P* value
Complete primary analysis population	59/170 (35%)	68/175 (39%)	-4.2 (-14.3-6.0)	0.42	-3.8 (-13.7-6.1)	0.45
All individuals with missing endpoint treated as failure	63/174 (36%)	71/178 (40%)	-3.7 (-13.8-6.5)	0.48	-3.6 (-13.6-6.4)	0.48
Missing in standard group treated as success, missing in combination group treated as failure	63/174 (36%)	68/178 (38%)	-2.0 (-12.1-8.1)	0.70	-1.8 (-11.6-8.0)	0.71
Including only those with bacterial isolates available[a]	54/156 (35%)	62/158 (39%)	-4.6 (-15.3-6.0)	0.40	-5.0 (-15.5-5.5)	0.35
Staphylococcus aureus isolates only (excludes *S. argenteus*)[b]	54/154 (35%)	62/157 (39%)	-4.4 (-15.2-6.3)	0.42	-4.8 (-15.5-5.8)	0.37
Methicillin-resistant *S. aureus* only *(*excludes *S. argenteus* & methicillin-susceptible *S. aureus*)[c]	54/153 (35%)	62/157 (39%)	-4.2 (-15.0-6.6)	0.44	-4.6 (-15.3-6.0)	0.39

a. There were 321 available bacterial isolates, for which 7 associated participants had missing follow-up data. Leaving 314 total participants included in this subgroup.
b. An additional 3 isolates were genotyped as *S. argenteus*, leaving 311 total participants included in this subgroup.
c. There were 2 isolates that had tested as methicillin-resistant at the study site laboratory, but as methicillin-susceptible at the central laboratory. One of the associated patients had missing follow-up data. Leaving 310 total participants included in this subgroup.

eTable 3: Secondary Outcomes in the Per Protocol Population, Unadjusted and Adjusted for Baseline Stratification Variables of Study Site and Hemodialysis

	No./Total No. (%)		Unadjusted		Adjusted	
	Combination	**Standard**	**Risk difference, % (95% CI)**	***P* value**	**Risk difference, % (95% CI)**	***P* value**
Secondary Outcomes[a]						
All-cause mortality						
Day 14	8/144 (6%)	13/174 (7%)	-1.9 (-7.3-3.5)	0.49	-2.0 (-7.2-3.2)	0.45
Day 42	16/144 (11%)	19/174 (11%)	0.2 (-6.7-7.1)	0.96	0.1 (-6.3-6.6)	0.97
Day 90	26/144 (18%)	28/174 (16%)	2.0 (-6.4-10.3)	0.64	1.8 (-6.0-9.5)	0.66
Persistent bacteremia						
Day 2	43/142 (30%)	61/173 (35%)	-5.0 (-15.4-5.4)	0.35	-4.6 (-14.9-5.7)	0.38
Day 5	16/141 (11%)	35/172 (20%)	-9.0 (-17.0--1.0)	0.03	-8.5 (-16.5--0.5)	0.04
Microbiological relapse[b]	11/143 (8%)	18/175 (10%)	-2.6 (-8.9-3.7)	0.42	-2.7 (-9.0-3.6)	0.40
Microbiological treatment failure[c]	14/144 (10%)	17/175 (10%)	0.0 (-6.5-6.5)	1.00	0.1 (-6.4-6.5)	0.99
Acute Kidney Injury (AKI)[d]	27/123 (22%)	9/145 (6%)	15.7 (7.4-24.0)	<0.001	15.8 (7.4-24.2)	<0.001
Duration of intravenous antibiotics, mean (SD), d	30.8 (19.6)	28.1 (17.4)		0.24		0.21

a. The per-protocol population was defined as (1) for the combination group: received at least 75% of study β-lactam doses; (2) for the standard treatment group: received ≤1 defined daily dose of study β-lactam; (3) for both groups: data available for the primary endpoint.
b. Microbiological relapse was defined as a positive blood culture for methicillin-resistant *Staphylococcus aureus* (MRSA) at least 72 hours after a preceding negative culture
c. Microbiological treatment failure was defined as a positive sterile site culture for MRSA at least 14 days after randomization.
d. Participants on dialysis at randomisation are excluded from the acute kidney injury (AKI) outcome. AKI was defined as at least stage 1 modified RIFLE criteria (1.5-fold increase in the serum creatinine) at any time within the first 7 days or new need for renal replacement at any time from days 1 to 90.

eTable 4: Subgroup Analyses for the Primary Outcome

Subgroup Analysis	Primary outcome, No./Total No. (%)		Risk difference, %	95% CI	*P* value for interaction
	Combination	Standard			
Backbone drug[a]					
Vancomcyin	56/165 (34%)	67/172 (39%)	-5.0	(-15.3-5.2)	0.39
Daptomycin	3/5 (60%)	1/3 (33%)	26.7	(-41.8-95.1)	
Dialysis at enrolment					
Not receiving	52/145 (36%)	54/145 (37%)	-1.4	(-12.5-9.7)	0.23
Receiving	7/25 (28%)	14/30 (47%)	-18.7	(-43.7-6.4)	
Received >24 hours of β-lactam within 72 hours of randomisation					
No	24/61 (39%)	36/73 (49%)	-10.0	(-26.8-6.8)	0.34
Yes	35/109 (32%)	32/102 (31%)	0.7	(-11.8-13.3)	
Complicated bacteremia[b]					
No	8/45 (18%)	10/43 (23%)	-5.5	(-22.3-11.4)	0.72
Yes	51/125 (41%)	58/132 (44%)	-3.1	(-15.2-8.9)	
Country of recruitment					
Australia/New Zealand	37/120 (31%)	43/125 (34%)	-3.6	(-15.3-8.2)	
Singapore	8/28 (29%)	13/28 (46%)	-17.9	(-42.8-7.1)	0.38
Israel	14/22 (64%)	12/22 (55%)	9.1	(-19.8-38.0)	
Baseline immunosuppression[c]					
No	54/153 (35%)	62/158 (39%)	-3.9	(-14.7-6.8)	0.90
Yes	5/17 (29%)	6/17 (35%)	-5.9	(-37.3-25.5)	
Endocarditis affecting the left side of the heart[d]					
No	53/159 (33%)	64/166 (39%)	-5.2	(-15.6-5.2)	0.50
Yes	6/11 (55%)	4/9 (44%)	10.1	(-33.7-53.9)	
Origin of MRSA infection					
Community-associated	17/65 (26%)	17/56 (30%)	-4.2	(-20.3-11.9)	0.85
Healthcare-associated	42/105 (40%)	51/119 (43%)	-2.9	(-15.8-10.1)	

Subgroup Analysis	Primary outcome, No./Total No. (%)				Risk difference, %	95% CI	*P* value for interaction
	Combination		Standard				
Vancomycin MIC of primary isolate[d]							
≤ 1.0µg/mL	57/162	(35%)	65/167	(39%)	-4.2	(-15.2-6.8)	0.72
≥ 2.0µg/ml	2/8	(25%)	3/8	(38%)	-12.5	(-57.5-32.5)	

a. The backbone drug is considered the drug for which the patient received the majority of doses in the first seven days following randomization (i.e., if they received both vancomycin and daptomycin, then it will typically be the drug received for ≥4 days).
b. Episodes were considered complicated unless all the following criteria for uncomplicated SAB defined as per IDSA guidelines were satisfied: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection.
c. Baseline immunosuppression is defined as participants receiving any of: Prednisone >0.5mg/kg/day for >14 days or the equivalent; Any immunosuppressive drugs for organ transplant; Any cancer chemotherapy; Any immunosuppressive biologic agent; Any other drug known to increase the risk of opportunistic infection.
d. The pre-specified subgroups in the protocol were vancomycin MIC <1.5µg/mL and ≥1.5µg/mL. As the broth microdilution assay used at the central reference laboratory determines the MIC in 2-fold dilutions, results obtained were for MICs in integer values starting at 1µg/mL. Therefore, the subgroups now used are ≤ 1.0µg/mL and ≥ 2.0µg/ml.

eTable 5: Reported Adverse Events Thought to Be Related to Study Drugs (Vancomycin, Daptomycin or β-Lactam)

	Standard N=178	**Combination N=174**
Acute kidney injury	1	13
Rash	4	9
Diarrhea	-	2
Raised liver enzymes	-	1
Thrombocytopenia	2	-
Thrombophlebitis	1	-
Drug fever	-	1
TOTAL with at least one adverse event	7	23

eTable 6: Reported Serious Adverse Events in the Combination Therapy Arm

Nature of serious adverse event	Suspected culprit drug	Relationship to culprit drug	Outcome at day 90
Acute kidney injury	Flucloxacillin	Possible	Recovered
Acute kidney injury	Flucloxacillin	Possible	Recovered
Acute kidney injury	Flucloxacillin	Possible	Recovered
Acute kidney injury	Flucloxacillin	Possible	Partially recovered
Seizure	Cloxacillin	Probable	Recovered

eTable 7: Occurrence of Acute Kidney Injury as Defined Using Modified Kidney Disease Improving Global Outcomes (KDIGO) Criteria[a]

	Combination therapy (n=145)[b]	Standard therapy (n=145)[b]
Acute Kidney Injury		
None	109 (75%)	132 (91%)
Stage 1	18 (12%)	8 (6%)
Stage 2	7 (5%)	3 (2%)
Stage 3	11 (8%)	2 (1%)

a. Acute kidney injury is defined using modified Kidney Disease Improving Global Outcomes (KDIGO) criteria: Stage 1 is serum creatinine 1.5-1.9 times baseline in the first 7 days OR ≥26.5 µmol/l increase from baseline in the first 48 hours; Stage 2 is serum creatinine 2.0-2.9 times baseline in the first 7 days; Stage 3 is serum creatinine ≥3.0 times baseline in the first 7 days OR ≥353.6 µmol/l increase from baseline in the first 48 hours OR new initiation of renal replacement therapy within 90 days. Urine output criteria have not been included as data on urine output was not collected.

b. There were 5 patients in the combination therapy group and 11 in the standard therapy group that did not have a baseline creatinine, but could still qualify for Stage 3 AKI if they required renal replacement therapy.

eTable 8: Characteristics of Patients in the Combination Treatment Group Who Received Only Flucloxacillin or Cloxacillin and Who Only Received Cefazolin, Excluding Those on Dialysis at Baseline[a]

Characteristic	Cefazolin only (n=27)		Flucloxacillin or cloxacillin only (n=111)	
Age, median (IQR), y	69	(59-80)	63	(48-74)
Male	16	(59%)	84	(76%)
Country				
Australia / New Zealand	13	(48%)	90	(81%)
Singapore	4	(15%)	13	(12%)
Israel	10	(37%)	8	(7%)
Acquisition[b]				
Nosocomial acquisition	11	(41%)	39	(35%)
Health-care Associated Infection	22	(81%)	65	(59%)
Time from index blood culture to randomization, median (IQR), d	2	(1-2)	2	(1-2)
Charlson comorbidity index, median (IQR)[c]	6	(4-7)	4	(2-7)
Pitt bacteremia score, median (IQR)[d]	2	(2-3)	2	(2-3)
SOFA score, median (IQR)[e]	2	(0-4)	1	(0-2)
Indwelling vascular device	12	(44%)	59	(53%)
Indwelling prosthetic valve or cardiac device	3	(11%)	13	(12%)
Other intravascular foreign material	0	(0%)	6	(5%)
Recognized infection foci at time of index blood culture				
Skin and soft tissue infection	3	(11%)	32	(29%)
Primary blood stream infection	4	(15%)	24	(22%)
Native Osteoarticular	7	(26%)	22	(20%)
Intravenous line related	3	(11%)	9	(8%)
Pleuropulmonary infection	3	(11%)	8	(7%)
Device-related	1	(4%)	6	(5%)
Infective endocarditis	0	(0%)	6	(5%)
Other	6	(22%)	4	(4%)
Final diagnosis of infective endocarditis[f]	2	(7%)	16	(14%)
Any antibiotic in 72h preceding randomization	24	(89%)	110	(99%)
Any β-lactam in 72h preceding randomization	14	(27%)	77	(69%)
Drugs affecting renal function in 48h preceding randomization[g]	14	(52%)	64	(58%)
Baseline creatinine, median (IQR), mg/dL[h]	1.93	(0.8-3.0)	0.95	(0.7-1.4)
Baseline c-reactive protein, median (IQR), mg/L	173	(80-230)	170	(110-270)
Received vancomycin[i]	27	(100%)	109	(98%)
Received daptomycin[i]	3	(11%)	8	(7%)
Trough vancomycin level at D1, mean (SD), µg/mL	16.9	(12.6)	14.1	(7.2)
Trough vancomycin level at D2, mean (SD), µg/mL	19.5	(10.3)	17.4	(8.9)
Trough vancomycin level at D3, mean (SD), µg/mL	18.9	(7.0)	20.3	(8.0)
Received any non-study antibiotic during D1-7	11	(41%)	34	(31%)
Infectious diseases consultation	27	(100%)	108	(97%)

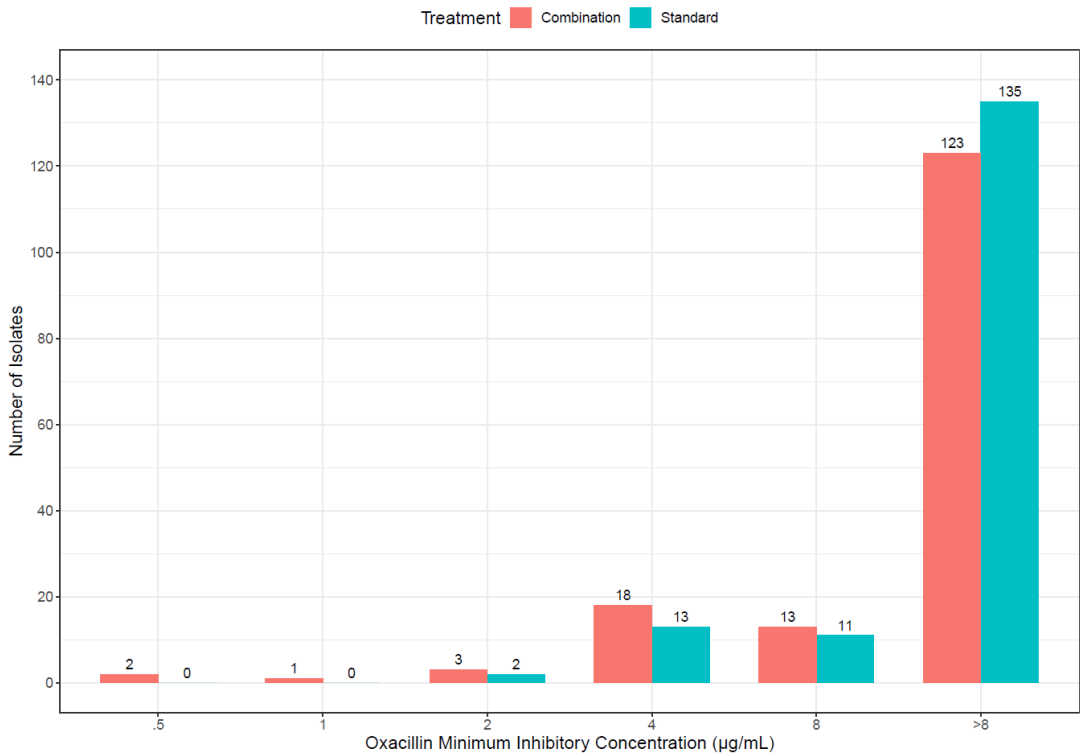
Characteristic	Cefazolin only (n=27)		Flucloxacillin or cloxacillin only (n=111)	
Infected source removed	10/13	(77%)	48/67	(72%)
Time to removal of infected source, median (IQR), d[j]	-0.5	(-2.0-2.0)	1.0	(-1.0-2.0)
Multilocus sequence type[k]				
ST22	5/23	(22%)	21/103	(20%)
ST93	3/23	(13%)	14/103	(14%)
ST45	5/23	(22%)	10/103	(10%)
ST5	4/23	(17%)	15/103	(15%)
ST239	1/23	(4%)	5/103	(5%)
ST1	0/23	(0%)	5/103	(5%)
ST30	0/23	(0%)	4/103	(4%)
Other	5/23	(22%)	29/103	(28%)
Vancomycin MIC[k,l]				
≤1 µg/mL	23/23	(100%)	97/103	(94%)
2 µg/mL	0/23	(0%)	6/103	(6%)

Abbreviations: IQR, interquartile range; SOFA, sequential organ failure assessment score; SD, standard deviation; ST, sequence type; MIC, minimum inhibitory concentration.

a. Data are expressed as No. (%) of participants unless otherwise indicated. The denominator for each cell is 23 for the cefazolin only and 111 for the flucloxacillin or cloxacillin only columns unless otherwise indicated.
b. Nosocomial acquisition if the patient had been an inpatient for >48 hours at the time of index blood culture collection. Health-care associated if the patient had been any of: admitted to hospital in the home in the past 30 days, >48 hours in hospital in the past 90 days, received outpatient chemotherapy in the past 30 days, lived in a residential care facility.
c. Provides a 10-year mortality risk, based on weighted comorbid conditions, ranging from 0 to 29, with a score of 4 associated with an estimated 10-year survival of 53%.
d. Provides a measure of in-hospital mortality risk in patients with bloodstream infections based on clinical variables, ranging from 0 to 14, with a Pitt score ≥4 associated with a risk of mortality of approximately 40%.
e. Provides a mortality prediction score based on the degree of dysfunction of six organ systems, ranging from 0 to 24, with a SOFA score of 6-7 associated with a risk of mortality of approximately 20%. The SOFA score was based on the worst recorded parameters in the 24 hours preceding randomization.
f. The final diagnosis of infective endocarditis was defined by modified Duke criteria. Numbers differ from those recognised with infective endocarditis at baseline as further investigations will have been performed
g. Drugs affecting renal function included: radiocontrast dye, amphotericin B, loop diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin 2 receptor blockers, non-steroidal anti-inflammatories, aminoglycosides, calcineurin inhibitors
h. To convert from conventional units (mg/dL) to Système International units (µmol/L) multiply by 88.4. The baseline creatinine was the worst creatinine measure in the 24 hours preceding randomization.
i. Some patients may have received both vancomycin and daptomycin during their time on the study.
j. The source may have been removed prior to randomization with days prior to randomization counted as a negative number of days.

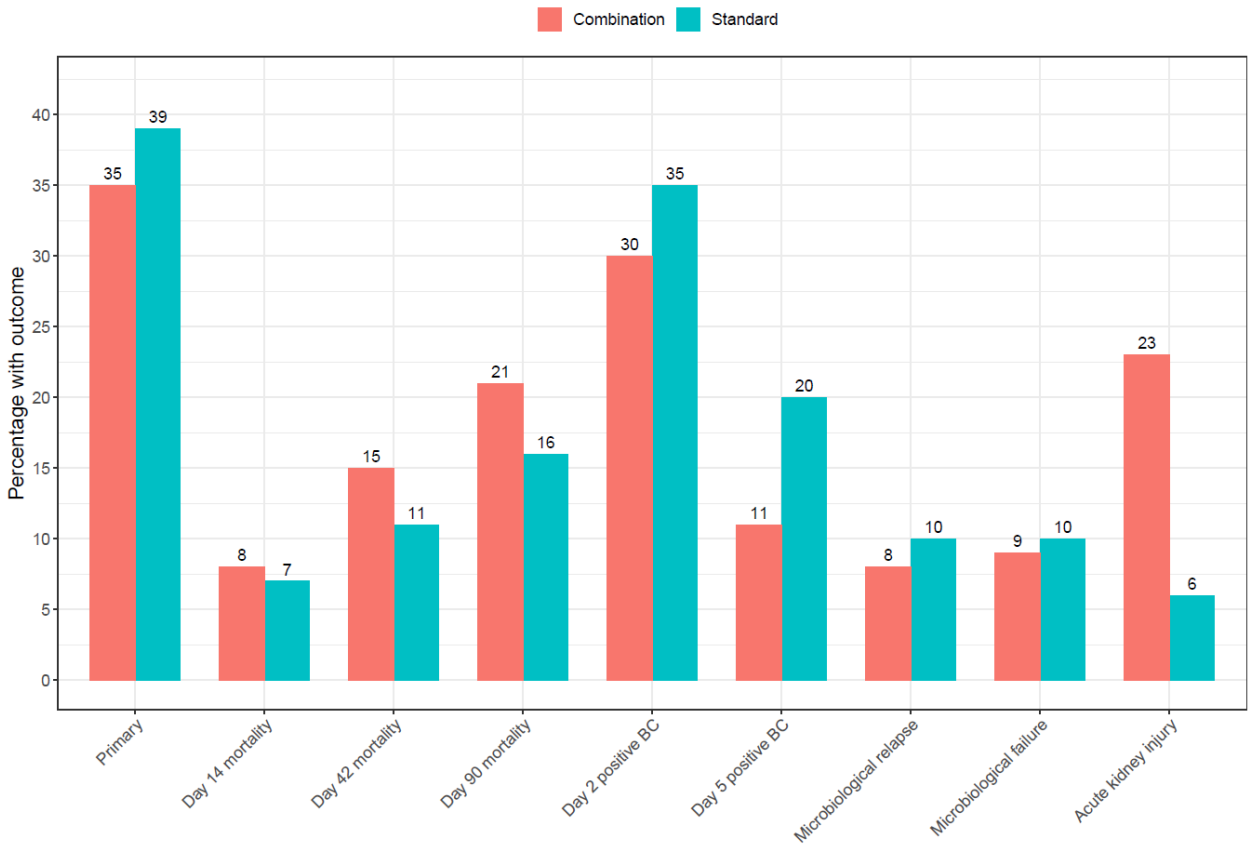
k. There were 126 isolates recovered for genotyping and determination of vancomycin minimum inhibitory concentration.
l. The pre-specified subgroups in the protocol were vancomycin MIC <1.5µg/mL and ≥1.5µg/mL. As the broth microdilution assay used at the central reference laboratory determines the MIC in 2-fold dilutions, results obtained were for MICs in integer values starting at 1µg/mL. Therefore, the subgroups now used are ≤ 1.0µg/mL and ≥ 2.0µg/ml.

eFigure 1: Distribution of Oxacillin Minimum Inhibitory Concentrations (MIC, µg/mL) by Treatment Allocation as Determined by a Central Laboratory Using Broth Microdilution



The following were phenotypically determined to be oxacillin susceptible: Two isolates were found to have an oxacillin minimum inhibitory concentration (MIC) of 0.5 µg/mL and for both of these, *mecA* was not detected. One isolate had an MIC of 1 µg/mL, and was *mecA* positive. Five isolates had an MIC of 2 µg/mL, and were *mecA* positive.

eFigure 2: Primary and Secondary Outcomes for the Primary Analysis Population, as Percentages of Participants Meeting Those Outcomes by Allocated Treatment Group



The primary outcome was a composite of Day 90 mortality, persistent bacteremia at Day 5 or beyond, microbiological relapse and failure. Numerator and denominators for each column can be found in Table 3.

eFigure 3: Forest Plot of Absolute Difference in Treatment Effect by Pre-specified Subgroups for the Primary Outcome

Definitions for subgroups are provided in eTable 4.