# Nephrotoxicity and Clinical Outcomes in Patients Treated with Nafcillin or Cefazolin

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## Abstract

**Background:** Antistaphylococcal ß-lactams are the mainstay of therapy for MSSA infections. There is considerable debate to which agent to use in various infections. This study examined the incidence of acute kidney injury (AKI) and in-hospital mortality in patients treated with nafcillin (NAF) or cefazolin (CFZ).

**Methods:** Electronic medical record data were obtained from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust from 9/1/2007 to 10/1/2015. Adult patients receiving NAF or CFZ for greater than 48 hours were included. Patients with renal dysfunction or vancomycin therapy were excluded. AKI was assessed with the RIFLE criteria. Patients were matched on baseline renal function, concomitant nephrotoxins, and comorbidities predisposing to AKI. Comparative statistics and multivariate logistic regression were performed.

**Results:** In total, 3,951 patients were evaluated, with 518 receiving NAF and 3,433 receiving CFZ. At baseline, the NAF group was younger (49.6±16.1 v 55.7±16.3 years old, p<0.0001), more likely to be male (62% v 57%, p=0.046) and had higher baseline renal function (101±41 v 92±36 mL/min, p<0.0001). AKI occurred in 29.2% of NAF patients compared to 14.8% of CFZ patients (p<0.0001). NAF patients were more likely to experience in-hospital mortality (14.3% v 4.9%, p<0.0001); however, when stratified by endocarditis, osteomyelitis, or bacteremia, this trend was not found. Following matching, the AKI rate for NAF patients remained 29.2%, and the rate in CFZ patients was 21.6% (p=0.007). Receipt of NAF was associated with an adjusted OR of 1.59 (95% CI 1.19-2.14) for AKI compared to CFZ. Other factors associated with increased odds of AKI were exposure to loop diuretics (OR 2.38, 95% CI 1.76-3.23) or hypotension (OR 2.17, 95% CI 1.6-2.97). Mortality remained higher in the NAF group (14.3% v 8.7%, p=0.006); however, no difference was noted in patients with endocarditis, osteomyelitis, or bacteremia. Similar numbers of patients in both groups were discharged healthy to home. Length of hospitalization was similar between groups.

**Conclusions:** NAF was associated with more AKI and in-hospital mortality compared to patients treated with CFZ, which suggests CFZ may be a reasonable alternative therapy.

## Background

- Nafcillin (NAF) and cefazolin (CFZ) are the mainstay of therapy for MSSA infections
- NAF use is impacted by significant adverse drug effects, such as acute kidney injury (AKI): whereas CFZ has been linked to treatment failures in high bacterial burden infections like endocarditis or osteomyelitis

## Objective

- Determine AKI incidence and mortality rate in patients treated with CFZ or NAF

## Results

**Table 1: Patient characteristics in unmatched and matched cohorts**

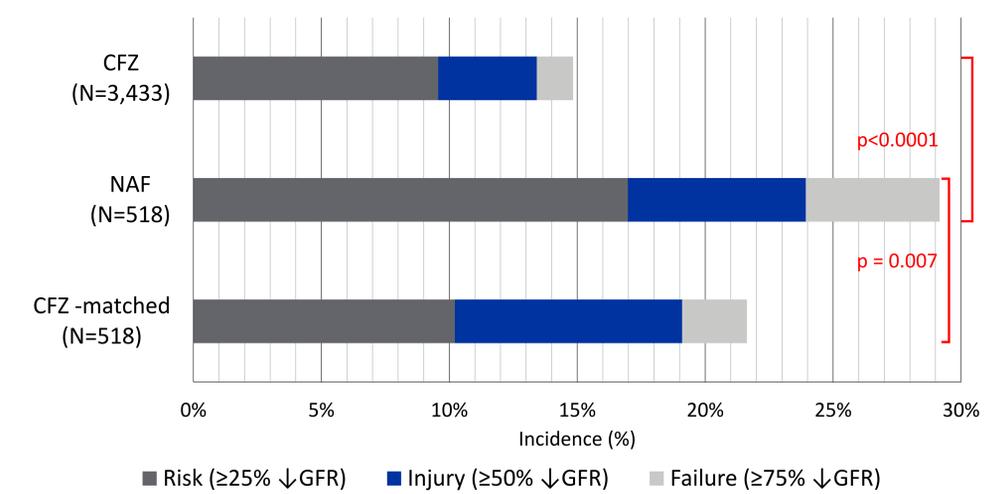| Variable | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| | CFZ (N=3,433) | NAF (N=518) | p | CFZ (N=518) | NAF (N=518) | p |
| Age (mean[SD]) | 55.7 (16.4) | 49.6 (16.1) | <0.00001 | 49.4 (17.2) | 49.6 (16.1) | 0.8 |
| Male | 1,951 (56.8%) | 319 (61.6%) | 0.046 | 327 (63.1%) | 319 (61.6%) | 0.7 |
| Caucasian | 3,146 (91.6%) | 476 (91.9%) | 0.9 | 487 (94.0%) | 476 (91.9%) | 0.2 |
| Weight (mean[SD]) | 85.9 (23.8) | 84.5 (24.6) | 0.3 | 87.5 (25.6) | 84.5 (24.6) | 0.1 |
| BMI (mean[SD]) | 29.4 (12.6) | 28.4 (8.1) | 0.04 | 30.2 (21.4) | 28.4 (8.1) | 0.1 |
| CCI (median [IQR]) | 3 (1-5) | 2 (1-4.75) | 0.3 | 2 (1-5) | 2 (1-4.75) | 0.8 |
| Baseline CrCl (median [IQR]) | 86.5 (66.4-111.6) | 100.3 (68.4-125.9) | <0.00001 | 96.9 (72.7-123.9) | 100.3 (68.4-125.9) | 0.96 |
| **Concomitant nephrotoxins** | | | | | | |
| Aminoglycosides | 341 (9.9%) | 78 (15.1%) | 0.0006 | 78 (15.1%) | 78 (15.1%) | 1 |
| Amphotericin B | 7 (0.2%) | 5 (1.0%) | 0.01 | 4 (0.8%) | 5 (1.0%) | 1 |
| ACE inhibitor | 517 (15.1%) | 123 (23.8%) | <0.00001 | 115 (22.2%) | 123 (23.8%) | 0.6 |
| ARB | 140 (4.1%) | 13 (2.5%) | 0.1 | 9 (1.7%) | 13 (2.5%) | 0.5 |
| Contrast Dye | 103 (3.0%) | 41 (7.9%) | <0.00001 | 31 (6.0%) | 41 (7.9%) | 0.3 |
| Loop diuretic | 1,322 (38.5%) | 220 (42.5%) | 0.09 | 262 (50.6%) | 220 (42.5%) | 0.01 |
| NSAID | 1,314 (38.3%) | 174 (33.6%) | 0.045 | 144 (27.8%) | 174 (33.6%) | 0.05 |
| Calcineurin inhibitor | 55 (1.6%) | 8 (1.5%) | 1 | 9 (1.7%) | 8 (1.5%) | 1 |
| Vasopressor | 646 (18.8%) | 129 (24.9%) | 0.001 | 151 (29.2%) | 129 (24.9%) | 0.1 |
| **Comorbidities** | | | | | | |
| Diabetes | 731 (21.3%) | 142 (27.4%) | 0.002 | 139 (26.8%) | 142 (27.4%) | 0.9 |
| Heart Failure | 385 (11.2%) | 73 (14.1%) | 0.07 | 88 (17.0%) | 73 (14.1%) | 0.2 |
| Hypertension | 2,011 (58.6%) | 259 (50.0%) | 0.0003 | 258 (49.8%) | 259 (50.0%) | 1 |
| Osteomyelitis | 119 (3.5%) | 85 (16.4%) | <0.00001 | 68 (13.1%) | 85 (16.4%) | 0.2 |
| Endocarditis | 48 (1.4%) | 59 (11.4%) | <0.00001 | 36 (7.0%) | 59 (11.4%) | 0.02 |
| Meningitis | 11 (0.3%) | 5 (1.0%) | 0.07 | 5 (1.0%) | 5 (1.0%) | 1 |
| Bacteremia | 476 (13.9%) | 305 (58.9%) | <0.00001 | 307 (59.3%) | 305 (58.9%) | 0.9 |
| Bacteremia – Staph | 43 (1.3%) | 107 (20.7%) | <0.00001 | 36 (7.0%) | 107 (20.7%) | <0.00001 |
| Bacteremia – MRSA | 13 (0.4%) | 5 (1.0%) | 0.1 | 12 (2.3%) | 5 (1.0%) | 0.1 |
| Hypotension | 1,249 (36.4%) | 290 (56.0%) | <0.00001 | 261 (50.4%) | 290 (56.0%) | 0.08 |

**Figure 1: AKI incidence between NAF and CFZ**



**Table 2: Multivariate regression results**

| Covariate | OR | CI | p |
|---|---|---|---|
| **Treatment** | | | |
| Cefazolin | | *(reference)* | |
| Nafcillin | 1.59 | 1.19 – 2.14 | 0.002 |
| Loop Diuretic | 2.38 | 1.76 – 3.23 | <0.001 |
| Hypotension | 2.17 | 1.60 – 2.97 | <0.001 |

**Table 3: Clinical outcomes in unmatched and matched cohorts**

| Variable | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| | CFZ (N=3,433) | NAF (N=518) | p | CFZ (N=518) | NAF (N=518) | p |
| Length of stay (median [IQR]) | 9 (4-19) | 16 (10-29) | <0.00001 | 16 (7-34) | 16 (10-29) | 0.3 |
| Discharge to home | 2,440 (71.1%) | 339 (65.4%) | 0.01 | 339 (65.4%) | 339 (65.4%) | 1 |
| Mortality | 167 (4.9%) | 74 (14.3%) | <0.00001 | 45 (8.7%) | 74 (14.3%) | 0.006 |
| Endocarditis* | 2 (4.2%) | 8 (13.6%) | 0.2 | 2 (5.6%) | 8 (13.6%) | 0.3 |
| Osteomyelitis* | 4 (3.4%) | 6 (7.1%) | 0.3 | 3 (4.4%) | 6 (7.1%) | 0.7 |
| Bacteremia* | 86 (18.1%) | 54 (17.7%) | 0.97 | 42 (13.7%) | 54 (17.7%) | 0.2 |

\* Percentage is patients who experienced mortality from those with the comorbid condition

## Methods

- Clinical data were collected from the UK Center for Clinical and Translational Science Enterprise Data Trust from 9/1/2007 to 10/1/2015
- Adult patients were included if they received NAF or CFZ for ≥48 hours
- Patients were excluded for: pregnancy, chronic kidney disease, baseline creatinine clearance (CrCl) < 30 mL/min, and vancomycin therapy
- CrCl was calculated with the adjusted Cockcroft-Gault equation
- Exposure to nephrotoxic drugs was defined as receiving at least 1 dose of the agent within 24 hours of treatment initiation through discontinuation
- Comorbidities were identified with ICD-9 codes
- Hypotension was defined as MAP<65 mmHg, SBP<90 mmHg, or vasopressor exposure during treatment
- Charlson Comorbidity index (CCI) was used to measure severity of illness
- AKI was defined as meeting any of the RIFLE criteria
- Patients were matched on: gender, age, CCI, baseline CrCl, endocarditis, osteomyelitis, bacteremia, diabetes, hypertension, and nephrotoxic drug exposures
- Univariate and multivariate logistic regressions were performed

## Conclusions

- After controlling for several factors associated with AKI, NAF patients experienced significantly more AKI compared to CFZ treated patients
- Mortality was more common in patients treated with NAF but infection-specific mortality was not different in the matched cohort, suggesting NAF patients were more ill at baseline; however, there were no differences in CCI between groups in both analysis