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

Authors:
Siyun Liao, Department of Pharmacy, University of Cincinnati Medical Center, Cincinnati, OH, USA
Judith Rhodes, Department of Pathology, University of College of Medicine, Cincinnati, OH, USA
Roman Jandarov, Division of Biostatistics and Bioinformatics, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH, USA
Zachary DeVore, University of Cincinnati College of Medicine, Cincinnati, OH, USA
Madhuri M. Sopirala, Division of Infectious Diseases, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA*

Contact Information:

*Corresponding Author:
Madhuri M. Sopirala, MD, MPH, FIDSA
E-mail: msopirala@gmail.com
Phone: 614-602-9064

Alternate Corresponding Author:
Siyun Liao, PPhD
E-mail: Siyun.liao@uchealth.com
Phone: 513-584-1073

Summary of the Article’s Main Point:
Cefepime utilization significantly decreased with the implementation of cascade reporting (CR) based on ceftriaxone susceptibility. We demonstrated the safety of de-escalation with LOS
significantly lower in post-CR period than in baseline period with no change in in-hospital mortality.

ABSTRACT

Background

There is 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 (e.g., 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 (CR) 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) to baseline (July 2013-June 2014) evaluating utilization of cefepime, cefazolin, ceftriaxone, ampicillin derivatives, fluoroquinolones, piperacillin/tazobactam, ertapenem and meropenem, and 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 among patients who received any antibiotic (DOT) for cefepime decreased from 1.229 days in baseline period to 0.813 days in post-CR (adjusted relative risk 0.668; P <0.0001). Mean DOT of ceftriaxone increased from 0.864 days to 0.962 days with the adjusted
relative risk of 1.113 (P = 0.004). No significant differences were detected in other antibiotics including ertapenem and meropenem demonstrating the direct association of the decrease in cefepime utilization to the cascade reporting based on ceftriaxone susceptibility. Average LOS in the study population decreased from 14.139 days to 10.882 days from baseline to post-CR was found to be statistically significant (P < 0.0001).

Conclusion

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 de-escalation with LOS significantly lower in post-CR period than in baseline period with no change in in-hospital mortality.

Key Words

Cascade reporting
Selective reporting
Suppression
Cefepime
Stewardship
Outcomes
INTRODUCTION

Broad-spectrum antibiotic use in hospitals is inevitable in the age of multidrug resistance. However best practice dictates that de-escalation 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 de-escalation to narrower spectrum antibiotics can prevent super-infections from bacteria such as *Clostridium difficile*, prevent toxicities associated with broad-spectrum agents, and reduce healthcare expenditure. The process of active audit of antibiotics to aid with de-escalation is very labor intensive thus limiting these efforts to focus on expensive and infrequently used antibiotics.\(^2,3\)

Clinical and Laboratory Standards Institute (CLSI) describes cascade reporting (CR) as a strategy of reporting antimicrobial susceptibility test results in which secondary (e.g., 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 (ASP) a less resource-intensive way to guide clinicians towards using narrower spectrum agents. However, there is paucity of data evaluating the outcomes of this approach in literature. Many of the published studies are descriptive studies without baseline data prior to 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 two prior studies have evaluated the clinical impact of this
approach comparing clinical outcomes before and after CR implementation. One of them reported dramatic changes in susceptibility patterns of certain antibiotics within a year period favoring the use of a restrictive reporting approach.\textsuperscript{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.\textsuperscript{11} In our CR, susceptibilities for cefepime and meropenem were release 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 \textit{Escherichia} and \textit{Klebsiella} clinical cultures.

**METHODS**

**Study design and patient population**

This is a retrospective cohort study comparing utilization of cefepime in the 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 five 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 patients. It used Epic as its electronic medical record (EMR). 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.

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 post-identification of ceftriaxone susceptible *Escherichia* spp. and *Klebsiella* spp., and

b) *Escherichia* spp. and *Klebsiella* spp are susceptible to ceftriaxone and not part of a polymicrobial culture. Each patient is counted only once per an episode of antibiotic treatment regardless of whether 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 by 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 warehouse has been 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 or less to ceftriaxone were reported to be susceptible, and an MIC of 8 mcg/ml or less to cefepime were reported to be susceptible in accordance with the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints from 2009.\(^\text{12}\)

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 CLSI. We developed and implemented a CR algorithm in collaboration with antimicrobial stewardship program and microbiology laboratory
for all Enterobacteriaceae in July 2014. We built suppression rules into the laboratory interface which 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, cefepime susceptibility result was released. If cefepime was resistant, 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 endpoint was the difference in mean days of therapy per encounter among patients who received any antibiotic (DOT) of cefepime in baseline and post-CR periods. Secondary endpoints included DOT of individual antibiotics, piperacillin/tazobactam, meropenem, ertapenem, ciprofloxacin, ceftriaxone, aminopenicillins with and without beta-lactamase inhibitors and cefazolin, incidence of *Clostridium difficile* infection within 30 days following 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 cascade reporting period and the days of therapy for each antibiotic were examined by performing a series of Poison regression analyses adjusting for age and sex of each
patient. Since six antibiotics were analyzed, the Bonferroni correction factor (alpha = 0.05/6=0.008) was utilized as the significance threshold. The binary secondary endpoints, 30-day readmission and all-cause mortality and incidence of \textit{C. difficile} infection, were analyzed using logistic regression models. The length of stay was considered as a continuous variable and analyzed using a multiple regression approach. For these secondary endpoints, the Bonferroni corrected significance level was equal to alpha = 0.05/4 = 0.01. The relative risks from Poisson regressions, odds ratios from logistic regressions, and beta coefficients from multiple regressions the corresponding intervals were calculated and reported at 95% level. All statistical analyses were two-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 \textit{Escherichia} and \textit{Klebsiella} spp. that met criteria for inclusion in the study. There were 852 episodes during baseline and 1049 episodes during 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 value <0.0001) with the 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 the adjusted relative risk of 1.113 (p value = 0.004). All other comparisons failed to detect any significant differences between mean DOT in baseline and post-CR periods. Our study population had median antibiotic days (interquartile range) of 5 (3, 9) during the study period.
Our prospective audit and feedback of our program included surveillance of meropenem, which continued during both baseline and post-CR periods with no changes in the process of review by ASP pharmacist. Only two patients in the baseline period and two patients during post-CR period received treatment with meropenem in the study population and none received ertapenem.

**Clostridium difficile infection, mortality, readmission and length of stay**

The results of the analysis of the secondary endpoints are presented in Table 3. Based on logistic regression, the decrease of the average length of stay from 14.139 days to 10.882 days from baseline to post-CR was found to be statistically significant (p value < 0.0001). The observed difference in average proportion of patients with *C. difficile* infection between the baseline and post-CR periods was not statistically significant (p value= 0.59). The observed difference in average proportion of patients with readmission within 30 days between baseline and post-CR periods was not statistically significant (p value= 0.073). There were no in-hospital deaths either in baseline or post-CR periods.

**DISCUSSION**

Antimicrobial stewardship programs face challenges in streamlining antimicrobial usage among clinicians. 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. In order to combat this, many ASP try to manually review broad spectrum antibiotic use and provide recommendations on de-escalation to narrower spectrum antibiotics when appropriate. This process is labor-intensive and thus limits the extent of de-escalation
recommendations that ASP can make to clinicians (2, 3). It is further dependent on the clinicians’ willingness to follow ASP’s recommendations.19 EMRs and computerized provider order entry have been used in antimicrobial stewardship.20

In this study, we used a ceftriaxone-based CR strategy removing broad-spectrum antibiotics out of sight of the prescribers who were prescribing antibiotics for the most common gram-negative organisms, Escherichia and Klebsiella spp. that were susceptible to ceftriaxone 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 were choosing the broad-spectrum antibiotics that they had most experience with and continuing the same antibiotic as the microbial susceptibility became available once it was confirmed that the organism being treated was susceptible to the antibiotic that was already being used. To address this observed pattern, we used a ceftriaxone-based CR strategy removing broad-spectrum antibiotics out of sight of the prescribers who were prescribing antibiotics for the most common gram-negative organisms, Escherichia and Klebsiella spp. that were susceptible to ceftriaxone and succeeded in significantly decreasing cefepime use by these prescribers.

In addition to finding a significant decrease in DOT with cefepime in post-CR period, we also found that ceftriaxone use has 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 use. However, the combined DOT of antibiotics other than cefepime has
increased. Cefepime mean DOT among all patients who received any antibiotic decreased by 0.416 in the post-CR compared to 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, 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 results, meropenem and ertapenem were minimally used at our institution throughout the study period (pre-CR and post-CR).

We demonstrated the safety of de-escalation in this study. If one fears that de-escalation to a narrower spectrum antibiotic was inadequate treatment, one could speculate that it would increase the LOS and mortality. In fact, LOS was significantly lower in post-CR period than in baseline period. This finding may be a surrogate marker for the ease of transition to outpatient with the once daily dosing of the antibiotic (ceftriaxone) rather than a switch from the broader spectrum, multiple daily dose antibiotic just before 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 pre-CR and post-CR periods given 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 highlights 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 de-escalation to them and remove any concerns. Other investigators have shown protective benefit of antibiotic de-escalation on in-hospital mortality.\textsuperscript{22} We did not see any difference in \textit{C. difficile} infections between 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 post discharge.

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 shared one electronic medical record and has constant cross-over 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 is a single-center study that included a diverse population of patients with a large sample size. The Medical Center where this study is 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 these findings may be generalizable to other medical centers. We believe that this intervention can be duplicated with ease in any hospital setting.

**CONCLUSIONS**

We demonstrated significant association of decreased cefepime utilization with the implementation of a CR based on ceftriaxone susceptibility. We also showed significant association of better LOS with the implementation of CR and did not see a change in in-hospital mortality with de-escalation. It is a valuable tool to promote better prescription practices among clinicians with minimal resource utilization.
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Figure 1

**Antimicrobial Agents Reported Through Cascade**

- Ceftriaxone
  - If resistant, report cefepime

- Cefepime
  - If resistant, report meropenem

- Meropenem

**Antimicrobial Agents Reported Without Cascade**

- Ampicillin
- Ampicillin/sulbactam
- Piperacillin/tazobactam
- Cefazolin
- Ciprofloxacin
- Tobramycin
- Gentamicin
- Trimethoprim/sulfamethoxazole
- Nitrofurantoin
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) | 59 (46, 70)    | 59 (47.5, 71)  |
| Male, n (%)      | 361 (42.3%)    | 431 (41.1%)    |
| **Source Infection n (%)**: | | |
| UTI             | 672 (78.9%)    | 839 (80.0%)    |
| Pneumonia       | 195 (22.3%)    | 177 (16.9%)    |
| Bacteremia      | 97 (11.4%)     | 129 (12.3%)    |

Table 1: Demographic information of each patient encounter with *Escherichia* or *Klebsiella* spp. culture and the source of cultures

Abbreviations: CR, Cascade reporting; SD, Standard deviation; UTI = Urinary tract infection
| Antibiotic                        | Mean$\# \pm$ SE | RR$^a$ (CI)       | $P$ Value$^a$ |
|----------------------------------|-----------------|------------------|--------------|
| **Piperacillin/tazobactam ($n = 474$)** |                 |                  |              |
| Baseline                         | 1.006 ± 0.083   | -                |              |
| Post-CR                          | 0.995 ± 0.064   | 0.998 (0.884, 1.128) | 0.973        |
| Cefepime ($n = 430$)             |                 |                  |              |
| Baseline                         | 1.229 ± 0.113   | -                |              |
| Post-CR                          | 0.813 ± 0.056   | 0.668 (0.592, 0.753) | <0.0001*     |
| **Ciprofloxacin ($n = 489$)**   |                 |                  |              |
| Baseline                         | 0.864 ± 0.075   | -                |              |
| Post-CR                          | 0.962 ± 0.065   | 1.112 (0.979, 1.264) | 0.028        |
| **Ceftriaxone ($n = 810$)**     |                 |                  |              |
| Baseline                         | 1.486 ± 0.086   | -                |              |
| Post-CR                          | 1.661 ± 0.076   | 1.113 (1.009, 1.227) | 0.004*       |
| **Aminopenicillins +/− beta-lactamase inhibitors ($n = 88$)** | | | |
| Baseline                         | 0.142 ± 0.026   | -                |              |
| Post-CR                          | 0.147 ± 0.026   | 1.033 (0.750, 1.423) | 0.790        |
| **Cefazolin ($n = 388$)**       |                 |                  |              |
| Baseline                         | 0.664 ± 0.069   | -                |              |
| Post-CR                          | 0.718 ± 0.056   | 1.086 (0.938, 1.258) | 0.138        |

Table 2: Mean levels and adjusted relative risks and corresponding confidence intervals for days of therapy in baseline and post-CR periods (significance threshold alpha = 0.008)

Abbreviations: SE, standard error; RR, relative risk; CI, confidence interval; CR, Cascade reporting

$^a$Mean days of therapy for each antibiotic among patients who received any antibiotic

$^a$Analyses are adjusted for age (continuous) and sex (male, female) of patients.

$^a$Statistically significant
|                          | Proportion ± SE | OR\textsuperscript{a} or Beta (CI) | P Value\textsuperscript{a,b} |
|--------------------------|-----------------|-----------------------------------|------------------------------|
| \textit{Clostridium difficile} |                 |                                   |                              |
| Baseline                 | 0.130 ± 0.012   | -                                 | 0.549                        |
| Post-CR                  | 0.115 ± 0.010   | 0.918 (0.652, 1.293)              |                              |
| \textit{Mortality}       |                 |                                   |                              |
| Baseline                 | 0               | -                                 | N/A                          |
| Post-CR                  | 0               | -                                 | N/A                          |
| \textit{Readmission within} \textit{30 days} | |             |                               |
| Baseline                 | 0.117 ± 0.011   | -                                 |                              |
| Post-CR                  | 0.091 ± 0.009   | 0.760 (0.513, 1.127)              | 0.073                        |
| \textit{Length of stay}  | Mean ± SE       | Beta\textsuperscript{a} (CI)     | P Value\textsuperscript{a,c} |
| Baseline                 | 14.139 ± 0.458  | -                                 |                              |
| Post-CR                  | 10.882 ± 0.344  | -2.767 (-4.021, -1.514)          | <0.0001*                     |

Table 3: Evaluation of \textit{Clostridium difficile}, mortality, readmission within 30 days and length of stay in baseline and post-CR periods

Abbreviations: SE, standard error; OR, odds ratio; RR, relative risk; CI, confidence interval; CR, Cascade reporting

\textsuperscript{a}Analyses are adjusted for age (continuous), sex (male, female) and DOT of each individual antibiotics.

\textsuperscript{b}significance threshold alpha = 0.01

\textsuperscript{c}significance threshold alpha = 0.017

\textsuperscript{*}Statistically significant