ORIGINAL ARTICLE

Antimicrobial Stewardship in Outpatient Settings: A Systematic Review

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OBJECTIVE. Evaluate the effect of outpatient antimicrobial stewardship programs on prescribing, patient, microbial outcomes, and costs.

DESIGN. Systematic review

METHODS. Search of MEDLINE (2000 through November 2013), Cochrane Library, and reference lists of relevant studies. We included English language studies with patient populations relevant to the United States (eg, infectious conditions, prescription services) evaluating stewardship programs in outpatient settings and reporting outcomes of interest. Data regarding study characteristics and outcomes were extracted and organized by intervention type.

RESULTS. We identified 50 studies eligible for inclusion, with most (29 of 50; 58%) reporting on respiratory tract infections, followed by multiple/unspecified infections (17 of 50; 34%). We found medium-strength evidence that stewardship programs incorporating communication skills training and laboratory testing are associated with reductions in antimicrobial use, and low-strength evidence that other stewardship interventions are associated with improved prescribing. Patient-centered outcomes, which were infrequently reported, were not adversely affected. Medication costs were generally lower with stewardship interventions, but overall program costs were rarely reported. No studies reported microbial outcomes, and data regarding outpatient settings other than primary care clinics are limited.

CONCLUSIONS. Low- to moderate-strength evidence suggests that antimicrobial stewardship programs in outpatient settings improve antimicrobial prescribing without adversely effecting patient outcomes. Effectiveness depends on program type. Most studies were not designed to measure patient or resistance outcomes. Data regarding sustainability and scalability of interventions are limited.

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Antimicrobial overuse, resistance to existing drugs, and the paucity of new agents under development have combined to form what the Centers for Disease Control and Prevention has termed "one of our most serious health threats."[1] The majority of antimicrobials administered to humans are prescribed in outpatient settings, and overuse is common. Approximately 80% of adults with rhinosinusitis are prescribed antimicrobials,[2,3] and >60% of patients with pharyngitis received antimicrobials despite data suggesting that only 10% have an antimicrobial-responsive infection.[4] Factors contributing to high rates of prescribing include patient expectations, patient and provider unawareness of antimicrobial resistance, and lack of appreciation regarding the seriousness of the threat posed by antimicrobial resistance.[5]

Antimicrobial stewardship programs (ASPs) are focused efforts by a health care system or a part of the system (eg, an outpatient clinic) to *optimize* antimicrobial use. Goals of ASPs include improving patient outcomes, decreasing negative consequences including adverse drug reactions and antimicrobial-associated infections (eg, *Clostridium difficile* infection), limiting antimicrobial resistance, and delivering cost-effective therapy.[6–9]

In a previous review,[10–12] quality improvement strategies (primarily clinician and/or patient education) were found to be moderately effective in reducing inappropriate antimicrobial prescribing and improving appropriate antimicrobial selection, but few studies reported patient or microbial outcomes. We conducted a systematic review of the recent evidence regarding the effectiveness of ASPs in outpatient settings, with an emphasis on patient outcomes and microbial outcomes, and including the more commonly reported prescribing outcomes. To avoid overlap with the existing review, we excluded any studies cited in the full Technical Review[10] or related publications.[11,12] This report is derived from work performed for a larger Department of Veterans Affairs Evidence-based Synthesis Program review.

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METHODS

Search Strategy

We based our search strategy on Cochrane reviews of antimicrobial stewardship[13,14] and searched MEDLINE (Ovid) from 2000 through November 2013, limited to English language studies enrolling human subjects (Appendix). We identified additional studies from the Cochrane Library, systematic reviews, reference lists, and suggestions from peer reviewers of the Evidence-based Synthesis Program review.

Study Selection

Titles, abstracts, and articles were reviewed by investigators and research associates. Included studies were (1) conducted in settings or enrolling patients relevant to the United States (eg, patients with infections likely in the United States; settings where antimicrobials are available only by prescription); (2) involving an intervention of interest with an assessment of intervention effects; (3) reporting outcomes of interest; (4) not involving prophylactic antimicrobials; (5) involving patients with bacterial (vs viral, fungal, or mycobacterial) infections; and (6) randomized controlled trials (RCTs), cluster randomized controlled trials (CRCTs), controlled clinical trial (CCTs), controlled before/after trial (CBAs), or interrupted times series (ITS) with at least 3 data points before and after intervention implementation. Interventions which did not meet inclusion criteria include national campaigns to educate clinicians and patients regarding optimizing antimicrobial use. These interventions are not implemented at the institution or system level, and thus were considered beyond the scope of this review.

Data Extraction and Synthesis

From eligible studies, we extracted study characteristics, outcomes (prescribing, patient, and microbial), costs, and harms. Categorization measures considered the primary focus of the intervention as described by study authors. Prescribing outcomes included percentage of subjects receiving antimicrobials, drug selection, therapy duration, and guideline-concordant use. Patient outcomes included return visits, hospitalizations, adverse events, delayed antimicrobial prescriptions, and patient satisfaction. Information regarding barriers to implementation, sustainability, and scalability was recorded. Data extraction was verified by the lead author. For categorical data, we report odds and risk ratios. For continuous data we report mean or median differences. From ITS studies, we report, where provided by study authors, level and trend (or slope) results.

We assessed risk of bias for individual studies using criteria developed for the Cochrane Effective Practice and Organization of Care reviews.[15] A study was rated as low risk if each of the individual criteria were scored as low, medium risk if one or two criteria were scored as unclear or high, and high risk if more than two criteria were scored as unclear or high. Quality of an existing systematic review was assessed using the measurement tool for assessment of multiple systematic reviews.[16]

We rated overall strength of evidence (high, medium, low, or insufficient) for prescribing, patient, and microbial outcomes for each intervention category using methods developed by the Agency for Healthcare Research & Quality (AHRQ) and the Effective Health Care Program.[17] Strength of evidence was evaluated based on four domains: (1) risk of bias, (2) consistency, (3) directness, and (4) precision. Due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting, results could not be accurately pooled. We compiled a summary of findings and drew conclusions based on qualitative synthesis of the findings. To minimize publication bias, we performed a comprehensive literature search, hand searched reference lists, and received input from content experts; however, funnel plots were not possible due to the small number of trials for each intervention.

RESULTS

We reviewed 6,694 titles and abstracts from the literature search. We excluded 6,125 after abstract review and an additional 529 after full text review, leaving 40 articles eligible for inclusion (Figure). Hand searching or reviewer suggestion identified 10 further articles, totaling 50 included articles (17 RCTs, 18 CRCTs, 3 CCTs, 6 CBA trials, and 6 ITS studies).[18–69] Studies were conducted in the United States or Canada (N = 21),[18–37] Europe or the United Kingdom (N = 24),[38–64] the Middle East (N = 3),[65–67] and the Asia/Pacific region (N = 2).[68,69] Of these, 14 studies that enrolled adults,[21,22,27,30,31,35,37,48–50,52,56] 5 enrolled children or adolescents,[18,20,57,65,68] and 31 enrolled all ages or did not specify age. Most enrolled patients with respiratory infections (29 trials).

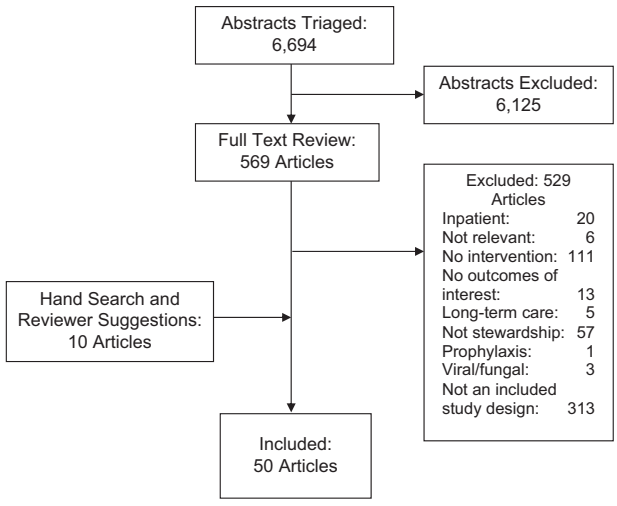

FIGURE. Literature Flow Diagram

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Summary data on prescribing and patient outcomes are presented in Tables 1 and 2; no study reported microbial outcomes. Although study heterogeneity precluded pooling results, the effects of individual studies are presented in Supplemental Tables 1 and 2, along with strength of evidence.

EFFECTIVENESS OF INTERVENTIONS ON PRESCRIBING AND PATIENT OUTCOMES

Provider and/or Patient Education

In 16 studies of provider and/or patient education (5 RCTs,[38,43,44,67,68] 6 CRCTs,[18,20,21,42,65,66] 1 CCT,[22] and 4 CBAs[19,23,29,40,41]), interventions were directed at providers in 13 of 16 studies and ranged from single to multiple sessions. Most provider education interventions were multifaceted and included discussion of current guidelines, feedback, patient education, communications skills training, or information regarding C-reactive protein (CRP) testing.

Antimicrobial prescribing was reported in 15 studies.[18–23,38–42,44,65–68] Of these, 6 found decreased prescribing[18,20,21,38,65,67] and 6 found no difference.[19,22,41,42,44,66] Of the remaining 3 studies, 1 study reported decreased prescribing for lower respiratory tract infections but not acute rhinosinusitis,[39,40] 1 study reported decreased prescribing for respiratory infections but not diarrhea,[68] and 1 study reported a 9.4% decrease in total antimicrobial prescribing during the study, but the significance of this finding was not reported.[23]

Patient outcomes were reported in 3 studies. In 1 RCT, a higher number of return clinic visits per patient was observed during the month after the initial visit in the group receiving a patient education leaflet.[44,70] No differences in hospitalizations (2 studies),[21,38] adverse events (1 study),[44] or satisfaction with care (1 study)[21] were observed.

Provider Feedback

In 3 of the 5 studies of provider feedback (1 RCT,[46] 2 CRCTs,[24,45] 1 CCT,[47] and 1 CBA[19]), individualized feedback regarding antimicrobial prescribing was associated with significant decreases in prescribing compared to more general feedback or usual care.[19,45,47] Prescribing outcomes were similar when postal feedback plus academic detailing (outreach visit from the research coordinator) was compared to postal feedback alone,[46] or when an electronic record component was compared to usual care.[24] No study reported patient outcomes.

Guidelines

Antimicrobial prescribing guidelines were assessed in 6 studies (1 CRCT,[50] 1 CCT,[51] 4 ITS[25,26,48,49]) for urinary tract infections (UTIs),[48] sexually transmitted infections,[25] acute dental pain,[50] acute rhinosinusitis,[49] and overall antimicrobial use.[26,51] In 4 studies detailing antimicrobial use following guideline introduction, 3 found significant decreases post-intervention.[26,49,50] In 1 study of guidelines to improve antimicrobial selection, mixed results across antimicrobials were reported,[48] while another reported no difference in patient satisfaction between those who did or did not receive an antimicrobial.[50]

Delayed Prescribing

Delayed prescribing was assessed in 4 RCTs,[27,44,52,64] wherein providers ask patients to fill a prescription only if symptoms persist or worsen. In 2 studies, delayed prescribing was the primary intervention. A significant reduction in antimicrobial use was found in 1 study of women with UTIs who received delayed prescriptions versus those who received immediate prescriptions.[52] A second study found no significant difference in prescriptions filled when patients were given post-dated (2-d delay) versus same-day prescription.[27]

Two other studies included a delayed prescribing component. One study, summarized under Provider and/or Patient Education because it included education versus no education groups, reported a significant reduction in antimicrobial use in the group assigned to delayed prescribing versus the immediate antimicrobial group.[44] Another study, summarized under Laboratory Tests (below) because it included CRP testing, found fewer patients in the CRP group receiving delayed prescriptions filled the prescriptions, versus control patients, who also received delayed prescriptions.[64]

One study found lower odds of return clinic visits in the delayed prescription group compared with immediate prescription for women with urinary tract infections (UTIs);[52] there were no major adverse events in either group. Another found that return clinic visits did not differ between groups assigned to delayed or immediate antimicrobial prescriptions.[44]

Communication Skills Training

Communication skill training for providers is intended to enhance patient–provider communication, address patient expectations for antimicrobial treatment, and foster a more "patient-centered" approach to care. All of the included studies (6 CRCTs[28,29,53–58]) involved multifaceted interventions. Of 6 eligible studies, 5 studies reported significantly reduced antimicrobial prescribing following the intervention.[28,53–58] For patient outcomes, the return clinic visit rate did not differ between intervention and control (3 studies).[28,54–57] Patient satisfaction was mixed, with improved satisfaction in the intervention group in 1 of 4 studies.[28]

Restriction Policies

Two studies (2 ITS[30,31]) assessed restriction policies. One was of fluoroquinolone restriction,[30] which was not associated with any significant change in the rate of fluoroquinolone prescribing but was associated with a significant increase in prescriptions consistent with formulary guidelines. There were

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TABLE 1. Overview of Prescribing Outcomes—Antimicrobial Stewardship Interventions for Outpatients

ASP Intervention (# studies)	Prescribing Rate/Use	Selection	Duration	Guideline Concordant Use	Summary
Provider and/or patient education (5 RCT, 6 CRCT, 1 CCT, 4 CBA)	Decreased: +9 studies[a,b] ≈6 studies	+3 studies[a] ≈5 studies	≈1 study	NR	Provider and/or patient education was associated with mixed results for prescribing outcomes.
Provider feedback (1 RCT, 2 CRCT, 1 CCT, 1 CBA)	Decreased: +3 studies ≈2 studies	+2 studies[a] ≈1 study	NR	≈1 study	Feedback on prescribing was associated with mixed results for prescribing outcomes.
Guidelines (1 CRCT, 1 CCT, 4 ITS)	Decreased: +3 studies ≈1 study	+3 studies[a] ≈1 study	≈1 study	NR	Introduction of guidelines was associated with decreased use and improved selection with no difference in duration.
Delayed prescribing (4 RCT)	Decreased: +3 studies ≈1 study	NR	NR	NR	Delayed prescribing was associated with decreased use of antimicrobials.
Communication skills training (6 CRCT)	Decreased: +5 studies ≈1 study	NR	NR	NR	Communication skills training was associated with a decrease in antimicrobial use.
Restriction (2 ITS)	Decreased: +/−2 studies	+/−2 studies	NR	+1 study	Restriction policies had mixed results for antimicrobial use and selection.
Decision support (2 RCT, 3 CRCT, 1 CBA)	Decreased: +4 studies[a] ≈2 studies	+2 studies	NR	+1 study	Decision support systems were associated with reduced antimicrobial prescribing and improved selection.
Financial incentive (1 CBA)	Decreased: 1 study[a]	NR	NR	NR	A provider incentive was associated with mixed results across antimicrobials.
Procalcitonin, rapid antigen detection tests, PCR assay, and CRP (6 RCT, 2 CRCT, 1 CBA)	Decreased[c]: +8 studies ≈1 studies	+1 study	NR	NR	Rapid antigen testing (sore throat) and C-reactive protein testing (respiratory or unspecified infection) were associated with decreased antimicrobial prescribing.

NOTE. ASP, antimicrobial stewardship program; NR, not reported; PCR, polymerase chain reaction; CRP, C-reactive protein; CBA, controlled before and after; CCT, controlled clinical trial; CRCT, cluster randomized controlled trial; ITS, interrupted time series; RCT, randomized controlled trial.

+ Indicates statistically significant difference favoring antimicrobial stewardship intervention.

≈ Indicates no statistically significant difference between antimicrobial stewardship intervention and control.

− Indicates statistically significant difference favoring control.

+/− Indicates mixed results across different antimicrobials studied or differences between level and trend outcomes in ITS analyses.

[a]Some studies with a "+" reported mixed results (ie, significant differences for some conditions or some age groups, no difference for others).

[b]Includes 1 study with significance not reported.

[c]Decreased antimicrobial use was also reported in 2 studies from an existing systematic review.

TABLE 2. Overview of Patient Outcomes—Antimicrobial Stewardship Interventions for Outpatients

ASP Intervention (No. studies)	Return Clinic Visits	Hospitalizations	Adverse Events	Late Antimicrobial Prescribing	Patient Satisfaction with Care	Summary
Provider and/or patient education (5 RCT, 6 CRCT, 1 CCT, 4 CBA)	≈2 studies −1 study	≈2 studies	≈1 study	NR	≈1 study	Provider and/or patient education did not affect patient outcomes.
Provider feedback (1 RCT, 2 CRCT, 1 CCT, 1 CBA)	NR	NR	NR	NR	NR	Patient outcomes were not reported.
Guidelines (1 CRCT, 1 CCT, 4 ITS)	NR	NR	NR	NR	≈1 study	One study reported no difference in patient satisfaction with treatment.
Delayed prescribing (4 RCT)	+1 study ≈1 study	NR	≈1 study	NR	NR	Two studies found mixed results for return clinic visits; no major adverse events were noted.
Communication skills training (6 CRCT)	≈3 studies	≈1 study p = NR, 1 study	≈4 studies	+1 study	≈3 studies +1 study	Communications skills training did not affect patient outcomes.
Restriction (2 ITS)	−1 study	−1 study	≈1 study	NR	NR	A restriction intervention was associated with small but significant increases in return outpatient visits and all-cause (but not infection-related) hospitalization.
Decision support (2 RCT, 3 CRCT, 1 CBA)	≈4 studies	≈2 studies	p = NR, 1 study	≈2 studies	NR	Decision support interventions did not affect patient outcomes.
Financial incentive (1 CBA)	NR	NR	NR	NR	NR	Patient outcomes were not reported.
Procilcitonin, rapid antigen detection tests, PCR assay, and CRP (6 RCT, 2 CRCT, 1 CBA)	≈4 studies	≈4 studies	≈6 studies	+2 studies ≈1 study	+1 study ≈2 studies	None of the laboratory tests studied affected most patient outcomes; 2 of 3 studies found fewer delayed prescriptions with CRP testing.

NOTE. ASP, antimicrobial stewardship program; NR, not reported; PCR, polymerase chain reaction; CRP, C-reactive protein; CBA, controlled before and after; CCT, controlled clinical trial; ITS, interrupted time series; RCT, randomized controlled trial.

+ Indicates statistically significant difference favoring antimicrobial stewardship intervention.

≈ Indicates no statistically significant difference between antimicrobial stewardship intervention and control.

− Indicates statistically significant difference favoring control.

no changes in mortality or infection-related hospitalizations, but small statistically significant increases in both return clinic visits and all-cause hospitalization were observed. A second study evaluated the effects of limiting reimbursement for fluoroquinolones to treatment of patients with specified conditions.[31] In this study, a decreasing trend in total antimicrobial prescriptions followed the introduction of the restriction policy, with mixed results for specific antimicrobials.

Computerized Clinical Decision Support

Computerized clinical decision support within an electronic medical record was evaluated in 6 studies (2 RCTs,[33,34] 3 CRCTs,[32,36,59] 1 CBA[35]), and was associated with decreased prescribing in 4 of 6.[32–35] Of the 2 remaining studies, 1 study reported no difference but also reported low uptake of the decision support by providers,[36] while another reported mixed results. Reminders were associated with increased adherence to only some of the prescribing recommendations.[59] Among patient outcomes, no significant differences were reported for return clinic visits (4 studies),[32–34,36] hospitalization (2 studies),[32,33] delayed antimicrobial prescriptions (2 studies),[33,34] or adverse events (1 study).[32]

Financial Incentives

A single study (CBA) described a one-time payment (independent of practice performance) improving the volume of prescribing and adherence to guidelines for just 2 of 7 antimicrobials studied; these researchers also noted that changes diminished during the first year.[60]

Procalcitonin, Rapid Antigen Detection Tests, Polymerase Chain Reaction Assay, and C-Reactive Protein

A high-quality systematic review found that procalcitonin testing in patients with acute respiratory tract infection was associated with decreased antimicrobial prescriptions.[71] In more recent studies (6 RCTs,[37,61–64,69] 2 CRCTs,[53–56] and 1 CBA[39,40]), rapid antigen detection and viral polymerase chain reaction (PCR) testing in patients with acute respiratory tract infection were associated with an initial decrease in antimicrobial prescriptions, although this was not sustained throughout the study period.[62] Testing for Group A *Streptococcus* antigen, either alone or in combination with pharyngitis decision rules, was associated with decreased antimicrobial prescriptions compared to usual care.[37] A second study of rapid antigen testing for patients with pharyngitis found that rapid testing combined with a clinical score was associated with decreased antimicrobial use compared to delayed prescribing, but the rapid test did not provide additive value to the clinical score alone.[61]

Of 6 studies of CRP testing (alone and in combination with communication skills training) in patients with acute respiratory tract or mixed infections, 5 studies showed decreased antimicrobial prescriptions and avoidance of newer broad-spectrum antimicrobials in select patients.[39,40,53,54–56,64,69]

No differences were observed between groups receiving any of the tests studied and comparator groups in return clinic visits,[54–56,61,63,64,69] hospitalizations,[54–56,61,64,69] modification of initial treatment,[69] duration of fever,[69] or performance of further testing.[69] CRP testing and communication skills training were associated with similar, or possibly increased, patient satisfaction with care.[54–56,64]

Costs

Dispensing costs were reported in 7 studies (3 RCTs,[38,67,68] 1 CCT,[47] 1 CRCT,[54,55] and 2 ITS[26,31]). Significant cost reductions associated with ASPs were found in 1 study of provider education,[68] a study of provider feedback,[47] and a study of guidelines for common infectious conditions.[26] One study of provider education reported greater savings with continuous medical education compared with seasonal medical education.[67] A "limited use" policy was associated with mixed findings (ie, decreased costs for some antimicrobials but not others).[31] One study reported that medication cost per patients decreased with communication skills training and with CRP testing.[54,55]

Three studies reported program costs (2 RCTs[38,46] and 1 CRCT[54,55]). A study of a provider education program reported a mean cost per practice of £2,923 (US$4,860 in 2014) covering administration costs, seminar preparation and seminar delivery.[38] A study of provider feedback reported total cost per practice of €175 (US$243) covering staff, equipment, and administrative costs.[46] The study of communication skills training and CRP testing reported per patient program costs ranging from €0.00 (usual care) to €10.06 (US$13.95) (combined CRP plus communication skills training).[54,55]

Key Intervention Components

Information on key intervention components is limited. Speculation by authors or reported data from individual provider[20,21,72,73] or focus group[45,74] interviews suggested that leadership, a team approach, patient education materials, provider reminders, user-friendly interfaces, and evidence-based materials may be key, but little evidence was presented to support such claims.

Effectiveness by Clinic Setting or Suspected Patient Condition

All but 7 studies were conducted in primary care clinics. Respiratory infections were the condition-of-interest in 29 studies. We found little information regarding the effectiveness of stewardship interventions in other settings or infections.

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TABLE 3. Overview of Strength of Evidence—Antimicrobial Stewardship Interventions for Outpatients

ASP Intervention (No. studies)[a]	Prescribing Outcomes (No. studies)	Patient Outcomes Return Clinic Visits, Hospitalizations (No. studies)	Microbial Outcomes (No. studies)
Provider and/or patient education (k = 16)	Low (k = 15)	Low for return clinic visits (k = 3); low for hospitalizations (k = 2)	Insufficient (k = 0)
Provider feedback (k = 5)	Low (k = 5)	Insufficient for return clinic visits and hospitalizations (k = 0)	Insufficient (k = 0)
Guidelines (k = 6)	Low (k = 4)	Insufficient for return clinic visits and hospitalizations (k = 0)	Insufficient (k = 0)
Delayed prescribing (k = 4)	Low (k = 4)	Low for return clinic visits (k = 1); insufficient for hospitalizations (k = 0)	Insufficient (k = 0)
Communication skills training (k = 6)	Medium (k = 6)	Low for return clinic visits (k = 2); low for hospitalizations (k = 2)	Insufficient (k = 0)
Restriction (k = 2)	Low (k = 2)	Low for return clinic visits (k = 1); low for hospitalizations (k = 1)	Insufficient (k = 0)
Decision support (k = 6)	Low (k = 6)	Low for return clinic visits (k = 4); low for hospitalizations (k = 2)	Insufficient (k = 0)
Financial incentive (k = 1)	Low (k = 1)	Insufficient for return clinic visits and hospitalizations (k = 0)	Insufficient (k = 0)
Procalcitonin, rapid antigen detection tests, polymerase chain reaction assay, and C-reactive protein (k = 9)	Medium (k = 9)	Low for return clinic visits (k = 5); low for hospitalizations (k = 4)	Insufficient (k = 0)

NOTE. ASP, antimicrobial stewardship program.
[a]Number of studies is >50; studies with multiple interventions are included under each intervention.

Harms of Antimicrobial Stewardship Programs in Outpatient Settings

No studies were powered to detect between-group differences in harms. In total, 20 studies reported return clinic visits, hospitalizations, and/or adverse events including mortality and only 3 found significant differences between intervention and control groups.[30,44,52]

Implementation Facilitators

In several studies, stewardship implementation was addressed. Providers reported being more likely to utilize a computer-based intervention if it was easy to access, similar to existing software, and not overly complex.[36] Similarly, convenient location and scheduling, interactive sessions, evidence-based information, and relevant topics were mentioned by participants as being important.[75]

Strength of Evidence

Only the associations between prescribing outcomes and communication skills training and laboratory testing were supported by medium-strength evidence (Table 3). Strength of evidence was low for associations between prescribing outcomes and other interventions, and it was low or insufficient for patient outcomes. Details regarding strength of evidence are presented in Supplemental Tables 1 (prescribing outcomes) and 2 (patient outcomes).

DISCUSSION

Our systematic review provides updated information on the impact of outpatient ASPs on prescribing, patient, microbial, and cost outcomes. We identified several main findings. First, outpatient antimicrobial stewardship interventions of all types were associated with favorable changes in antimicrobial prescribing. Second, changes in prescribing did not adversely affect patient outcomes or drug costs, although these outcomes were not universally reported. Third, no study reported the effect of outpatient stewardship interventions on microbial outcomes. Fourth, studies of outpatient antimicrobial stewardship predominantly involve respiratory infections; therefore, we have little information is available regarding antimicrobial stewardship for other common outpatient infections. Importantly, few interventions were supported by medium-strength evidence, and none by high-strength evidence. Additionally, many interventions in the included studies were multifaceted, and few provided separate results for different intervention components.

Given the high rate of unnecessary prescribing for respiratory infections in outpatient settings, it is not surprising that the majority of included studies were designed to address that concern. As a result, little information is available regarding whether the stewardship interventions would be effective with other infections or settings, including common infections such as cellulitis or other skin/soft-tissue infections. Urinary tract infections, which are commonly misdiagnosed and overtreated, are also underrepresented in studies of

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antimicrobial stewardship. These conditions may represent promising areas for both achieving further reductions in antimicrobial use and further stewardship studies. In addition to the lack of data on nonrespiratory infections, we also found limited information on scalability and sustainability of interventions. While many interventions were conducted at multiple sites, few were replicated or provided long-term results after the initial research team was no longer present. Future research should focus on assessing long-term sustainable improvements in clinically meaningful outcomes, should expand stewardship programs to non-respiratory infections, and should assess patient and microbial outcomes, in addition to the usual prescribing outcomes.

Laboratory testing to aid antimicrobial stewardship, especially procalcitonin and CRP assays, appears to be a promising tool that can be used to significantly decrease antimicrobial prescribing. Their objective results are likely a welcome aid to clinicians, who often must assess the risk/benefit ratio of antimicrobial treatment largely on subjective data. Similarly, efforts to improve provider communication with patients around antimicrobial use also showed promising results. As efforts from the CDC and others to educate the public about the growing risk of antimicrobial resistance[1] reach more patients, clinicians may find that patients will respond even more favorably to communication-based stewardship efforts.

In conclusion, a wide variety of stewardship efforts are associated with decreased antimicrobial prescribing, without evidence of harms or increased costs, although these outcomes were not universally assessed. Importantly, in this era of increasing antimicrobial resistance, the effects of outpatient stewardship programs on antimicrobial resistance are unknown. However, the ecological evidence linking increasing antimicrobial use and antimicrobial resistance is robust and biologically plausible.[76] Accordingly, the reductions in antimicrobial use are likely to offer a clinical benefit—albeit one that is yet unquantified. Future large-scale studies that assess the effect of outpatient antimicrobial stewardship and clinically relevant outcomes, including antimicrobial resistance, are needed. In the interim, the growing threat from antimicrobial resistance combined with the available evidence supporting outpatient ASPs makes a compelling argument for the widespread implementation of such programs, even as we await further data.

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SUPPLEMENTARY MATERIALS

To view Supplementary Materials for this article, please visit http://dx.doi.org/10.1017/ice.2014.41

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APPENDIX

Search Strategy
Database: Ovid MEDLINE(R)

1. antibiot$.mp. or exp antibiotics/
2. antimicrob$.mp.
3. exp Anti-Bacterial Agents/
4. exp Anti-Infective Agents, Urinary/
5. exp Cross Infection/
6. exp Community-Acquired Infections/
7. exp Respiratory Tract Infections/
8. exp Wound Infection/
9. exp Catheter-Related Infections/
10. exp Vancomycin Resistance/ or exp Vancomycin/ or vancomycin.mp.
11. aminoglycosides.mp. or exp Aminoglycosides/
12. fluoroquinolones.mp. or exp Fluoroquinolones/
13. broad spectrum antibiotics.mp.
14. carbapenems.mp. or exp Carbapenems/
15. exp Cephalosporins/or broad spectrum cephalosporins.mp.
16. or/1-15
17. exp Education/or education.mp.
18. information campaign.mp.
19. audit.mp.
20. feedback.mp. or exp Feedback/
21. dissemination.mp. or exp Information Dissemination/
22. provider reminders.mp.
23. computerized medical records.mp. or exp Medical Records Systems, Computerized/
24. exp Physician Incentive Plans/ or financial incentives.mp.
25. discharge planning.mp.
26. guideline implementation.mp.
27. guideline adherence.mp. or exp Guideline Adherence/
28. exp Quality Assurance, Health Care/ or quality assurance.mp.
29. program evaluation.mp. or exp Program Evaluation/
30. exp Practice Guideline/
31. exp Physician's Practice Patterns/
32. exp Drug Prescriptions/
33. exp Drug Utilization/
34. or/17-33
35. randomized controlled trial.mp. or exp Randomized Controlled Trial/
36. controlled clinical trial.mp. or exp Controlled Clinical Trial/
37. intervention study.mp. or exp Intervention Studies/
38. Comparative Study/
39. experiment.mp.
40. time series.mp.
41. pre-post test.mp.
42. (randomized controlled trial or controlled clinical trial).pt.
43. (randomized controlled trials or random allocation or clinical trial or double blind method or single blind method).sh.
44. exp clinical trial/
45. (clin$ adj25 trial$).ti,ab.
46. ((singl$ or doubl$ or trebl$ or trip$) adj25 (blind$ or mask$)).ti,ab.
47. (research design or placebos).sh.
48. (placebo$ or random$).ti,ab.
49. exp Double-Blind Method/
50. exp cohort studies/ or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or comparative study/ or follow-up studies/ or prospective studies/ or cohort.mp. or compared.mp. or multivariate.mp. (4148897)
51. ("time series" or pre-post or "Before and after" or intervention).tw.
52. or/35-51
53. 16 and 34 and 52
54. limit 53 to english language
55. limit 54 to humans
56. limit 55 to yr = "2000 -Current"
57. (influenza$ or antimalar$ or malaria$ or prophylax$).mp.
58. 56 not 57

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