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Twice daily cefazolin is effective for treatment of serious methicillin-sensitive *Staphylococcus aureus* infection in an outpatient parenteral antimicrobial therapy program

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Abstract

Background: The use of cefazolin for infections caused by *Staphylococcus aureus* has been demonstrated to be effective, and associated with fewer adverse effects compared with anti-staphylocccal penicillins; however, use of cefazolin on outpatient parenteral antimicrobial therapy (OPAT) programs often requires the use of continuous infusions. We report the outcomes of patients with serious infections caused by methicillin-sensitive *S. aureus* (MSSA) treated using twice daily cefazolin by a large tertiary hospital OPAT program. The aim of this study was to evaluate the safety, efficacy and outcomes after 90 days of follow up for patients with serious infections caused by MSSA treated with twice daily cefazolin by our OPAT program.

Methods: A retrospective analysis of clinical outcomes of cases treated for a serious infection proven to be caused by MSSA treated with cefazolin monotherapy on the OPAT program at a tertiary hospital between January 2010 and July 2016 (6.5 years). Outcome measures included readmission rate, adverse drug reactions and clinical cure.

Results: A total of 111 cases of serious MSSA infection were treated with cefazolin in the OPAT service during the study period, including 52 with peripheral or vertebral osteomyelitis and 13 with infective endocarditis; 56 patients had bacteraemia. Median duration of intravenous antibiotic therapy was 41 days, and the median proportion of intravenous therapy administered *via* OPAT was 69%. Two patients had recurrence of infection within 90 days, but were in the setting of retained prosthetic material. A total of 4% of patients experienced an adverse drug reaction. No cases of antibiotic failure were identified.

Conclusions: The use of twice daily cefazolin for serious MSSA infection on an OPAT program is safe and effective. Further study is needed to assess for noninferiority to conventional treatment regimes.

Keywords: antimicrobial stewardship, cefazolin, OPAT, sepsis, *Staphylococcus aureus*

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Introduction

Methicillin-sensitive *Staphylococcus aureus* (MSSA) is a pathogen that causes significant infection in both the community and hospitals, accounting for a significant proportion of presentations with community-acquired sepsis, and is a major cause of infection-related morbidity and mortality.[1–3]

Historically, anti-staphylococcal penicillins such as flucloxacillin, nafcillin or oxacillin have been the treatment of choice for methicillin-sensitive staphylococcus[4–6]; however, a recent study has identified that using cefazolin for MSSA infections in hospital-based therapy may lead to a lower risk of mortality, as well as a significant decrease in adverse effects.[7]

Similar findings have also been seen in a large outpatient-based study, which found increased rates of premature antimicrobial discontinuation as well as drug-emergent events when using naficillin in preference to cefazolin.[8] This study utilised a 2 g every 8 h dosing schedule for cefazolin; however, this is not practical for all outpatient parenteral antimicrobial therapy (OPAT) programs.

Many different delivery models have been described worldwide for OPAT programs, including treatment being delivered in an infusion centre, patients self-administering their medications, or administration in a patient's home by a visiting nurse or medical practitioner,[9] which is the predominant model used in Australia. This home-based model has been shown to lead to both high patient satisfaction as well as a significantly lower cost to the health care system.[10,11]

In an OPAT program that requires staff to visit patients at home, cefazolin's usual 8-h dosing is not practical due to a requirement for sufficient nursing staff to administer therapy, and limitations regarding staffing availability. Cefazolin can be administered by continuous infusion or intermittently dosed *via* a pump; however, this requires a patient to carry a pump or infuser, which may limit their ability to perform their activities of daily living, or return to work. Additionally, the use of continuous infusion has been shown to be associated with frequent adverse effects.[12] Our centre has for many years utilised a dosing schedule of up to 3 g of cefazolin every 12 h for patients when being treated by the OPAT service, however, the safety and equivalence of this dosing schedule has not been previously validated.

The objective of this retrospective single-centre observational study was to assess the clinical outcomes in using a 12-h dosing schedule of cefazolin after initial clinical improvement to the point that a patient can be safely managed in the community, for invasive MSSA infection in the OPAT setting.

Methods

This study was performed at Alfred Health, a 638-bed tertiary medical service for adults in Melbourne, Australia.

The Alfred Health 'Hospital in the Home' program was established in 1995 and provides community-based therapy for patients who no longer require hospital admission but are prescribed specific therapy that is not able to be provided by outpatient-based services. This program includes an OPAT service, as well as management of numerous other conditions such as acute wound management and management of anticoagulation. At any one time there are approximately 60–70 patients being managed under the 'Hospital in the Home' program for a variety of indications. All antibiotics are administered through peripherally inserted silastic central catheters. Patients receiving antibiotics on the OPAT program were reviewed at least weekly by the infectious diseases unit.

Cases were identified through the use of the Alfred Health Hospital in the Home database. All patients admitted to the Alfred Health OPAT program from 1 January 2010 until 31 July 2016 with a positive culture result demonstrating MSSA, without the presence of other organisms, were identified and screened for inclusion. Patients were included if they received definitive therapy with cefazolin on the OPAT program, and had an invasive infection due to MSSA, defined as any infection other than cellulitis or bursitis. Definitive antimicrobial therapy was defined as the antimicrobial agent that was prescribed in hospital after 72 h of therapy, when susceptibility results were available. Patients were excluded if they had another organism isolated on culture, received any other antimicrobial as part of their OPAT therapy, or received part of their care during the definitive antimicrobial therapy at an alternative health service. The primary source of infection was determined by concurrent microbiologic specimens positive for MSSA from the clinically suspected site of infection.

Cases received treatment with intermittent dose cefazolin while they were managed *via* OPAT. Patients who weighed 80 kg or more received a dose of 3 g twice daily, whereas those who weighed less than 80 kg were treated with 2 g twice daily. These doses were subsequently adjusted for patients with significantly impaired renal function, defined as a creatinine clearance of 40 ml per minute or less, with dosage reduced according to the product information.

Data was collated retrospectively by a single researcher. After identification, the case records from that episode of care were assessed, and data including indication for treatment, choice of

antimicrobial and dates of therapy and of readmission, were collected. Readmissions to Alfred Health were noted within 90 days of completion of the entire antimicrobial course, including any oral agents given.

The primary outcome was treatment success, defined as completing the antimicrobial regimen without premature discontinuation or change of therapy, and without treatment relapse or recurrence within 90 days of ceasing antibiotics. Secondary outcomes included complications observed whilst being treated *via* OPAT, readmission rates and adverse drug reactions. Given the retrospective nature of the study, adverse drug reactions were defined by a need to either change the antimicrobial, or by an increased frequency of monitoring, either by clinical assessment or pathology tests.

Continuous variables are presented as median and interquartile range. Categorical variables are presented as number and percentage of total.

The study was approved by the Alfred Health Ethics Committee (Project 350/17).

Results

The Alfred Health Hospital in the Home database identified 11451 patients who were treated during the period of 1 January 2010 and 31 July 2016. After excluding patients receiving treatment for noninfective diagnoses and those with infections either with an alternative causative organism or no organism identified, as well as excluding two patients who received part of their definitive antimicrobial therapy at an alternative health service, a total of 111 patients met all criteria for inclusion.

The median age at time of hospitalisation was 61 years (IQR 44–77 years), with 80 (72%) males. 107 cases lived in private homes, with the remainder in forms of supported accommodation. The median Charlson Comorbidity Index for the included patients was 3 (IQR 0–5). Baseline characteristics are listed in Table 1.

Sites of infection

The most common site of infection was peripheral osteomyelitis (32%), followed by infective endocarditis/endovascular infection (11%) and vertebral osteomyelitis (10%). 46% of cases had a positive blood culture for MSSA; 20% of these cases (9% of the total cohort) had no other identifiable site of infection, and 41% of patients had any prosthetic material *in situ* at the time of infection.

Antibiotic use

A majority of cases (50.5%) received flucloxacillin as directed therapy in hospital, rather than cefazolin (37%) or any other agent (13%). Only 1 case reported an allergy to an alternative cephalosporin; 21 cases (19% of cohort) had an allergy to any beta-lactam antibiotic (Table 2). The median duration of antimicrobial therapy received in hospital before transfer to the OPAT program was 9 days (IQR 6–14 days).

Upon transfer to the OPAT service, 65% were treated with 3 g twice daily of cefazolin, 29% were treated with 2 g twice daily, and the remainder had reduced doses in the setting of decreased renal function. The median total duration of intravenous therapy was 41 days (IQR 25–45 days), with 69% of this administered *via* the OPAT program following discharge from hospital (IQR 50–82%). Many patients (59%) received follow-up oral antibiotics after completing the intravenous proportion of therapy; the median total duration of antibiotics was 46 days (IQR 35–81 days).

Treatment outcomes

A total of 96.4% of patients were able to complete the prescribed antibiotic course without evidence of relapsed or recurrent infection within 90 days of completing their antimicrobial course (Table 3).

A total of 16 patients (14%) were identified to have complications while receiving cefazolin on the OPAT program (Table 4). The most common complication was an adverse drug reaction, in four cases (Rash ×2, neutropaenia, itch) with therapy changed as a result in only two cases. No patients developed clinically significant renal impairment or liver derangement. There were no deaths whilst being treated by the OPAT program.

There were 16 patients (13%) who were readmitted to an Alfred Health inpatient ward from the OPAT program whilst on cefazolin (Table 4); the

Table 1. Baseline demographics.

Number	111
Age (years)	61 (IQR 44–77)
Male gender	80 (72%)
Location of OPAT care	
Home	107 (96%)
Aged care facility	2 (2%)
Other	2 (2%)
Primary infection site	
Peripheral osteomyelitis	36 (32%)
Infective endocarditis/endovascular	12 (11%)[a]
Vertebral osteomyelitis	11 (10%)[b]
Unknown	10 (9%)
Line-related	10 (9%)
Skin/soft tissue	7 (6%)
Septic arthritis	7 (6%)
Epidural abscess	5 (5%)
Intra-abdominal/pelvis	4 (4%)
Other	9 (8%)
Positive blood culture	51 (46%)
Charlson comorbidity index	3 (IQR 0–5)

[a]Includes one patient with prosthetic valve endocarditis, and two patients with prosthetic endovascular graft infections.
[b]Three patients had vertebral metalware *in situ* at the time of infection; Eight patients had native tissue only.
IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy.

most common reason was for management of an acute medical condition not related to their infection (four cases). One case managed for infective endocarditis required readmission from the OPAT service for heart failure in the setting of a failing mitral valve. This patient proceeded to have a mitral valve replacement; however, blood cultures at the time of readmission and tissue culture of the valve were negative. Given these results, it was not felt that this case reflected antibiotic failure. No patients were admitted to alternative health facilities during their OPAT treatment period.

Of the 20 patients (17%) who required readmission within 90 days of completing their antimicrobial course (Table 4), 11 were for management of another medical condition, and 2 were identified to be related to a relapse of infection in the setting of retained prosthetic material. Of these, one case was initially managed for a bacteraemia with no known source of infection, and was later found to have an infected femoral artery graft; the other was for a patient that was initially treated for a pacemaker pocket infection, and had recurrent bacteraemia with pacemaker lead infection. Given that both cases were felt to have relapsed due to retained infected prosthetic material, neither was felt to reflect antibiotic failure.

High-risk subgroups

Of the 12 patients with infective endocarditis/endovascular infection, 9 were infections of native valves, 1 case had prosthetic valve endocarditis, and there were 2 cases of vascular graft infections. Only two cases of native valve endocarditis and the two vascular graft infections underwent planned surgical management; the remainder were treated with antibiotic therapy alone. As already detailed, one of the cases of native valve endocarditis required emergent valve replacement whilst being treated by the OPAT program after developing heart failure from mitral regurgitation; however the other cases were able to complete their treatment as planned and achieved treatment success.

On subgroup analysis of the 11 patients with vertebral osteomyelitis, 3 had vertebral prosthetic material *in situ* at the time of diagnosis, and 8 had native tissue only. The one patient with prosthetic material and two patients with native tissue only underwent surgical debridement; an additional case with prosthetic material had their prosthetic material removed and underwent additional debridement. The remaining cases were managed with antibiotic therapy alone. All patients were able to complete their treatment as planned with resolution of infection.

Discussion

This descriptive study evaluates a group of patients treated for invasive MSSA infection with twice daily dosing of cefazolin through an OPAT program. We found that 96.4% of patients had

cure of infection at 90 days, with no clearly demonstrable cases of antibiotic failure, and a low rate of adverse drug reaction (3.6%) in this cohort. Of the two cases of recurrent infection, retained prosthetic material was thought to be the cause of relapse, although the patient with recurrent pacemaker lead endocarditis received only a short duration of treatment (4 days) before transfer to the OPAT service, and this may be a contributing factor.

These findings are compatible with previous studies that have used cefazolin for OPAT therapy using a conventional 8-h dosing schedule,[8] that reported a 6.7% rate of premature antibiotic discontinuation when using cefazolin.

Given a usual duration of intravenous therapy of 2–6 weeks for invasive staphylococcal aureus infection,[4,6] OPAT services provide a crucial service to allow home-based care, which in turn can decrease overall cost of treatment,[11,13,14] as well as decreased mortality and higher levels of patient and carer satisfaction.[10,15] Previous studies have established a high degree of clinical success for patients who traditionally require prolonged intravenous antibiotics. Large cohort studies have shown that rates of successful treatment for bone and joint infections can be as high as 86%,[13,16] and for infective endocarditis clinical cure rates of up to 94% are reported.[17] OPAT therapy is now recommended as part of routine clinical care for infective endocarditis in US, European and UK guidelines.[18–20]

Whilst continuous infusions or intermittent pump services are available as an alternative method of antibiotic administration, they have issues with malfunctioning, and previous studies have shown adverse events to be common amongst patients receiving continuous antibiotic infusions.[12] Additionally, continuous infusion therapy has not been validated as an equivalent modality of therapy for many indications for OPAT, although there is some data for its use in infective endocarditis.[21] Furthermore, an antibiotic dosing schedule that requires three or more doses in a day can have limited utility on an OPAT program if a patient is unable or unwilling to self-administer medication due to the impractical nature of visits this frequently.

This study demonstrates a high rate of clinical success in a broad patient cohort using a dosing

Table 2. Antibiotic therapy.

Initial antibiotic choice in hospital	
Flucloxacillin	56 (50%)
Cefazolin	41 (37%)
Piperacillin/Tazobactam	4 (4%)
Ticarcillin/Clavulanate	3 (3%)
Vancomycin	2 (2%)
Other	5 (5%)
Reported β-Lactam allergy	
Nil	90 (81%)
Penicillin	13 (12%)[a]
Amoxycillin/Ampicillin	3 (3%)[b]
Flucloxacillin	2 (2%)[c]
Piperacillin/Tazobactam	2 (2%)[d]
Cephalexin	1 (1%)[e]
Cefazolin dose during OPAT	
3 g twice daily	72 (65%)
2 g twice daily	32 (29%)
1.5 g twice daily	2 (2%)
1 g twice daily	2 (2%)
1 g daily	3 (3%)
Total duration of intravenous antibiotics (days)	41 (25–45)
Proportion of intravenous antibiotics delivered *via* OPAT	69% (50–82%)
Total antibiotic duration (days)	46 (35–81)

[a]Reported penicillin reaction: 9 rash, 3 unknown, 1 Drug reaction with eosinophilia and systemic symptoms.
[b]Reported amoxicillin/ampicillin reaction: 1 rash/fever, 1 rash/nausea, 1 unknown.
[c]Reported flucloxacillin reaction: 1 acute interstitial nephritis, 1 unknown.
[d]Reported piperacillin/tazobactam reaction: 1 anaphylaxis, 1 itch/rash.
[e]Reported cephalexin reaction: skin peeling.
OPAT, outpatient parenteral antimicrobial therapy.

Table 3. Treatment outcomes.

Premature antibiotic switch/discontinuation	2 (2%)
Infection recurrence within 90 days follow-up	2 (2%)[a]
Treatment success	107 (96%)

[a]Both cases in setting of retained prosthetic material.

Table 4. Complications and readmissions during OPAT.

Complications during OPAT	
Adverse drug reaction	4 (4% of patients)[a]
Fall requiring hospital assessment	3 (3%)
Clostridium difficile colitis	2 (2%)
Venous access issues	2 (2%)
Treatment failure	1 (1%)[b]
Diarrhoeal illness (other than *Clostridium difficile*)	1 (1%)
Line infection	1 (1%)
Postoperative collection	1 (1%)
Total	16 (14%)
Readmission whilst on OPAT program	
Acute medical condition (not directly related to initial infection)	4 (4% of patients)
Fall requiring hospital assessment	3 (3%)
Line related complication	2 (2%)
Medication related complication	2 (2%)
Surgical procedure; planned	2 (2%)
Surgical procedure; unplanned	1 (1%)
Postoperative complication	1 (1%)
Complication of initial infection	1 (1%)
Total	16 (14%)
Readmission within 90 days of completion of antimicrobials	
Acute medical condition (not directly related to initial infection)	11 (10%)
Elective surgical procedure	4 (4%)
Relapse of infection	2 (2%)
Clostridium difficile colitis	1 (1%)
New alternative infection	1 (1%)
Complication of previous surgery	1 (1%)
Total	20 (18%)

[a]Rash (2), neutropaenia (1), itch (1).
[b]Failure of conservative management in infective endocarditis requiring surgery; no evidence of recurrence of infection.
OPAT, outpatient parenteral antimicrobial therapy.

schedule that requires only twice daily visits, and allows patients to be independent for the rest of the day, without the need to be continuously connected to an antibiotic pump or infusion.

Strengths of this study include its large patient numbers with variable indications for treatment, and detailed interrogation of patient records. The exclusion of patients receiving any antibiotic other than cefazolin means the findings accurately represent the effect of cefazolin on cure rates. In addition, this study reflects 'real-world' treatment courses and prescribing habits in a complex patient group, providing generalisability for other centres.

This study does have a number of limitations. Firstly, it was a single-centre retrospective review of clinical data, and it is possible an observational bias exists. The information reported on was collected for clinical utility and not for research purposes. We have attempted to minimise this by having a single researcher entering and validating data, to standardise data entry. Secondly, a treatment selection bias may exist, in which some patients might have been treated with either an alternative agent, such as an antistaphylocccal penicillin, or an alternative drug delivery system such as a continuous infusion, or by pump. If present, this effect is likely minimised due to a single clinical service director of the OPAT program over this time who has advocated a consistent approach. Finally, some follow-up data may be incomplete if a patient received treatment at an alternative health service of hospital within the 90-day follow-up period, which could have an impact on the reported treatment success.

Conclusion

This single-centre retrospective observational study demonstrates a high rate of clinical success by using twice-daily cefazolin for serious MSSA infection, as part of an OPAT program. There were no demonstrable cases of antibiotic failure and a low rate of premature antimicrobial discontinuation. It could be considered as a treatment option when deciding on long-term parenteral treatment for MSSA in the OPAT setting; however, further studies using a comparator arm are needed.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Consent statement

This study was approved by the Alfred Health Ethics Committee (Project 350/17). Due to the retrospective nature of this study, individual consent from patients was not required.

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