

Implementation of Veterans Affairs Primary Care Antimicrobial Stewardship Interventions For Asymptomatic Bacteriuria And Acute Respiratory Infections

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Background. Outpatient antimicrobial prescribing is an important target for antimicrobial stewardship (AMS) interventions to decrease antimicrobial resistance. The objective of this study was to design, implement, and evaluate the impact of AMS interventions focused on asymptomatic bacteriuria (ASB) and acute respiratory infections (ARIs) in the primary care setting.

Methods. This stepped-wedge trial evaluated the impact of multifaceted educational interventions to providers on adult patients presenting to primary care clinics for ARIs and ASB. The primary outcome was percentage of overall antibiotic prescriptions as a composite of prescriptions for ASB, acute bronchitis, upper respiratory infection not otherwise specified, uncomplicated sinusitis, and uncomplicated pharyngitis. Secondary outcomes were the individual components of the primary outcome; a composite safety endpoint of related hospital, emergency department, or primary care visits within 4 weeks; antibiotic selection appropriateness; and patient satisfaction surveys.

Results. A total of 887 patients were included (405 preintervention and 482 postintervention). After controlling for type I error using Bonferroni correction, the primary outcome was not significantly different between groups (56% vs 49%). There was a statistically significant decrease in prescriptions for acute bronchitis (20.99% vs 12.66%; $P = .0003$). Appropriateness of antibiotic prescriptions for uncomplicated sinusitis (odds ratio [OR], 4.96 [95% confidence interval {CI}, 1.79–13.75]; $P = .0021$) and pharyngitis (OR, 5.36 [95% CI, 1.93–14.90]; $P = .0013$) was improved in the postintervention vs the preintervention group. The composite safety outcome and patient satisfaction surveys did not differ between groups.

Conclusions. Multifaceted educational interventions targeting providers can improve antibiotic prescribing for indications rarely requiring antimicrobials without increasing re-visits or patient satisfaction surveys.

Keywords. antimicrobial drug resistance; bacteriuria; outpatient care; upper respiratory infections.

Antibiotic resistance is a growing threat leading to resistant infections in the United States. It is estimated that there are 2 million infections and about 23 000 deaths per year in the United States attributable to resistant infections [1]. While there are many factors that contribute to the rise in drug-resistant infections, one notable cause is the inappropriate prescribing of antibiotics, particularly in the ambulatory care setting. Approximately 60% of antibiotic expenditure in the United States occurs in the outpatient setting. The Centers for Disease

Control and Prevention (CDC) estimates that 50% of these prescriptions are inappropriate and 30% are unnecessary, making outpatient antimicrobial prescribing an important target for antimicrobial stewardship (AMS) interventions [1].

Several studies aim to identify risk factors for patients who may receive inappropriate antimicrobials and barriers to implementation of effective outpatient antimicrobial stewardship programs [2–5]. Toolkits have been published by the MITIGATE group [6], the CDC, and the national Veterans Affairs (VA) AMS Task Force (ASTF) [1, 2]. The use of clinical decision support tools has also been a target of intervention and investigation, but with mixed results [7, 8]. Numerous systematic reviews and individual studies have identified outpatient AMS interventions to be effective at improving outpatient provider prescribing practices; however, the most optimal interventions have not been identified [1, 9–13]. These systematic reviews evaluated approaches such as education for patients, family, and clinicians; procalcitonin testing; and electronic clinical decision support [9–12, 14]. It was also identified that active clinician

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education, such as educational outreach or interactive workshops, was more effective than passive educational interventions [11, 15–17].

While there have been small strides in improving outpatient antimicrobial prescribing for acute respiratory tract infections, a larger impact is needed to create lasting change and prevent further antimicrobial resistance and adverse events. There is a lack of data demonstrating the impact of outpatient stewardship interventions targeting inappropriate prescribing of antimicrobials for asymptomatic bacteriuria (ASB). The Infectious Diseases Society of America (IDSA) recently updated guidelines addressing the overtreatment of ASB and recognizes this as a stewardship opportunity to help decrease resistance and *Clostridioides difficile* rates [18].

At the Milwaukee Veterans Affairs Medical Center (VAMC), the antimicrobial stewardship program (ASP) evaluated 200 prescriptions from associated primary care clinics for appropriateness of antibiotic prescribing for acute respiratory infections (ARIs). Antibiotics prescribed for acute bronchitis were always deemed inappropriate according to the American College of Clinical Pharmacy guidelines [19]. Antibiotics prescribed for acute bacterial rhinosinusitis (ABRS) were considered indicated if patients experienced persistent symptoms, severe symptoms, or double sickening according to IDSA guidelines [20]. ABRS prescriptions were considered appropriate according to a guidance document based on local antibiogram data and IDSA guidelines. Three pharmacist reviewers independently reviewed a subset of patients using the guidance document. Results showed that for patients with prescriptions for sinusitis (n = 61), 46% (28/61) of prescriptions were not indicated and 79% (48/61) of antibiotic prescriptions were inappropriate (drug selection and/or duration of therapy). The group also identified 96 cases of acute bronchitis that were inappropriately treated with antibiotics. This data revealed a need for AMS education in our primary care setting at the Milwaukee VAMC and associated community-based outpatient clinics.

ASB is the fourth most common indication intervened on by the ASP at the Milwaukee VAMC with ≥ 30 interventions annually. ASP recommendations for ASB are accepted <50% of the time; therefore, it was decided to include ASB-targeted interventions in this study in addition to ARIs.

This stepped-wedge trial aimed to improve antimicrobial prescribing in the outpatient setting by primary care providers

through implementation of a multifaceted education intervention targeting ARIs and ASB.

METHODS

Inclusion Criteria

Patients who were included in this study were adults (≥ 18 years of age) who had a primary care visit at a Milwaukee VAMC primary care clinic or community-based clinic with a diagnosis of uncomplicated ARI, acute bronchitis, upper respiratory infection not otherwise specified (URI-NOS), uncomplicated sinusitis, or uncomplicated pharyngitis identified through the VA ASTF dashboard using *International Classification of Diseases, Tenth Revision* codes or adult patients (aged ≥ 18 years) who had a positive urine culture from a primary care visit, identified using a microbiology report from the VA Corporate Data Warehouse.

Exclusion Criteria

Patients were excluded from the ARI group if they had complicated infections such as pneumonia (as documented in the medical record by the provider or on chest radiograph), influenza or pertussis documented by the provider in the medical record with laboratory testing, a past medical history of chronic obstructive pulmonary disease as documented in the medical record, or immunosuppression as defined by the 2013 IDSA clinical practice guideline for vaccination in the immunocompromised host (those with combined primary immunodeficiency disorder, receiving cancer chemotherapy, within 2 months after solid organ transplant, human immunodeficiency virus infection with a CD4 count < 200 cells/ μL , receiving daily corticosteroid therapy with a dose of ≥ 20 mg of prednisone or equivalent for 14 days or more, receiving certain biologic immunomodulators such as tumor necrosis factor- α blockers or rituximab) [21]. Patients were excluded from the ASB group if they had abnormal urologic anatomy or an upcoming urologic procedure, were known to be pregnant, or had significant immunosuppression as defined above.

Patient Consent Statement

The design of this work was approved by the Milwaukee VAMC Institutional Review Board (IRB), which determined that this study presents no more than minimal risk. The IRB approved a waiver of consent for this study.

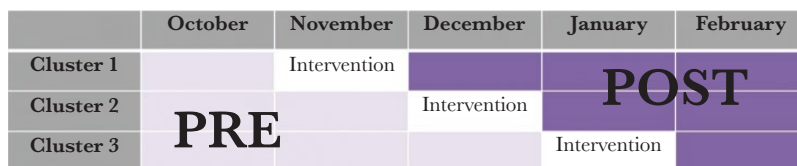


Figure 1. The above figure depicts the stepped wedge study design. Time-frame for data collected from the preintervention group is highlighted in light purple and the postintervention group is highlighted in dark purple. Abbreviations: POST, postintervention; PRE, preintervention.

Design

The study design is a stepped-wedge trial as depicted in [Figure 1](#). The intervention was implemented at the Appleton clinic, Green Bay clinic, Cleveland clinic, Union Grove clinic, and Milwaukee VAMC primary care clinics from November 2019 through January 2020. Clinics were split into 3 clusters according to expected number of patients based on a sample of data for ARI diagnoses and positive urine cultures associated with primary care visits. Cluster 1 consisted of 4 primary care clinics on the main Milwaukee VAMC campus, cluster 2 included the Green Bay and Cleveland clinics, and cluster 3 included the Appleton and Union Grove clinics. Clusters were entered into a random number generator to determine the order of intervention implementation. Implementation was completed in a stepwise fashion and data were collected on preintervention and postintervention groups as depicted in [Figure 1](#). Data were omitted from the month of the intervention for each cluster.

Intervention

Report cards ([Supplementary Figure A](#)) were prepared for each individual provider and included data regarding their prescribing patterns for ARIs (collected from the VA ASTF dashboard) and positive urine cultures (collected via medical record review by primary investigator) and compared them to de-identified peer providers at the same clinic location. Report cards also included “quick facts” about the true incidence of bacterial infection in acute respiratory tract infections according to the literature and when to treat bacteriuria according to IDSA ASB guidelines. These report cards were sent to providers 3–7 days prior to the scheduled educational session. A provider education session was provided in-person to providers focusing on guideline-recommended prescribing for ARIs and urinary tract infections focused on local antibiogram trends and antimicrobial formulary. The presentation also reviewed available resources and communication strategies to educate patients on AMS. The presentation can be viewed in [Supplementary Figure B](#). Pocket cards with local prescribing guidelines were provided at the education sessions ([Supplementary Figure C](#)). Clinical decision support within the electronic health record was updated to include order sets reflecting the references for ARI including links to quick orders for symptomatic treatment (cough suppressants, etc). Each clinic was also provided with locally created patient education brochures “How Do You Know if Antibiotics Are Right for You?,” the CDC “Be Antibiotics Aware” campaign symptomatic relief prescription pads, and posters for patient rooms.

Primary Outcome

The primary outcome of this study was a composite outcome of the overall antibiotic prescribing rate for bronchitis, URI-NOS, sinusitis, pharyngitis, and ASB.

Secondary Outcomes

The secondary outcomes evaluated were the individual components of the primary outcome; a composite safety endpoint of hospital admission, primary care visit, or emergency department visit within 4 weeks for the same infection; and patient satisfaction surveys. After initial analysis of data, it was also decided to include a post hoc analysis of antimicrobial appropriateness for all studied infections, defined as having all 3 of the following: correct antimicrobial (assessed as appropriate if it was concordant with provided guideline), correct dose, and correct duration. Overall appropriateness calculations considered antibiotic prescriptions for infections in which antibiotics are not indicated as inappropriate. Following this calculation, further analysis was done to calculate an odds ratio (OR) for all indications individually. Because antibiotics are only indicated in sinusitis and pharyngitis, there were 0 appropriately written scripts for the remaining indications and these analyses led to meaningless unbounded ORs. Thus, ORs for sinusitis and pharyngitis only are reported in this article.

Statistical Analysis

Univariate analyses were performed using χ^2 test, Fisher exact test, and 1-way analysis of variance as appropriate. Conditional logistic regression was used to examine prescribing habits. All analyses were conducted using SAS version 9.4 software. Type I error was controlled using Bonferroni correction.

RESULTS

A total of 887 patients were included for analysis. There were 405 patients in the preintervention group and 482 patients in the

Table 1. Patient Characteristics

Characteristic	Preintervention (n = 405)	Postintervention (n = 482)	PValue ^a
Cluster, No. (%)			
1	156 (39)	248 (51)	<.0001
2	109 (27)	159 (33)	<.0001
3	140 (35)	75 (16)	<.0001
Visit diagnosis, No. (%)			
Acute bronchitis	112 (28)	98 (20)	NS
URI-NOS	112 (28)	154 (32)	NS
Uncomplicated sinusitis	89 (22)	142 (29)	NS
Uncomplicated pharyngitis	39 (10)	42 (9)	NS
Asymptomatic bacteriuria	2 (1)	4 (1)	NS
Male sex, No. (%)	355 (88)	396 (82)	.0057
White race, No. (%)	348 (86)	397 (82)	NS
Age, y, mean (SD)	59 (18)	58 (16)	NS
BMI, kg/m ² , mean (SD)	31 (7)	31 (6)	NS
CrCl, mL/min, mean (SD)	94 (35)	95 (35)	NS
CCI, mean (SD)	2 (1.76)	2 (1.53)	.0070

Abbreviations: BMI, body mass index; CrCl, creatine clearance; CCI, Charlson comorbidity index; NS, not significant; SD, standard deviation; URI-NOS, upper respiratory infection not otherwise specified.

^aUnivariate analyses were performed using χ^2 test, Fisher exact test, or 1-way analysis of variance as appropriate. Type I error was controlled for using Bonferroni correction.

postintervention group. The patient population was a VAMC population consisting mostly of elderly white males. Baseline characteristics are included in Table 1. There was a statistically significant difference in number of patients in each cluster and in Charlson Comorbidity Index; however, the mean was the same [22] for both groups and the standard deviation was small. There were also significantly more males in the preintervention group than in the postintervention group.

After Bonferroni correction, there was no significant difference in the primary outcome of overall antibiotic prescribing rate (224 [56%] vs 235 [49%]). There was a statistically significant decrease in prescriptions for acute bronchitis (85 [21%] vs 61 [13%]; $P = .0003$). There was no statistically significant difference in any of the other components of the primary outcome, details of which are reported in Table 2. There was no statistically significant difference in the composite safety outcome of related primary care visit, emergency department visit, or hospitalization within 4 weeks (38 [9%] vs 41 [9%]). There was no statistically significant difference in patient care satisfaction scores between the preintervention and postintervention groups.

Appropriateness of prescriptions was significantly improved in the postintervention group compared to the preintervention group (23 [10%] vs 5 [2.2%]; $P = .0004$). Of the indications where prescriptions could be appropriate according to the pocket guides provided, there was a significant improvement in appropriate prescriptions in the postintervention group compared to the preintervention group. The OR for receipt of an appropriate prescription for uncomplicated sinusitis in the postintervention group compared to the preintervention group was 4.961 (95% confidence interval [CI], 1.789–13.754; $P = .0021$). The same was true for uncomplicated pharyngitis, with an OR of 5.359 (95% CI, 1.927–14.903; $P = .0013$). These results are noted in Table 3.

DISCUSSION

This stepped-wedge study found no difference in the primary endpoint of overall antibiotic prescriptions; however, a

significant difference was seen for acute bronchitis and in appropriateness of prescriptions after intervention for sinusitis and pharyngitis. While the number of appropriate prescriptions for antibiotic indications remains low, the improvement is encouraging. This study was not designed to detect differences in the secondary outcomes or patient satisfaction surveys, but the lack of significant difference supports further investigation of the pharmacist-led antimicrobial stewardship interventions. The results from this study showed observed improvement in primary care prescribing patterns following multifaceted pharmacist-led AMS interventions. However, continued primary care stewardship campaigns are likely needed to significantly change prescribing practices rather than 1-time educational interventions.

A statistically significant decrease in antibiotic prescriptions was observed only in bronchitis. This is likely due to the straightforward recommendation from CDC adult treatment recommendations and existing VA educational materials recommending against the treatment of bronchitis with antibiotics. Indications such as rhinosinusitis, pharyngitis, and asymptomatic bacteriuria can be less straightforward, requiring antibiotics in select situations suggesting bacterial etiology [23]. A similar study conducted by Butler et al [24] found a similarly low but statistically significant reduction in total antibiotic prescribing for acute respiratory tract infections (4.2%) with no differences in hospital admissions or return visits for respiratory tract infection [13]. This is contrasted with Harris et al, who implemented more engaging interactions with patients and focused on acute respiratory tract infections never requiring antibiotics (bronchitis and URI-NOS) and found a more profound and statistically significant decrease in antibiotic prescriptions [16]. This further supports that interventions targeted at indications never requiring antibiotics is more effective at consistently decreasing overall antibiotic prescribing in the outpatient setting. However, unlike Harris et al, our study found no statistically significant difference in prescribing patterns for URI-NOS, which is likely due to the fact that our clinical education

Table 2. Primary and Secondary Endpoints

Endpoint	Preintervention (n = 405)	Postintervention (n = 482)	P Value ^a
Overall antibiotic prescribing rate	225 (56)	235 (49)	NS
Asymptomatic bacteriuria prescribing rate	12 (3)	8 (2)	NS
Acute bronchitis prescribing rate	85 (21)	61 (13)	.0003
URI-NOS prescribing rate	35 (9)	27 (6)	NS
Uncomplicated sinusitis prescribing rate	69 (17)	105 (22)	NS
Uncomplicated pharyngitis prescribing rate	20 (5)	23 (5)	NS
Related hospitalization, ED visit, or primary care visit within 4 wk	38 (9)	41 (9)	NS
Patient satisfaction scores, average score (100-point scale)	91	89	NS
Appropriate prescriptions	5 (2)	23 (10)	.0004

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ED, emergency department; NS, not significant; URI-NOS, upper respiratory infection not otherwise specified.

^aUnivariate analyses were performed using χ^2 , Fisher exact test, and 1-way analysis of variance as appropriate. Type I error was controlled for using Bonferroni correction.

Table 3. Ad Hoc Antibiotic Appropriateness Analysis

Variable	OR	(95% CI)	PValue
Appropriate uncomplicated sinusitis prescription	4.961	(1.789–13.754)	.0021
Appropriate uncomplicated pharyngitis prescription	5.359	(1.927–14.903)	.0013

Conditional logistic regression was used to examine prescribing habits. Abbreviations: CI, confidence interval; OR, odds ratio.

focused on avoiding antibiotics specifically for bronchitis, sinusitis, and pharyngitis.

The baseline rate of antibiotics prescriptions for bronchitis is markedly lower than what has been observed in the published literature. An audit performed after this study was completed revealed coding inaccuracies in the ARI dashboard resulting in omitted prescriptions, which likely impacted the results of this study. Additionally, the VA Academic Detailing Service launched a campaign to improve the management of ARIs, occurring at this VA from 15 November 2019 through 31 March 2020. This relatively recent education could have impacted baseline prescribing rates. This may make extrapolating these findings to institutions without academic detailing services difficult.

It should also be noted that a study by Juzych et al observed a reduction more robust than the reduction in the present study when implementing changes in prescribing practices after education using interactive and case-based learning [17]. This difference could be partly due to our study's inclusion of acute respiratory tract infections that sometimes require antibiotics, but also may highlight the effectiveness of interactive learning experiences. The present study incorporated interactive portions to education; however, practice cases were not included due to a limited amount of time with providers.

Of note, no specific studies regarding AMS interventions in the primary care setting targeting inappropriate prescriptions for ASB were found. Unfortunately, in comparison to acute respiratory tract visits, the number of visits for ASB were much fewer and no significant difference was found. It should be noted this education was well received by physicians at educational sessions and they requested that additional services be provided education about when it is appropriate to order urinalyses and prescribe antimicrobials. Results from this study suggest that ASB may not represent as significant a proportion of inappropriate prescriptions in the primary care setting as investigators anticipated. Additional studies focusing on interventions regarding ASB in primary care are needed to identify opportunities for education.

There are several limitations to this study. Due to its retrospective nature for data collection, there are inherent biases and data are limited to what has been included in the electronic health record. This study is also subject to the Hawthorne effect as providers are aware that their prescribing patterns are being observed after receiving report cards and thus are more likely

to adhere to guidance presented in the intervention. Without sustained intervention, regression to the mean is very possible given the 1-time nature of the intervention and likelihood of new providers entering the workforce. Another drawback to this study was the lack of needs assessment conducted prior to implementation. While we have identified a lack of appropriate antimicrobial prescribing in the outpatient setting, the reasons for this remain unknown. This intervention focused on increasing the knowledge base of the providers; however, other barriers could be present that are unaddressed by the current intervention. Also of note, specific provider groups (ie, midlevel practitioners vs physicians) were not evaluated; however, there could be distinct differences among these groups that remain undefined. There are many unique barriers to effective outpatient AMS practices within the VA system including rapidly changing primary care administrative policies that impact provider time, which would be better defined by a needs assessment. This represents an important step that can be taken by our AMS team moving forward to help target future AMS interventions.

Stepped-wedge trials are uniquely designed to evaluate policy changes or service delivery methods using a fair yet robust study design [25]. The strongest study design would be to implement the intervention in half of the population and use the other half as a comparator group. Quasi-experimental design studying outcomes pre- and postimplementation is subject to temporal bias and is logistically difficult when rolling out interventions to several different geographic locations. The stepped-wedge study design controls for this potential bias by randomizing start dates and its unique pre- and postintervention groups, allowing for a more pragmatic intervention timeline. Although an uneven number of patients were included in each cluster, there was a relatively even number of patients in the pre- and postintervention groups.

Data from this study add to the current body of evidence supporting the effectiveness of AMS interventions in the primary care setting. Outcomes were not as significantly impacted as some previously published data, possibly due to the limited amount of time spent with providers rolling out this intervention and the 1-time nature of the intervention. The importance of AMS in the outpatient setting is clearly established, but defining the optimal role of the ASP remains to be determined. Highly interactive and continual interventions are likely needed to make a lasting, impactful change in the primary care setting.

Increasingly more institutions are hiring pharmacists and/or clinicians to promote outpatient AMS, which will allow for the more targeted and sustained interventions that are desperately needed to make lasting change and preserve one of our most important resources: antimicrobials.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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