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## CASE REPORT

**Continuous Infusion of Nafcillin for Sternal Osteomyelitis in an Infant After Cardiac Surgery**

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We report the use of the continuous infusion of nafcillin for the treatment of an infant who had methicillin-susceptible *Staphylococcus aureus* sternal osteomyelitis not responsive to traditional nafcillin dosing. The patient was successfully treated with surgical debridement and the continuous infusion of nafcillin. To our knowledge, this is the first report describing the successful use of the continuous infusion of nafcillin to treat an infant who had sternal osteomyelitis after cardiac surgery.

**KEYWORDS** congenital heart disease, continuous infusion, nafcillin, sternal wound infection

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**BACKGROUND**

Surgical site infections account for approximately 16% of hospital-acquired infections and remain a concern in the treatment of children undergoing surgery for the repair of congenital heart disease.<sup>1</sup> Sternal wound infections occur in 5% of children who have undergone median sternotomy. For children who have undergone cardiac surgery, incidence of such infections is 3% for superficial sternal infections, 2% for deep sternal infections, and 0.04%–3.9% for mediastinitis.<sup>2–5</sup> Surgical debridement and prolonged durations of the intravenous (IV) administration of antibiotics are the mainstays of treatment. Because of the organisms that commonly precipitate mediastinal infections, antistaphylococcal or broad spectrum beta-lactam antibiotics are often used to treat these infections.<sup>3</sup> In contrast with a similar regimen applied in the adult population, there are few reports of the administration of beta-

lactam antibiotics via continuous IV infusion in children and in practice is rarely used.<sup>6–8</sup> To our knowledge, our report is the first published case

**ABBREVIATIONS** ASD, atrial septal defect; CoA, coarctation of the aorta; CPB, cardiopulmonary bypass; DOL, day of life; IV, intravenous; MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *Staphylococcus aureus*; VSD, ventricular septal defect; WBC, white blood cell

of a patient treated with a continuous infusion of nafcillin for sternal osteomyelitis after surgery for congenital heart disease.

**CASE REPORT**

A 12-day-old, full-term, male infant with congenital heart disease that had features consistent with Shone's complex—coarctation of the aorta (CoA), a hypoplastic and bicuspid aortic valve, a mildly hypoplastic aortic arch, a secundum atrial septal defect (ASD), and a paramembranous ventricular septal defect (VSD)—was admitted for increased work of breathing, shortness of breath, and diaphoresis with feeding. His CoA was surgically repaired on the 15th day of life

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**Table.** Laboratory Parameters After ASD and VSD Repair

DOL	POD ASD/VSD	WBC Count* (N/B)†	Platelet Count‡	Culture Analysis Results
31	3	11.5 (58/6)	106	N/A
32	4	23.9 (77/17)	61	Blood, MSSA (+)§ Chest tube fluid, MSSA (+)
33	5	13.3 (52/33)	48	Blood, MSSA (+)
34	6	9.4 (79/14)	25	Blood, no growth
35	7	6.1 (80/0)	39	N/A
36	8	3.4 (61/0)	64	no growth
37	9	6.5 (77/0)	79	N/A
38	10	7.4 (29/18)	167	N/A
39	11	11.1 (74/0)	174	no growth
40	12	20.2 (66/16)	174	N/A
41	13	16.9 (88/0)	176	N/A
42	14¶	16.9 (90/0)	180	Bone, MSSA (+) Wound, MSSA (+)
43	15	13 (85/0)	174	N/A

ASD, atrial septal defect; B, bands; DOL, day of life; MSSA, methicillin-susceptible *Staphylococcus aureus*; N, neutrophils; N/A, not applicable because no specimen taken, POD, postoperative day; VSD, ventricular septal defect; WBC, white blood cells.

\* Calculated as No.  $\times 10^3/\text{mm}^3$

† Percentage of neutrophils/percentage of bands

‡ Calculated as No.  $\times 10^3/\text{mm}^3$

§ (+) Symbol indicates positive

¶ Continuous infusion of nafcillin initiated

(DOL), and he received an extended end-to-end anastomosis through a thoracotomy incision. He was admitted to the pediatric intensive care unit for postoperative care. On the second postoperative day (DOL 17), the patient was begun on inotropic support for hemodynamic instability; vancomycin (30 mg/kg/d divided every 12 hours) and piperacillin-tazobactam (300 mg/kg/d divided every 8 hours) were initiated to rule out sepsis. The patient was afebrile at this time, and his white blood cell (WBC) count was normal. Blood and urine cultures tested negative for the presence of bacteria, and the antibiotics were discontinued after 48 hours. Over the next several days, the patient continued to exhibit signs of heart failure and ultimately did not wean

from mechanical ventilation. Echocardiogram findings showed significant left-to-right shunting through the ASD and VSD. The patient was taken to surgery on DOL 28 for repair of his ASD and VSD. Cardiopulmonary bypass (CPB) and moderate hypothermia were required for surgical repair.

After ASD and VSD repair, the infant remained mechanically ventilated in the pediatric intensive care unit. The patient received 24 hours of postoperative cefuroxime sodium prophylaxis. On the fourth postoperative day (DOL 32), the patient's WBC count increased to  $23.9 \times 10^3/\text{mm}^3$  from  $11.5 \times 10^3/\text{mm}^3$ , with a differential of 77% neutrophils and 17% bands. The platelet count decreased to  $61 \times 10^3/\text{mm}^3$  from

$106 \times 10^3/\text{mm}^3$  (Table). Chest tube (placed during ASD/VSD repair) drainage at that time was observed to be milky in appearance, although there was not an increase in output. Analysis of this fluid revealed a triglyceride concentration of 85 mg/dL, and chylothorax was ruled out.<sup>9,10</sup> Because the patient was afebrile, antibiotics were not started, but blood and urine cultures were obtained. On DOL 33, the microbiological analysis showed that 3 of 4 bottles of blood from the previous day had tested positive for Gram-positive cocci, which were subsequently identified as methicillin-susceptible *Staphylococcus aureus* (MSSA). The MSSA was resistant to penicillin but retained susceptibility to oxacillin with a minimum inhibitory concentration (MIC) of 0.5 mg/L. Additional blood and urine cultures were obtained. There was a moderate amount of milky-appearing drainage from the chest tube had a strong odor and was also sent for culture. Vancomycin (30 mg/kg/d divided every 12 hours), gentamicin (4.3 mg/kg every 24 hours), and piperacillin (250 mg/kg/d divided every 8 hours) were initiated after the new cultures were obtained. The second set of blood cultures and cultures of the chest tube drainage from DOL 33 also tested positive for MSSA. Vancomycin and piperacillin were discontinued on DOL 35, and nafcillin was initiated at 170 mg/kg/d divided every 6 hours. The maximum dose of nafcillin was not initiated because of concerns for potential hematologic and hepatic toxicities. Gentamicin was continued as a 4.3 mg/kg dose every 24 hours. Serum concentrations of gentamicin were obtained weekly and were at so-called "therapeutic values" for low-dose gentamicin MSSA therapy.

Over the next 2 days, the infant remained afebrile and had a decreasing WBC count. The chest tube output was thick and brownish. The patient again did not wean to extubation from mechanical ventilation on DOL 39. Erythema was observed on DOL 41, spreading out from the sternal wound with an area of fluctuance under the dressing. The sternal incision had reddened, and it had a dime-sized, fluid pocket on the upper third of the incision site. The patient went for mediastinal exploration and debridement the next day. Intraoperative findings showed purulent material beneath the skin and anterior to the sternum and it was exposed to the lower half of the sternum. The wound infection also ap-

peared to tract down toward the chest tube site. The lowermost sternal wire was removed, as it was partially loose, along with a small bone flap that appeared to be partially disengaged from the rest of the sternum. The purulent material and bone fragment were sent for culture; they tested positive for MSSA.

On the basis of the positive results for the wound culture and intraoperative observations from the mediastinal exploration, on DOL 42, intermittent administration of nafcillin was stopped, and continuous infusion dosing was started to optimize the drug's pharmacodynamic profile. The nafcillin was dosed to provide 185 mg/kg/d, delivered as a continuous IV infusion. This dosage was approximately the same total daily dose that was being administered with intermittent dosing. Over the subsequent days, the patient's condition was stable, and the incision had no signs of infection. An additional wound culture obtained on DOL 49 (7 days after surgical debridement) was negative for the presence of bacteria. The patient was treated for an additional 12 days with gentamicin (26 days total) and 35 days of continuous infusion nafcillin (49 days total duration). No additional signs of wound infection were present.

The continuous infusion of nafcillin was well tolerated. We observed no clinically significant changes in the patient's hepatic or hematologic laboratory values. Although the patient had a maculopapular rash 2 days after the initiation of the continuous infusion of nafcillin, the rash appeared to be caused by external contact, and it subsided over the next several days without discontinuation of nafcillin.

The patient had one subsequent episode of bacteremia that occurred 14 days after discontinuation of nafcillin. Blood cultures from DOL 97 and 100 tested positive for coagulase-negative staphylococci, which were methicillin-resistant; the patient received treatment with vancomycin for 10 days. Although the patient had received antibiotics on several occasions after the discontinuation of nafcillin, no cultures yielded recurrence of MSSA.

The patient continued with a prolonged hospitalization because of secondary developmental and respiratory issues. He continued to require mechanical ventilation and underwent a tracheostomy on DOL 112. The patient was discharged home on DOL 284 on a laptop ventilator.

## DISCUSSION

Surgical site infections remain a serious and frequent complication of cardiac surgery. Of particular concern are deep sternal wound infections and mediastinitis that can lead to significant morbidity and mortality. The incidence of sternal wound infections has been shown to be greater in neonates (5.5%) than in older children (0.5%) and has been associated with increased morbidity and mortality in neonates.<sup>11</sup> Incisional cellulitis and fever are common signs of sternal wound infection in children, and in multiple series, *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most common pathogens.<sup>3-5,11-14</sup>

Risk factors for sternal wound infection in children who have undergone cardiac surgery include younger age, prolonged ventilation, length of surgery, duration of central venous catheterization, and deep hypothermic circulatory arrest.<sup>4,14,15</sup> Our patient had multiple risk factors for infection. After the initial CoA repair, our patient underwent surgical repair of his ASD and VSD and had progressive heart failure in addition to a prolonged need for mechanical ventilation. Repair of the ASD and VSD required CPB with moderate hypothermia. The use of CPB with hypothermia may result in decreased immune function postoperatively. Decreased immune function may also occur because of prolonged periods of diminished cardiac output coupled with the young age of the patient.<sup>16</sup>

Treatment for deep sternal wound infection, mediastinitis, and sternal osteomyelitis include both surgical debridement and prolonged antibiotic therapy.<sup>11-13,17-19</sup> Optimization of antibiotic dosing is critical. Nafcillin, a beta-lactam antibiotic, exhibits time-dependent bacterial killing; the amount of time the drug serum concentration is above the MIC is the main predictor of efficacy.<sup>20,21</sup> Bacteria regrowth can occur when the drug serum concentration falls below the MIC.<sup>21</sup> In children, nafcillin is typically dosed every six hours, but this empiric dosing strategy may not optimize the duration of drug exposure at the source of infection in cases of deep sternal wound infection such as osteomyelitis. Rather, relative to the MIC, continuous infusion of nafcillin—as with other beta-lactam antibiotics—may more reliably provide adequate drug concentrations at the site of infection.<sup>21,22</sup> Although optimization of antibiotic dosing is critical in patients

with surgical wound infections, no reports have been published about the continuous infusion of antibiotics in children with secondary sternal osteomyelitis.

Continuous infusion of beta-lactam antibiotics such as nafcillin, piperacillin-tazobactam, and ceftazidime is used in adult patients to optimize each drug's pharmacodynamic profile, to take advantage of their convenience, and to reduce the consumption of health care resources.<sup>20,22,23</sup> Compared with intermittent dosing, this administration method has been shown to lead to cost reductions.<sup>24,25</sup> Reports of the continuous infusion of nafcillin in children are unavailable, but the medical literature regarding this population includes a few reports of other beta-lactam antibiotics and vancomycin being dosed as continuous infusions for indications other than sternal osteomyelitis.<sup>6-8</sup> Dalle and colleagues studied the pharmacokinetic profile of ceftazidime continuously administered by IV in 20 febrile children (median age, 5.4 years) who had neutropenia.<sup>7</sup> Administration of a 65 mg/kg loading dose and continuous infusion of ceftazidime (200 mg/kg/d) resulted in mean serum concentrations of 30.4-33 mg/L at 23-43 hours after initiation of the infusion.<sup>7</sup> Authors of another study reported the efficacy of the continuous infusion of ceftazidime in 14 children (mean age, 12.6 years) who had cystic fibrosis.<sup>8</sup> Compared with ceftazidime administered at 200 mg/kg/day 3 times a day, the continuous infusion of ceftazidime at 100 mg/kg/d provided similar effects on pulmonary, inflammatory, and nutritional status markers.<sup>8</sup> Continuous infusions were well tolerated in both studies.<sup>7,8</sup> Vancomycin, cefuroxime, and piperacillin-tazobactam also have been administered successfully as continuous infusions in 13 children, aged 2 months to 14 years, who were treated for persistent, central intravenous catheter-related infections due to Gram-positive organisms.<sup>6</sup>

After multiple cultures tested positive for MSSA, including a positive result for a wound specimen that was taken while the patient was receiving intermittent administration of nafcillin, the continuous infusion of nafcillin was initiated to optimize our patient's nafcillin exposure. Although the medical literature includes reports of children being treated with continuous infusions of other beta-lactam antibiotics or vancomycin, which have shown activity against MSSA, we

elected to use nafcillin for our patient because of the narrow spectrum of bacterial coverage and the drug's effectiveness against MSSA. We considered switching to an intermittent dosing regimen of every 4 hours rather than the continuous infusion of nafcillin. However, given the nursing and pharmacy resources required for intermittent administration versus continuous infusion and the anticipated prolonged duration of therapy, we elected to administer nafcillin as a continuous infusion. One bag containing a 24-hour supply (nafcillin 24 mg/mL in 5% dextrose) was compounded daily by the inpatient pharmacy, and the nursing staff changed the infusion once per day to limit IV line interruptions. The total daily dose of nafcillin was divided by 24 hours and administered as a continuous infusion. Specific nafcillin concentrations were not targeted. The benefit of such concentrations is questionable since our patient's infection involved primary bone and was not a blood stream infection. Also, our laboratory was not able to analyze serum nafcillin concentrations; hence, samples would have to be sent to a referral laboratory. The significant delay in acquiring results diminished the utility of trying to active certain concentrations.

### CONCLUSIONS

To our knowledge, our case is the first report of the use of a continuous infusion of nafcillin in an infant who had sternal osteomyelitis after cardiovascular surgery. The diagnosis of the sternal wound infection was confirmed using laboratory and clinical criteria. The infection did not respond to initial antimicrobial therapy administered via a traditional dosing strategy. After receiving surgical debridement and continuous infusion nafcillin, the patient was successfully treated.

**DISCLOSURE** The authors declare no conflicts or financial interests in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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