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Antimicrobial Stewardship in the Microbiology Laboratory: Impact of Selective Susceptibility Reporting on Ciprofloxacin Utilization and Susceptibility of Gram-Negative Isolates to Ciprofloxacin in a Hospital Setting

B. J. Langford,[a] J. Seah,[a] A. Chan,[a] M. Downing,[a,b] J. Johnstone,[a,b,c] L. M. Matukas[a,b]

St. Joseph's Health Centre, Toronto, Ontario, Canada[a]; Department of Medicine, University of Toronto, Toronto, Ontario, Canada[b]; Public Health Ontario, Toronto, Ontario, Canada[c]

The objective of this study was to determine the impact of selective susceptibility reporting on ciprofloxacin utilization and Gram-negative susceptibility to ciprofloxacin in a hospital setting. Historically at our institution, the microbiology laboratory practice was to report ciprofloxacin susceptibility for all *Enterobacteriaceae* regardless of susceptibility to other agents. A selective reporting policy was implemented which involved the suppression of ciprofloxacin susceptibility to *Enterobacteriaceae* when there was lack of resistance to the antibiotics on the Gram-negative panel. Ciprofloxacin utilization (measured in defined daily doses [DDD] per 1,000 patient days) was collected before and after the intervention and compared to moxifloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, and amoxicillin-clavulanate. Monthly susceptibility of *Pseudomonas aeruginosa* and *Escherichia coli* to ciprofloxacin was tabulated. An interrupted time series analysis using segmented regression was performed. The mean monthly ciprofloxacin utilization decreased from 87 (95% CI, 83.7 to 91.2) to 39 (95% CI, 35.0 to 44.0) DDD per 1,000 patient days before and after the implementation of selective reporting, respectively. There was an immediate and sustained reduction in ciprofloxacin usage at 1, 3, 6, 12, and 24 months postintervention ($P < 0.001$). A compensatory increase in amoxicillin-clavulanate use was noted starting at 6 months postintervention and persisted for the study period ($P < 0.027$). Susceptibility of *E. coli*, but not that of *P. aeruginosa*, to ciprofloxacin was higher than predicted starting 12 months after the intervention ($P < 0.05$). In conclusion, selective reporting of ciprofloxacin susceptibly may be a useful intervention to reduce targeted antimicrobial utilization and improve Gram-negative susceptibility to ciprofloxacin. This approach should be considered as part of a broader multimodal antimicrobial stewardship program.

According to the World Health Organization, antimicrobial resistance (AMR) is considered one of the most serious threats to public health globally (http://www.who.int/mediacentre/multimedia/amr-transcript.pdf). Given the lack of new antimicrobial classes available, preservation of existing classes is a key measure to managing and preventing AMR. Fluoroquinolones (FLQ) are broad-spectrum antibiotics useful for a wide range of bacterial infections. Hence, they have been used extensively since their introduction. As with other antibiotic classes, overuse of these agents is common. A recent prospective analysis in a tertiary medical center found that 39% of FLQ days of therapy were unnecessary (1). As a result of overuse, resistance to this class emerged rapidly after these agents became available (2). FLQ have also been linked with *Clostridium difficile* infection (CDI) (3), cardiac arrhythmia (4), and collagen-associated adverse events, such as tendon rupture and aortic aneurysm (5). Given these concerns, limiting the use of FLQ is a prudent strategy.

Antimicrobial stewardship is a multimodal, multidisciplinary approach to improving the appropriateness of antimicrobial use. It focuses on optimizing antibiotic therapy while limiting adverse effects in the individual patient as well as reducing the emergence of resistance in both the patient and the population. One of the many interventions recommended by the Infectious Diseases Society of America (IDSA) antimicrobial stewardship guidelines is to provide selective or cascade reporting to help guide appropriate antimicrobial use. However, this is listed as a weak recommendation supported by low-quality evidence (6).

Selective susceptibility reporting has been shown to alter prescribing decisions on an individual patient level (7–9). One study found an increase in inpatient rifampin utilization after the microbiology laboratory started routinely reporting susceptibility to this agent for all Gram-positive isolates (10). Additionally, McNulty et al. showed that reporting susceptibility to cephalexin in place of amoxicillin-clavulanate altered prescribing practices in the primary care setting (11). There is a lack of data, however, on the impact of selective reporting on reducing utilization of a targeted antibiotic across an entire health center.

Our site is a large community teaching hospital in Toronto, Canada. As a result of two hospital-wide CDI outbreaks in 2010

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Address correspondence to B. J. Langford, brad.langford@gmail.com.

and 2011, and because of high rates of resistance of *Pseudomonas aeruginosa* to ciprofloxacin, we chose to target the FLQ class with the goal of reducing utilization.

In 2011, as a quality improvement initiative, we implemented a selective reporting policy for all *Enterobacteriaceae* to ciprofloxacin. The purpose of this study was to determine the impact of this policy on ciprofloxacin utilization as part of a hospital-wide antimicrobial stewardship program.

MATERIALS AND METHODS

Setting. St. Joseph's Health Centre is a 400-bed community teaching hospital in Toronto, Canada. There is an on-site microbiology laboratory, with staff available during daytime and evening hours. Microbiology results are reported electronically on the electronic health record (Eclipsys Sunrise Clinical Manager; Allscripts Healthcare).

Intervention. Prior to the intervention, for adult patients, the microbiology laboratory practice was to report ciprofloxacin susceptibility for all *Enterobacteriaceae* regardless of susceptibility to other agents. A selective reporting policy was created and implemented by the antimicrobial stewardship program in collaboration with the microbiology laboratory in February 2011. The policy involved the suppression (i.e., nonreporting) of ciprofloxacin susceptibility to *Enterobacteriaceae*, for all sites of infection, when there was susceptibility to all agents (except ampicillin) on the Gram-negative panel. This panel included ampicillin, nitrofurantoin (for urinary isolates), cefazolin, trimethoprim-sulfamethoxazole (TMP-SMX), gentamicin, tobramycin, and ciprofloxacin. If the organism was intermediate or resistant to ciprofloxacin, the policy was to report ciprofloxacin nonsusceptibility.

Outcomes. The primary outcome was inpatient ciprofloxacin utilization as measured in defined daily doses (DDD) per 1,000 inpatient days, tabulated on a monthly basis between April 2008 and March 2015. This was compared to moxifloxacin (the other FLQ on formulary, which was not targeted by this intervention), TMP-SMX, nitrofurantoin, and amoxicillin-clavulanate (oral agents with *Enterobacteriaceae* activity) as control groups. Pharmacy dispensing data (GE Centricity) was the source of the drug utilization data.

Secondary outcomes were *Pseudomonas aeruginosa* and *Escherichia coli* susceptibility to ciprofloxacin. These data were tabulated monthly using inpatient specimens (sterile and nonsterile sites). Only one isolate from the same patient per year was recorded unless there was a change in susceptibility. The source of these data was SoftMic from SCC Soft Computer.

Statistical analysis. Interrupted time series analysis with segmented regression was performed to determine the impact of the policy on antimicrobial utilization (primary outcome) and antimicrobial susceptibility (secondary outcomes). There were a total of 35 and 49 monthly data points before and after the intervention, respectively. The slopes (trend) before and after the intervention were calculated. Additionally, the 1-month postintervention level for drug utilization and the 3-, 6-, 12-, and 24-month postintervention levels for drug utilization and susceptibility were calculated and compared to predicted levels, to determine if there was an immediate and sustained effect. The Cochrane Effective Practice and Organisation of Care (EPOC) method for interrupted time series analysis was used (http://epoc.cochrane.org/epoc-specific-resources-review-authors). For each variable, autoregressive integrated moving average models were generated and analyzed using IBM SPSS v23.0.

RESULTS

Drug utilization. The mean monthly ciprofloxacin utilization dropped from 87 DDD per 1,000 patient days (95% CI, 83.7 to 91.2) before the implementation of selective reporting to 39 DDD per 1,000 patient days (95% CI, 35.0 to 44.0) after the intervention. In the time series analysis, postintervention, there was an immediate and sustained reduction in ciprofloxacin utilization at 1, 3, 6, 12, and 24 months ($P < 0.001$). Additionally, there was a steeper decline in the trend of utilization ($P = 0.002$) after the intervention (Fig. 1).

There was also a significant reduction in the slope for the utilization of moxifloxacin ($P = 0.012$) and TMP-SMX ($P = 0.002$) after the intervention. However, despite the change in trend, there was no significant change in the level of utilization of these agents (with the exception of TMP-SMX utilization, which was significantly lower than predicted at the 24-month postintervention mark). There was no significant change in the slope of nitrofurantoin usage before and after the intervention. However, at 1 month, there was a significant rise in nitrofurantoin utilization ($P = 0.04$), but this was not sustained at subsequent time points. For amoxicillin-clavulanate, there was an incline in the slope of utilization ($P = 0.003$) postintervention. Mean amoxicillin-clavulanate utilization prior to the intervention was 3.1 DDD per 1,000 patient days (95% CI, 2.4 to 3.8), whereas it increased after the intervention to 29.8 DDD per 1,000 patient days (95% CI, 25.8 to 33.9). Starting at 6 months postintervention, amoxicillin-clavulanate usage was significantly higher than predicted, and this persisted throughout the study period ($P < 0.027$).

Susceptibility. Prior to the intervention, there were 1.8 and 6.5 isolates tested per 1,000 patient days per month for *P. aeruginosa* and *E. coli*, respectively. After the intervention, the number of *P. aeruginosa* isolates tested remained stable at 1.7 per 1,000 patient days per month. However, there was a slight increase for *E. coli* to 7.4 isolates tested per 1,000 patient days per month. The majority of *P. aeruginosa* and *E. coli* isolates were from urinary tract sources, at 73% and 80%, respectively.

Before selective reporting, the average monthly susceptibility of *P. aeruginosa* and *E. coli* to ciprofloxacin was 53% (95% CI, 48 to 57%) and 69% (95% CI, 66 to 71%), respectively. After the intervention, susceptibility was 65% (95% CI, 62 to 69%) and 68% (95% CI, 66 to 70%), for *P. aeruginosa* and *E. coli*, respectively.

In the time series analysis, after the implementation of selective susceptibility reporting, there was no statistically significant change to the slope or level of *P. aeruginosa* susceptibility to ciprofloxacin. However, for *E. coli*, the slope of susceptibility changed from declining to stable after the intervention ($P = 0.036$). Additionally, starting at 6 months, there was a trend toward higher-than-predicted susceptibility for *E. coli* ($P = 0.08$). *E. coli* susceptibility was significantly higher than predicted at the 12- and 24-month postintervention time points ($P < 0.05$) (Fig. 2).

DISCUSSION

This is the first study, to our knowledge, to show an impact of selective reporting on targeted antimicrobial usage and resistance rates across a health center.

Selective reporting of *Enterobacteriacae* susceptibility to ciprofloxacin was associated with an immediate and sustained reduction in the volume of ciprofloxacin utilization. This intervention was also associated with higher-than-predicted *E. coli* susceptibility to ciprofloxacin, possibly due to reduced selective pressure in the hospital setting.

This presents an opportunity for antimicrobial stewardship programs to implement an effective intervention in collaboration with the clinical microbiology laboratory. This approach would be considered front end, as it prevents the initiation of ciprofloxacin use. This is in contrast to back-end approaches, such as a prospec-

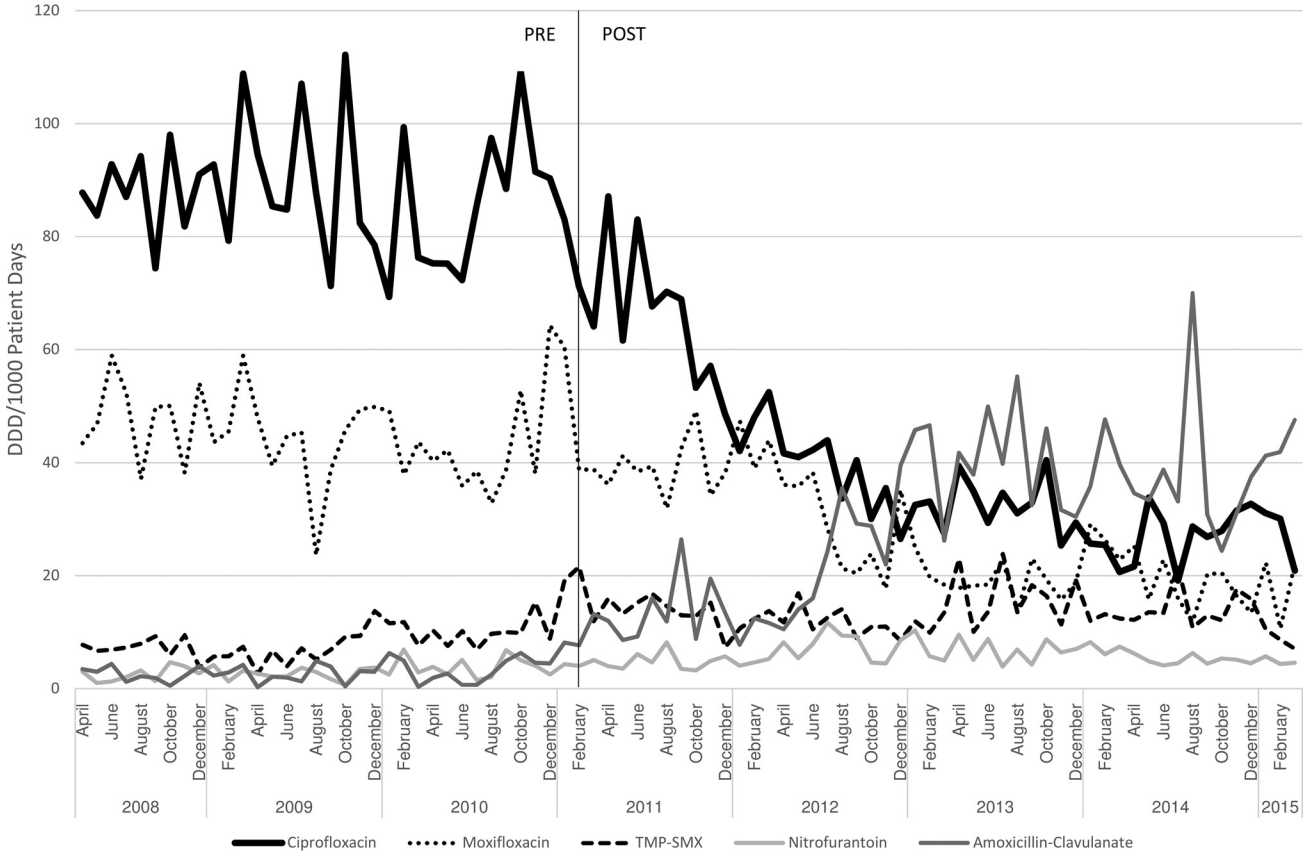

FIG 1 Antimicrobial utilization before and after ciprofloxacin selective reporting.

tive audit and feedback, which are often highly resource intensive from an antimicrobial stewardship perspective. Selective reporting may also be seen as a restrictive method to address overuse of a particular antimicrobial agent. However, given that susceptibility is hidden or suppressed, it may cause less interprofessional friction than other restrictive approaches, such as preauthorization programs, because the prescriber will often simply choose a different agent from the Gram-negative susceptibility panel. One

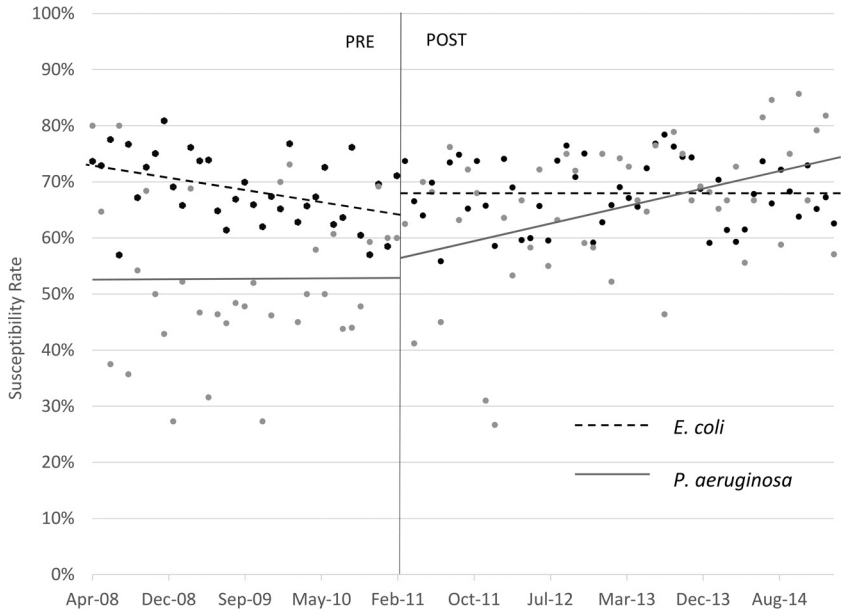

FIG 2 *E. coli* and *P. aeruginosa* susceptibility to ciprofloxacin before and after selective susceptibility reporting.

concern with restrictive approaches is the concept of squeezing the balloon: a shift of utilization from one class to another. This may have been the case in our setting. As ciprofloxacin usage declined, there appeared to be a compensatory increase in utilization of amoxicillin-clavulanate. However, this was delayed until 6 months after the intervention and may have also been affected by other factors. These factors include the introduction of internal guidelines recommending amoxicillin-clavulanate as first line for non-intensive care unit community-acquired pneumonia therapy as well as the addition of this agent to the Gram-negative Vitek panel in June 2012.

There are a number of limitations to this study. First, it is a quasiexperimental retrospective analysis. As a result, there are numerous possible confounding factors. Our antimicrobial stewardship program was implemented gradually during 2010 to 2011. The program included multiple interventions consistent with IDSA guidelines (6), such as prospective audit and feedback, verbal and written education, guidelines, and order sets. Hence, it is difficult to determine with certainty that selective reporting was the sole cause for the reduction in ciprofloxacin utilization. However, even though our program aggressively targeted all FLQ usage through education and feedback, only ciprofloxacin, but not moxifloxacin, use declined significantly in the interrupted time series analysis. This suggests a possible additional effect of selective reporting over and above any effects associated with the antimicrobial stewardship program in general.

Urinary tract infection is a common indication for ciprofloxacin utilization. During the study period, there were a number of changes that affected the treatment of UTI that may have contributed to changes in prescribing patterns. IDSA guidelines were published in March 2011 discouraging the use of FLQ for the first-line treatment of uncomplicated cystitis in women (12). The IDSA guidelines were not disseminated widely throughout our institution. However, our institutional UTI guidelines were published in November 2010, with a bulletin in May 2011 reinforcing IDSA recommendations to avoid FLQ for this indication. These interventions may have contributed to the reduction in utilization of ciprofloxacin. It has been noted, however, that dissemination of printed materials alone is unlikely to alter prescribing practices (13). Additionally, when persuasive interventions, such as guidelines, are effective, they are less likely to have an immediate impact on prescribing practices. We noted a significant reduction in utilization as early as 1 month postintervention. As a result, it is unlikely the distribution of guidelines or written materials alone explains the changes in utilization.

It is important to note that, although our selective ciprofloxacin reporting policy included all sites, it is likely most applicable to urinary isolates. Since 80% of *E. coli* isolates were from the urinary tract, selective reporting in this group likely drove the majority of changes in antibiotic utilization. Additionally, there may be some value to reporting ciprofloxacin for nonurinary isolates, due to the good bioavailability and tissue penetration of this agent for deep-seated infections (14).

The selective reporting policy was not automated. As a result, human error may have led to overreporting of ciprofloxacin when the policy dictated it was to be suppressed. Alternatively, there were instances when laboratory staff suppressed ciprofloxacin susceptibility when policy indicated it should have been reported. An automated rule-based cascade reporting system would be ideal to prevent such errors.

Because of the retrospective design and the potential for multiple confounding factors, the changes in ciprofloxacin susceptibility over time should be interpreted with caution. Other antimicrobial stewardship interventions, changes in prescribing patterns outside the hospital, and shifts in patient demographics may also be contributing factors. Although there was an absolute increase in *P. aeruginosa* susceptibility to ciprofloxacin after the intervention, this difference was not statistically significant in the time series analysis. On the other hand, *E. coli* susceptibility to ciprofloxacin was significantly higher than predicted after the intervention in the time series analysis. The lack of statistically significant increase for *P. aeruginosa* may be related to a type II error (due to a smaller sample size and larger month-to-month variability compared to *E. coli*) or it may reflect that this intervention in fact has no effect on *P. aeruginosa* susceptibility to ciprofloxacin. For *E. coli*, however, the change in slope after the intervention from declining to stabilized susceptibility, as well as a trend toward improved susceptibility at 6 months and a sustained improvement in susceptibility at 12 to 24 months, supports the possibility that selective reporting indeed played a role in these changes. These results are in line with a recent Cochrane EPOC group meta-analysis indicating that restrictive antimicrobial stewardship initiatives have resulted in significant reductions in colonization or infection with antibiotic-resistant organisms (15).

Another limitation is that selective reporting has no direct impact on the empirical choice of antimicrobial therapy. It is only when the culture and sensitivity results are available that definitive therapy is selected. However, selective reporting still has a significant impact on the overall use of antimicrobial therapy, as most results are available within 48 to 72 h of collection and many prescribing decisions, including streamlining or deescalating, are made at this juncture. Additionally, with selective reporting, prescribers will likely become more familiar and comfortable with alternative agents, and this may subsequently reduce empirical ciprofloxacin usage in subsequent patient cases. There is also the concern that, if ciprofloxacin was chosen as empirical therapy, selective reporting would hinder an appropriate assessment of whether initial therapy was adequate, because ciprofloxacin was hidden on the susceptibility report. Our microbiology laboratory is not available 24 h per day, but the prescriber could call during normal business hours to determine susceptibility results. Additionally, part of the policy was to report ciprofloxacin susceptibility if the organism was nonsusceptible to this agent.

Furthermore, selective reporting of susceptibility is unlikely to reduce the overall volume of antimicrobial use but, rather, is likely to shift it from one agent or class to another. This is an important concern given the prevalence of overutilization in general and overtreatment of conditions such as asymptomatic bacteriuria (ASB). This problem may require a slightly different strategy to address. For example, in a prospective before-and-after proof-of-concept study, nonreporting of urine culture and susceptibility results for noncatheterized medical and surgical inpatients resulted in a significantly reduced rate of ASB treatment (16). This more aggressive variant of selective reporting will likely be further validated in future studies and may have a substantial impact on overutilization in many settings.

Finally, selective reporting of susceptibility results does not ensure appropriateness of antibiotic therapy for each individual patient case. It is a method to guide the prescriber away from less desirable options. As a result of these limitations, selective report-

ing should be considered carefully in antimicrobial stewardship programs.

Conclusion. Selective reporting of *Enterobacteriaceae* susceptibility to ciprofloxacin was associated with an immediate and sustained reduction in ciprofloxacin usage at our health center. However, a compensatory increase in amoxicillin-clavulanate utilization was identified. This intervention was associated with a statistically significant improvement in *E. coli* susceptibility to ciprofloxacin. This collaborative intervention with clinical microbiology should be considered an effective approach to reduce targeted antimicrobial utilization as part of a broader antimicrobial stewardship program.

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