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MAJOR ARTICLE

Out of Sight—Out of Mind: Impact of Cascade Reporting on Antimicrobial Usage

Siyun Liao,[1] Judith Rhodes,[2] Roman Jandarov,[3] Zachary DeVore,[4] and Madhuri M. Sopirala[5]

[1]Department of Pharmacy, University of Cincinnati Medical Center, Cincinnati, Ohio, USA, [2]Department of Pathology, University of College of Medicine, Cincinnati, Ohio, USA, [3]Division of Biostatistics and Bioinformatics, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA, [4]University of Cincinnati College of Medicine, Cincinnati, Ohio, USA, and [5]Division of Infectious Diseases, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Background. There is a paucity of data evaluating the strategy of suppressing broader-spectrum antibiotic susceptibilities on utilization. Cascade reporting (CR) is a strategy of reporting antimicrobial susceptibility test results in which secondary (eg, broader-spectrum, costlier) agents may only be reported if an organism is resistant to primary agents within a particular drug class. Our objective was to evaluate the impact of ceftriaxone-based cascade reporting on utilization of cefepime and clinical outcomes in patients with ceftriaxone-susceptible *Escherichia* and *Klebsiella* clinical cultures.

Methods. We compared post-CR (July 2014–June 2015) with baseline (July 2013–June 2014), evaluating utilization of cefepime, cefazolin, ceftriaxone, ampicillin derivatives, fluoroquinolones, piperacillin/tazobactam, ertapenem, and meropenem; new *Clostridium difficile* infection; and length of stay (LOS) after the positive culture, 30-day readmission, and in-hospital all-cause mortality.

Results. Mean days of therapy (DOT) among patients who received any antibiotic for cefepime decreased from 1.229 days during the baseline period to 0.813 days post-CR (adjusted relative risk, 0.668; $P < .0001$). Mean DOT of ceftriaxone increased from 0.864 days to 0.962 days, with an adjusted relative risk of 1.113 ($P = .004$). No significant differences were detected in other antibiotics including ertapenem and meropenem, demonstrating the direct association of the decrease in cefepime utilization with CR based on ceftriaxone susceptibility. Average LOS in the study population decreased from 14.139 days to 10.882 days from baseline to post-CR and was found to be statistically significant ($P < .0001$).

Conclusions. In conclusion, we demonstrated significant association of decreased cefepime utilization with the implementation of a CR based on ceftriaxone susceptibility. We demonstrated the safety of deescalation, with LOS being significantly lower during the post-CR period than in the baseline period, with no change in in-hospital mortality.

Keywords. cascade reporting; cefepime; selective reporting; suppression; stewardship.

Broad-spectrum antibiotic use in hospitals is inevitable in the age of multidrug resistance. However, best practice dictates that deescalation of antibiotics occur as soon as the organism is identified and susceptibility results are available. This provides an opportunity for physicians to limit population exposure to broad-spectrum antibiotics and combat development of antimicrobial resistance [1]. Active deescalation to narrower-spectrum antibiotics can prevent superinfections from bacteria such as *Clostridioides difficile*, prevent toxicities associated with broad-spectrum agents, and reduce health care expenditure. The process of active audit of antibiotics to aid with deescalation is very labor-intensive, thus limiting these efforts to focus on expensive and infrequently used antibiotics [2, 3].

The Clinical and Laboratory Standards Institute (CLSI) describes cascade reporting (CR) as a strategy of reporting antimicrobial susceptibility test results in which secondary (eg, broader-spectrum, costlier) agents may only be reported if an organism is resistant to primary agents within a particular drug class [4]. This offers antimicrobial stewardship programs (ASPs) a less resource-intensive way to guide clinicians toward using narrower-spectrum agents. However, there is a paucity of data evaluating the outcomes of this approach in literature. Many of the published studies are descriptive studies without baseline data before implementation [5, 6], or small studies that used survey questionnaires from prescribers instead of using actual antimicrobial usage data [7, 8], or case vignette studies using hypothetical patients instead of real patients [9]. To our knowledge, only 2 prior studies have evaluated the clinical impact of this approach by comparing clinical outcomes before and after CR implementation. One of them reported dramatic changes in susceptibility patterns of certain antibiotics within a 1-year

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Correspondence: M. M. Sopirala, MD, MPH, FIDSA, 5323 Harry Hines Blvd, Dallas, TX 75390-9113 (msopirala@gmail.com).

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period, favoring the use of a restrictive reporting approach [10]. The other study evaluated the outcomes of CR of multiple antibiotic classes for positive blood cultures with any Gram-negative organism and showed promising results [11]. In our CR, susceptibilities for cefepime and meropenem were released only if the organism was resistant to ceftriaxone and cefepime, respectively. Our objective was to evaluate the impact of ceftriaxone-based CR on utilization of cefepime and on clinical outcomes in patients with ceftriaxone-susceptible *Escherichia* and *Klebsiella* clinical cultures.

METHODS

Study Design and Patient Population

This is a retrospective cohort study comparing utilization of cefepime during baseline (July 2013–June 2014) and post-CR (July 2014–June 2015) periods at a 699-bed tertiary care academic medical center. The hospital provides care to a wide range of patients including those in 5 intensive care units (ICUs)—medical, surgical, cardiovascular, neurosurgical, and burns surgical care. It is a level 1 trauma center with wide range of patients in medicine, general surgery, trauma, hematology/oncology, neurology, bone marrow transplant, and solid organ transplant. It uses Epic as its electronic medical record (EMR). The ASP consisted of an infectious diseases physician and an infectious diseases pharmacist. Five infectious diseases physicians, a clinical microbiologist, and clinical pharmacists from all specialties in the hospital served on the antimicrobial stewardship committee.

The study period was from July 2013 to June 2015. All patient encounters with the following criteria were included in the study: (a) physician prescription of antimicrobial treatment within 7 days pre- and postidentification of ceftriaxone-susceptible *Escherichia* spp. and *Klebsiella* spp. and (b) *Escherichia* spp. and *Klebsiella* spp. susceptible to ceftriaxone and not part of a polymicrobial culture. Each patient was counted only once per episode of antibiotic treatment regardless of whether the patient grew the organism from multiple sources. All cultures positive for ceftriaxone-susceptible *Escherichia* spp. and *Klebsiella* spp. were extracted from the electronic medical record using the Health System's Data Warehouse, and S.L. manually confirmed "a" and "b" by reviewing the extracted data and performing a chart review. Data extracted from the electronic medical record using the Data Warehouse included demographic information, antimicrobial therapy, microbiological data, new *C. difficile* infection up to 30 days after the positive *Escherichia* or *Klebsiella* culture, length of stay (LOS), 30-day readmission, and in-hospital all-cause mortality. Data extracted from the warehouse were validated by S.L. for antimicrobial stewardship. The study was determined to be not human subjects research by our institution's institutional review board.

Antibiotic Susceptibility Reporting and CR Schema

Organism identification and antibiotic susceptibilities were determined using VITEK. Organisms with an MIC of ≤8 mcg/mL to ceftriaxone were reported to be susceptible, and those with an MIC of ≤8 mcg/mL to cefepime were reported to be susceptible, in accordance with the CLSI susceptibility breakpoints from 2009 [12]. Before the implementation of CR, results from VITEK were directly captured through an interface and reported through the hospital's electronic medical record. Susceptibility results were reported for all antibiotics tested; the specific grouping of antibiotics chosen for testing was based on the organism group, as recommended by the CLSI. We developed and implemented a CR algorithm in collaboration with the antimicrobial stewardship program and microbiology laboratory for all Enterobacteriaceae in July 2014. We built suppression rules into the laboratory interface that were reflected in electronic antibiotic susceptibility reports. CR was based on the susceptibility of ceftriaxone and cefepime (Figure 1). If ceftriaxone was susceptible, cefepime and meropenem susceptibilities were not released. If ceftriaxone was resistant, the cefepime susceptibility result was released. If cefepime was resistant, the meropenem susceptibility result was released. For Enterobacteriaceae, the results for ampicillin, ampicillin/sulbactam, cefazolin, piperacillin/tazobactam, ciprofloxacin, gentamicin, tobramycin, trimethoprim/sulfamethoxazole, and nitrofurantoin (urine isolates only) susceptibilities were always reported. Of note, our institution was not affected by any antibiotic shortage during the study period.

Outcomes

The primary end point was the difference in mean days of therapy of cefepime per encounter among patients who received any antibiotic (DOT) during the baseline and post-CR periods. Secondary end points included DOT of individual antibiotics, piperacillin/tazobactam, meropenem, ertapenem, ciprofloxacin, ceftriaxone, aminopenicillins with and without beta-lactamase inhibitors and cefazolin, incidence of *C. difficile* infection within 30 days of reporting of a positive culture for *Enterobacter* or *Klebsiella* spp., length of stay (LOS) following reporting of a positive culture, 30-day readmission, and all-cause mortality during the same admission.

Statistical Analysis

Statistical analyses were performed using R, version 3.3.0.28. The associations between the baseline and post-sCR period and the days of therapy for each antibiotic were examined by performing a series of Poison regression analyses adjusting for the age and sex of each patient. As 6 antibiotics were analyzed, the Bonferroni correction factor ($\alpha = .05/6 = .008$) was utilized as the significance threshold. The binary secondary end points, 30-day readmission and all-cause mortality and incidence of *C. difficile* infection, were analyzed using logistic regression

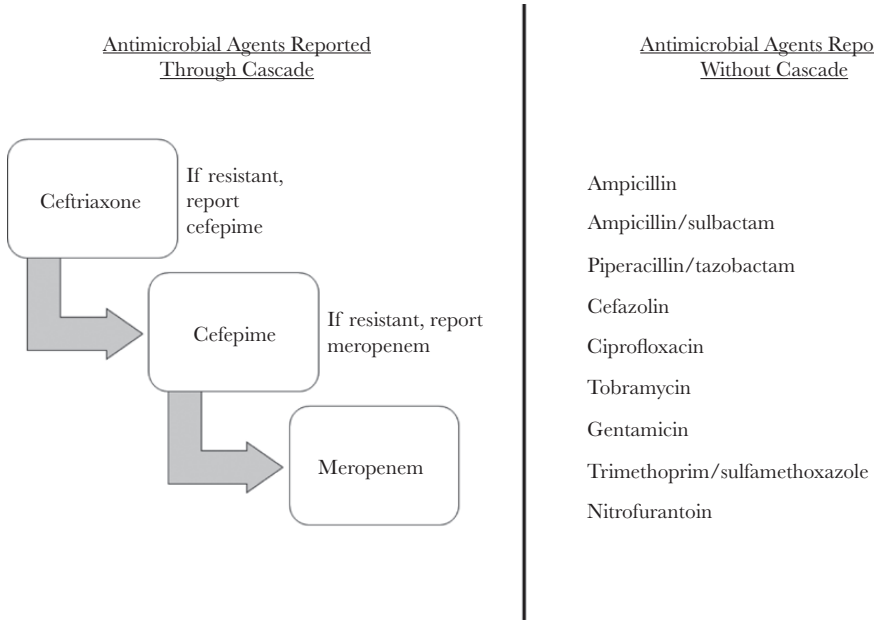

Figure 1. Cascade Reporting for Enterobacteriaceae.

models. The length of stay was considered a continuous variable and analyzed using a multiple regression approach. For these secondary end points, the Bonferroni-corrected significance level was equal to α = .05/4 = .01. The relative risks from Poisson regressions, odds ratios from logistic regressions, and beta coefficients from multiple regressions and corresponding intervals were calculated and reported at 95% level. All statistical analyses were 2-sided, and the *P* values below the Bonferroni-adjusted thresholds were considered statistically significant.

RESULTS

There were 1901 episodes of antibiotic treatment in response to a positive clinical culture for *Escherichia* and *Klebsiella* spp. that met criteria for inclusion in the study. There were 852 episodes during the baseline period and 1049 episodes post-CR (Table 1).

Days of Therapy for Cefepime and Other Antibiotics

As can be seen in Table 2, the decrease in mean DOT for cefepime from baseline to post-CR was from 1.229 days to 0.813 days. This decrease was found to be statistically significant ($P < .0001$), with an adjusted relative risk of 0.668. There was also a small but statistically significant increase in days of therapy for ceftriaxone from 0.864 days to 0.962 days, with an adjusted relative risk of 1.113 ($P = .004$). All other comparisons failed to detect any significant differences between mean DOT during the baseline and post-CR periods. Our study population had a median number of antibiotic days (interquartile range) of 5 (3–9) during the study period. Our prospective audit and feedback for our program included surveillance of meropenem, which continued during both the baseline and post-CR periods with no changes in the process of review by the ASP pharmacist. Only 2 patients in the baseline period and 2 patients during the post-CR period received treatment with meropenem in the study population, and none received ertapenem.

Table 1. Demographic Information of Each Patient Encounter With *Escherichia* or *Klebsiella* spp. Culture and the Source of Cultures

	Baseline (852)	Post-CR (1049)
Age, median (IQR), y	59 (46–70)	59 (47.5–71)
Male, No. (%)	361 (42.3)	431 (41.1)
Source infection, No. (%)		
UTI	672 (78.9)	839 (80.0)
Pneumonia	195 (22.3)	177 (16.9)
Bacteremia	97 (11.4)	129 (12.3)

Abbreviations: CR, cascade reporting; IQR, interquartile range; UTI, urinary tract infection.

Clostridium difficile Infection, Mortality, Readmission, and Length of Stay

The results of the analysis of the secondary end points are presented in Table 3. Based on logistic regression, the decrease in average length of stay from 14.139 days to 10.882 days from baseline to post-CR was found to be statistically significant ($P < .0001$). The observed difference in the average proportion of patients with *C. difficile* infection between the baseline and post-CR periods was not statistically significant ($P = .59$). The observed difference in average proportion of patients with readmission within 30 days between the baseline and post-CR periods was not statistically significant ($P = .073$). There were no in-hospital deaths either in the baseline or post-CR period.

Table 2. Mean Levels and Adjusted Relative Risks and Corresponding Confidence Intervals for Days of Therapy During the Baseline and Post-CR Periods (Significance Threshold α = 0.008)

Antibiotic	Mean[a] ± SE	RR[b] (95% CI)	*P*[b]
Piperacillin/tazobactam (n = 474)			
Baseline	1.006 ± 0.083	-	
Post-CR	0.995 ± 0.064	0.998 (0.884 to 1.128)	.973
Cefepime (n = 430)			
Baseline	1.229 ± 0.113	-	
Post-CR	0.813 ± 0.056	0.668 (0.592 to 0.753)	<.0001[c]
Ciprofloxacin (n = 489)			
Baseline	0.864 ± 0.075	-	
Post-CR	0.962 ± 0.065	1.112 (0.979 to 1.264)	.028
Ceftriaxone (n = 810)			
Baseline	1.486 ± 0.086	-	
Post-CR	1.661 ± 0.076	1.113 (1.009 to 1.227)	.004[c]
Aminopenicillins ± beta-lactamase inhibitors (n = 88)			
Baseline	0.142 ± 0.026	-	
Post-CR	0.147 ± 0.026	1.033 (0.750 to 1.423)	.790
Cefazolin (n = 388)			
Baseline	0.664 ± 0.069	-	
Post-CR	0.718 ± 0.056	1.086 (0.938 to 1.258)	.138

Abbreviations: CI, confidence interval; CR, cascade reporting; RR, relative risk.

[a]Mean days of therapy for each antibiotic among patients who received any antibiotic.

[b]Analyses are adjusted for age (continuous) and sex (male, female) of patients.

[c]Statistically significant.

DISCUSSION

Antimicrobial stewardship programs face challenges in streamlining antimicrobial usage among clinicians [13, 14]. Despite studies showing broad-spectrum antimicrobial usage resulting in multidrug resistance, clinicians continue using these antibiotics for the entire duration of antibiotic treatment regardless of susceptibility pattern of the organism causing the infection [15, 16]. To combat this, many ASPs try to manually review broad-spectrum antibiotic use and provide recommendations on deescalation to narrower-spectrum antibiotics when appropriate [17, 18]. This process is labor-intensive and thus limits the extent of deescalation recommendations that ASPs can make to clinicians [2, 3]. It is further dependent on the clinicians' willingness to follow ASPs' recommendations [19]. EMRs and computerized provider order entry have been used in antimicrobial stewardship [20].

Table 3. Evaluation of *Clostridium difficile*, Mortality, Readmission Within 30 Days, and Length of Stay During the Baseline and Post-CR Periods

	Proportion ± SE	OR[a] or Beta (95% CI)	*P*[a,b]
Clostridium difficile			
Baseline	0.130 ± 0.012	-	
Post-CR	0.115 ± 0.010	0.918 (0.652 to 1.293)	.549
Mortality			
Baseline	0	-	
Post-CR	0	-	N/A
Readmission within 30 d			
Baseline	0.117 ± 0.011	-	
Post-CR	0.091 ± 0.009	0.760 (0.513 to 1.127)	.073
	Mean ± SE	Beta[a] (95% CI)	*P*[a,c]
Length of stay, d			
Baseline	14.139 ± 0.458	-	
Post-CR	10.882 ± 0.344	–2.767 (–4.021 to –1.514)	<.0001[d]

Abbreviations: CI, confidence interval; CR, cascade reporting; OR, odds ratio; RR, relative risk.

[a]Analyses are adjusted for age (continuous), sex (male, female), and days of therapy of each individual antibiotic.

[b]Significance threshold α = .01.

[c]Significance threshold α = .017.

[d]Statistically significant.

In this study, we used a ceftriaxone-based CR strategy removing broad-spectrum antibiotics from the sight of the prescribers who were prescribing antibiotics for the most common gram-negative organisms that were susceptible to ceftriaxone, *Escherichia* and *Klebsiella* spp., and succeeded in significantly decreasing cefepime use by these prescribers.

There is evidence suggesting that physicians choose antibiotics based on their experience as trainees, with their prescribing behaviors modeled after their supervisors or attending physicians [21]. In our experience, clinicians' empiric antibiotic choice depended on their familiarity with that antibiotic. Once chosen, the same antibiotic was being continued if culture result indicated that the organism was susceptible to it were more familiar. To address this observed pattern, we used a ceftriaxone-based CR strategy removing broad-spectrum antibiotics from the sight of the prescribers and succeeded in significantly decreasing cefepime use.

In addition to finding a significant decrease in DOT with cefepime in the post-CR period, we also found that ceftriaxone use significantly increased during this period, supporting the conclusion that CR drove up the use of ceftriaxone, the antimicrobial that the cascade reporting was based upon in our study. There was no statistically significant change in the utilization of other antibiotics including piperacillin/tazobactam, ampicillin/sulbactam, cefazolin, and fluoroquinolone. However, the combined DOT of antibiotics other than cefepime increased. The cefepime mean DOT among all patients who received any antibiotic decreased by 0.416 in the post-CR compared with the pre-CR period. At the same time, we saw an overall increase in the combined mean DOT of ceftriaxone, ciprofloxacin, aminopenicillins ± beta-lactamase inhibitors, and cefazolin/cephalexin by 0.332. We do not have data on whether there was an increase in the use of other oral antibiotics that were not included in the study. As discussed in the "Results" section, meropenem and ertapenem were minimally used at our institution throughout the study period (pre-CR and post-CR).

We demonstrated the safety of deescalation in this study. If one fears that deescalation to a narrower-spectrum antibiotic would be inadequate treatment, one could speculate that it would increase the LOS and mortality. In fact, LOS was significantly lower during the post-CR period than in the baseline period. This finding may be a surrogate marker for the ease of transition to outpatient with once-daily dosing of the antibiotic (ceftriaxone), rather than a switch from the broader-spectrum, multiple-daily-dose antibiotic just before the patient is discharged, which could potentially delay discharge procedures and lengthen hospital stay. This finding has not been adjusted for severity of illness. It is less likely that there were differences in severity of illness in the pre-CR and post-CR periods, given that our hospital quality data did not indicate a change in hospital-wide severity of illness through the study period (data not shown). Nevertheless, our data highlight that there was no increase in mortality or 30-day hospital readmissions as a result of cascade reporting. We were able to show these results to our clinicians to demonstrate the benefits of deescalation to them and remove any concerns. Other investigators have shown protective benefit of antibiotic deescalation on in-hospital mortality [22]. We did not see any difference in *C. difficile* infections between the baseline and post-CR periods. Our resistance patterns did not change throughout the study period based on our institutional antibiogram (not shown). We followed patients for development of *C. difficile* infection for 30 days postdischarge.

Our study has its limitations. First, being a retrospective study, it did not allow for the advantages of a randomized controlled trial. Randomization was not feasible, because the health system shares 1 electronic medical record and has constant crossover of clinicians between different patient care units. In addition, the ethical acceptability of control groups in situations perceived as threatening to patients (such as broader-spectrum antibiotic usage leading to unfavorable outcomes) was another obstacle, as described in other studies [23, 24]. Second, this was a single-center study that included a diverse population of patients with a large sample size. The medical center where this study was conducted is similar to national benchmarks in many patient outcomes in the metrics included in the Medicare Hospital Compare website (http://www.medicare.gov/hospitalcompare), suggesting that these findings may be generalizable to other medical centers. We believe that this intervention could be duplicated with ease in any hospital setting.

CONCLUSIONS

We demonstrated a significant association of decreased cefepime utilization with the implementation of a CR based on ceftriaxone susceptibility. We also showed a significant association of better LOS with the implementation of CR and did not see a change in in-hospital mortality with deescalation. It is a valuable tool to promote better prescription practices among clinicians with minimal resource utilization.

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