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Cefazolin as second line treatment for invasive Methicillin-susceptible Staphylococcus aureus infection in a UK cohort of patients

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Corresponding Author:	Nicola Jones, MB BS Oxford University Hospitals NHS Foundation Trust Oxford, UNITED KINGDOM
First Author:	Bernadette C Young
Order of Authors:	Bernadette C Young
	Louise Dunsmure
	Louise Downs
	Kornelija Kildonaviciute
	Nicola Jones, MB BS
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Bernadette C Young,[a,b] Louise Dunsmure,[c] Louise Downs,[a] Kornelija Kildonaviciute,[c] Nicola Jones [a]

Affiliations:

[a] Microbiology and Infectious Diseases Department, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford OX3 9DU, UK
[b] Nuffield Department of Medicine, Experimental Medicine Division, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
c Antimicrobial Pharmacy, Department of Pharmacy, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford OX3 9DU, UK

Corresponding author: Nicola Jones

Nuffield Department of Medicine, Experimental Medicine Division, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
Nicola.jones@ouh.nhs.uk +44 1865 221918

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Dear Editor,

Worldwide, cefazolin is one of the most commonly used antibiotics, as revealed in a recent article in this Journal,[1] but until recently has had limited availability in the United Kingdom. We became interested in using cefazolin in the treatment of invasive Methicillin-susceptible Staphylococcus aureus (MSSA) infections, particularly bloodstream infections (BSI). Accumulating evidence suggests cefazolin is better tolerated than anti-staphylococcal penicillins(e.g. flucloxacillin, nafcillin, oxacillin),[2,3] equally efficacious in the treatment of BSI due to MSSA,[4,,5] and may improve outcomes in MSSA BSI.[6,7] We submitted a successful application to our local therapeutics committee for use of cefazolin as an unlicensed agent.

We applied to use cefazolin as treatment for invasive MSSA infections (MSSA cultured from blood culture or deep-seated focus) for patients with documented penicillin allergy, or developing adverse effects on anti-staphylococcal penicillin (ASP). Patients with MRSA infection, a history of anaphylaxis or immediate hypersensitivity to penicillin or cephalosporin allergy were excluded. We started using cefazolin in January 2018. Summary of product characteristics were variable, particularly regarding renal dosing, we therefore followed published guidelines for dosing in renal impairment (Table 1).[8,9] We followed our Trust's procedure for the use of unlicensed and off-label medicines.

We have undertaken a retrospective audit of all cefazolin treatment in our acute hospital trust between 01/1/2018 and 01/11/2020. Electronic patient records were reviewed for all patients prescribed cefazolin. Over this time 79 patients received at least one dose of cefazolin. Most (50/79, 63%) were male. Patient ages ranged from 17 to 95 years of age (median 70 years, IQR 52-80).

The most frequent indication for antibiotics was invasive MSSA infection (n=75), including MSSA-BSI without deep focus (n=17), MSSA-BSI with endovascular infection (n=22), MSSA-BSI with another deep focus of infection (n=30), invasive MSSA infection without BSI (n=6). Deep foci included septic arthritis, vertebral discitis, epidural abscess, psoas abscess, respiratory tract infection and soft tissue infection (Figure 1A). Cefazolin was also used four further patients, one with endocarditis caused by Staphylococcus lugdunensis, as procedural prophylaxis, for cellulitis and for BSI later confirmed as MRSA. These latter three cases were reviewed for adverse events only.

Duration of cefazolin treatment ranged from 1-42 days (median 13 days, IQR 6-21). The indications for selecting cefazolin were: documented penicillin allergy (27/76, 35%), development of adverse reaction to ASP (36/76, 48%), and to facilitate outpatient parenteral antibiotic therapy (OPAT) (6/76, 7.9%) (Figure 1B). Seven patients received cefazolin for indications outwith guidelines, being assessed as at increased risk of harm from penicillin-related nephrotoxicity due to acute kidney injury (n=6), and to broaden antimicrobial spectrum in polymicrobial infection (n=1).

In 75/76 patients, (98.7%) cefazolin was the second or subsequent antibiotic treatment. Treatment regimens used prior to use of cefazolin included flucloxacillin (n=41), vancomycin or teicoplanin (n=42), ceftriaxone (n=28), co-amoxiclav, (n=25), and others (gentamicin, meropenem, ertapenem, clindamycin, daptomycin)).

In 45/72 patients (62.5%) intravenous therapy was completed with cefazolin (information about final therapy was incomplete for 4 patients transferred to other inpatient trusts), with 27/72 (37.5%) patients switched to another intravenous agent. Therapy was changed to facilitate OPAT with a once daily agent (n=11, 15%), to broaden antimicrobial treatment for an intercurrent infection (n=6, 8%), or because

cefazolin was not indicated on review (n = 4, 5.6%). Interruption to cefazolin supply led to substitution of another suitable agent in 2/72 (2.8%). Treatment was only stopped due to adverse events in 2/72 (2.8%), detailed further below. Subsequent intravenous treatment options included ceftriaxone (n=17), flucloxacillin (n=7), and others (piperacillin/tazobactam, ceftazidime, dalbavancin, daptomycin, tigecycline, meropenem). Oral conversion at the end of intravenous treatment was not reviewed.

We reviewed documented adverse effects in all 79 patients receiving any dose of cefazolin. Adverse effects were recorded in 5/79 (6.3%). Two patients (2/79, 2.5%) reported diarrhoea, not resulting in changed therapy. Cefazolin was discontinued due to adverse effects in 3/79 (3.8%) patients due to hypersensitivity with (rash) (n=1), Clostridoides difficile infection (CDI) (n=1), and drug induced liver injury (n=1), which developed during flucloxacillin therapy and progressed on treatment with cefazolin. All patients with suspected adverse drug reactions on cefazolin recovered from these reactions. There were no additional cases of CDI within 90 days of cefazolin treatment. No patients with reported penicillin allergy developed symptoms of hypersensitivity to cefazolin. While electronic records may under-report side effects, it is notable that 48% of this cohort experienced significant adverse effects necessitating discontinuation of ASP, while only 3.8% of patients required a change of therapy due to adverse effects on cefazolin. In this cohort, two patients developed CDI prior to cefazolin, while only one case of CDI was observed after receiving a dose of cefazolin. No concerning signal of excess CDI was seen in this group.

Outcomes recorded were inpatient mortality, survival to 30 days after diagnosis, and readmission within 30 days of discharge. Thirteen (13/76, 17%) patients died in hospital during the admission with invasive MSSA infection. Data on survival to 30 days from diagnosis of infection was available in 74 patients, of whom 13/74 (17.6%) died

within 30 days of diagnosis. Among patients surviving to discharge, 13/63 (20.6%) were readmitted within 30 days. Of these 4/63 (6.3%) were re-admitted with relapse or recurrence of MSSA infection.

These outcomes compare favourably with a recent cohort of 1459 UK S. aureus BSI cases, reporting 30-day mortality of 22.2%.[10] Our lower observed mortality might be attributed to selection effect: patients with early mortality may not receive cefazolin, which was usually a second-line treatment. However, most patients in this cohort had complicated MSSA-BSI with endovascular infection or deep foci of infection, which are associated with poorer outcomes.[10] Frequent re-admissions may reflect the age and medical comorbidity of the cohort, because the low rate of early re-admission with recurrent infection suggests treatment failure was not common in this cohort.

In our setting, cefazolin is an effective, well-tolerated agent for patients with invasive MSSA infection and non-severe penicillin hypersensitivity or experiencing adverse effects with ASP. Further evidence to assess the comparative clinical efficacy is urgently needed. Other UK institutions should consider adding cefazolin to their armamentarium for treatment of MMSA infections.

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Figures and Table

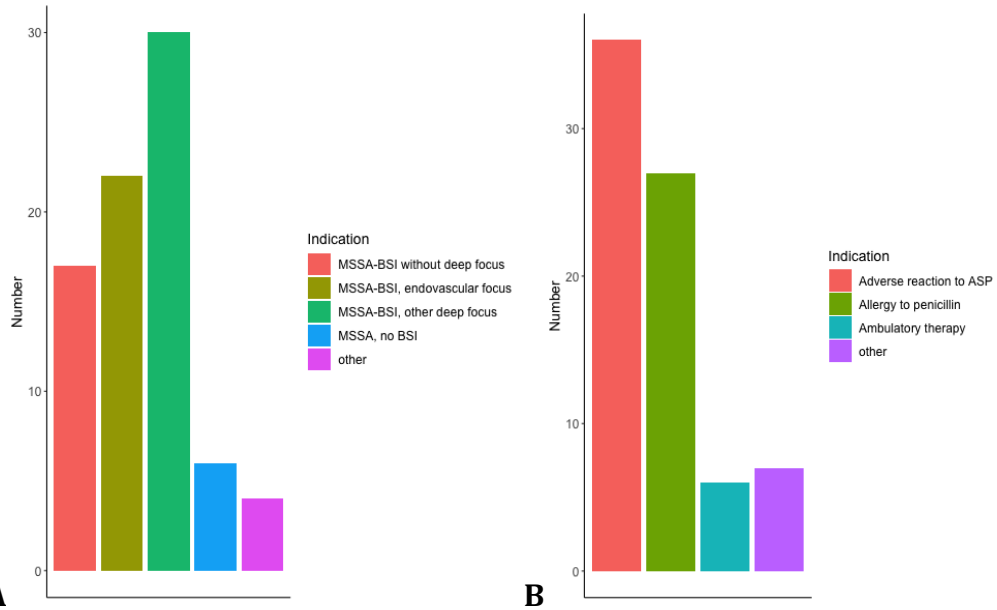

Figure 1 Use of cefazolin in adults from 2018-2020 in an acute hospital trust in the UK. 1a) Infections for antibiotics in patients receiving cefazolin 1b) Indication for cefazolin as agent of choice. (MSSA – Methicillin-susceptible S. aureus, BSI – bloodstream infection, ASP – anti-staphylococcal penicillin)

Creatinine clearance (ml/min)	**Dose of cefazolin**
50 or more	2g every 8 hours
10-50	1g - -2g every 12 hours*
less than 10	1g every 24 hours
Haemodialysis	1g daily or dose after each dialysis session, according to number of days between sessions. E.g. Mon-Wed-Fri dialysis is 2g-2g-3g

Table 1: Dosing regimens of cefazolin for invasive MSSA infections.

*In patients with creatinine clearance 10-50/min, 12 hourly dosing was selected to facilitate ambulation and OPAT.