A Cluster of Cefepime-induced Neutropenia During Outpatient Parenteral Antimicrobial Therapy

Kap Sum Foong,¹ Kevin Hsueh,¹ Thomas C. Bailey,¹ Lan Luong,² Ayesha Iqbal,² Christine Hoehner,² Lee Connor,¹ Ed Casabar,³ Michael Lane,¹ Yvonne Burnett,^{1,4} David Ritchie,^{3,4} Tamara Krekel,³ Helen Newland,³ Lori Weilmuenster,⁵ Brett Heuring,⁵ Michael J. Durkin,¹ and Yasir Hamad¹

¹Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, ²Center for Clinical Excellence, BJC HealthCare, ³Department of Pharmacy, Barnes-Jewish Hospital, ⁴Department of Pharmacy Practice, St. Louis College of Pharmacy, and ⁵BJC Home Care Services, St. Louis, Missouri

A cluster of cefepime-induced neutropenia (CIN) was identified from June 2017 to May 2018 in a regional outpatient parenteral antimicrobial therapy population. Our data suggest prolonged courses of cefepime (≥ 2 weeks), administered by rapid intravenous push, were associated with a higher risk of CIN.

Keywords. cefepime; cefepime-induced neutropenia; drug-induced neutropenia; adverse drug event; OPAT.

Cefepime is a fourth-generation cephalosporin antibiotic that is commonly used for outpatient parenteral antimicrobial therapy (OPAT) [1]. Neutropenia is reported in fewer than 1% of cefepime courses from post-marketing studies [2]. In published studies, neutropenia has been associated with prolonged cefepime usage (range, 17–30 days) and is reversible upon discontinuation [3–6]. In March 2018, we observed a cluster of neutropenia events among our patients receiving cefepime for OPAT. In this report, we describe the verification of this cluster and characterize the risk factors associated with this adverse drug event.

METHODS

To verify a cluster of cefepime-induced neutropenia (CIN), we conducted a retrospective cohort study of all outpatients ≥ 18 years old who received cefepime through BJC Home Care Services (BJC-HCS) from January 2016 to May 2018. BJC-HCS is a comprehensive home-health agency that provides home infusion services for a 15-hospital network in the St Louis, Missouri, region. Patients were excluded if they had any of the following: (1) missing lab, drug, or therapy data; (2) pre-existing

neutropenia, defined as an absolute neutrophil count (ANC) ≤ 1700 cells/mm³ (institutional lower limit of normal) for ≤ 2 weeks before starting cefepime; (3) persistent neutropenia, defined as an ANC of ≤ 1000 cells/mm³ for > 2 weeks after cefepime discontinuation; or (4) chemotherapy or bone marrow transplantation ≤ 21 days before starting cefepime.

As some patients received more than 1 course of cefepime during the study period, each course of cefepime (defined as administration of cefepime without interruption for ≥ 48 hours) was analyzed separately. Probable CIN was defined as (1) a reduction of ANC during a course of cefepime to ≤ 1000 cells/mm³ from a baseline of > 1700 cells/mm³ (institutional lower limit of normal); and (2) a complete recovery of neutropenia after the discontinuation of cefepime. This case definition is in accordance with the Naranjo adverse drug reaction probability scale [7]. The method of cefepime administration was categorized as either an intravenous push (IVP) or standard infusion. The IVP of cefepime was performed using a syringe and was given over 3–5 minutes. The standard infusion of cefepime was administered over 30–60 minutes via mini-bag, an elastomeric device, or a syringe pump. The collected variables for each participant included demographics, the Charlson comorbidity index, the primary diagnosis at the start of cefepime course, the cefepime dose, the duration of therapy, the method of administration, the cefepime distributor, the National Drug Code (NDC), and lot numbers.

Fisher's exact and Wilcoxon rank sum tests were used for categorical and continuous variables, respectively. A log-linked binomial regression model was conducted to identify the risk factors associated with CIN (SAS Version 7.1, SAS Institute Inc., Cary, NC). All regression models were binomial, with 1 risk factor. A sensitivity analysis was performed at the patient level after adjusting for the number of cefepime courses to address the assumption of independence when fitting a binomial regression model. Multivariable models were not used, due to the small sample size and the low number of CIN cases. This study was approved by the Human Research Protection Office at Washington University in St. Louis.

RESULTS

A total of 326 patients received 402 treatment courses of cefepime during the study period (Supplementary Figure 1). Of these, 11 patients met the case definition of CIN. As depicted in the epidemic curve (Figure 1), the clustering of CIN suggested that there were 2 time periods of interest (Period 1, January 2016 to May 2017; Period 2, June 2017 to May 2018). The incidence of CIN increased significantly, from 0.9% (2 cases per 234 courses) during Period 1 to 5.4% (9 cases per 168

Received 9 November 2018; editorial decision 14 December 2018; accepted 21 December 2018; published online December 24, 2018.

Correspondence: Y. Hamad, Division of Infectious Diseases, Washington University School of Medicine, Campus Box 8051, 4523 Clayton Ave, St. Louis, MO 63110 (yhamad@wustl.edu). *Clinical Infectious Diseases*® 2019;69(3):534–7

© The Author(s) 2018. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/ciy1112

Figure 1. Epidemic curve of cefepime-induced neutropenia from January 2016 to May 2018.

courses) during Period 2. Based on the clustering of cases, further analyses were restricted to Period 2. Of the 168 treatment courses in Period 2, all patients with CIN had only 1 treatment course, while 20 patients (14.7%) with non-CIN had >1 treatment course (Supplementary Figure 1). The median duration difference between the treatment courses was 62 days.

Baseline demographics are summarized in Table 1. Patients with CIN had a lower Charlson comorbidity index ($P = .001$), compared to non-CIN cases. The median cumulative cefepime dose for the CIN and non-CIN groups were 102.9g (interquartile range [IQR] 59.1–136.3) and 67.0g (IQR 39.4–118.3), respectively ($P = .25$). All CIN cases received ≥ 2 week courses of therapy ($P = .014$). CIN cases were 3 times more likely than non-CIN cases to receive IVP (77.8% vs 24.5%, respectively; $P = .002$). Among patients with CIN, the 30-day mortality was 0%. Correlations identified between CIN and the distributor, NDC codes, or lot numbers were considered uninterpretable, due to the small numbers involved.

In a log-linked binomial regression model, cefepime administered by IVP was associated with a significantly higher risk of developing neutropenia (relative risk [RR] 9.28, 95% confidence interval [CI] 2.00–43.06). A sensitivity analysis at the patient level, after adjusting for the number of cefepime courses, yielded a similar result (RR 7.0, 95% CI 1.56–31.72). Other covariates were not significantly associated with CIN in our regression model (Supplementary Table 1). In a further subgroup analysis among patients receiving cefepime therapy for ≥ 2 weeks, IVP's risk for CIN was 7.42 times higher (95% CI 1.63–33.81). Lastly, examination by stratification did not

indicate the presence of confounding factors, nor suggest the need for statistical adjustment.

We also explored the characteristic differences in covariates by infusion type. Males were more likely to receive IVP ($P = .005$). However, there were no other significant differences in age, race, Charlson comorbidity index, baseline ANC, and cumulative cefepime dose (Supplementary Table 2).

DISCUSSION

To date, CIN has been reported in individual cases and small cohorts [3–6]. Our findings showed an increased incidence of CIN from a baseline of 0.9% to 5.4% during the 2 time periods. Only a single other published report describes an elevated rate of CIN (62%, $n = 8/13$). However, this low-volume case series of cefepime, used to treat osteomyelitis, lacked rigorous case definitions and statistical analyses [4]. The clustering of CIN observed in Period 2 in our study has not been described previously. The risk factors associated with CIN remain poorly understood. Our study identified rapid IVP as a potential novel and modifiable risk factor for CIN. Given the strength of the association and the negligible logistical differences between the methods of administration, our institution no longer administers cefepime via IVP. Since that time, we have not identified any cases of CIN through our ongoing surveillance effort.

Various studies of rapid cefepime administration via IVP for short-term therapy have concluded that it is safe, practical, and cost-effective, without compromising its pharmacokinetics [8–10]. Limited data are available regarding the long-term safety

Table 1. Demographic and Clinical Characteristics of the Study Groups from June 2017 to May 2018 (Period 2)

	CIN (n = 9)	Non-CIN (n = 159)	P Value ^a
Age, median (IQR)	54 (33–66)	54 (31–59)	.54
Gender	...	...	.30
Male, n (%)	7 (77.8)	87 (54.7)	...
Female, n (%)	2 (22.2)	72 (45.3)	...
Race	...	...	.20
White, n (%)	5 (55.6)	123 (77.3)	...
Black, n (%)	3 (33.3)	26 (16.3)	...
Other, n (%)	1 (11.1)	10 (6.4)	...
Charlson comorbidity index scoring	...	...	.001
0, n (%)	7 (77.8)	34 (21.4)	...
1–2, n (%)	0 (0)	66 (41.5)	...
3–4, n (%)	1 (11.1)	29 (18.2)	...
≥5, n (%)	1 (11.1)	30 (18.9)	...
Baseline ANC, as cells/mm ³ , median (IQR)	4.9 (4.3–5.8)	5.7 (4.2–8.3)	.24
Duration of cefepime therapy	...	...	.014
< 2 weeks, n (%)	0 (0)	65 (40.9)	...
≥ 2 weeks, n (%)	9 (100)	94 (59.1)	...
Cumulative cefepime dose, in g, median (IQR)	102.9 (59.1–136.3)	67.0 (39.4–118.3)	.25
Mode of administration of cefepime	...	...	.002
Standard infusion, n (%)	2 (22.2)	120 (75.5)	...
IVP, n (%)	7 (77.8)	39 (24.5)	...
Syringe utilization	...	...	.038
Yes, n (%)	8 (88.9)	85 (53.5)	...
No, n (%)	1 (11.1)	74 (46.5)	...
Simultaneous use of other antibiotic therapy	...	...	.32
Yes, ^b n (%)	5 (55.6)	61 (38.4)	...
No, n (%)	4 (44.4)	98 (61.6)	...

Abbreviations: ANC, absolute neutrophil count; CIN, cefepime-induced neutropenia; IQR, interquartile range; IVP, intravenous push.

^aFor continuous variables, *P* values were determined by the Wilcoxon rank sum test; for categorical variables, *P* values were determined by Fisher's exact test (all categorical variables had at least 25% of the cells with an expected count less than 5). Variables were not normally distributed; thus, non-parametric tests were used.

^bOther antimicrobials include intravenous vancomycin, daptomycin, metronidazole, fluconazole, and trimethoprim-sulfamethoxazole.

profile of cefepime IVP. Briggs et al reported a 3% incidence of β -lactam-induced neutropenia among patients who received prolonged β -lactams therapy administered by IVP [11]. Similarly, we found that administration via IVP was significantly associated with CIN in patients who received prolonged cefepime therapy. Further studies are required to explore this association, including the investigation of a plausible biological basis for this phenomenon.

This potential link between CIN and the administration of cefepime via IVP highlights a significant risk of the increasingly frequent pharmaceutical shortages occurring in the United States.

Hurricane Maria's devastation on Puerto Rico further exacerbated the pharmaceutical manufacturing capacity of an already-depleted national shortage of small-volume parenteral solutions in September 2017 [12, 13]. This necessitated the implementation of conservation measures of small-volume parenteral solutions at our institution. Thus, certain medications, including cefepime, were changed to IVP administration. This led to a rise of cefepime IVP from 24.3% (January 2016 through September 2017) to 33.3% (October 2017 through May 2018).

Our study clinically links cefepime exposure, particularly the rapid infusion of cefepime, to a risk of neutropenia. The biologic mechanism behind CIN is unknown, though it is postulated to be due to a direct hemotoxic effect or an immune-mediated response [14, 15]. Bone marrow aspirates in patients with β -lactam-induced neutropenia demonstrated a lack of well-differentiated myeloid elements in the setting of numerous granulocyte precursors, suggesting inhibition of the proliferation stage of myelopoiesis. In vitro data revealed similar findings, in which the addition of β -lactam resulted in the dose-dependent inhibition of granulopoiesis [14]. An early study by Olaison et al found a significant correlation between antibodies directed against penicillin and delayed adverse reactions during β -lactam treatment, favoring the hypothesis of an immune mechanism [15]. How the rapid infusion of cefepime could influence either of these mechanisms is unclear.

The morbidity and mortality of β -lactam-induced neutropenia is not well elucidated in the current literature [4, 11, 16, 17]. Although this adverse drug event is generally reversible, the development of severe neutropenia is potentially dangerous and may lead to life-threatening complications. Consistent with

previous studies of β -lactam-induced neutropenia, there were no deaths observed in this cohort [4, 11, 16, 17]. In addition, the small number of cases and the fact that cefepime is indicated for the treatment of febrile neutropenia may have contributed to the apparently benign nature of CIN in our patients.

In conclusion, our data demonstrate that prolonged use of cefepime, administered via IVP, may be a risk factor for CIN. Not only does this have clinical implications for the safe treatment of complex infections, it underscores the potential, indirect public health impacts of intravenous fluid and other medical supply shortages.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The content in this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial support. This work was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (award number KL2TR002346 to M. J. D.).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Norris AH, Shrestha NK, Allison GM, et al. IDSA clinical practice guideline for the management of outpatient parenteral antimicrobial therapy. *Clin Infect Dis* **2019**; 68:e1–35.
- Hospira. Maxipime (cefepime) [prescribing information]. Lake Forest, Illinois: Hospira, **2017**.
- Dahlgren AF. Two cases of possible cefepime-induced neutropenia. *Am J Health Syst Pharm* **1997**; 54:2621–2.
- Wong BB, Ko GJ. Neutropenia in patients receiving long-term cefepime therapy for osteomyelitis. *Am J Health Syst Pharm* **2003**; 60:2229–32.
- Hettmer S, Heeney MM. Cefepime-induced neutropenia in a teenager. *Pediatr Blood Cancer* **2008**; 51:715–6.
- Malincarne L, Francisci D, Martinelli L, Masini G, Baldelli F. A case of severe cefepime-related neutropenia in a 15-year-old patient. *Scand J Infect Dis* **2010**; 42:156–7.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* **1981**; 30:239–45.
- Garrelts JC, Wagner DJ. The pharmacokinetics, safety, and tolerance of cefepime administered as an intravenous bolus or as a rapid infusion. *Ann Pharmacother* **1999**; 33:1258–61.
- Butterfield-Cowper JM, Burgner K. Effects of i.v. push administration on β -lactam pharmacodynamics. *Am J Health Syst Pharm* **2017**; 74:e170–5.
- McLaughlin JM, Scott RA, Koenig SL, Mueller SW. Intravenous push cephalosporin antibiotics in the emergency department: a practice improvement project. *Adv Emerg Nurs J* **2017**; 39:295–9.
- Briggs S, Smith S, Ritchie S, Fitzharris P, Ellis-Pegler R. Late-onset bolus intravenous beta-lactam antibiotic adverse reaction: short-lived symptoms during drug administration and associated laboratory abnormalities. *Scand J Infect Dis* **2014**; 46:14–20.
- US Food and Drug Administration. Updates on some ongoing shortages related to IV fluids. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592617.htm>. Accessed 16 July 2018.
- Sacks CA, Kesselheim AS, Fralick M. The shortage of normal saline in the wake of Hurricane Maria. *JAMA Intern Med* **2018**; 178:885–6.
- Neftel KA, Hauser SP, Müller MR. Inhibition of granulopoiesis in vivo and in vitro by beta-lactam antibiotics. *J Infect Dis* **1985**; 152:90–8.
- Olaisson L, Belin L, Hogevis H, Alestig K. Incidence of beta-lactam-induced delayed hypersensitivity and neutropenia during treatment of infective endocarditis. *Arch Intern Med* **1999**; 159:607–15.
- Peralta FG, Sánchez MB, Roíz MP, Pena MA, Tejero MA, Arjona R. Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis* **2003**; 37:1568–72.
- Furtek KJ, Kubiak DW, Barra M, Varughese CA, Ashbaugh CD, Koo S. High incidence of neutropenia in patients with prolonged ceftaroline exposure. *J Antimicrob Chemother* **2016**; 71:2010–3.