ORIGINAL ARTICLE

Audit and Feedback to Reduce Broad-Spectrum Antibiotic Use among Intensive Care Unit Patients: A Controlled Interrupted Time Series Analysis

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OBJECTIVE. We aimed to rigorously evaluate the impact of prospective audit and feedback on broad-spectrum antimicrobial use among critical care patients.

DESIGN. Prospective, controlled interrupted time series.

SETTING Single tertiary care center with 3 intensive care units.

PATIENTS AND INTERVENTIONS. A formal review of all critical care patients on their third or tenth day of broad-spectrum antibiotic therapy was conducted, and suggestions for antimicrobial optimization were communicated to the critical care team.

OUTCOMES. The primary outcome was broad-spectrum antibiotic use (days of therapy per 1000 patient-days; secondary outcomes included overall antibiotic use, gram-negative bacterial susceptibility, nosocomial *Clostridium difficile* infections, length of stay, and mortality.

RESULTS. The mean monthly broad-spectrum antibiotic use decreased from 644 days of therapy per 1,000 patient-days in the preintervention period to 503 days of therapy per 1,000 patient-days in the postintervention period ($P < .0001$); time series modeling confirmed an immediate decrease ($\pm$ standard error) of 119 $\pm$ 37.9 days of therapy per 1,000 patient-days ($P = .0054$). In contrast, no changes were identified in the use of broad-spectrum antibiotics in the control group (nonintervention medical and surgical wards) or in the use of control medications in critical care (stress ulcer prophylaxis). The incidence of nosocomial *C. difficile* infections decreased from 11 to 6 cases in the study intensive care units, whereas the incidence increased from 87 to 116 cases in the control wards ($P = .04$). Overall gram-negative susceptibility to meropenem increased in the critical care units. Intensive care unit length of stay and mortality did not change.

CONCLUSIONS. Institution of a formal prospective audit and feedback program appears to be a safe and effective means to improve broad-spectrum antimicrobial use in critical care.

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Inexorable increases in antibiotic use in hospitals over the past few decades have driven increases in rates of resistance among hospital-acquired pathogens.[1,2] However, up to half of antibiotic use in hospitals is unnecessary or inappropriate, suggesting that it still may be possible to reverse this trend through the promotion of more judicious antimicrobial use.[3,4]

In response to this crisis of antibiotic overuse and increases in the prevalence of antibiotic resistance, North American and European infectious diseases societies have published guidelines for the introduction of multidisciplinary hospital antimicrobial stewardship programs.[4,5] An antimicrobial stewardship program aims to reduce inappropriate antimicrobial use while optimizing antimicrobial drug selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection and to limit antibiotic costs, adverse drug events, cases of *Clostridium difficile* infection, and selection of antibiotic-resistant organisms.[4]

Although antibiotic stewardship programs should strive to improve rational antimicrobial use throughout a facility, the greatest potential impact may lie in the critical care unit,[6] because this is the location in which, in most hospitals, antimicrobial use and antimicrobial resistance is the greatest.[7,8] However, the obstacles to antibiotic stewardship are significant in this vulnerable and complex patient population.[6]

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A recent systematic review of antibiotic stewardship in critical care documented that antimicrobial stewardship programs have been associated with reductions in antibiotic use, costs, adverse events, and antimicrobial resistance without compromising clinical outcomes, such as nosocomial infection rates, length of stay, and mortality.[9] However, this review also demonstrated that most earlier research involved uncontrolled before and after studies, which are prone to bias and temporal confounding.[9,10] Therefore, we aimed to rigorously evaluate the impact of a formal prospective audit and feedback program of broad-spectrum antimicrobial use among critical care patients using a controlled interrupted time series analysis.

METHODS

Study Design and Setting

The study was performed at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada, across 3 level III intensive care units, including (1) a 20-bed general critical care unit (CRCU), which treats medical and surgical patients as well as regional trauma patients; (2) a 14-bed cardiovascular intensive care unit (CVICU), which treats cardiac and vascular surgery patients; and (3) the 14-bed Ross Tilley Burn Centre (RTBC), which serves as Canada's largest burn center. The preintervention period spanned from October 1, 2008, through September 30, 2009, and the intervention period spanned from October 1, 2009, to September 30, 2010. Ethics approval for this study was obtained from the Sunnybrook Research Ethics Board.

Intervention

Beginning in October 2009, records for all patients who had received 3 days of therapy with broad-spectrum antimicrobials in the intensive care units were reviewed by the antimicrobial stewardship pharmacist. The targeted antimicrobials included third-generation cephalosporins (ceftriaxone and ceftazidime), β-lactam and β-lactamase inhibitor combinations (piperacillin-tazobactam), carbapenems (meropenem and ertapenem), fluoroquinolones (levofloxacin and ciprofloxacin), and vancomycin. In consultation with the senior infectious disease pharmacist, each patient was reviewed for optimization of antimicrobial therapy. If an opportunity for optimization was identified, the case was reviewed with an infectious diseases staff physician. Once the suggestion was approved, it was entered into the stewardship database, a computer generated progress note was placed in the patient chart, and the stewardship pharmacist provided verbal feedback to available members of the critical care team. Assessment, review, and feedback were completed rapidly and within the day. The decision to implement suggestions from the antimicrobial stewardship team rested with the most responsible physician or delegate. In a similar manner, reviews were also conducted on the tenth day of therapy in critical care to prevent excessive durations of treatment with these targeted broad-spectrum drugs. The audit and feedback intervention was only performed during weekdays, so patients who received their third or tenth day of therapy on a weekend were reviewed on the following Monday. The acceptance or rejection of each suggestion was tracked. Reasons for rejection of suggestions were recorded during the first 6 months of the program to ensure adequate uptake of the intervention.

Outcome Assessment

The primary outcome was the use of targeted antimicrobials in the level III intensive care units (ICUs), which was measured in days of therapy per 1,000 patient-days per month.[11] Days of therapy were collected monthly from the pharmacy computer system, and patient-days per month were collected from mandatory data reported to the Ontario Ministry of Health and Long Term Care Critical Care Information System (CCIS) and Sunnybrook Health Sciences Centre health data records.

Secondary drug use outcomes included use of targeted antibiotics within each of the 3 individual ICUs, nontargeted antibiotic use, and overall antibiotic use (the sum of targeted and nontargeted agents) measured in days of therapy per 1,000 patient-days across the units as well as overall drug acquisition costs. Gram-negative antibiotic resistance was assessed as a secondary microbiologic outcome. Gram-negative susceptibility data were obtained from the microbiology laboratory information software system. The first isolate of each organism from each patient was included in the analysis. However, to ensure that antimicrobial susceptibility was not overestimated by excluding hospital-acquired organisms, organisms were also included if they were isolated multiple times if the susceptibility profile changed with respect to any of the targeted antimicrobials. To ensure a reasonable sample size for each month, overall gram-negative susceptibility (weighted by the frequency of each pathogen) was reported. The incidence of nosocomial *C. difficile* infection was determined prospectively by dedicated infection prevention and control practitioners who were not affiliated with this study.[12] Secondary clinical outcomes included the incidence of *C. difficile* infection in the ICU, length of stay, and overall ICU (all cause) mortality.

Covariates

Prospective data collection for the CCIS provided important information regarding patient risk factors in the preintervention and postintervention period, including age, sex, admitting service, diagnosis category, multiorgan dysfunction score, and use of mechanical ventilation and central venous catheters.

Controls

Two controls were used to improve the specificity of the evaluation: a control group of patients and a control class of medications. First, the use of the same targeted antibiotics, calculated in days of therapy per 1,000 patient-days, was collected from the non-ICU medical and surgical wards, where patients and prescribers were not subject to the audit and feedback intervention. Second, the days of therapy per 1,000 patient-days of agents for stress ulcer prophylaxis (oral or intravenous ranididine and oral lansoprazole) dispensed in the level III ICUs was used as a control medication class to ensure that changes in drug use within the ICUs were not an artifact of methods used to measure days of therapy or patient-days.

Statistical Analysis

Patient characteristics in the preintervention and postintervention periods were compared using χ^2 statistic for binary variables and Student*t* tests or Wilcoxon rank-sum tests for normally distributed and nonnormally distributed continuous variables, respectively.

The days of therapy per 1,000 patient-days of targeted antimicrobials in the preintervention period and postintervention period were compared using Student *t* test. However, this test relies on an assumption of independence between observations, which is violated by this longitudinal data within the same ICUs. Therefore, in the primary analysis, the impact of the audit and feedback intervention on targeted drug use was analyzed using segmented regression, in which the autocorrelations were modeled using a second-order autoregressive model.[13] The residuals obtained from the model were checked for autocorrelation using Q-statistics. The residuals were also inspected for normality. A total of 12 monthly data points were available for analysis in the preintervention period (October 1, 2008, through September 30, 2009), and 12 monthly data points were available for analysis in the postintervention period (October 1, 2009, to September 30, 2010). The model can be formulated as follows:

$$Y_t = \beta_0 + \beta_1 * T_t + \beta_2 * I_t + \beta_3 * TI_t + \varepsilon_t, \quad (1)$$

where β_0 is the intercept, β_1 is the slope before the intervention, β_2 is the change in the number of days of therapy per 1,000 patient-days immediately following the intervention, and β_3 is the change in slope from the preintervention period to the postintervention period. Similar models were applied to days of therapy per 1,000 patient-days of targeted antibiotics used in the level III ICUs and days of therapy per 1,000 patient-days of targeted antibiotics among non-ICU ward patients. No autocorrelation was identified in the analysis of monthly days of therapy per 1,000 patient-days of stress ulcer prophylaxis medications used in the level III ICUs, and therefore a simple regression model was used for this analysis.

The proportion of gram-negative bacteria susceptible to each of meropenem, ciprofloxacin, ceftriaxone, ceftazidime, and piperacillin-tazobactam were compared between the preintervention and postintervention time periods by χ^2 test. Differences in monthly nosocomial *C. difficile* cases per month in the preintervention and postintervention periods (in level III ICUs and non-ICU wards) were compared using a one-tailed paired Student *t* test. Mortality and length of stay were evaluated using χ^2 tests. Statistical analyses were performed in SAS, version 9.2 (SAS).

RESULTS

Patient Characteristics

During the 12-month preintervention period, 2,358 patients were admitted to the 3 level III ICUs for a total of 14,225 patient-days; during the 12-month postintervention period, 2,339 patients were admitted to these same units for a total of 15,431 patient-days. The baseline characteristics were similar between the 2 time periods, including patient demographic characteristics, diagnoses at hospital admission, severity of illness, receipt of mechanical ventilation, and central venous catheter use (Table 1).

Nature and Uptake of the Intervention

During the intervention period, the stewardship team evaluated 717 antibiotic prescriptions and made a suggestion for optimization in 247 (34%) of these orders. The critical care staff accepted 82% of the suggestions made (Table 2). The most common suggestion was to discontinue the antibiotic (56% of the suggestions), followed by suggestions to change to an alternate agent (26%) and suggestions to change dose, frequency, or route of administration (8%). Acceptance rates were similar for these categories of suggestions (81% for discontinuing the antibiotic, 84% for changing the agent, and 84% for other suggestions). The most commonly cited reasons for rejection of recommendations included suspicion of additional pathogens (21%), suspicion of an additional site of infection (14%), patient allergies (11%), patient nearing the end of planned therapy (7%), patient to be transferred (7%), and suspicion of antibiotic resistance (4%). However, in many cases, the team's reasons for rejection could not be articulated or classified (35%).

Impact on Targeted Broad-Spectrum Antibiotic Use

The mean monthly broad-spectrum antibiotic use decreased from 644 days of therapy per 1,000 patient-days in the preintervention period to 503 days of therapy per 1,000 patient-days in the postintervention period ($P < .0001$). Time series modeling demonstrated a significant decrease of 119 days of therapy per 1,000 patient-days (standard error [SE], 37.9; $P = .0054$) in the use of targeted antimicrobials immediately after the intervention was implemented. The trend of targeted

TABLE 1. Baseline Characteristics of Critical Care Patients before and after the Antimicrobial Stewardship Intervention

Variable	Preintervention period[a] (n = 2,358)	Postintervention period[b] (n = 2,339)	P
Age, mean years (± SD)	63.8 ± 16.9	63.3 ± 17.9	.28
Male sex, %	67	69	.12
Medical ward	741 (31)	764 (33)	.38
Surgical ward	1,617 (69)	1,574 (67)	
Unit			
Critical care unit	1,013 (43)	1,000 (43)	.91
Ross Tilley Burn Centre	154 (7)	178 (8)	.17
Cardiovascular ICU	1,191 (50)	1,161 (50)	.57
Diagnosis at hospital admission			
Trauma	287 (12)	251 (11)	.13
Respiratory	348 (15)	355 (15)	.72
Neurological	85 (4)	104 (4)	.16
Genitourinary	6 (0)	9 (0)	.59
Cardiovascular/cardiac/vascular	1,168 (49)	1,110 (47)	.16
Oncology/hematology	45 (2)	29 (1)	.09
Gastrointestinal	36 (2)	38 (2)	.88
Musculoskeletal or skin	133 (6)	161 (7)	.04
Metabolic or endocrine	5 (0)	7 (0)	.76
Other	245 (10)	275 (12)	.15
Multiorgan dysfunction score	4.43	4.64	.27
Mechanical ventilation, days	17,692	21,075	.11
Central venous catheter use, days	21,373	23,904	.63

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit; SD, standard deviation.

[a] October 1, 2008, through September 30, 2009.

[b] October 1, 2009, through September 10, 2010.

antimicrobial use was flat before the intervention (slope, 1.9 days of therapy per 1,000 patient-days; SE, 3.66; P = .52). After the intervention, the slope changed to −6.1 days of therapy per 1,000 patient-days (SE, 3.82; P = .12), and the overall change in trend of targeted antimicrobial use was nonsignificant at −8.0 days of therapy per 1,000 patient-days (SE, 5.0; P = .1278), which suggests that the impact of the stewardship intervention was immediate rather than gradual (Figures 1 and 2).

Control Wards and Medications

Within the time series model, the use of these same targeted antimicrobials did not change in the medical and surgical units that did not receive the audit and feedback intervention. There was a nonsignificant increase of 14.4 days of therapy per 1,000 patient-days associated with the implementation of the intervention (SE, 9.5; P = .1482), and the slope did not change significantly between the preintervention period and the postintervention period (change in slope, −1.0; SE, 1.26; P = .41; Figure 1).

The specificity of our findings was also tested by repeating the analysis using the outcome of days of therapy of stress ulcer prophylaxis, which is another common and expensive class of medications in the ICU that was not subject to audit and feedback. No autocorrelation was identified in the monthly use of stress ulcer prophylaxis medications in these units; therefore, a simple regression model was fitted to the data. This identified a nonsignificant increase in the use of stress ulcer prophylaxis medications (increase, 71.0 days of therapy per 1,000 patient-days; SE, 70.3; P = .32), with a nonsignificant trend before the intervention of 2.5 days of therapy per 1,000 patient-days (SE, 7.2; P = .32), and a nonsignificant change in trend after the intervention of −6.3 days of therapy per 1,000 patient-days (SE, 10.1; P = .54; Figure 2).

Overall Antibiotic Use, Nontargeted Antibiotic Use, and Costs

Overall antibiotic use decreased from 1,134 days of therapy per 1,000 patient-days in the preintervention period to 985 days of therapy per 1,000 patient-days in the postintervention period (P = .003). This was driven by decreased use of targeted antibiotics, because the use of nontargeted antibiotics did not change from the preintervention period to the postintervention period (490 vs 482 days of therapy per 1,000 patient-days; P = .80). Antibiotic expenditures decreased by $95,000 in the postintervention period, compared with the

preintervention period. This represented an average decrease of 23.7% in antimicrobial acquisition cost across all 3 units.

Antimicrobial Resistance among Gram-Negative Bacterial Isolates

There was a significant increase in overall gram-negative susceptibility to meropenem in the postintervention period, compared with the preintervention period (83.4% vs 78.2%; $P = .03$), and the susceptibility of gram-negative bacteria to ceftriaxone, piperacillin-tazobactam, ciprofloxacin, and ceftazidime remained unchanged (Figure 3).

C. difficile Infection

The number of monthly nosocomial *C. difficile* infections decreased by 31%, from 16 cases during the preintervention period to 11 cases in paired calendar months during the postintervention period. In contrast, the number of cases increased in the control non-ICU wards by 33%, from 87 to 116 cases ($P = .04$).

Clinical Outcomes

ICU length of stay and crude mortality rates did not change in the postintervention period, compared with the preintervention period. Mean length of stay (± standard deviation) was identical during both time periods at 6.9 ± 23 days ($P = .92$). The crude mortality rate was 13.1% before the intervention and 14.4% during the postintervention period ($P = .20$).

DISCUSSION

Our antibiotic stewardship audit and feedback intervention was associated with an immediate, substantial, sustained, and specific reduction in the use of broad-spectrum antimicrobial agents in intensive care. The total days of therapy with broad-spectrum antibiotics decreased abruptly by 22% (from 644 to 503 days of therapy per 1,000 patient-days per month) and remained low for the 12-month duration of the intervention. As expected, the benefit was seen for the targeted broad-spectrum antibiotics in critical care, whereas no change was seen for the same antibiotics in control non-ICU wards or for a control class of medications within the ICU. Reductions in antibiotic use were associated with cost savings ($95,000 per year, or $3.20 per patient-day), reductions in rates of *C. difficile* infection, and increased gram-negative bacterial susceptibility to meropenem without any compromise in clinical end points, such as length of stay or mortality.

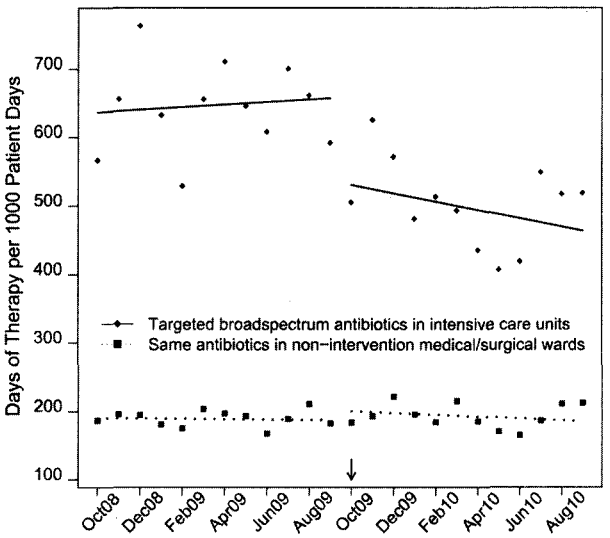

FIGURE 1. Monthly use of broad-spectrum antibiotics in critical care patients and control medical and surgical ward patients. This autoregressive integrated moving average model demonstrated a significant decrease of −119 days of therapy per 1,000 patient-days (standard error, 37.9; $P = .0054$) in the use of targeted antimicrobials immediately after the audit and feedback intervention was implemented in October 2009. The use of these same targeted antimicrobials did not change in those medical and surgical units that did not receive the audit and feedback intervention (dotted line).

The beneficial impact of our antimicrobial stewardship intervention is in keeping with the findings of a recent systematic review.[9] Among 16 earlier studies that reported on the impact of stewardship on antibiotic use in critical care, the median reduction in antibiotic use was 13.5% (interquartile range, 10%–35%).[14] Three of these studies involved interventions similar to our intervention, with formal reassessment of antibiotic use on a prespecified day of therapy.[15-17] A reevaluation of antibiotic therapy at 2 days was associated with a 17% reduction in the number of antibiotic prescriptions, from 1.8 to 1.5 prescriptions per patient.[17] Formal reevaluation at 14 days was associated with a 12% reduction in overall antibiotic use, from 1,265 to 1,112 defined daily

TABLE 2. Number of Antimicrobial Stewardship Recommendations and Rate of Acceptance by Critical Care Team

Unit	No. of orders reviewed	No. of suggestions (%)	No. accepted (%)	No. rejected (%)
CrCU	433	124 (29)	104 (84)	20 (16)
CVICU	156	60 (39)	42 (70)	18 (30)
RTBC	128	63 (49)	57 (90)	6 (10)
Overall	717	247 (34)	203 (82)	44 (18)

NOTE. CrCU, critical care unit (including medical, surgical, and trauma intensive care units); CVICU, cardiovascular intensive care unit; RTBC, Ross Tilley Burn Centre.

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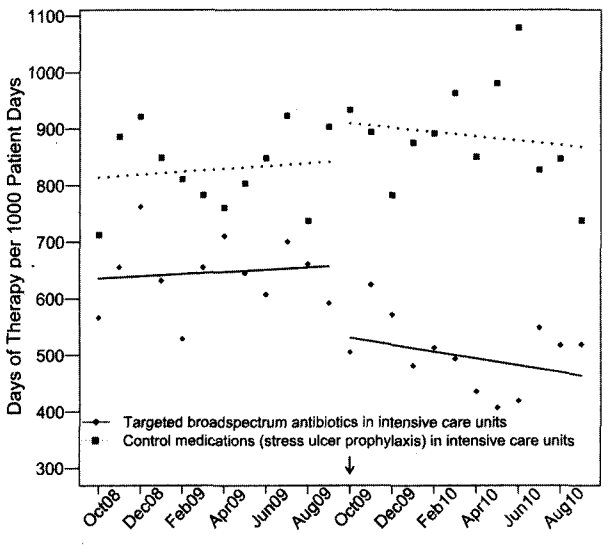

FIGURE 2. Monthly use of broad-spectrum antibiotics and control medications (stress ulcer prophylaxis) in critical care patients. The reduction in targeted antibiotics is once again displayed (solid line), this time in comparison with the use of a control medication. Use of stress ulcer prophylaxis (dotted line) exhibited a nonsignificant immediate increase of 71.0 days of therapy per 1,000 patient-days after the antibiotic stewardship intervention (standard error, 70.3; $P = .32$).

doses per 1,000 patient-days.[16] The intervention most similar to our own (with reassessment on days 3, 7, and 10) was credited with a 35% reduction in antibiotic use, from 940 to 610 days of therapy per 1,000 patient days.[15] All 3 earlier studies employed an uncontrolled before and after design, and thus our study provides more rigorous confirmation of the benefit of this approach to antibiotic stewardship.

The reductions in antimicrobial resistance in our study were similar to gains reported by previous studies of formal antibiotic reassessment. Earlier studies have detected decreases in extended-spectrum β-lactamase-producing Enterobacteriaceae[15-17] as well as carbapenem, ceftazidime, and ciprofloxacin resistance among *Pseudomonas* and *Acinetobacter* species.[16,17] However, our report represents, to our knowledge, the first examination of the impact of critical care antibiotic stewardship on the risk of *C. difficile* infection. The small reduction in the number of cases of *C. difficile* infection within our critical care units, which coincided with the introduction of antibiotic stewardship, is intriguing, particularly because a steep increase in the number of cases of *C. difficile* infection occurred in our nonintervention medical and surgical wards during the same time period. This supports the notion that a reduction in patient susceptibility to *C. difficile* through antibiotic avoidance may be as important as reducing the transmission of *C. difficile* through traditional infection control measures, such as hand hygiene, contact precautions, and isolation.[18,19]

The success of our antibiotic stewardship program in critical care hinged on the active and interactive design of our intervention. We involved the critical care team (physicians and pharmacists) from the early stages of program planning and strived for a mutual reflection around the need for antibiotics in each individual case. The uptake of our program in the critical care unit is illustrated by the high acceptance rate for our individual antimicrobial suggestions. In contrast, passive programs based on antibiotic restriction may be less effective and can result in unintended increases in use and resistance for unrestricted classes of agents.[20,21] The high uptake of our intervention may also be owing to our targeting the third and tenth day of broad-spectrum therapy (rather than the initial day of therapy). In this manner, we were able to incorporate microbiologic data and the early clinical trajectory of the patient to provide cogent recommendations.

Our intervention was not administered in the context of a randomized controlled trial and therefore can be subject to selection bias or temporal confounding. However, our con-

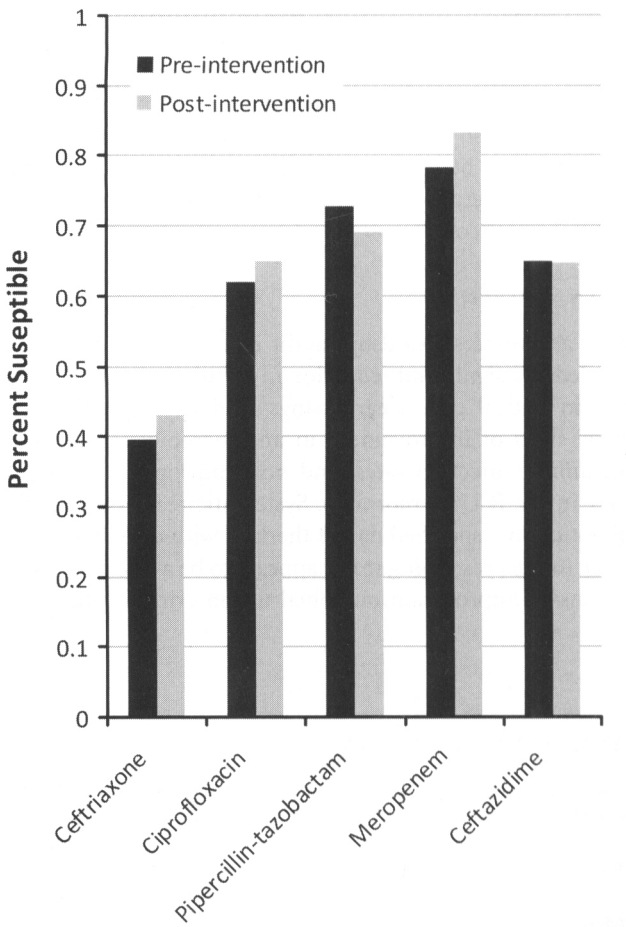

FIGURE 3. Overall susceptibility of gram-negative bacteria isolated from intensive care unit patients during the preintervention period versus during the postintervention period. The increase in meropenem susceptibility (from 78.2% to 83.4% of isolates) was statistically significant ($P = .03$).

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trolled interrupted time series analysis provides much greater evidence of causality than the uncontrolled before and after studies that comprise the earlier literature regarding antibiotic stewardship in critical care.[9] The measurement of 12 monthly data points, both preintervention and postintervention, demonstrates that the reduction in antibiotic use occurred immediately coinciding with the implementation of our program. The absence of change in the use of antibiotics among control patients (non-ICU medical and surgical wards) or control medications (stress ulcer prophylaxis in the ICU) further strengthens the causal inference.

Another important limitation of our study is that it was a single-center study, so it is uncertain whether our findings can be generalized to other centers. For example, other institutions may lack experienced infectious diseases consultants and senior infectious diseases pharmacists, commitment from hospital administration, or buy-in from the critical care unit.[22] Although our 3 ICUs are large, they still afford only a small sample size for microbiologic outcomes (antibiotic resistance and *C. difficile* infection) and are underpowered to detect small but meaningfully important improvements. Our time series design is an improvement upon earlier research in this field but does not altogether rule out temporal confounding. Our analysis extends to only 12 months after the intervention, so additional analyses will be required to ensure that ongoing benefit is maintained in future years and to assess for emergence of additional benefits in antimicrobial resistance outcomes.

CONCLUSIONS

Our antibiotic stewardship audit and feedback intervention has led to a significant reduction in broad-spectrum antibiotic use in critical care, clear savings in drug acquisition costs, early signs of improvement in antimicrobial resistance and *C. difficile* infection rates, and no compromise in length of stay in the ICU or mortality. Systematic reassessment of antibiotics on a specified day of therapy, with case by case feedback to the prescribing team, appears to be a safe and effective means to improve antimicrobial use in critical care.

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