Healthcare Improvement Scotland | SAPG Safeguarding antibiotics

Evidence and economic review: Comparison of flucloxacillin and cefazolin in methicillin-sensitive *Staphylococcus Aureus* (MSSA) bacteraemia

Cefazolin clinical effectiveness and economic evaluation report

May 2026

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Evidence review and recommendation summary	
Population	Adults with Methicillin-sensitive *staphylococcus aureus* (MSSA) bacteraemia
Intervention	Form: Intravenous (IV) cefazolin Dose: 2 g three times daily (TDS) Higher dose not required for patients with obesity (1) IV antimicrobial therapy continues for 14 days after clearance of bacteraemia*
Comparator	Form: Intravenous (IV) flucloxacillin Dose: 2 g four times daily (QDS) – for patients less than 85 kg Dose 2 g six times daily for patients over 85 kg IV antimicrobial therapy continues for 14 days after clearance of bacteraemia*
Outcomes	Clinical efficacy, safety and cost evaluation
Findings	Cefazolin was non-inferior to flucloxacillin or cloxacillin for the clinical efficacy outcomes of all-cause mortality at 90 days, therapeutic success and survival at day 90. Patients treated with cefazolin reported fewer serious adverse events and lower acute kidney injury (AKI) rates compared to flucloxacillin or cloxacillin. Cost comparisons showed that cefazolin will increase the net medicines cost in patients with MSSA bacteraemia when compared with flucloxacillin. However, when considering the cost of administration and treatment of AKIs, cefazolin is expected to result in cost savings.
Recommendation	Scottish Antimicrobial Prescribing Group (SAPG) Committee endorse cefazolin as first-line antibiotic in the treatment of adults with MSSA bacteraemia SAPG *Staphylococcus aureus* bacteraemia (SAB) quality of care indicators to be updated to reflect change.

* Economic evaluation based on 14 days antibiotic treatment

Overview

Cefazolin is a first-generation cephalosporin, recently reclassified as an Access category (first-line) agent as per WHO AwARe category. Cefazolin has good activity against methicillin-sensitive *Staphylococcus aureus* (MSSA).

In Scotland, flucloxacillin is currently the first-line antibiotic recommended for treating MSSA bacteraemia, however flucloxacillin is associated with increased risk of acute kidney injury (AKI). For this reason, SAPG reviewed switching from flucloxacillin to cefazolin in MSSA bacteraemia guidance. This publication reports findings from the clinical evidence review and economic evaluation which were completed to assess the practicality and appropriateness of the proposed switch.

1. Introduction

The Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) Scotland Annual Report identified 1,715 cases of *Staphylococcus aureus* bacteraemia in Scotland in 2024, with 1,654 of these cases identified to be MSSA bacteraemia (SAB) (2). Notably, 37.7% of SAB cases were in female patients and 51.1% were in individuals aged 65 and over.

SAPG *Staphylococcus aureus* bacteraemia (SAB) quality of care indicators (3) currently recommend intravenous (IV) flucloxacillin for treating MSSA bacteraemia in patients without a penicillin allergy. The suggested dosage is 8 g daily (divided into four doses) for patients under 85 kg and 12 g daily (divided into six doses) for patients over 85 kg.

Renal impairment is a well recognised side effect of flucloxacillin, and national surgical prophylaxis policy was changed in Scotland in 2012 (4) following identification of increased post-operative AKI in orthopaedic patients. The policy at that time changed from recommending flucloxacillin and gentamicin to co-amoxiclav in this group of patients to reduce AKI.

Emerging evidence suggests that cefazolin is non-inferior to flucloxacillin in treating MSSA bacteraemia but with a significant reduction in AKI.

There is no published international consensus guideline on the optimal first-line treatment of MSSA bacteraemia. If recommendations were to be extrapolated from native valve MSSA infective endocarditis guidelines, then the European Society of Cardiology recommends cefazolin and (flu)cloxacillin as first-line therapy for methicillin-sensitive native valve *S. aureus* infective endocarditis in Europe (5).

A review of the clinical evidence and an economic assessment has been completed to assess the clinical and economic impact of switching from flucloxacillin to cefazolin in MSSA SABs.

2. Evidence review approach

With support from the Research and Information Service (RIS), SAPG completed three reviews to identify clinical and economic evidence that would guide decisions on the proposed switch from flucloxacillin to cefazolin. Relevant evidence sources were searched in September 2025. Searches were re-run in April 2026 and no additional evidence was identified.

a. Clinical evidence review (focus on Medline, Embase and Cochrane databases)

b. Grey literature search and summary (including unpublished work or published through non-commercial channels, including pre-prints, conference proceedings, unpublished manuscripts)

c. Economic evaluation

3. Clinical evidence review summary

3.1. Clinical efficacy evidence

Three clinical efficacy studies were identified from the database and grey literature searches.

1. Prosty et al, 2025 (6): A systematic literature review and meta-analysis
2. The Staphylococcus aureus Network Adaptive Platform (SNAP) trial abstract (2025) (7): A multicentre, pragmatic, multi-arm, open-label adaptive platform trial
3. Burdet et al, 2025 (8): A prospective, open-label, multicentre, non-inferiority, randomised clinical trial

Summary of findings

3.1.1. Prosty et al, 2025 (6)

The Prosty et al., 2025 study is a systematic review and meta-analysis that compared cefazolin with anti-staphylococcal penicillins (ASPs) in patients with MSSA bacteraemia. This study currently provides the most comprehensive and up-to-date synthesis of evidence available and includes studies that are directly relevant to this review. Although other systematic reviews were identified during the literature search, none matched the methodological quality or scope of the Prosty et al, 2025 study.

The Prosty et al study screened 263 records and included 30 studies that were published between 2011 to 2024 in 10 high-income countries. The studies included were observational studies and were all assessed as having moderate or high risk of confounding bias based on the Cochrane Risk of Bias in Non-Randomised Studies I (ROBINS-I) tool. A total of 3,869 patients received cefazolin and 11,644 received ASPs. Flucloxacillin was the most administered ASP (N= 6,721, 4 studies).

The primary outcome was **30-day all-cause mortality** assessed for non-inferiority using pre-specified non-inferiority margin of a pooled Odds Ratio (OR) <1.2. This threshold was for the upper limit of the 95% CI of the OR for cefazolin versus the ASPs. The secondary outcome for clinical efficacy was **90-day all-cause mortality**.

Cefazolin was associated with a reduced odds of **30-day all-cause mortality** (OR = 0.73, 95% CI: 0.62–0.85, I^2 (heterogeneity between studies) = 0%, 16 studies, low-certainty evidence) compared with ASPs. Results remained in favour of cefazolin when cefazolin was compared with individual ASPs, however the differences were not statistically significant, including the difference between cefazolin and flucloxacillin (10.6% [92/865] versus 11.3% [752/6665], OR = 0.92, 95% CI: 0.73–1.16, I^2= 0%, 3 studies). Cefazolin therefore met the pre-specified margin for non-inferiority compared with ASPs as a group and with flucloxacillin as an individual ASP.

The **90-day all-cause mortality** results were in favour of cefazolin and point estimates met the pre-specified non-inferiority margin (17.1% [359/2,097] versus 24.1% [801/3,318], OR= 0.80, 95% CI: 0.61-1.05, 14 studies, I^2 = 29%, very low-certainty evidence). Results were consistently in favour of cefazolin when compared with the individual ASPs, however the differences were not statistically significant, including the difference between cefazolin and flucloxacillin (OR= 0.77, 95% CI: 0.13-4.40, I^2= 0%, 2 studies).

Conclusion: In this meta-analysis based on observational studies, cefazolin met the pre-specified non-inferiority standards in 30 day and 90 day all-cause mortality compared with ASPs.

3.1.2. The Staphylococcus aureus Network Adaptive Platform (SNAP) trial (7)

This trial included adults across 92 sites in eight countries including the UK. An abstract from the trial was presented at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) global conference in 2025. The full results from the trial are not yet published.

Within the SNAP trial, participants with MSSA were assigned to receive (flu)cloxacillin (ie. flucloxacillin or cloxacillin) or cefazolin. The primary outcome was **90-day all-cause mortality**.

Enrolment started in February 2022, was paused in June 2024 because of an excess of AKI cases in the (flu)cloxacillin group and was closed in August 2024 after the non-inferiority criterion was achieved.

1,341 adults were enrolled, 671 were randomised to the cefazolin group and 670 to the (flu)cloxacillin group. 90-day all-cause mortality was 15.0% (97/645) in the cefazolin group and 17.0% (109/642) in the (flu)cloxacillin group, adjusted OR=0.81, 95% Credible Interval (CrI) 0.59–1.12, P non-inferiority of cefazolin=0.992, P superiority of cefazolin= 0.898.

Conclusion: Cefazolin is non-inferior to (flu)cloxacillin for 90-day all-cause mortality in adults with MSSA bacteraemia.

3.1.3. Burdet et al, 2025 (8)

This open-label, non-inferiority, randomised controlled trial (RCT) was conducted across in 21 hospitals in France. Adults aged 18 years or over with MSSA bacteraemia were randomly assigned (1:1) to receive either IV cefazolin (25–50 mg/kg every 8 h) or cloxacillin (25–50 mg/kg every 4–6 h) for the first 7 days of treatment. Antibiotic treatment was given for at least 14 days, however subsequent treatment given to the participant after the first 7 days was left to the choice of the investigator. A non-inferiority margin of 12% was chosen for the primary and secondary efficacy outcomes. Non-inferiority of cefazolin over cloxacillin was based on the lower limit of the 95% CI of the difference of proportions of participants who met each outcome.

315 participants were randomised, 23 were excluded from the analysis (12 from the cefazolin group and 11 from the cloxacillin group), and 146 participants were included in the intention to treat analysis in each group (146 in the cefazolin group and 146 in the cloxacillin group). The mean age of participants was 62.7 years, and 215 (74%) participants were male. The mean duration of treatment with study-assigned antibiotic was 12.9 days (standard deviation [SD] 8.2) in the cefazolin group and 11.6 days (SD 6.5) in the cloxacillin group. Following randomisation, the mean total duration of antibiotic treatment was 27.4 days (SD 19.6) in the cefazolin group and 27.0 days (SD 19.5) in the cloxacillin group.

The primary endpoint of **therapeutic success** was met in 109/146 (75%) participants in the cefazolin group versus 108/146 (74%) participants in the cloxacillin group (treatment difference –1%; 95% CI –11 to 9, p-value 0.012). In addition, the secondary efficacy outcome of **survival rate at day 90** was met in 134/146 (91.8%) participants in the cefazolin group versus 134/146 (91.8%) in the cloxacillin group (treatment difference 0%; 95% CI –7 to 7, p-value 0.0005).

The paper reported that at day 8, only 68% and 57% in the cefazolin and cloxacillin groups, respectively, received their allocated treatments exclusively. However, the study did not assess if this had any impact on the outcomes of interest.

Conclusion: In adults with MSSA bacteraemia, cefazolin was non-inferior to cloxacillin for therapeutic success and survival at day 90.

A summary of the clinical results from the 3 studies is provided in table 2.

Table 2: Clinical efficacy results

Study	Outcome	No. of studies (no. of patients)	Odds ratio (95% CI)	Summary
Prosty et al, 2025 (6) Critically appraised as high quality paper.	30-day all-cause mortality	16 (11,969)	OR= 0.73, 95% CI: 0.62 to 0.85, I^2 = 0%, 16 studies, low-certainty evidence. Favoured cefazolin compared with ASPs as a group. Cefazolin met the pre-specified margin for non-inferiority (of OR <1.2 for the upper bound of the 95% CI) compared with ASPs as a group. Favoured cefazolin compared with individual ASPs but differences were not statistically significant. For example, difference between cefazolin and flucloxacillin was OR = 0.92, 95% CI: 0.73–1.16, I^2 = 0%, 3 studies. Cefazolin met the pre-specified margin non-inferiority (of OR <1.2 for the upper bound of the 95% CI) compared with flucloxacillin.	Lower odds of all-cause mortality at 30 days for cefazolin compared with ASPs. Cefazolin non-inferior to ASPs group and non-inferior to flucloxacillin for all-cause mortality at 30 days.
	90-day all-cause mortality	14 (5,415)	OR= 0.8, 95% CI= 0.61 to 1.05, I^2=29%, 14 studies, very low-certainty evidence. Favoured cefazolin compared with ASPs as a group and met the pre-specified non-inferiority margin. Favoured cefazolin compared with individual ASPs, but difference was not statistically significant. Difference between cefazolin and flucloxacillin was OR= 0.77, 95% CI: 0.13-4.40, I^2 = 0%, 2 studies.	Cefazolin non-inferior to ASPs for all-cause mortality at 90 days.

Study	Outcome	No. of studies (no. of patients)	Odds ratio (95% CI)	Summary
SNAP trial group, 2025 (7) Critically appraised as uncertain quality as full text not available.	90-day all-cause mortality	1 (1,287)	97/645 (15.0%) in the cefazolin group versus 109/642 (17.0%) in the (flu)cloxacillin group. aOR=0.81, 95% credible interval 0.59-1.12, P non-inferiority of cefazolin = 0.992, P superiority of cefazolin = 0.898.	Cefazolin non-inferior to (flu)cloxacillin.
Burdet et al, 2025 (8) Critically appraised as acceptable quality paper.	Therapeutic success	1 (292)	109/146 (74.7%) in cefazolin group versus 108/146 (74.0%) in the cloxacillin group, treatment difference –1%; 95% CI –11 to 9, p-value* = 0.012.	Cefazolin non-inferior to cloxacillin.
	Survival at day 90	1 (292)	134/146 (91.8%) in cefazolin versus 134/146 (91.8%) in cloxacillin, treatment difference 0%; 95% CI –7 to 7, p-value* = 0.0005.	Cefazolin non-inferior to cloxacillin.

*In Burdet et al, 2025 study, p values for clinical efficacy outcomes refer to test for non-inferiority of cefazolin over cloxacillin; p values for safety outcomes refer to test for superiority. Non-inferiority margin was based on the lower limit of the 95% CI of the difference of proportions of participants who met each outcome.

3.2. Safety evidence

3.2.1. The Prosty et al, 2025 (6)

The systematic review and meta-analysis also evaluated safety outcomes that included treatment-related adverse events (TRAEs), discontinuation due to toxicity and nephrotoxicity. These were assessed as secondary outcomes.

Cefazolin was associated with a reduced odds of TRAEs compared with ASPs (11.0% [116/1052] versus 23.5% [412/1755], OR= 0.33, 95% CI: 0.18-0.63, I^2 = 75.8%, 14 studies, low-certainty evidence). Subgroup analysis did not compare cefazolin with flucloxacillin because flucloxacillin studies did not report TRAEs.

Discontinuation due to toxicity was lower in the cefazolin group compared with ASPs (2.1% [14/669] versus 16.8% [142/843], OR = 0.13, 95% CI: 0.06–0.27, I^2= 20.4%, 10 studies, high-certainty evidence). In subgroup analysis, only one flucloxacillin study reported on discontinuation due to toxicity. Compared with flucloxacillin, the result favoured cefazolin but the difference was not statistically significant.

Nephrotoxicity was lower in the cefazolin group when compared with ASPs (4.4% [48/1103] versus 13.7% [205/1498], OR= 0.30, 95% CI: 0.20-0.46, I^2 =13.6%, 13 studies, moderate-certainty evidence). Subgroup analysis for nephrotoxicity did not compare cefazolin with flucloxacillin.

Conclusion: Point estimates favoured cefazolin over ASPs for TRAEs, discontinuation due to toxicity and nephrotoxicity.

3.2.2. The SNAP trial (7)

The SNAP trial reported **AKI** of 14.0% (92/659) in the cefazolin group and 19.7% (127/646) in the (flu)cloxacillin group (aOR 0.67; 95% CrI 0.50–0.90; P superiority 0.997).

Conclusion: In adults with MSSA bacteraemia, cefazolin was associated with less AKI risks compared with (flu)cloxacillin.

3.2.3. Burdet et al, 2025 (8)

Safety outcomes reported included serious adverse events, AKI and *C. difficile* infection. P values for safety outcomes refer to test of superiority.

By the end of study treatment, **serious adverse events of any type** were reported in 22/146 (15%) in the cefazolin group versus 40/146 (27%) in the cloxacillin group (treatment difference –12%; –22 to –3; p=0·01).

AKI in the cloxacillin group was significantly more frequent compared with the cefazolin group. At day 7, AKI occurred in 1/134 (1%) of participants in the cefazolin group versus 15/128 (12%) participants in the cloxacillin group (treatment difference –11%; –18 to –6; p=0·0002). By the end of the study treatment, AKI occurred in 4/111 (4%) in the cefazolin group versus 17/99 (17%) in the cloxacillin group (treatment difference -13%; -23 to -6, p= 0.0008).

***C. difficile* infection** occurred in 3/146 (2%) in cefazolin group versus 3/146 (2%) in the cloxacillin group (treatment difference 0%; –4 to 4; p>0·99).

Conclusion: In adults with MSSA bacteraemia, cefazolin was associated with lower serious adverse events and AKI rates compared with cloxacillin. *C. difficile* infection rates were the same in both cefazolin and cloxacillin groups.

A summary of the safety results from the 3 studies is provided in table 3.

Table 3: Safety results

Study	Outcome	No. of studies (no. of patients)	Odds ratio (95% CI)	Summary
Prosty et al, 2025 (6) Critically appraised as high quality paper.	Treatment related adverse events (TRAE)	14 (2,807)	OR= 0.33, 95% CI= 0.18 to 0.63, I^2= 75.8%, 14 studies, low-certainty evidence. Favoured cefazolin compared with ASPs group. Subgroup analysis did not compare cefazolin with flucloxacillin.	Lower rates of TRAEs in cefazolin group compared with ASPs.
	Discontinuation due to toxicity	10 (1,512)	OR= 0.13, 95% CI= 0.06 to 0.27, I^2= 20.4%, 10 studies, high-certainty evidence. Favoured cefazolin compared with ASPs. One flucloxacillin study reported on this outcome. Result favoured cefazolin but difference was not statistically significant.	Lower discontinuations due to toxicity in cefazolin group compared with ASPs.
	Nephrotoxicity	13 (2,601)	OR= 0.30, 95% CI= 0.20 to 0.46. I^2= 13.6%, 13 studies, moderate-certainty evidence. Favoured cefazolin compared with ASPs. Subgroup analysis did not compare cefazolin with flucloxacillin.	Lower rates of nephrotoxicity in cefazolin group compared with ASPs.
SNAP trial group, 2025 (7)	AKI	1 (1,305)	AKI occurred in 14.0% (92/659) in cefazolin group versus 19.7% (127/646) in the (flu)cloxacillin group (aOR 0.67; 95% CrI 0.50–0.90; P superiority 0.997).	Lower AKI rates in cefazolin group compared with (flu)cloxacillin group.

Study	Outcome	No. of studies (no. of patients)	Odds ratio (95% CI)	Summary
Critically appraised as uncertain quality as full text not available.				
Burdet et al, 2025 (8) Critically appraised as acceptable quality paper.	Serious adverse events	1 (292)	By the end of study treatment, 22/146 (15%) in cefazolin group versus 40/146 (27%) in cloxacillin group (treatment difference –12%; –22 to –3; p=0·01*).	Fewer serious adverse events in cefazolin group versus cloxacillin group.
	AKI	1 (292)	At day 7, 1/134 (1%) in cefazolin group versus 15/128 (12%) in cloxacillin group (treatment difference –11%; –18 to –6; p=0·0002*) By the end of the study treatment, 4/111 (4%) in cefazolin group versus 17/99 (17%) in cloxacillin group (treatment difference -13%; -23 to -6, p= 0.0008*).	Lower AKI rates in cefazolin group versus cloxacillin group.
	C. difficile infection	1 (262)	3/146 (2%) in cefazolin group versus 3/146 (2%) in cloxacillin group (treatment difference 0%; –4 to 4; p>0·99*).	*C. difficile* infection rates the same in both cefazolin and cloxacillin groups.

*In Burdet et al, 2025 study, p values for clinical efficacy outcomes refer to test for non-inferiority of cefazolin over cloxacillin; p values for safety outcomes refer to test for superiority. Non-inferiority margin was set at 12% based on the lower limit of the 95% CI of the difference of proportions of participants who met each outcome.

3.2.4. Clinical benefit-risk balance

In patients with MSSA bacteraemia, cefazolin was found to be non-inferior to (flu)cloxacillin for all-cause mortality at 90 days. Cefazolin was also non-inferior to cloxacillin for therapeutic success and survival at day 90.

The cefazolin group reported fewer serious adverse events compared with the cloxacillin group, and lower AKI rates compared with (flu)cloxacillin. Reduction in AKI, reported in the SNAP trial as a 5.7% reduction, will mean less morbidity, reduced treatment costs and reduced length of stay. Lastly, *C. difficile* infection rates were the same in both cefazolin and cloxacillin groups.

4. Economic evidence review summary

4.1. Type of economic evaluation

No relevant published economic analysis was identified in the literature search. Prosty et al 2025 (6) and the SNAP study (7) demonstrated non-inferior mortality outcomes for cefazolin compared with flucloxacillin in the treatment of MSSA bacteraemia. Given there were no published economic evaluations and based on the non-inferiority conclusions of the studies, a de-novo cost-comparison was performed.

4.2. Population, intervention, comparator and outcomes

The participant population consisted of patients with MSSA SAB. The intervention was cefazolin 2 g three times daily (TDS) and the comparator was flucloxacillin 2 g four times daily (QDS). As a cost-comparison analysis was performed, quality-adjusted life-years were not included in the analysis.

4.3. Costs

The cost-comparison included acquisition costs, administration costs and costs associated with AKI.

The list price of cefazolin was £183.90 per 10-pack of 2 g vials (British National Formulary (BNF), April 2026). The national framework contract price of cefazolin is commercial in confidence (CIC).

The list price of flucloxacillin was £34.50 per 10-pack of 1 g vials (BNF, April 2026). The national framework price of flucloxacillin is CIC.

The duration of treatment applied for each treatment was 14 days based on SAPG quality of care indicators.

Administration costs were defined in three components. Firstly, Band 5 nursing time for an IV administration was included, estimated at 22 minutes per dose. The Band 5 nurse costs were sourced from the Unit Costs of Health and Social Care 2024, a standard staffing cost source in Scottish Medicines Consortium (SMC) guidance, with 22 minutes per IV administration from Jenkins 2023 (9). Secondly, the cost of a set of consumables per dose was included. Finally, IV administration costs were estimated using NHS reference costs (2023/2024) for chemotherapy delivery (10), a standard cost source in SMC guidance. However, as these costs are defined per day and were identical for both the cefazolin and flucloxacillin treatment arms, they were ultimately excluded from the cost-comparison analysis as they had no impact on the results.

The costs associated with AKI were estimated using a cost sourced from the NHS reference costs based on the lowest level of AKI complexity (£4,817) (11) as a conservative assumption. The AKI

rates for cefazolin and flucloxacillin were sourced from the SNAP study (7) of 14% for cefazolin and 19.7% for flucloxacillin.

4.4. Results

All results in the cost-comparison exclude VAT. The base case results are shown in the table below. Confidential NHS Scotland medicine pricing agreements were considered in decision making. SAPG is unable to publish the results using national framework pricing as they are CIC.

Table 4: Base case results (list prices, British National Formulary (BNF) April 2026)

Medicine	Med acquisition costs	Administration cost components		Admin. total costs	AKIs	Total	Incremental cost of cefazolin versus flucloxacillin
		Band 5 nurse time	Consumables				
Cefazolin	£772	£724	£47	£770	£674	£2,217	-£145
Flucloxacillin	£386	£965	£62	£1,027	£949	£2,363	

Abbreviations: AKI = acute kidney injury; Incr = incremental.
Prices have been rounded to the nearest pound

Table 5: Base case results (national framework commercial in confidence prices)

Medicine	Med acquisition costs (£)	Administration cost components		Admin. total costs	AKIs	Total	Incremental cost of cefazolin versus flucloxacillin
		Band 5 nurse time	Consumables				
Cefazolin	CIC	£724	£47	£770	£674	CIC	Cost-saving
Flucloxacillin	CIC	£965	£62	£1,027	£949	CIC	

Abbreviations: AKI = acute kidney injury; CIC = commercial in confidence; Incr = incremental.
Prices have been rounded to the nearest pound

Using list prices, cefazolin was associated with cost savings of £145 compared with flucloxacillin. Using national framework CIC prices, cefazolin was associated with cost savings versus flucloxacillin.

To understand uncertainty in the cost-comparison analysis, a series of scenarios were considered. Each row represents a scenario in which a single parameter is varied to assess its impact on the base case results.

Table 6: Scenario analysis

#	Parameter	Base case	Scenario	Incremental cost of cefazolin versus flucloxacillin (national framework CIC pricing)	Incremental cost of cefazolin versus flucloxacillin (list)
	Base case			Cost-saving	-£145
1	Band 5 nursing time for IV administration	22 minutes per dose	12 minutes per dose	Cost-saving	-£36
2	AKI cost	NHS reference costs (2023/2024) for AKI for the lowest level of complexity (£4,817)	NHS reference costs (2023/2024) for AKI for the highest level of complexity (£7,756)	Cost-saving	-£313
3	AKI	Included in the cost-comparison	Excluded from the cost-comparison	Cost-saving	£129
4	Flucloxacillin dosing	2 g four times daily	2 g six times daily	Cost-saving	-£339

Abbreviations: AKI = acute kidney injury; CIC= commercial in confidence; IV = intravenous. Prices have been rounded to the nearest pound

5. Cost-effectiveness considerations

Generalisability of the cost-comparison

NHS Scotland national framework and confidential prices were considered in confidence to increase the generalisability of the net costs.

Limitations

The mean duration of nursing time for an IV administration varied in the literature between 12 and 22 minutes per dose (9, 12). Therefore, a scenario was considered applying the shorter Band 5 nursing time for an IV administration of 12 minutes per dose (Scenario 1). In this scenario cefazolin generated cost savings using national framework CIC pricing.

There were limitations of including AKI in the cost-comparison analysis. NHS reference costs (2023/2024) do not provide granular definitions for different levels of AKI complexity. Therefore, the base case used the minimum reported cost associated with the lowest level of AKI complexity, a conservative assumption. To understand this parameter uncertainty, a scenario considered the maximum reported cost for the highest level of AKI complexity (Scenario 2). In this scenario cefazolin generated cost savings under national framework CIC pricing. In addition, it is uncertain whether the AKI rates reported in SNAP are applicable to the 14-day treatment period of the costing analysis, or if these would be realised over a longer period. To consider this uncertainty, a conservative scenario excluded AKI entirely from the cost-comparison analysis (Scenario 3). In this scenario cefazolin generated cost savings under national framework CIC pricing.

Due to an absence of a cost-utility analysis, the cost-comparison analysis only compared costs, with no consideration of the potential difference in benefits associated with the two treatments. However, the SNAP study noted AKI rates were lower in the cefazolin group and found a favourable point estimate for 90-day-all-cause mortality (OR=0.81, 95% CrI 0.59–1.12). The 90-day-all-cause mortality point estimate was also in favour of cefazolin in Prosty et al 2025 (OR= 0.77, 95% CI: 0.13-4.40). Although the 90-day all-cause mortality in these studies was not statistically significant, the favourable point estimates and the reduction in AKI may indicate improved health outcomes for patients that are not captured in the cost-comparison.

The base case dosing of flucloxacillin was 2 g QDS. As patients over 85 kg receive flucloxacillin 2 g six times daily, this was considered in a scenario analysis (Scenario 4). In this scenario cefazolin generated cost savings under national framework CIC pricing.

Band 5 nursing time was sourced from the Unit Costs of Health and Social Care 2024. Whilst a component of these costs are based on NHS England pay scales, reducing generalisability to NHS Scotland, this is a standard staffing cost source in SMC guidance that reflects the full economic costs of employing staff in the NHS.

The analysis focused on three key cost areas, medicine acquisition, IV administration and AKIs. The implementation costs of training, protocol updates and stock management, were not explicitly reflected in this analysis.

6. Budget impact

Patient uptake

The number of patients expected to be treated with cefazolin was estimated to be 1,656 per year in Scotland. The figure was from the ARHAI Annual Report 2023-2024 (2). Discontinuation and mortality rates were assumed to not be included.

Per patient medicine cost and treatment duration

These prices include VAT.

The list price of cefazolin was £220.68 per 10-pack of 2 g vials (BNF, April 2026). The national framework price of cefazolin is CIC.

The list price of flucloxacillin was £41.40 per 10-pack of 1 g vials (BNF, April 2026). The national framework price of flucloxacillin is CIC.

The duration of treatment applied for each treatment was 14 days based on the SAPG quality of care indicators.

Comparator displacement

It was assumed that the introduction of cefazolin would displace 100% of flucloxacillin in the proposed patient population.

Results

All figures in the budget impact include VAT. The budget impact results include medicine acquisition costs only. Confidential NHS Scotland medicine pricing agreements were considered in decision making. SAPG is unable to publish the results using national framework pricing because of CIC pricing contracts.

Table 7: Budget impact results

	List prices	National framework CIC pricing
Acquisition cost		
Cefazolin is 2 g TDS (3x)	£927	CIC
Flucloxacillin is 2 g QDS (4x)	£464	CIC
Budget impact		
Number of patients treated	1656	1,656

	List prices	National framework CIC pricing
Budget impact - net medicine costs (difference of the two multiplied by patient count)	£767,019	Cost-increasing

Abbreviations: CIC = commercial in confidence; TDS = three times daily; QDS = four times daily. Prices have been rounded to the nearest pound.

Using list prices, the net medicines budget impact was estimated to be £767,019, based on an uptake of 1,656 patients. Based on the national framework CIC prices, the net medicines budget impact was cost-increasing.

7. Summary

Based on the national framework CIC pricing, the use of cefazolin will increase the net medicines cost for this patient group when compared with flucloxacillin. However, when considering the cost of administration and AKIs, cefazolin is expected to result in cost savings.

SAPG considered CIC NHS Scotland medicine pricing agreements in decision making. SAPG is unable to publish resulting using confidential pricing because of CIC issues.

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8. Appendix

8.1. Appendix 1: Search strategy

a. Clinical and economic evidence database search

- **Medline and Embase. first search 17/09/2025 and updated 20/04/2026**

This stem search was combined with a reviews filter, a guidelines filter and an economics filter for other aspects of the key questions.

1 *cefazolin/ (8469)
2 cefazolin.tw. (8619)
3 or/1-2 (13747)
4 (anti-staphylococcal adj penicillin$).tw. (83)
5 *oxacillin/ (4924)
6 oxacillin.tw. (7268)
7 *cloxacillin/ (3742)
8 cloxacillin.tw. (2558)
9 *dicloxacillin/ (1648)
10 dicloxacillin.tw. (816)
11 *flucloxacillin/ (2033)
12 flucloxacillin.tw. (1929)
13 *nafcillin/ (2002)
14 nafcillin.tw. (1012)
15 or/4-14 (20881)
16 3 and 15 (1782)
17 *Staphylococcus aureus/ (45781)
18 "staphylococcus aureus".tw. (171938)
19 or/17-18 (182393)
20 3 and 15 and 19 (600)
21 limit 20 to english language (522)

- **Cochrane, first search 16/09/2025 and updated 20/04/2026**

ID	Search	Hits
#1	cefazolin	1436
#2	oxacillin	186
#3	cloxacillin	274

#4 dicloxacillin 134
#5 flucloxacillin 266
#6 nafcillin 70
#7 (2-#6) 752
#8 MeSH descriptor: [Staphylococcus aureus] this term only 864
#9 staphylococcus aureus 4451
#10 (4-#9) 4451
#11 #1 and #7 and #10 52 (20 revs, 31 trials)

b. Grey literature search, first search 17/09/2025 and updated 20/04/2026

Database: Embase <1974 to 2025 September 15>

1 "SNAP Trial".mp. (52)

2 "NCT05137119".tw. (5)

3 "Staphylococcus aureus Network Adaptive Platform".tw. (15)

4 or/1-3 (53)

8.2. Appendix 2: Quality Appraisal

- The Scottish Intercollegiate Guidelines Network (SIGN) checklist for systematic reviews and meta-analyses was used to critically appraise the Prosty et al, 2025 paper and the methodological quality of this review was assessed as high. It was a well conducted systematic review with a clearly defined research question and comprehensive literature searches. The included studies were relevant, and their scientific quality and risk of bias were assessed.

  The Prosty et al, 2025 review also completed GRADE evaluation to assess the certainty of evidence for the efficacy and safety outcomes. For efficacy outcomes, the evidence for 30-day mortality and 90-day mortality were assessed as low-certainty and very low-certainty respectively. For safety outcomes, the evidence for TRAEs, nephrotoxicity, and discontinuation due to toxicity were reported as low-certainty, moderate-certainty, and high-certainty respectively. However, we query the high-certainty evidence given to the discontinuation due to toxicity outcome. This is because of the very serious risk of bias associated with the studies in the review, assessed using the Cochrane Risk of Bias tool for non-randomised studies.

- The Authority, Accuracy, Coverage, Objectivity, Date and Significance checklist was used to critically appraise the SNAP trial abstract. The methodological quality of this evidence was assessed as uncertain as it did not include study aims, information to assess adherence to study protocol, data collection processes and evidence of peer review. However, the SNAP

trial protocol (14) was very detailed and included information on the trial aims, outcomes of interest and data collection processes.

- The SIGN methodology checklist for controlled trials was used to appraise the quality of the Burdet et al, 2025 RCT and the methodological quality of the study was assessed as acceptable. This is because the processes of randomisation, allocation concealment and data analysis were well documented. However, there is uncertainty in the conclusions reached because at day 8, only 68% and 57% in the cefazolin and cloxacillin groups (respectively) received their allocated treatments exclusively. This raises concern as to whether the effects seen can be truly attributed to the treatment received.

8.3. Appendix 3: Clinical effectiveness considerations

- The population in the Prosty et al 2025 study did not include the UK, but included participants from USA (15 out of 30 studies), Europe including France, Spain, and Germany (7 studies), South Korea (2 studies), Australia and New Zealand (2 studies), Singapore (2 studies), Canada (1 study) and Isreal (1 study). All study participants had MSSA bacteraemia and had received treatment with either cefazolin or an ASP. The population in this study was predominantly male (67.1%), which is comparable to the 62.3% male SAB cases in Scotland. In addition, the mean or median ages in the Prosty et al, 2025 study ranged from 50 to 71 years. Mean or median ages for Scotland were not reported in the ARHAI Scotland report for 2024, however, the report stated that 51.1% of SAB cases in Scotland were aged 65 years and over.
- Participants in the SNAP trial were recruited from 92 sites in eight countries, including the UK. All participants had *staphylococcus aureus* bacteraemia, and those with MSSA were treated with cefazolin or (flu)cloxacillin.
- Participants in the Burdet et al 2025 study were adults hospitalised in France hospitals. Participants had MSSA bacteraemia and were assigned to receive either cefazolin or cloxacillin treatment. The population in this study was predominantly male (73%), and mean age of participants was 62.7 years.

8.4. Appendix 4: Table of abbreviations

Abbreviation	Definition
AKI	Acute kidney injury
ARHAI	Antimicrobial resistance and healthcare associated infection
ASP	Anti-staphylococcal penicillins
BNF	British national formulary
CIC	Commercial in confidence
ESCMID	European society of clinical microbiology and infectious diseases
MSSA	Methicillin-sensitive staphylococcus aureus
OR	Odds ratio
QDS	Four times daily
RCT	Randomised controlled trial
SAB	Staphylococcus aureus bacteraemia
SAPG	Scottish antimicrobial prescribing group
SNAP	Staphylococcus aureus network adaptive platform
TDS	Three times daily
TRAE	Treatment-related adverse events

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