Cefazolin-Induced Neutropenia Development and Evaluation of Risk Factors in Home Infusion (CINDER-FHI)

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ABSTRACT

Background

Beta-lactam-induced neutropenia (BLIN) is a serious adverse reaction associated with extended treatment courses. For many severe infections, guideline-directed medical therapy frequently involves weeks or months of IV antibiotics. To avoid health care costs associated with hospitalization and as a method to improve hospital bed capacity, clinicians are encouraged to discharge patients to receive IV antibiotics in the ambulatory setting once clinically stable. The purpose of this study was to compare the incidence of cefazolin-induced neutropenia between intravenous push (IVP) administration and intermittent infusions among home infusion patients. This study is unique in its analysis of neutropenia monitoring and interventions in a pharmacist-led outpatient parenteral anti-infective therapy (OPAT) model. Cefazolin was examined over other beta-lactams due to high utilization in home infusion and administration methods by IVP and intermittent infusion at this institution.

Methods

This was a retrospective cohort study within a single large health system that includes an associated home infusion pharmacy. Patients were included for analysis if they met the following criteria: ≥18 years of age, received cefazolin through the home infusion pharmacy between July 1, 2017, and July 1, 2022, and were discharged from an acute care site within the health system for index cefazolin episode to the home or an affiliated long-term care facility. Lab values within 2 weeks of the cefazolin treatment course were evaluated for neutropenia. The primary outcome was the incidence of neutropenia by the method of administration: IVP versus intermittent infusion. Patients who received intermittent infusions in this study utilized elastomeric devices or ambulatory infusion pumps. Duration of IVP and intermittent infusion were defined as being given over 10 minutes and 30 minutes, respectively.

Results

A total of 431 patients were included in the study. Home infusion pharmacists recorded 18 BLIN events. All patients were asymptomatic. Fourteen events were classified as mild, with an absolute neutrophil count (ANC) nadir of 1.1-1.5 cells×1000/μL. Two events were considered moderate and 2 were considered severe, with ANC nadirs between 0.5 to 1.0 cells×10^3/μL and <0.5 cells×10^3/μL, respectively.

Conclusions

The relationship between baseline ANC and the development of BLIN later in treatment reported a 3.4-fold increased risk of cefazolin-induced neutropenia, and individuals with neutrophil counts between 1.6×10^3 cells/μL and 3.9×10^3 cells/μL at baseline require the highest degree of care. Our data suggests that low absolute neutrophil count (ANC) at cefazolin initiation is the strongest risk factor for subsequent development of neutropenia.

Keywords: beta-lactams, home infusion, neutropenia, intravenous push, infusion.

Background

Beta-lactam-induced neutropenia (BLIN) is a serious adverse reaction associated with extended treatment courses. It is characterized by decreased levels of neutrophils, often defined as absolute neutrophil count (ANC) ≤1.5 with at least 10-12 days of beta-lactam therapy.[1,2] Numerous proposed mechanisms exist, including immune-mediated hypersensitivity reaction, direct cellular toxicity, and suppressed humoral immunity.[3-5] For cephalosporins, the prevailing theory involves the formation of haptens (protein adducts) with neutrophils, which prompts an immune response, resulting in neutropenia, particularly with durations of therapy exceeding 2 weeks.[6-10] Modifications of the cephalosporin chemical structure occur at R sites on the core beta-lactam ring and differentiate the spectrum of activity. Both R1 and R2 side chains on the beta-lactam ring have been implicated in the process of immune recognition.[10,11] Suggested risk factors for BLIN include increased cumulative exposure and prolonged treatment durations.[11] One recent study showed a correlation between cefepime-induced neutropenia and intravenous push administration, and another study of hospitalized pediatric patients found younger age was associated with neutropenia development.[12,13] Incidence of BLIN varies based on the beta-lactam utilized and the total duration of therapy. Approximate incidence based on duration of therapy greater than 2 weeks is 10%.[11]

For many severe infections, such as osteomyelitis, endocarditis, and bacteremia, guideline-directed medical therapy frequently involves extended courses of IV antibiotics.[11,14] To avoid health care costs associated with extended hospitalization and as a method to improve hospital bed capacity, clinicians are encouraged to discharge patients to receive IV antibiotics in the ambulatory setting once clinically stable. Home infusion represents a rapidly growing industry where patients can receive IV antibiotics safely, effectively, and conveniently in their homes.[15] Due to decreased costs and patient convenience, home infusion has become the standard of care for outpatient parenteral antibiotic therapy (OPAT).[11,15]

Several methods of medication administration seen in home infusion are intravenous push (IVP), elastomeric devices, dial-regulated gravity infusions, and ambulatory pumps.[16] Many patients prefer IVP because of its ease of use. Once connected to the patient's indwelling line, IVP is usually given over 2-10 minutes, depending on the medication. Elastomeric devices are available in a variety of administration rates and can be used for short intermittent infusions as well as extended continuous infusions of 3 hours or more. Ambulatory pumps are programmed for the prescribed administration rate and can be used for short infusions or extended infusions. Infusion duration and frequency of drug administrations are important considerations when selecting between administration methods. The efficacy of cephalosporin antibiotics is dependent upon maximizing the duration of time that drug concentrations remain above the minimum inhibitory concentration (MIC) of the target pathogen.[17] Data shows that either IVP or intermittent infusion are appropriate for cephalosporin administration.[17]

Cefazolin is commonly dosed 3 times daily, and it is a good candidate to be administered via IVP in the home, although it may also be given via an elastomeric device or ambulatory pump. Cefazolin covers *Streptococci*, methicillin-susceptible *Staphylococci* (MSSA), and some Gram-negative organisms. It also has enhanced patient convenience compared to penicillinase-resistant semisynthetic penicillins such as nafcillin and oxacillin, which are dosed every 4-6 hours or as a continuous infusion, necessitating more frequent administrations or attention to the administration device.[18] These factors have quickly made cefazolin a drug of choice in home infusion for management of bloodstream infections, endocarditis, and bone or joint infections, especially those due to MSSA.

The aim of this study was to compare the incidence of cefazolin-induced neutropenia between IVP and intermittent administration among home infusion patients. The secondary outcome of the study was to explore additional risk factors for cefazolin-induced neutropenia. Herein we address a gap of evidence evaluating risk factors for BLIN in the home infusion setting. This study is also unique in its analysis of neutropenia monitoring and interventions in a pharmacist-led OPAT model. Cefazolin was examined over other beta-lactams due to high utilization in home infusion and adequate administration by both IVP and intermittent infusion at this institution.

Methods

Study Setting and Population.

This was a retrospective cohort study within a single large health system that includes an associated home infusion company. Patients were included for analysis if they met the following criteria: ≥18 years of age, received cefazolin through the home infusion pharmacy between July 1, 2017, and July 1, 2022 and were discharged from an acute care site within the health system for index cefazolin episode to the home or an affiliated long-term care facility. Race was self-reported and extracted from the electronic medical record. Similarly, the total duration of therapy was identified via addition of both inpatient and outpatient antibiotic course durations via electronic medical record. Patients without a documented stop date were defined as having an indeterminate treatment duration. Patients were excluded if they had neutropenia at baseline prior to OPAT, a history of any chemotherapy or bone marrow transplantation within 90 days prior to or during cefazolin treatment or had inadequate lab data to assess for neutropenia throughout treatment. The University of Minnesota institutional review board (IRB) approved this study.

ANC at cefazolin initiation was interpreted as being on the low end of normal for values 1.6-3.9 cells×1000/μL. ANC values 4.0-6.9 cells×1000/μL were considered normal. ANC greater than 7.0 cells×1000/μL was considered elevated. All lab values within 2 weeks of the cefazolin treatment course were evaluated for neutropenia, defined as ANC ≤1.5 and further classified into one of several categories. Mild, moderate, and severe neutropenia were defined as 1.5-1.0, <1.0-0.5, and <0.5 cells×1000/μL, respectively. For logistic regression analysis, patients were categorized into groups based on age, ANC, and duration of treatment to determine whether these factors impact the incidence of BLIN. Grouping criteria seen in Table 4 were selected by investigator choice a priori. Reference ranges were selected as comparators based on the hypotheses that incidence of neutropenia would increase with older age, longer treatment durations, and decreased baseline ANC. Upon identification of cefazolin-induced neutropenia, a chart review was conducted to identify management strategies and assess for potential symptomatic neutropenia, characterized by new fevers or new or worsening infection.

Data Collection and Variables of Interest

Study data were collected and managed using the Research Electronic Data Capture (REDCap®). Patient race, sex, age, research authorizations, hospital admission discharge dates, and method of administration were retrieved via pharmacy analytics report. Manual chart review was conducted to confirm and document laboratory data and duration of cefazolin treatment. Chart reviews were conducted independently by 2 investigators. Upon identification of neutropenic events, pharmacist and provider interventions were assessed. Any discrepancies were resolved via discussion and consensus with a third pharmacist within the research team.

The primary outcome was incidence of neutropenia by method of administration: IVP versus intermittent infusion. Patients who received intermittent infusions in this study utilized elastomeric devices or ambulatory infusion pumps. Duration of IVP and intermittent infusion was defined as being given over 10 minutes and 30 minutes, respectively. As a secondary outcome, the following covariates were analyzed for correlations with incidence of neutropenia: duration of OPAT, sex, age, race, and baseline ANC.

Statistical Analysis

The distribution of continuous variables was examined for normality. Categorical variables were compared with neutropenia status using chi-squared tests. Univariate logistic regression models estimated the odds of becoming neutropenic by each variable of interest, with 95% confidence intervals reported. Statistical significance was determined a priori at $\alpha=0.05$ for all comparisons. All analyses were conducted in SAS®, version 9.4 (SAS®, Inc., Cary, NC).

Results

A total of 431 patients were included in the study. Baseline characteristics are listed in Table 1 by the characteristic variable, and by infusion method of either infusion (30 minutes) or IV push (10 minutes).

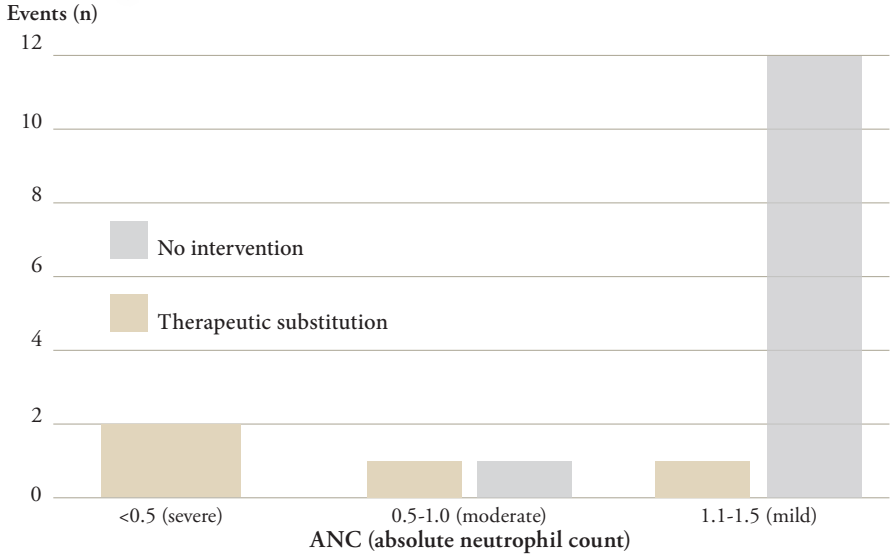
Home infusion pharmacists recorded 18 BLIN events as visualized in Figure 1. In each scenario, home infusion pharmacists notified providers of neutropenic events and engaged in shared decision-making. All patients were asymptomatic. Fourteen events were classified as mild, with an ANC nadir

TABLE 1 | Baseline and Descriptive Characteristics

Characteristic	Infusion n= 80 (%)	IV Push n=351 (%)	Total n=431 (%)
Male sex	39 (48.8)	210 (59.8)	249 (57.8)
Female sex	41 (51.2)	141 (40.2)	182 (42.2)
Age, years; mean (std dev)	72 (11.8)	54 (14.9)	57 (16.1)
18-49, years	4 (5.0)	130 (37.0)	134 (31.1)
50-64, years	16 (20.0)	151 (43.0)	167 (38.7)
65+, years	60 (75.0)	70 (20.0)	130 (30.2)
Race			
White	70 (87.5)	298 (84.9)	368 (85.4)
Black or African American	2 (2.5)	22 (6.3)	24 (5.6)
Asian	1 (1.3)	15 (4.3)	16 (3.7)
Undisclosed	4 (5.0)	11 (3.1)	15 (3.5)
Other	3 (3.7)	5 (1.4)	8 (1.8)
Baseline ANC, ×103 cells/μL; median (IQR)	8.0 (7.5)	7.3 (6.9)	7.4 (6.9)
Low: 1.6-3.9 cells×1000/μL	10 (12.5)	52 (14.8)	62 (14.4)
Normal: 4-6.9 cells×1000/μL	20 (25.0)	110 (31.3)	130 (30.2)
Elevated: >7 cells×1000/μL	50 (62.5)	189 (53.8)	239 (55.5)
ANC reduction, cells ×1000 /μL; median (IQR)	4.3 (5.1)	3.3 (5.8)	3.3 (5.7)
OPAT Duration, days; median (IQR)	36 (16.0)	28 (22.0)	29 (21.0)
0-4 weeks	22 (27.5)	158 (45.0)	180 (41.8)
4-6 weeks	25 (31.2)	83 (23.6)	108 (25.1)
>6 weeks	20 (25.0)	64 (18.2)	84 (19.5)
Indeterminate	13 (16.3)	46 (13.1)	59 (13.6)

Std dev= standard deviation; IQR= interquartile range

FIGURE 1 | Management of Neutropenia by Neutropenic Event Severity (n=18)



X axis = ANC nadir given in cells×103/μL (interpretation). Y axis = incidence of event.

of 1.1-1.5 cells×1000/μL. Two events were considered moderate and 2 were considered severe, with ANC nadirs between 0.5-1.0 cells×10^3/μL and <0.5 cells×10^3/μL, respectively. Figure 1 shows that 14% of all mild events led to an intervention compared to 50% of moderate events and 100% of severe events. When therapeutic substitution was considered necessary per prescriber discretion, new antibiotic therapy was restarted as soon as feasible. This strategy was effective, as patient ANC counts spontaneously recovered without any additional intervention. Across all neutropenic events, the mean time to recovery was 9.1 days (range 1-28 days). Two neutropenic events occurred at the end of therapy, where no lab data was available to assess neutrophil recovery after discontinuation.

The primary outcome of neutropenia incidence by administration type did not generate statistically significant results, as seen in Table 2. These results are contrary to previous studies demonstrating higher rates of neutropenia with more rapid IVP administration of beta-lactams.[12]

TABLE 2 | Primary Outcome: Neutropenia Incidence by Administration Type

Administration Type	Neutropenic Events	Incidence	*p*-Value
Infusion	4/80	5.0%	0.683
IV Push	14/351	4.0%	

Additional covariates were analyzed for correlations with incidence of BLIN in Table 3 and Table 4, including sex, race, baseline ANC, treatment duration, and patient age. Sex, race, treatment duration, and patient age demonstrated no statistically significant correlation with BLIN incidence. In addition, having a low baseline ANC (1.6-3.9×10^3 cells/μL) was the covariate that was most closely correlated with development of BLIN later in treatment and was statistically significant (OR 3.41; 95% CI 1.03 – 11.28).

Discussion

In this retrospective cohort study of patients receiving OPAT with cefazolin, baseline ANC was the greatest predictor for risk of neutropenic events. Patients with a baseline ANC between 1.6 and 3.9 were roughly 3.4 times more likely to experience a neutropenic event. In contrast to previous studies, no statistically significant differences in the incidence of neutropenia based on the method of delivery (IV push vs. intermittent infusion) were observed.

This study represents important progress for OPAT in home infusion. In the context of acute infection, neutrophil counts generally remain within normal ranges. Low neutrophil levels can indicate an underlying condition predisposing the patient to future neutropenic events. All events observed in this study were asymptomatic, and most were mild (ANC 1.5-1.1), requiring no intervention. Key cutoffs for neutropenia necessitating intervention are not well established and may be patient specific. Pharmacists play a critical role in monitoring labs, assessing risk for neutropenia, and relaying concerns to providers. Out of 18 incidents of BLIN, 5 led to an intervention. The pharmacist was responsible for monitoring for BLIN and reporting patient lab results to the prescriber. In conjunction with the prescriber, the pharmacist coordinated medication interventions. This finding supports the safe and effective practice of a pharmacist-led home infusion service for monitoring response to treatment in OPAT.

While a past medical history of antibiotic allergy was not included in the statistical analysis, investigators observed little correlation between allergy history and neutropenic events. If an immunologic mechanism is responsible for cefazolin-induced neutropenia, one might expect a prior antibiotic allergy to be a predisposing factor in the risk of developing antibiotic-induced neutropenia, particularly if the allergy were to a cephalosporin. This correlation was not observed, and since immune recognition has been associated with variations in R side chains of the beta-lactam ring, the research acknowledged that cefazolin does not share any similar or identified R1 or R2 side chains with other beta-lactams.

This study has several limitations. BLIN is rare and multifactorial; establishing a correlation with any 1 covariate is challenging. Thus, this study was underpowered to detect statistically significant differences in several key metrics. Statistically nonsignificant primary outcome results may be due to several factors. Patient preference for IVP administration makes adequately powering an IV infusion group challenging. Furthermore, age distributions between IVP and infusion groups

TABLE 3 | Incidence of BLIN Based on Sex and Race

Characteristics		Neutropenic Events	Incidence	*p*-Value
Sex	Female	8/180	4.4%	0.827
	Male	10/249	4.0%	
Race	White	15/368	4.1%	0.913
	African American	1/24	4.2%	
	Asian	1/16	6.3%	

TABLE 4 | Risk of BLIN Based on Age, Baseline ANC, and Cefazolin Duration

Characteristics		Neutropenic Events	Incidence	OR (95% CI)
Age (years)	18-49	6/134	4.5%	*reference*
	50-64	7/167	4.2%	0.96 (0.31, 2.93)
	65+	5/130	3.8%	0.89 (0.27, 3.01)
Baseline ANC (cells×1000/μL)	Low: 1.6-3.9	7/62	11.3%	3.41 (1.03, 11.28)
	Normal: 4-6.9	5/130	3.8%	*reference*
	Elevated: ≥7	6/239	2.5%	0.65 (0.19, 2.18)
Cefazolin duration (weeks)	0-4	5/180	2.8%	*reference*
	4-6	7/108	6.5%	2.51 (0.78, 8.11)
	>6	6/84	7.1%	2.81 (0.83, 9.47)

OR= odds ratio; CI= confidence interval; ANC= absolute neutrophil count. Patients were excluded from this analysis if total duration of cefazolin treatment was indeterminate.

must be considered. Generally, both geriatric and pediatric populations are more susceptible to adverse effects.[19] This has been seen with BLIN, specifically in pediatric patients; although, as of now, no study has been identified showing older age to be associated with BLIN.[13] Still, the potential for confounding with distributions of geriatric patients differing between groups (75% vs. 20%) must be considered.

Additionally, patients in the IVP group were educated to administer cefazolin over 10 minutes, on the conservative end of the IVP administration range. A recent study associated rapid IV push of cefepime with the rate of infusion administered IVP mediation over 3-5 minutes.12 The conservative approach for IVP administration in this study may indicate that a slower administration rate for IVP medications may mitigate the adverse effect. Furthermore, generalizability of these results to other sites may be limited by the observed patient characteristics. Overall, 85.4% of patients in this study were self-reported as white race. Thus, these results may translate differently to more racially diverse patient populations.

Neutropenic events increase in frequency with increasing antibiotic durations. In most cases, neutropenic events occurred at or near the end of therapy. As a result, therapy was discontinued as planned, and ANC was rechecked at the follow-up appointment to confirm resolution, often 1-2 weeks later. However, ANC may have recovered well before the follow-up level was drawn. As a result, data on the duration of neutropenia was imprecise. Documentation of antibiotic stop dates for patients transferred to affiliated long-term care facilities was often not well documented within electronic health records. While these patients were not excluded from the study, they could not be included in logistic regression analysis without an appropriate duration of therapy.

Other covariates will be reassessed for correlations with BLIN in a follow-up study. Duration of treatment was of particular interest. Despite being underpowered to detect statistical differences, we observed odds ratios of 2.5 and 2.8 for durations of 4-6 weeks and 7+ weeks, respectively. If these results hold up to a larger sample size, this will confirm

previous literature identifying longer treatment durations as a significant risk factor for BLIN. Notably, this study excluded patients with baseline ANCs below 1.5×10^3 cells/μL. Thus, additional studies are necessary to address optimal OPAT management for patients with baseline neutropenia or those receiving myelosuppressive chemotherapy.

Current recommendations for the management of BLIN are nonspecific and leave much to provider assessment based on ANC cutoffs and current risk of decompensation. Management strategies often start with careful laboratory monitoring in long-term beta-lactam treatment courses. In mild and asymptomatic BLIN, discontinuation of the offending agent is not always necessary. Watchful waiting and more frequent monitoring may prevent further decompensation. For patients at higher risk, transitioning to a beta-lactam containing an alternative R1 side chain is common. Finally, providers may utilize G-CSF to bolster the immune system and minimize infection risk; however, this was not observed in our study and is typically reserved for severe symptomatic neutropenia.[11] Future development of a management algorithm for BLIN may hasten the continued success of OPAT in a home infusion setting.

Conclusions

The primary takeaway from this study is the relationship between baseline ANC and the development of BLIN later in treatment. With a 3.4-fold increased risk of cefazolin-induced neutropenia, individuals with neutrophil counts between 1.6×10^3 cells/μL and 3.9×10^3 cells/μL at baseline require the highest degree of care. Based on these results, we recommend these patients get a baseline ANC measurement during the inpatient period and a thorough screening to identify other possible sources of neutropenia. Once discharged to home infusion, laboratory monitoring should be continued for cefazolin courses with durations greater than 2 weeks. Secondarily, this study provides valuable insight into neutropenia monitoring and interventions in a pharmacist-led OPAT model.

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