Clinical Outcomes With Continuous Nafcillin Infusions in Children

Chad A. Knoderer, PharmD; Lauren C. Karmire, PharmD; and Kristen R. Nichols, PharmD

OBJECTIVES The primary objective of this study was to describe the clinical outcomes of continuous nafcillin infusion in pediatric patients.

METHODS This was a retrospective case study performed at a freestanding, tertiary care children's hospital. Subjects were included if they were at least 30 days old and had received more than 1 dose of nafcillin by continuous infusion (CI) between January 1, 2009, and December 31, 2012. Clinical and microbiological data were extracted from the medical record. Documented adverse events potentially associated with nafcillin were recorded. Treatment success was defined by any one of the following outcomes without the presence of conflicting data: microbiological cure, prescriber-documented treatment success, or normalization of abnormal clinical or laboratory parameters.

RESULTS Forty subjects with a median of 9 (interquartile range [IQR], 2.3–12) years of age were included. Median length of stay (in days) for all indications observed was 7 (IQR, 5–21.8) days. Extended lengths of stay, indicated by ≥ 10 days, were more common in cases of endocarditis, skin and soft tissue infection, and bacteremia. Adverse reactions were documented in 20% of patients.

CONCLUSIONS In this pediatric study, overall treatment success was observed in 92.5% of patients. Microbiological cure was documented in 91.3% of patients by using follow-up cultures. Length of stay may be positively impacted by CI nafcillin. Continuously infused nafcillin appears to be an acceptable alternative to intermittently infused nafcillin in children. Further studies are needed to address the question of whether clinical outcomes of CI nafcillin are superior to those of conventional infusion.

ABBREVIATIONS CI, continuous infusion; IQR, interquartile range; MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *Staphylococcus aureus*; PD, pharmacodynamics; PK, pharmacokinetic

KEYWORDS antibiotic; continuous infusion; methicillin-susceptible *Staphylococcus aureus*, MRSA; nafcillin

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Introduction

Nafcillin is an antistaphylococcal penicillin antibiotic frequently used in the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. Nafcillin has a very short half-life of approximately 45 minutes in children and is commonly administered as 30-minute intermittent infusions every 4–6 hours.^{1,2} Beta-lactam pharmacodynamics (PD), including those of nafcillin, are characterized by time-dependent bacterial killing. Bactericidal activity is dependent upon the percentage of time that free drug concentrations exceed the minimum inhibitory concentration ($fT > MIC$) of the pathogen.^{3–6} Efficacy is best predicted when $fT > MIC$ is at least 50% of the dosage interval for penicillin antibiotics, including nafcillin.^{3,4} Pharmacodynamic targets may not be achievable when penicillin antibiotics are given according to the recommendations found in commonly used dosage references, and this may be associated with poor clinical outcomes.^{7–9}

Use of CI and extended infusions of beta-lactams

have been reported in children and adults as a means of optimizing the pharmacokinetic (PK) and PD parameters.^{7,9–22} Continuously infused beta-lactams have been shown to attain target PD parameters and achieve clinical success in adult patients.^{16–22} Despite PK and PD justifications for using CI nafcillin in children, there is a general lack of pediatric data examining outcomes or efficacy with CI nafcillin, and this has been the reason cited for not using the dosage strategy.^{5,10,23} The objective of the present study was to describe the clinical outcomes of CI nafcillin in pediatric patients.

Materials and Methods

This was a retrospective, single-center case series of children receiving CI nafcillin. Eligible patients 30 days through 17 years of age were identified using a pharmacy computer system-generated report of patients who received more than 1 nafcillin dose while admitted to the hospital from January 1, 2009, to December 31, 2012. Patients were categorized as receiving CI nafcillin

if the total daily dose of nafcillin was administered over a minimum of 24 hours. Patients receiving nafcillin as antimicrobial prophylaxis or who received both intermittent and CI nafcillin dosage regimens were excluded.

Medical records were reviewed for demographic information, nafcillin indication and dosage information, concomitant medications, infection-attributed length of stay, and clinical and laboratory markers of infection or adverse reactions to nafcillin. Microbiological data including days and sites of positive cultures and isolated organisms were also recorded. Data were collected throughout inpatient stay while receiving nafcillin, but no data following transition to oral therapy or hospital discharge were collected. The primary outcome was treatment success defined by any 1 of the following outcomes without the presence of conflicting data: microbiological cure, prescriber-documented treatment success, or normalization of abnormal clinical or laboratory parameters. In the setting of conflicting data, for example, clearing of microbiological cultures but persistently elevated temperature, the outcome was classified as unsuccessful. Secondary outcomes included microbiological cure determined by the presence of negative follow-up cultures when obtained; infection-attributed length of stay; days to normalization of limb movement; skin appearance; erythrocyte sedimentation rate; and C-reactive protein concentration; and adverse events determined by medical record documentation or laboratory changes. Neutropenia was defined as an absolute neutrophil count less than 500 cells/ μ L. Statistical analyses were conducted using Statistical Package for Social Sciences version 19.0 software (SPSS, Inc., Chicago, IL). The study was approved by Indiana University and Butler University institutional review boards.

Results

A total of 40 patients received CI nafcillin. Baseline demographics and culture sites are summarized in Table 1. Median age of patients was 9 (interquartile range [IQR], 2.3–12) years of age, and 82.5% were male. Patients received nafcillin for a median duration of 4 (IQR, 3–12.5) days. Infection indications are displayed in Table 2. Isolated bacteremia occurred in 10% of the group ($n = 4$), although a total of 62.5% of patients ($n = 25$) were reported to have some bacteremia, either isolated or in addition to another indication. Thirty-nine patients (97.5%) had a positive culture, with MSSA (87.2%, $n = 34$) most commonly isolated, followed by coagulase-negative *Staphylococcus* species (7.7%, $n = 3$). A nutritionally deficient *Streptococcus* organism and a polymicrobial mixed growth were encountered in 1 patient each. Patients might have had more than 1 culture source of MSSA. Of the patients with MSSA infection, 58.8% of infections (20 of 34) were isolated from blood. Follow-up cultures were obtained in 23 patients with culture clearance documented in 91.3% ($n = 21$) (Table 2).

Table 1. Baseline Demographics (N = 40)

Demographics	Continuous Infusion Patients
Males, n (%)	33 (82.5)
Age (yr)*	9 (2.3–12)
Weight (kg)*	24.8 (13.4–40.6)
Empiric dose (mg/kg/day) [†]	190 $\pm$ 36.4
Therapy duration (days)*	4 (3–12.5)
Culture sites, n (%)	
Blood	18 (45)
Wound	13 (32.5)
Blood and wound	7 (17.5)
Bone	1 (2.5)
Missing information	1 (2.5)

IQR, interquartile range; LOS, length of stay; SD, standard deviation

* Values are medians (IQR).

[†] Values are means $\pm$ SD.

Criteria for treatment success was met in 92.5% of patients ($n = 37$). The 3 patients in whom treatment success was not achieved were receiving nafcillin for indications of skin and soft tissue infection ($n = 1$) and endocarditis ($n = 2$). Incision and drainage procedure was documented in 45% ($n = 18$) of those who were candidates for incision and drainage based on infectious indications, which were osteomyelitis, septic arthritis, and skin and soft tissue infection. Length of stay ranged from 3 to 69 days with a median of 7 (IQR, 5–21.8) days. Concurrent vancomycin and rifampin therapy regimens were used in 20% ($n = 8$) and 15% ($n = 6$) of courses, respectively. Additional secondary efficacy outcomes are summarized in Table 3.

Adverse events were documented in 20% of patients ($n = 8$) receiving CI nafcillin. Of the patients who experienced an adverse event, the most common adverse event experienced was hypokalemia in 3 patients (7.5%). Other documented adverse events included elevated liver transaminases (25%, $n = 2$), diarrhea (25%, $n = 2$), and neutropenia (12.5%, $n = 1$). There were no cases of interstitial nephritis or rash. There were no differences in median ages (median, 9.5; IQR, 3–12.8 years; vs. 9; IQR, 2.3–12 years, respectively; $p = 0.630$) or treatment duration (median, 10; IQR, 2.3–25.5 days; vs. 4; IQR, 3–10.8 days; $p = 0.475$) in patients with and without adverse events, respectively. However, infection-attributed length of stay was greater in patients experiencing adverse events (median 17; IQR, 7.3–40.8 days versus median 6; IQR, 5–15 days, respectively; $p = 0.027$). No patients required discontinuation of nafcillin or other treatment due to adverse events.

Discussion

The ability of CI beta-lactams to achieve goal PD

Table 2. Treatment Duration, LOS, Microbiologic Success, and Overall Treatment Success Per Indication (N = 40)

Site of Infection	n	Treatment Duration (days)*	LOS (days)*	Microbiologic Success, n (%)†	Treatment Success, n (%)
Bacteremia	4	8 (3.5-12.5)	19 (9.3-33.3)	4/4 (100)	4 (100)
Central Nervous System	1	2 (NC)	3 (NC)	‡	1 (100)
Endocarditis	8	28 (11.25-35.75)	39 (12-62.5)	6/7 (85.7)	6 (75)
Musculoskeletal	11	3 (2-4)	5 (4-6)	7/7 (100)	11 (100)
Pneumonia	2	4 (NC)	5 (NC)	1/1 (100)	2 (100)
Skin/Soft Tissue	14	4 (2-11.7)	7.5 (5-15)	3/4 (75)	13 (92.9)
Total	40	4 (3-12.5)	7 (5-21.8)	21/23 (91.3)	37/40 (92.5)

IQR, interquartile range; LOS, length of stay; NC, not able to calculate

* Values are medians (IQR).

† Values were calculated from those with a follow-up culture obtained.

‡ No follow-up cultures were available.

targets is unlikely to be disputed. However, evidence of clinical success is more difficult to find. Many available studies are limited to PK or mathematical simulation studies or focus on infections caused by Gram-negative pathogens.^{7,13,16,18} A search of PubMed and EMBASE databases revealed no published studies describing clinical outcomes with CI antistaphylococcal penicillins in children. The outcomes in these cases suggest that CI nafcillin in children can result in positive treatment success and microbiological cure.

Knoderer et al¹¹ reported a single case of an infant who received CI nafcillin for MSSA infectious sternal osteomyelitis after not responding to conventional nafcillin therapy. The patient received 185 mg/kg/day delivered continuously and appeared to tolerate therapy well with resolution of infection.¹¹ The dosage in that case is similar to the mean dosage of 190 mg/kg/day received by patients in the present series. Several studies in adult patients have reported clinical outcomes with CI flucloxacillin and oxacillin.^{18,20–22} Leder et al²⁰ demonstrated the feasibility and efficacy of using CI flucloxacillin in 20 adult patients with documented MSSA infections. Clinical and microbiological cure was characterized in 14 of 17 patients (82%) who successfully completed CI flucloxacillin. Similarly, Howden et al²¹ studied 62 adult patients with either cellulitis or other MSSA infection and found that CI resulted in infection resolution in 92% and 96% of those patients, respectively, although 2 patients developed transient neutropenia with CI therapy. Continuously infused oxacillin, 12 g per day, was reported to result in resolution of infection in 73% of adults (19 of 26) with burn cellulitis.²²

In the present case series, 92.5% of patients met criteria for treatment success, with 91.3% experiencing microbiological cure. This finding suggests similarities between our pediatric cohort and those in previous studies in adults. Patients receiving CI nafcillin in this cohort were older children with a median 9 years of age, with 75% older than 3 years of age. It is possible that fewer young children received CI nafcillin at our

institution because of prescribers' concerns about intravenous access and that these concerns have been previously cited as a common reason for not using CI beta-lactams.²³ Although we cannot definitively extrapolate similar efficacy to younger children, it is anticipated that similar clinical and microbiological cure rates would be observed. Continuously infused nafcillin appeared to be well tolerated in this cohort. Hypokalemia was the most commonly documented adverse event, although none of the events required additional treatment or nafcillin discontinuation. In this cohort, dosage was aggressive at the higher end of the recommended range, suggesting acceptable tolerability, even with larger doses. Because we did not evaluate patients who received intermittent nafcillin dosages, it is impossible to determine whether this adverse event was more likely with CI dosage.

Even with limited clinical efficacy data for CI nafcillin in children, there are some potential benefits that should be considered. Particularly in pediatrics, where each dose frequently must be prepared for a specific patient, pharmacy preparation of 1 dose per day (to be infused over 24 hours) may save time and money. Additionally, nursing time could be saved with less time spent starting and stopping infusions. Finally, limiting intravenous catheter manipulations by starting 1 dose per day instead of 4 or 6 could have implications for prevention of infection.

The retrospective nature of this study limits the ability to most accurately determine clinical outcomes and causes of adverse events. There were potentially other contributing factors that were not considered in the study, and a severity scoring system could have answered valuable questions regarding whether severity of illness influenced the decision to choose CI nafcillin and ultimately the treatment success. The study was not a comparative study, and we are not able to comment on a likely comparison with conventionally infused nafcillin. Time and economic considerations limit the ability to conduct a prospective multicenter

Table 3. Secondary Efficacy Outcomes and Adverse Effects in Patients Receiving Continuous Infusion (N = 40)

Secondary Clinical Outcomes	Results
Length of stay (days)*	7 (5-21.8)
Time to culture clearance (days)*	2 (1.5-4)
Time to defervescence (days)*	3 (1.5-4.5)
Time to CRP normalization (days)*	14 (12-30)
Time to ESR normalization (days)*	21 (14-23)
Time to limb movement normalization (days)*	17 (12-30)
Time to skin appearance normalization (days)*	11 (4-21.5)
Adverse Events, n (%)	
Any event	8 (20)
Hypokalemia	3 (37.5)
Increased transaminases	2 (25)
Diarrhea	2 (25)
Neutropenia	1 (12.5)
Rash	0
Seizure	0

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range

* Values are medians (IQR).

† Values are medians (minimum-maximum).

study with adequate power. The limitations of our study are acknowledged, but we believe that the information reported in this study is useful as it is the first description of experience using CI nafcillin in 40 children.

Outcomes of our cohort of patients who received CI suggest that CI nafcillin is an effective alternative dosage regimen to that of intermittent infusion, with efficacy similar to descriptions from adult studies. Continuously infused nafcillin appeared to be well tolerated in our cohort. Further studies are needed to address the question of whether clinical outcomes of CI nafcillin are superior to those of conventional infusion.

ARTICLE INFORMATION

Affiliations Department of Pharmacy Practice (CAK, LCK, KRN), College of Pharmacy and Health Sciences, Butler University Indianapolis, Indiana; Department of Pharmacy (KRN), Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana; Department of Pediatrics, Ryan White Center for Pediatric Infectious Disease, Indiana University School of Medicine, Indianapolis, Indiana

Correspondence Chad Knoderer, PharmD, cknodere@butler.edu

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