Using audit-and-feedback to improve antimicrobial-prescribing in Emergency Departments: a multicenter quasi-experimental study in the Veterans Health Administration

The clinical trial was registered on ClinicalTrias.gov, NCT03349567.

This document was last revised December 24, 2020 to modify statistical methods for the interrupted time-series analysis of the primary outcome.

All outcomes were defined prior to study initiation.

INTRODUCTION

Antimicrobial use is a major contributor to the spread and emergence of antimicrobial resistance, a persistent public health problem. Antimicrobials are frequently prescribed in both hospitals and ambulatory care, but the majority of antimicrobial-prescribing is in outpatient settings.[1] An estimated 30% of all outpatient antimicrobial use is unnecessary.[2, 3]

Audit-and-feedback is an effective strategy for improving antimicrobial-prescribing.[4] Audit-and-feedback involves reviewing a clinician's antimicrobial-prescribing behavior and providing feedback to help the clinician adjust his/her performance. The use of audit-and-feedback for outpatient antimicrobial stewardship has been largely studied in primary care clinics[5-9] with limited data in Emergency Departments and urgent care centers.[10-12]

The Emergency Department (ED) is a major provider of medical care in the United States and, in turn, an important partner in efforts to improve antimicrobial-prescribing. The use of EDs has been increasing steadily over the past decade.[13] In 2016, there were 145.6 million visits to EDs in the United States, or 46 visits per 100 persons.[14] During these visits, ED clinicians prescribed 29 million antimicrobials.[14] Prior studies have demonstrated several opportunities to improve antimicrobial-prescribing in EDs.[15-19]

In this quasi-experimental pilot study, we evaluated whether the use of audit-and-feedback with peer-to-peer comparisons could reduce unnecessary antimicrobial use at 2 intervention EDs compared to 2 matched control EDs.

METHODS

Study design: We performed a quasi-experimental pilot study with an interrupted time-series design and a matched-pair non-equivalent control group to evaluate the effect of a pilot intervention on clinicians at 2 participating EDs versus 2 control EDs. All EDs were affiliated with Veterans Affairs Medical Centers (VAMCs) in the midwestern United States.

Ethics approval: The clinical trial was registered on ClinicalTrias.gov, NCT03349567. The Institutional Review Boards (IRB) at the University of Iowa and Indiana University as well as the

Research & Development Committee of the Iowa City and Indianapolis VAMCs approved this study and waived written informed consent. All other sites were not engaged in research activities, so local IRB approval was not sought.

Site selection: First, we contacted VAMCs within two midwestern Veterans Integrated Service Networks (VISNs) to assess their interest in participating in this study. These 2 VISNs were chosen because they were among the few VISNs that had not implemented regional initiatives to improve antimicrobial use in ambulatory care.

Once two intervention sites were identified, we pulled a year of antimicrobial-prescribing data for all EDs within these same two midwestern VISNs. Eligible control sites had a baseline antimicrobial-prescribing rate (outpatient antimicrobial prescriptions dispensed per total ED patient-visits) that was similar to the intervention sites. Selection of controls on the pre-intervention outcome of interest minimized bias and reduced the impact of regression to the mean, which is a key threat when selecting poor performers in non-randomized trials.[20] To further ensure that intervention and control sites were as similar as possible, control and intervention sites were also matched on their hospital complexity level, as defined by the VHA.

Intervention: The entire study period was 2-years in duration. The baseline period covered 1-year between 10/01/2017 through 09/30/2018, the implementation phase lasted one month (10/2018), and the intervention period spanned another 11 months, 11/01/2018 through 09/30/2019.

In 10/2018, the study team had meetings with all willing ED clinicians at the intervention sites. At intervention site 1, these meetings were face-to-face and took place during a two-day time frame when D.J.L., an Infectious Disease (ID) physician, was present on-site. These one-on-one meetings with each clinician lasted 10-15 minutes and included a review of the clinician's individual antimicrobial-prescribing data (see feedback metrics), an anonymous comparison to his/her local peers, and a review of antimicrobial-prescribing guidelines. At intervention site 2, D.J.L. enrolled ED clinicians by telephone while an on-site ID physician

(A.D.) met with clinicians in-person. The content of these meetings was identical to those at intervention site 1.

After the initial meeting, the study team e-mailed updated data to each participating clinician on his/her antimicrobial use. These e-mails were sent once every quarter. Overall, three e-mails were sent over the 12-month study period. E-mails were not sent after the fourth quarter, as the study had concluded by that point.

Beginning in late September 2018, a clinical pharmacist was assigned to the ED at intervention site 2 from 10a-10p every day. One of the clinical pharmacist's responsibilities was to ensure adequate antimicrobial selection. These pharmacists were not part of this trial, and the study team was only made aware of their presence as the intervention period was about to begin. To account for this, separate analyses were performed for intervention sites 1 and 2.

Feedback metrics: Feedback at the enrollment visit and in each quarterly e-mail update consisted of two metrics: 1) the clinician's total antimicrobial-prescribing volume adjusted for the total number of ED patient-visits, i.e. a total antimicrobial prescribing rate, and 2) the clinician's rate of prescribing antibiotics for uncomplicated viral acute respiratory infections (ARI), based on data from the VA's internal Academic Detailing website. The ARI metric included visits for acute bronchitis and non-specific upper respiratory tract infections but excluded visits for patients who were immunosuppressed, had chronic lung disease, or had a concurrent infection.

For the enrollment meeting with clinicians, both metrics were based on the year preceding the initiation of the study. Once the intervention period began, data on the clinician's total antimicrobial-prescribing rate was only drawn from the intervention period, which could include more than one quarter. Data on the ARI metric was only provided if the patient had seen ≥8 eligible ARI cases during the prior quarter; if there were not 8 eligible visits during the prior quarter, then more than one quarter of data could be included as long as the data was all from the intervention period.

At enrollment, clinicians were compared to their peers for both metrics. In subsequent e-mail communications, clinicians were compared to their peers and to their own prior performance for the ARI metric. For the total antimicrobial-prescribing rate, e-mails only compared clinicians to their personal baseline performance. The wording used in all feedback reports was based on the MITIGATE toolkit (Supplemental Table 1).[21] All peer-to-peer comparisons were also demonstrated graphically in an attachment to the e-mail (Supplemental Figure 1).

To assess whether the clinician received the e-mail feedback, we requested a read receipt for all e-mail communication. The percentage of read receipts that were acknowledged was tracked over time.

We did not educate or provide feedback to ED clinicians at the two control sites. The control sites were not aware that there antimicrobial-prescribing was being monitored.

Outcomes: The primary outcome was the cumulative frequency of an outpatient antimicrobial prescription within 24 hours of the ED visit. ED visits that resulted in an inpatient admission within 24 hours after the visit were not eligible for inclusion in the outcome. Antimicrobials were defined as all agents included in the National Healthcare Safety Network's (NHSN) Antimicrobial Use and Resistance Module.[22] On a monthly basis, the cumulative number of outpatient antimicrobials prescribed by the ED and the total number of eligible ED visits were used as the numerator and denominator, respectively. This outcome was chosen as it would not be influenced by diagnostic shifting.[12, 23]

The secondary outcome was the proportion of ED visits associated with an outpatient antibiotic prescription within 24 hours of the ED visit; it was calculated similar to antimicrobial use. Antibiotics were defined as all antibacterial agents, as defined by the NHSN's Antimicrobial Use and Resistance Module.[22]

The ARI metric, as defined above, was captured across all clinicians at the control and intervention sites. Guideline-concordant management was assessed using manual chart

reviews (see below). Other secondary outcomes were measured from 24 hours after the ED visit up to 30 days after the visit. These secondary outcomes included testing for the presence of *Clostridioides difficile*, confirmed *C. difficile* infection (CDI), return ED visit, late antimicrobial use, late antibiotic use, and admission to a VHA acute-care facility. CDI linked to a visit was confirmed if the patient had a positive *C. difficile* test and a qualifying antibiotic (metronidazole, oral vancomycin, or fidaxomicin) was dispensed to the patient within 7 days of the positive *C. difficile* test. Visits that occurred from 24 hours up to 30 days after the prior visit were recorded as a return ED visit. ED visits that occurred after 30 days from the prior ED visit were considered as independent visits. Primary and secondary outcomes, except return ED visits, included all eligible visits in the denominator.

Data on oral antimicrobial prescriptions, demographics, comorbidities, infections, and laboratory data for *Clostridioides difficile* for ED visits during the study period were extracted from the Corporate Data Warehouse (CDW) using the VA Informatics and Computing Infrastructure (VINCI). The *International Classification of Diseases*, Tenth Revision (ICD-10) codes were used to identify existing comorbidities and infection diagnoses linked to the ED visit.

Statistical Analysis: An interrupted times series analysis was used to evaluate the effect of audit-and-feedback between the intervention and control sites. The crude differences in patient characteristics from baseline to intervention periods were assessed for intervention and control sites using Fisher's exact test and Wilcoxon rank-sum test. Monthly proportions of antimicrobial and antibiotic use were calculated at each site for the baseline and intervention time periods. Segmented regression analysis was conducted using generalized linear models to estimate change in monthly antimicrobial and antibiotic prescription rates between baseline and intervention periods for intervention and control sites, respectively. Models were adjusted for continuous variables for time (months before, during, and after implementation). The estimate for time during implementation was used to calculate the immediate change in prescription rates and was reported as incident rate ratios (IRR) with 95% confidence intervals (CI). Indicator

variables for the four seasons were also included in each model to adjust for seasonal trends. An R-side random statement was included in each model to vary the degree of overdispersion for each facility. Finally, a difference-in-difference estimate was reported for the change in monthly prescription rates between intervention and control sites in the intervention period while controlling for changes in the baseline period. A Poisson regression model with log link was used to estimate the rate of secondary outcomes. Models were adjusted for time as a continuous covariate, an indicator for month of implementation of intervention (October 2018), and included random effects to account for repeated measures among sites each month during the study period. An interaction variable for the study period (baseline or intervention) and site (intervention or control) was included in the model to estimate the IRR and 95% CIs.

Manual chart reviews to assess guideline-concordant management: Patient-visits were eligible for manual chart review if the visit met the following criteria: 1) a patient's first ED visit during the study period; 2) a qualifying infection diagnosis, as defined by ICD-10 codes, and 3) no evidence of immunosuppression. Qualifying diagnoses were acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease (AE-COPD), acute sinusitis, cystitis, pharyngitis, and upper respiratory tract infection (URI) (Supplemental Table 2). Immunosuppression was defined as having a diagnosis of lymphoma, leukemia, HIV/AIDs, or organ transplantation during the 12 months prior to presentation or receipt of an immunosuppressive medication, which was defined as follows: prednisone or steroid equivalent at a dose ≥20 mg/day during the 30 days prior to admission, chemotherapy within the 30 days prior to admission, or an anti-rejection medication, biologic agent or a disease-modifying anti-rheumatic drug within the 3 month prior to admission. At each of the 4 EDs, eligible patient-visits were randomly chosen for review. Two independent, blinded reviewers evaluated selected medical records while using defined algorithms (Supplemental Figures 2-7). Reviewers assessed the accuracy of the diagnosis and, if necessary, re-classified the infection type; they also evaluated a decision to prescribe or not prescribe antibiotics as well as the appropriateness

of antibiotic selection and duration. Reviewers consisted of a fourth-year medical student, an Internal Medicine resident physician, and an Infectious Disease fellow physician. If the initial reviewers' assessment were discordant, a third reviewer, who was not blinded, reviewed the medical record. The third reviewer (D.J.L.) had to evaluate 128 (26.7%) charts during the baseline period and 135 (29.7%) during the intervention period. The goal was to include at least 110 adjudicated charts per site for the baseline and intervention periods.

Guideline-concordant management was defined as either prescribing an antibiotic when indicated or not prescribing an antibiotic when not indicated. Guideline-concordant antibiotic selection was defined as prescribing an antibiotic recommended by professional guidelines, as defined by our protocols (Supplemental Figures 2-7). Guideline-concordant duration was defined as prescribing an antibiotic for a duration that was ≤2 days shorter and ≤2 days longer than what is recommended by professional guidelines.

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