REVIEW ARTICLE

Antimicrobial Stewardship Programs in Inpatient Hospital Settings: A Systematic Review

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OBJECTIVE. Evaluate the evidence for effects of inpatient antimicrobial stewardship programs (ASPs) on patient, prescribing, and microbial outcomes.

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 (ie, infectious conditions and prescriptions required for antimicrobials) that evaluated ASP interventions and reported outcomes of interest. Study characteristics and outcomes data were extracted and reviewed by investigators and trained research personnel.

RESULTS. Few intervention types (eg, audit and feedback, guideline implementation, and decision support) substantially impacted patient outcomes, including mortality, length of stay, readmission, or incidence of *Clostridium difficile* infection. However, most interventions were not powered adequately to demonstrate impacts on patient outcomes. Most interventions were associated with improved prescribing patterns as measured by decreased antimicrobial use or increased appropriate use. Where reported, ASPs were generally associated with improvements in microbial outcomes, including institutional resistance patterns or resistance in the study population. Few data were provided on harms, sustainability, or key intervention components. Studies were typically of short duration, low in methodological quality, and varied in study design, populations enrolled, hospital setting, ASP intent, intervention composition and implementation, comparison group, and outcomes assessed.

CONCLUSIONS. Numerous studies suggest that ASPs can improve prescribing and microbial outcomes. Strength of evidence was low, and most studies were not designed adequately to detect improvements in mortality or other patient outcomes, but obvious adverse effects on patient outcomes were not reported.

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BACKGROUND

More than 3 million kilograms of antimicrobials were administered to humans in the United States in 2009.[1] Although the benefits of appropriate antimicrobial prescribing are indisputable, major harms are associated with use and misuse, and antimicrobial resistance is compounding. Major concerns include microbial resistance, antimicrobial-associated *Clostridium difficile* infection (CDI), adverse events, and increased antimicrobial and nonantimicrobial healthcare costs.[2-9]

Antimicrobial stewardship programs (ASPs) are focused efforts by healthcare organizations or sections of organizations (eg, intensive care units) to optimize antimicrobial use and thus to improve patient outcomes, reduce adverse consequences (emergence of resistance, selection of pathogenic organisms, or toxicity), and deliver cost-effective therapy.[2,10-12] The emphasis is on appropriate selection, dosing, route, and duration of antimicrobial therapy.[11,12] Despite recognition of the growing problem of antimicrobial resistance, a 2008 survey estimated that only 48% of hospitals in the United States had an ASP.[13]

A recent Cochrane review of studies published through 2009 categorized hospital-based ASP interventions as persuasive, restrictive, or structural, and disparate outcome measures were used to assess ASP effectiveness.[14] Few of the 89 studies included in the review reported patient outcomes.

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However, both persuasive and restrictive interventions were associated with improved prescribing outcomes and desired microbial outcomes.[14]

The purposes of the present review were to summarize evidence on ASPs not reviewed in or published since the last Cochrane review[14] and to identify differences between ASP interventions by grouping studies according to key intervention components.[11] This report is part of a larger US Department of Veterans Affairs evidence-based synthesis program review available at http://www.hsrd.research.va.gov/publications/esp/reports.cfm.

METHODS

Search Strategy

We searched MEDLINE (Ovid) from 2000 through November 2013 (Appendix). The search was limited to studies published in English language and enrolling human subjects. We identified additional studies from systematic reviews, reference lists of retrieved articles, and suggestions made by experts in the field.

Study Selection

Titles, abstracts, and articles were reviewed by investigators and trained research associates. We excluded studies for the following reasons: (1) settings or patient populations not relevant to the United States (ie, patients with infections unlikely in the United States; settings where antimicrobials are available without a prescription); (2) no intervention or not an intervention of interest (eg, studies of interventions involving education only were excluded); (3) intervention with no assessment of the effects of the intervention; (4) did not report at least 1 of the patient outcomes of interest, prescribing outcomes, microbial outcomes, or harms; (5) antimicrobial therapy for medical or surgical prophylaxis; (6) patients with viral or fungal infection or tuberculosis; (7) outpatient, extended care, nursing home, or pediatric settings. We included studies if they were a randomized controlled trial (RCT), controlled clinical trial (CCT), controlled before/after trial (CBA), or interrupted times series (ITS) with at least 3 data points before and after implementation of the intervention.

Data Abstraction

We extracted, in duplicate, study characteristics, patient (primary) outcomes, prescribing outcomes, microbial outcomes, and harms from eligible studies. Discrepancies were resolved by consensus. Patient outcomes included mortality, length of stay, readmissions, CDI, and adverse effects. Antimicrobial prescribing outcomes included timing, use, selection, dose, route, and duration. Microbial outcomes included institutional resistance patterns and resistance in the study population. Information on implementation barriers, sustainability, and scalability were also extracted, if reported.

Quality Assessment

Risk of bias of individual studies was assessed using criteria developed for Cochrane Effective Practice and Organization of Care (EPOC) reviews.[15] A study was rated as low risk of bias if each of the individual criteria were scored as low risk and as high risk of bias if more than 2 criteria were scored as unclear or high risk. We determined quality of systematic reviews using the measurement tool for assessment of multiple systematic reviews (AMSTAR).[16]

Data Synthesis

We constructed evidence tables showing the study characteristics and results for all included studies, organized by intervention category. If feasible, data were analyzed in Review Manager (RevMan) version 5.2 software (Nordic Cochrane Centre, Copenhagen, Denmark). We were unable to pool results quantitatively due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting among studies for each intervention. Instead, we compiled a summary of findings and drew conclusions based on qualitative synthesis of the findings.

Rating the Body of Evidence

We assessed overall strength of evidence for patient outcomes for each intervention category using methods developed by the Agency for Healthcare Research and Quality and the Effective Health Care Program.[17] The strength of the evidence was evaluated on the basis of 4 domains: (1) risk of bias, (2) consistency, (3) directness, and (4) precision.

RESULTS

Our literature search yielded 6,334 titles and abstracts (Figure 1), of which 37 studies (11 RCTs or cluster RCTs, 4 CCTs, 2

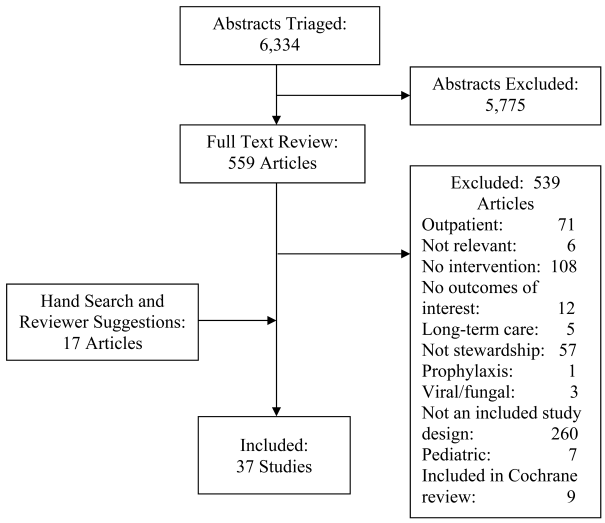

FIGURE 1. Literature flow diagram.

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CBAs, and 20 ITS studies) met eligibility criteria.[18-54] To avoid duplication, we included only studies meeting the eligibility criteria described above and not included in the Cochrane review.[14]

Effectiveness of Inpatient Antimicrobial Stewardship Programs

Of the 29 studies that reported patient outcomes, nearly 60% ($k = 17$) found no significant differences in any patient outcome (mortality, length of stay, readmission, or incidence of CDI). However, improvements in at least 1 patient outcome were observed in 11 (38%). Of 31 studies that measured antimicrobial outcomes, improvements in at least 1 outcome (antimicrobial use, selection, timing, or duration) were observed in 23 (74%). Of the 9 studies that measured microbial outcomes, improvements in at least 1 outcome (institutional or study population resistance) were observed in 7 studies (78%). No studies clearly identified barriers to implementation. A handful of authors expressed opinions about how program impacts might be enhanced. Nearly all study periods were short, and there was no systematic evidence on sustainability or scalability.

Most of the 37 included studies were conducted at university-affiliated or teaching hospitals. Among studies reporting intervention site, 10 were conducted in intensive care units (ICUs),[21,23,26,33,42,44,48,51,53,54] 7 in medical wards,[19,22,27,30,31,38,50] 12 in multiple sites (medical, surgical, ICU),[18,20,24,25,28,29,32,35,36,40,45,47] and 1 in acute care.[39] Seven studies focused on treatment of respiratory illness,[37,38,43,44,47,49,50] 27 included patients with any type of infection,[18-29,31,32,34-36,39-42,45,46,48,51,52,54] 1 study included only bloodstream infections,[33] and 2 did not report infection site.[30,53]

We categorized studies by primary intervention, including 14 studies of audit and feedback programs,[18-31] 5 studies of formulary restriction or preauthorization programs,[32-36] 4 studies of guideline implementation with feedback,[37-40] 4 studies of guideline implementation with no feedback,[41-44] 4 studies of computerized decision support,[45-48] and 4 studies of protocol or policy implementation.[49-52] We also identified 2 recent systematic reviews and 2 trials published after these reviews that focused on procalcitonin monitoring to guide antimicrobial therapy.[53-56]

Patient and prescribing outcome findings are summarized in Tables 1 and 2, with more detailed information, including strength of evidence for patient outcomes, in Tables 3 and 4. Microbial outcome findings are presented in Table 5. Strength of evidence for all patient outcomes was rated as low because of small numbers of studies of each intervention type that reported each outcome, inconsistency across studies, and medium-to-high risk of bias.

Audit and feedback. In all 14 studies of audit and feedback (3 RCTs, 2 CCTS, 1 CBA, and 8 ITS studies),[18-31] a pharmacist and/or physician reviewed management of individual cases in real time and provided advice to clinicians during a course of antimicrobial therapy. Studies were dispersed geographically, but most were conducted in urban, university-affiliated hospitals.

Of 10 studies reporting mortality, only 1 CCT reported a significant reduction in risk-adjusted odds of death in the intervention group compared with the control group (Figure 2; Tables 1 and 3), and that study was of use of a checklist with only 1 item on antimicrobial use.[21] Length of stay, reported in 10 studies, did not differ between intervention and control groups or pre- and postintervention periods. One RCT reported a significant difference in 60-day readmission for relapsing infection favoring the intervention group (3.4% intervention, 7.9% control, $P = .01$).[18]

Audit and feedback programs decreased use of targeted antimicrobials and decreased excessive use (Tables 2 and 4). Effects of audit and feedback on increasing appropriate use varied across studies with a significant increase in appropriate therapy in an RCT study[19] but no differences in an ITS study.[26] Five studies reported improved durations of therapy after the intervention.[18,19,20,22,27] Improvements in antimicrobial selection were reported in 1 study,[30] whereas another reported mixed results for targeted antimicrobials.[29]

Two studies reported decreased incidence rates of selected antimicrobial-resistant bacteria after implementation of an ASP (Table 5),[29,30] however, one of these studies also reported that the incidence of another antimicrobial-resistant organism had increased.[30] Of 3 other studies, 1 found increased susceptibility to 1 of 6 antimicrobials studied;[23] no other differences were reported.[18,31]

Formulary restriction and preauthorization. We identified 5 studies (1 RCT, 4 ITS) evaluating restrictive interventions; 2 evaluated preauthorization, and 3 evaluated formulary restriction.[32-36] One study used administrative health care databases;[34] others were conducted in university-affiliated or teaching hospitals (3 studies) or a community hospital (1 study).

Formulary restriction and preauthorization interventions were associated with no change in mortality or hospital length of stay (Figure 1; Tables 1 and 3).[32-34] CDI incidence was reduced after intervention in 1 study.[35] Four studies reported decreased antimicrobial use or inappropriate use after intervention (Tables 2 and 4),[33-36] and 1 study reported lower defined daily dose and duration of antimicrobial treatment in the intervention group.[32] One study of ciprofloxacin restriction reported decreases in the percentage and rate of carbapenem- and ciprofloxacin-resistant *Pseudomonas aeruginosa* isolates (Table 5).[36]

Guidelines implemented with feedback. Four studies (2 RCTs, 2 ITS) implemented guidelines and provided feedback to guideline users.[37-40] Mortality and length of stay were unchanged following guideline implementation for management of respiratory illnesses or to reduce broad-spectrum antimicrobial prescribing in patients with unspecified infection (Figure 1; Tables 1 and 3).[37-39] CDI incidence was significantly

TABLE 1. Overview of Patient Outcomes, Antimicrobial Stewardship Interventions for Inpatients

ASP intervention (no. of studies)	Mortality	Length of stay	Readmission	CDI	Summary
Prospective audit and feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	Favored ASP, 1 study; NS, 9 studies	NS, 9 studies	Favored ASP, 1 study; NS, 2 studies	p NR,[a] 1 study	Patient outcomes were generally unchanged
Formulary restriction and preauthorization (1 RCT, 4 ITS)	NS, 3 studies	NS, 2 studies	NR	Favored ASP, 1 study	Mortality and length of stay were unchanged; CDI was decreased
Guidelines with feedback (2 RCT, 2 ITS)	NS, 3 studies	NS, 3 studies	NR	Favored ASP, 2 studies	Mortality and length of stay were unchanged; CDI was decreased in 2 studies
Guidelines without feedback (1 CCT, 1 CBA, 2 ITS)	Favored ASP, 1 study; NS, 1 study; favored control, 1 study	Favored ASP, 1 study; NS, 1 study; favored control, 1 study	NS, 1 study	NR	Inconsistent findings from 3 studies assessing mortality or length of stay; no difference in readmissions
Computerized decision support (1 RCT, 1 CCT, 2 ITS)	NS, 3 studies	Favored ASP, 1 study; NS, 2 studies	NS, 1 study	Favored ASP, 1 study; NS, 1 study	No differences in mortality or readmissions; mixed results for length of stay and CDI
Protocols (2 RCT, 2 ITS)	Favored ASP, 1 study; NS, 2 studies	Favored ASP, 2 studies; NS, 1 study	NS, 1 study	NR	Results were mixed for mortality and length of study; no difference in readmissions
Procalcitonin (2 RCT)	NS, 2 studies	NS, 1 study; favored control, 1 study	NR	NR	No difference in mortality; one study reported longer ICU length of stay in the procalcitonin group

NOTE. ASP, antimicrobial stewardship program; CBA, controlled before and after; CCT, controlled clinical trial; CDI, incidence of *Clostridium difficile* infection; ICU, intensive care unit; ITS, interrupted time series; NR, not reported; NS, no statistically significant difference between antimicrobial stewardship intervention and control; RCT, randomized controlled trial.

[a] Statistical significance between groups not reported.

TABLE 2. Overview of Prescribing Outcomes, Antimicrobial Stewardship Interventions for Inpatients

ASP intervention (no. of studies)	Use	Selection	Timing	Duration	Summary
Prospective audit and feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	Decreased: favored ASP, 8 studies; appropriate: favored ASP, 1 study; NS, 1 study	Favored ASP, 1 study; NS, 1 study	NR	Favored ASP, 5 studies	Improvement in prescribing outcomes
Formulary restriction and preauthorization (1 RCT, 4 ITS)	Decreased: favored ASP, 4 studies	NR	NR	Favored ASP, 1 study	Improvement in prescribing outcomes.
Guidelines with feedback (2 RCT, 2 ITS)	Decreased: favored ASP, 1 study; compliant/appropriate: favored ASP, 2 studies	NS, 1 study	Favored ASP, 1 study	NS, 2 studies	Mixed results; some studies reporting improvements in adherence to guideline recommended treatments and appropriate early initiation of therapy
Guidelines without feedback (1 CCT, 1 CBA, 2 ITS)	Decreased: favored ASP, 1 study; compliant/appropriate: favored ASP, 2 studies; NS, 1 study	NR	Favored control, 1 study	Favored ASP, 1 study; NS, 1 study	Improvement in prescribing use but not timing or duration
Computerized decision support (1 RCT, 1 CCT, 2 ITS)	Decreased: favored ASP, 1 study; NS, 1 study	NR	NR	NR	Two studies reported mixed results for antimicrobial use
Protocols (2 RCT, 2 ITS)	Appropriate: NS, 1 study	NR	NS, 1 study	Favored ASP, 2 studies	No difference in appropriate use or timing but reduced duration of use
Procalcitonin (2 RCT)	NS, 1 study	NR	NS, 1 study mixed, 1 study	NR	No difference in use of antimicrobials; one study reported a difference in time to appropriate prescribing across infection sites; another found no difference in time on antimicrobials

NOTE. ASP, antimicrobial stewardship program; CBA, controlled before and after; CCT, controlled clinical trial; ITS, interrupted time series; NR, not reported; NS, no statistically significant difference between antimicrobial stewardship intervention and control; RCT, randomized controlled trial.

TABLE 3. Strength of Evidence for Patient Outcomes

Study, year (reference)	Study design	Purpose	Risk of bias	Outcome	Finding vs control or prior to implementation	Strength of evidence, by outcome
Audit and feedback studies						
Lesprit 2013[18]	RCT	Improve quality of antimicrobial use	Medium	Mortality	NS, RR = 0.98 (0.64, 1.50)	Low for mortality
Camins 2009[19]	RCT	Improve appropriateness	High		NS, RR = 0.62 (0.30, 1.29)	
Masia 2008[20]	RCT	Decrease targeted antimicrobials	Medium		NS, RR = 1.12 (0.75, 1.66)	
Weiss 2011[21]	CCT	Improve mortality	High		Reduced, OR = 0.48 (0.26, 0.88)	
Manuel 2010[22]	CCT	Improve appropriateness	High		NS	
Elligsen 2012[23]	ITS	Decrease targeted antimicrobials	Medium		NS, 13% pre, 14% post	
Standiford 2012[24]	ITS	Decrease ineffective/ excessive	High		NS	
Teo 2012[25]	ITS	Improve appropriateness	High		NS, 0.44 deaths per 100 inpatient-days (pre and post)	
Bornard 2011[26]	ITS	Improve quality of antimicrobial use	High		NS, RR = 0.84 (0.05, 12.99)	
Dunn 2011[27]	CBA	Increase switch rate from IV to oral	High		NS	
Lesprit 2013[18]	RCT	Improve quality of antimicrobial use	Medium	Length of stay	NS, 15 days (median) both groups	Low for length of stay
Camins 2009[19]	RCT	Improve appropriateness	High		NS, 7 days intervention, 8 days control (medians)	
Masia 2008[20]	RCT	Decrease targeted antimicrobials	High		NS, 14 days (median) both groups	
Weiss 2011[21]	CCT	Improve mortality	High	Length of stay (ICU)	NS, 4 days intervention, 5 days control (P = .07)	
Manuel 2010[22]	CCT	Improve appropriateness	High	Length of stay	NS	
Elligsen 2012[23]	ITS	Decrease targeted antimicrobials	Medium		NS, 6.9 days (pre and post)	
Standiford 2012[24]	ITS	Decrease ineffective/ excessive	High		NS	

Bornard 2011[26]	ITS	Improve quality of antimicrobial use	High		NS, 18 days pre, 19 days post	
Dunn 2011[27]	CBA	Increase switch rate from IV to oral	High		NS	
Lesprit 2013[18]	RCT	Improve quality of antimicrobial use	Medium	Readmission[a]	Reduced, RR = 0.43 (0.23, 0.82)	Low for readmission
Masia 2008[20]	RCT	Decrease targeted antimicrobials	High		NS, RR = 1.40 (0.84, 2.33)	
Standiford 2012[24]	ITS	Decrease ineffective/excessive	High		NS	
Elligsen 2012[23]	ITS	Decrease targeted antimicrobials	Medium	Incidence of CDI	Significance not reported; 16 cases pre, 11 cases post	Low for incidence of CDI
Formulary restriction and preauthorization interventions						
Rattanaumpawan 2010[32]	RCT	Preauthorization	High	Mortality	NS, RR = 1.04 (0.90, 1.20)	Low for mortality
Peto 2008[33]	ITS	Preauthorization	Medium		NS, 64.3 per 1,000 patients (after) vs 66.2 per 1,000 patients (before; $P = .44$)	
Mamdani 2007[34]	ITS	Formulary restriction	Low		NS ($P = .62$)	
Rattanaumpawan 2010[32]	RCT	Preauthorization	High	Length of stay	NS ($P = .80$)	Low for length of stay
Peto 2008[33]	ITS	Preauthorization	Medium		NS, 2.4 days (after) vs 2.6 days (before; $P = .44$)	
Aldeyab 2012[35]	ITS	Restriction	High	Incidence of CDI	Reduced *trend* ($P = .008$), NS change in *level*	Low for incidence of CDI
Guidelines with feedback studies						
Schnoor 2010[37]	RCT	Improve adherence to pneumonia guidelines	High	Mortality	NS, RR = 0.97 (0.43, 2.17)	Low for mortality
Schouten 2007[38]	RCT	Appropriate use	High		CAP: NS, RR = 0.87 (0.45, 1.66); COPD: NS, RR = 1.76 (0.61, 5.08)	
Fowler 2007[39]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium		Rates reported only	
Schnoor 2010[37]	RCT	Improve adherence to pneumonia guidelines	High	Length of stay	NS	Low for length of stay
Schouten 2007[38]	RCT	Appropriate use	High		NS ($P = .89$)	
Fowler 2007[39]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium		Significance not reported	
Talpaert 2011[40]	ITS	Reduce broad-spectrum antimicrobial use	Medium	Incidence of CDI	Decreased, IRR = 0.34 (0.20, 0.58)	Low for incidence of CDI

TABLE 3 (*Continued*)

Study, year (reference)	Study design	Purpose	Risk of bias	Outcome	Finding vs control or prior to implementation	Strength of evidence, by outcome
Fowler 2007[39]	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium		Decreased, IRR = 0.35 (0.17, 0.73)	
Guidelines without feedback studies						
Goldwater 2001[41]	CCT	Reducing costs without sacrificing patient care	High	Mortality	NS, RR = 1.07 (0.63, 1.82)	Low for mortality
Meyer 2007[42]	ITS	Reduce duration	Medium		Increased ($P < .05$)	
Capelastegui 2004[43]	CBA	Appropriateness, timing, duration	High		Reduced, OR = 1.8 (1.1, 2.9)[b]	
Goldwater 2001[41]	CCT	Reducing costs without sacrificing patient care	High	Length of stay	Increased ($P < .05$)	Low for length of stay
Meyer 2007[42]	ITS	Reduce duration	Medium		NS	
Capelastegui 2004[43]	CBA	Appropriateness, timing, duration	High		Reduced ($P < .001$)	
Capelastegui 2004[43]	CBA	Appropriateness, timing, duration	High	Readmission	NS, OR = 0.8 (0.3, 2.0)[b]	Low for readmission
Computerized decision support studies						
McGregor 2006[45]	RCT	Appropriateness	High	Mortality	NS, RR = 1.11 (0.80, 1.53)	Low for mortality
Barenfanger 2001[46]	CCT	Lower mortality, cost, and duration	High		NS, RR = 1.12 (0.62, 2.01)	
Nowak 2012[47]	ITS	Appropriateness, cost	High		NS sepsis: RR = 0.50 (0.18, 1.38) pneumonia: RR = 0.96 (0.63, 1.47)	
McGregor 2006[45]	RCT	Appropriateness	High	Length of stay	NS, 3.8 days intervention, 4.0 days control (medians)	Low for length of stay
Barenfanger 2001[46]	CCT	Lower mortality, cost, and duration	High		Reduced ($P = .035$)	
Nowak 2012[47]	ITS	Appropriateness, cost	High		NS sepsis: 7.2 (pre), 7.4 (post); pneumonia: 5.9 (pre), 5.5 (post)	
Nowak 2012[47]	ITS	Appropriateness, cost	High	Readmission	NS sepsis: RR = 0.83 (0.46, 1.49); pneumonia: RR = 1.02 (0.83, 1.25)	Low for readmission
Nowak 2012[47]	ITS	Appropriateness, cost	High	Incidence of CDI	Decreased ($P = .018$)	Low for incidence of CDI
McGregor 2006[45]	RCT	Appropriateness	High		NS ($P = .49$)	

Protocol studies						
Carratalà 2012[49]	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR = 2.01 (0.37, 10.85)	Low for mortality
Oosterheert 2006[50]	RCT	Evaluate effectiveness of early switch	Medium		NS, RR = 0.63 (0.21, 1.88)	
Pulcini 2011[51]	ITS	Appropriateness	Medium		Reduced (P = .03)	
Carratalà 2012[49]	RCT	Evaluate effectiveness of early switch	Medium	Length of stay	Reduced, WMD = 2.1 (1.7, 2.7)	Low for length of stay
Oosterheert 2006[50]	RCT	Evaluate effectiveness of early switch	Medium		Reduced, WMD = 1.9 (0.6, 3.2)	
Pulcini 2011[51]	ITS	Appropriateness	Medium		NS (P = .99)	
Carratalà 2012[49]	RCT	Evaluate effectiveness of early switch	Medium	Readmission	NS, RR = 1.21 (0.63, 2.33)	Low for readmission
Procalcitonin monitoring						
Annane 2013[54]	RCT	Evaluate procalcitonin-based algorithm for antimicrobial use	Medium	Mortality	NS, RR = 1.00 (0.22, 4.58)	Low for mortality
Jensen 2011[53]	RCT	Evaluate procalcitonin testing to increase early antimicrobials	Medium		NS, HR = 0.98 (0.83, 1.16)	
Annane 2013[54]	RCT	Evaluate procalcitonin-based algorithm for antimicrobial use	Medium	Length of stay	NS ICU: 22 days (intervention), 23 days (control) (medians; P = .58); hospital: 27 days (intervention), 33 days (control) (medians; P = .22)	Low for length of stay
Jensen 2011[53]	RCT	Evaluate procalcitonin testing to increase early antimicrobials	Medium		ICU: 6 days (intervention), 5 days (control) (medians; P = .004)	

NOTE. CAP, community-acquired pneumonia; CBA, controlled before and after study; CCT, controlled clinical trial; CDI, *Clostridium difficile* infection; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ITS, interrupted time series; IRR, incidence rate ratio; IV, intravenous; NS, not statistically significant; OR, odds ratio (95% confidence interval); RCT, randomized controlled trial; RR, rate ratio (95% confidence interval); WMD, weighted mean difference.

[a] Lesprit reported 60-day readmission for relapsing infection; other studies report 30-day readmission for any cause.

[b] In this study, the postintervention cohort was the reference group.

TABLE 4. Prescribing Outcomes

Study, year (reference)	Study design	Purpose	Outcome	Finding vs control or prior to implementation
Audit and feedback studies				
Cairns 2013[28]	ITS	Evaluate effect of program on broad-spectrum antimicrobial use	Use	Reduced total broad-spectrum use by 16.6%; $P < .001$
Lesprit 2013[18]	RCT	Improve quality of antimicrobial use	Duration	Reduced days of total use (6 vs 7; $P < .001$), broad-spectrum use (2 vs 4; $P < .001$), and IV use (3 vs 4; $P = .004$). NS for oral use
Ellingson 2012[23]	ITS	Decrease targeted antimicrobials	Use	Reduced mean monthly broad-spectrum use
Magedanz 2012[30]	ITS	Improve appropriateness	Use	Reduced, 48.9 to 36.9 DDD/100 patient-days; $P = .001$
Standiford 2012[24]	ITS	Decrease ineffective/excessive	Use	Reduced total antimicrobial use by 29%; $P = .014$; reductions also noted for antifungals and antivirals
Yeo 2012[31]	ITS	Improve appropriateness	Use	Reductions in audited antimicrobials (cephalosporins and vancomycin) and evaluated antimicrobials
Bonnard 2011[26]	ITS	Improve quality of antimicrobial use	Use	NS for appropriate therapies
Dunn 2011[27]	CBA	Increase switch rate from IV to oral	Use	72% of IV use switched on appropriate day; $P = .02$
			Duration	Reduced duration of IV use, 72 vs 96 hours; $P = .02$
Manuel 2010[22]	CBA	Improve appropriateness	Duration	Reduced time to antimicrobial therapy modification, 3.9 vs 5 days; $P = .007$
Camins 2009[19]	RCT	Improve appropriateness	Use	Improved appropriate initial use, 78 vs 58%; $P < .001$
			Duration	Reduced time of inappropriate use, 2 vs 5 days; $P < .001$
Liebowitz 2008[29]	ITS	Reduce cephalosporin and ciprofloxacin prescribing to reduce MRSA	Selection	Hospital-wide reduction in third-generation cephalosporins (37 to 9 DDD/1,000 bed-days); NS reduction in ciprofloxacin use
Masia 2008[20]	RCT	Decrease targeted antimicrobials	Use	Reduced, 8 vs 10 DDD patient-days; $P = .04$
			Duration	Reduced days receiving targeted antimicrobials (4 vs 6; $P = .002$) and carbapenem (4 vs 8; $P < .0001$)

Formulary restriction and preauthorization interventions				
Aldeyab 2012[35]	ITS	Restriction	Use	Reduced level of use of high-risk antimicrobials ($P < .001$) and total antimicrobial use ($P = .007$); trend changes were not significant
Lewis 2012[36]	ITS	Restriction	Use	Reduced use of ciprofloxacin, 87.09 vs 8.04 DDD/1,000 patient-days; $P = .003$; increased use of carbapenems, 11.96 vs 28.19 DDD/1,000 patient-days; $P = .013$
Peto 2008[33]	ITS	Preauthorization	Use	Reduced, 163 to 101 DDD/100 patient-days
Mamdani 2007[34]	ITS	Formulary restriction	Use	Reduced, 17.1 prescriptions vs predicted use of 43.6 prescriptions per 1,000 elderly persons per quarter; $P < .01$
Rattanaumpawan 2010[32]	RCT	Preauthorization	Duration	Reduced days for all antimicrobials (12.7 vs 16.4 days; $P < .01$) and targeted antimicrobials (7.5 vs 9.3 days; $P < .01$)
Guidelines with feedback studies				
Talpaert 2011[40]	ITS	Reduce broad-spectrum antimicrobial use	Use	Reduced use of targeted antimicrobials (fluoroquinolone by 59%, $P = .006$ and cephalosporin by 46%, $p < .001$); total antimicrobial use did not change significantly; increased level of use antimicrobials targeted for increased use (penicillin, macrolides, gentamicin, nitrofurantoin, trimethoprim; $P < .05$)
Schnoor 2010[37]	RCT	Improve adherence to pneumonia guidelines	Use	Reduced inappropriate use, OR = 1.8 (95% CI, 1.1–2.8)
Schouten 2007[38]	RCT	Appropriate use	Use	Increased indicated use and use according to guidelines, OR = 2.6 (95% CI, 1.6–4.4)
			Timing	Improved initiation of antimicrobial use within 4 hours of presentation for CAP patients, OR = 3.6 (95% CI, 1.0–12.6)
			Dose	Improved dosage and dose interval based on renal function, OR = 12.9 (95% CI, 3.6–45.8)
			Duration	NS improvement in increase of optimal duration for patients with COPD/CB, OR = 2.2 (95% CI, 0.96–5.1)
Fowler 2007[39]	ITS	Reinforce narrow-spectrum antimicrobial policy	Use	Reduced use of targeted antimicrobials (cephalosporins and amoxicillin/clavulanate); $P = .035$; increased use of antimicrobials targeted for increased use (amoxicillin, $P = .001$; benzyl penicillin, $P = .012$)
Guidelines without feedback studies				
Mangino 2011[44]	ITS	Assess and improve outcomes in adults with HAP	Use	Use of empirical antimicrobials, 44% vs 31%; $P = .01$
Meyer 2007[42]	ITS	Reduce duration	Use	Reduction in antimicrobial use density total from 949.8 to 626.7 DDD/1,000 patient-days
Capelastegui 2004[43]	CBA	Appropriateness, timing, duration	Use	NS in increased appropriate antimicrobial use, OR = 1.1 (95% CI, 0.7–1.7)
			Timing	Improved initiation of antimicrobial use within 8 hours of presentation, OR = 2.3 (95% CI, 1.7–3.0)

TABLE 4 (*Continued*)

Study, year (reference)	Study design	Purpose	Outcome	Finding vs control or prior to implementation
Goldwater 2001[41]	CCT	Reducing costs without sacrificing patient care	Use	Reduced use of levofloxacin, 96% vs 48%; $P < .001$
			Duration	NS, 5.3 vs 5.3 days
Computerized decision support studies				
Nowak 2012[47]	ITS	Appropriateness, cost	Use	Decreased use of quinolones (total), vancomycin, carbapenems, and piperacillin-tazobactam (*P* values not reported)
Yong 2010[48]	ITS	Reduce use of broad-spectrum antimicrobials	Use	NS, trend analysis: antimicrobials to cover gram-negative bacteria remained stable during study period
Protocol studies				
Carratalà 2012[49]	RCT	Reduce duration of IV antimicrobial therapy and length of stay	Timing	NS, time to antimicrobial therapy: 3.3 vs 4 days
			Duration	Reduced, difference −2.0 days (95% CI, −2.0 to −1.0); $P < .001$
Pulcini 2011[51]	ITS	Improve quality of prescriptions	Use	NS
Oosterheert 2006[50]	RCT	Evaluate effectiveness of early switch	Duration	NS for overall antimicrobial treatment; reduced IV treatment days, 3.6 vs 7; $P < .05$
Procalcitonin monitoring				
Annane 2013[54]	RCT	Evaluate procalcitonin-based algorithm for antimicrobial use	Use	NS, RR = 0.83 (0.60, 1.14)
			Timing	NS, 5 days of antimicrobial therapy (median), both groups ($P = .52$)
Jensen 2011[53]	RCT	Evaluate procalcitonin testing to increase early antimicrobials	Timing	Nonbloodstream infections: NS, 0.2 days (intervention), 0.4 days (control; $P = .61$); bloodstream infections: −0.1 days (intervention), 0.8 days (control; $P = .02$)

NOTE. CAP, community-acquired pneumonia; CBA, controlled before and after; CCT, controlled clinical trial; CI, confidence interval; COPD/CB, chronic obstructive pulmonary disease/chronic bronchitis; DDD, defined daily dose; HAP, hospital-acquired pneumonia; ITS, interrupted time series; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, not statistically significant; OR, odds ratio; RCT, randomized controlled trial.

reduced after interventions to decrease broad-spectrum antimicrobial prescribing for patients with any infection site.[39,40]

In these studies, antimicrobial use significantly decreased while appropriate/compliant prescribing, selection, and timing improved (Tables 2 and 4).[37-39] Duration of antimicrobial use for treatment of respiratory infections was unchanged in 2 studies that evaluated this outcome.[37,38] No studies reported microbial outcomes.

Guidelines implemented without feedback. Four studies (2 ITS, 1 CCT, 1 CBA) evaluated guidelines developed and implemented without feedback.[41-44] Studies of guidelines created and implemented for various purposes (eg, conversion from intravenous to oral therapy and increasing concordant therapy) found few differences in mortality or length of hospital stay (Figure 1; Tables 1 and 3). One study in a neurosurgical ICU reported higher ICU mortality in the intervention group;[42] 2 non-ICU studies reported either no difference[41] or reduced mortality in the intervention group.[43] One study in community and rehabilitation hospitals reported longer length of stay for patients in the intervention group,[41] whereas the ICU study reported no differences,[42] and a non-ICU study reported shorter length of stay after intervention.[43]

Improvements in antimicrobial use and/or appropriate use and compliance were noted in 3[41,42,44] of the 4 studies (Tables 2 and 4).[43] Treatment duration was shorter in 1 study[43] and unchanged in a second study.[41] One study reported improved timing of initiation of antimicrobials in the intervention group.[43] One ITS study from an ICU reported a decrease in the proportion of *Staphylococcus aureus* isolates resistant to methicillin after intervention (from 8.4% to 2.9%; $P < .05$), but whether the decrease was associated with the intervention was unclear (Table 5).[42]

Computerized decision support. Three studies (1 RCT, 1 CCT, 1 ITS) of computerized systems to identify cases for possible antimicrobial intervention or to link susceptibility test results to pharmacy orders found no significant effect on mortality (Figure 1; Tables 1 and 3).[45-47] One study of a system linking laboratory results and pharmacy orders found a shorter length of stay in the intervention group,[46] but 2 studies of systems for case identification found no differences.[45,47] Readmission rates were unchanged following implementation of a system to identify cases for intervention.[47] Incidence of CDI was decreased in 1 study of a computerized case identification system[47] but unchanged in a second study.[45]

Mixed results for antimicrobial use were reported in 2 ITS studies (Tables 2 and 4).[47,48] A computerized decision support system aimed at reducing broad-spectrum antimicrobial use improved susceptibility of ICU gram-negative isolates (Table 5).[48]

Protocols. Four studies (2 RCTs, 2 ITS) evaluated implementation of protocols.[49-52] In clinically stable adults with CAP, protocols for switching from intravenous to oral antimicrobials did not have an effect on mortality.[49,50] However, hospital length of stay was significantly shorter in the early switch groups (Figure 1; Tables 1 and 3) and duration of intravenous therapy was reduced (Tables 2 and 4).[49,50]

Systematic reassessment at 72 hours was associated with reduced mortality but was not associated with change in length of stay or improved appropriateness of prescribing.[51] In 1 study reporting microbial outcomes, susceptibility of *P. aeruginosa* to imipenem increased after autosubstitution of ertapenem for ampicillin-sulbactam (Table 5).[52]

Procalcitonin monitoring. Two systematic reviews[55,56] and 2 more recent trials[53,54] of procalcitonin testing for patients with sepsis syndromes (including respiratory infections) in ICUs have concluded that procalcitonin is not useful for aiding decisions about whether to initiate antimicrobial therapy, accelerate such therapy, or intensify testing. Used in this way, procalcitonin testing was associated with increased length of ICU stays and more days with decreased renal function and severe sepsis/septic shock. Procalcitonin testing is useful as an aide in deciding when to stop antimicrobial therapy when bacterial infection has not been proved in ICU patients, and testing in this way is associated with fewer antimicrobial days.

Intervention Components Associated with Effective Inpatient Antimicrobial Stewardship

In 6 of the studies included in the review, investigators described intervention components that they thought were associated with effective antimicrobial stewardship.[23,25,41,42,45,46] These included a consistent and persistent effort involving qualified personnel using effective communication skills and use of electronic medical records or computerized decision-support systems.

Harms of Inpatient Antimicrobial Stewardship Programs

We found no reports of harms associated with implementation of ASPs.

Barriers to Inpatient Antimicrobial Stewardship Program Implementation, Sustainability, and Scalability

Barriers were not specifically identified. However, in 4 trials, investigators suggested ways to improve acceptance or impact.[25,37,38,47] Suggestions included involving representatives of relevant clinical services in the development and implementation of evidence-based guidelines,[37] providing opportunity for iterative feedback,[37] and adding audits or continuous quality improvement cycles.[38] Understanding the local prescribing culture,[47] fostering an environment of appropriate prescribing,[25] and increasing collaboration between infectious diseases physicians and pharmacists[47] were also suggested.

Most reviewed studies of ASPs were 1 year or less in duration and therefore provided little information on sustainability. One audit and feedback study reported decreased antimicrobial use during the 7-year life of the intervention followed by a 5.2% increase after study termination.[24] No study commented on scalability.

DISCUSSION

Our findings suggest that ASPs can improve prescribing and microbial outcomes without significant adverse impact on

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TABLE 5. Microbial Outcomes

Study, year (reference)	Study design	Purpose	Outcome	Finding versus control or prior to implementation
Audit and feedback studies				
Lesprit 2013[18]	RCT	Improve quality of antimicrobial use	Resistance in study population	NS for secondary infection and/or colonization in 6 months after randomization; MRSA, 2.9% vs 2.6%; $P = .82$; ESBLE, 3.2% vs 4.5%; $P = .34$
Ellingson 2012[23]	ITS	Decrease targeted antimicrobials	Institutional resistance	Increase in gram-negative susceptibility to meropenem in postintervention period (83.4% vs 78.2%; $P = .03$); no change for ceftriaxone, piperacillin-tazobactam, ciprofloxacin, or ceftazidime
Magedanz 2012[30]	ITS	Improve appropriateness	Institutional resistance	Ceftazidime-resistant *Klebsiella* increased from 12% to 16% (stages 1 and 2) to 42% (stage 3). Carbapenem-resistant *Pseudomonas* decreased from 6% and 7% (stages 1 and 2) to 1% (stage 3)
Yeo 2012[31]	ITS	Improve appropriateness	Resistance in study population	NS
Liebowitz 2008[29]	ITS	Reduce cephalosporin and ciprofloxacin prescribing to reduce MRSA	Institutional resistance	Hospital-wide: change in level of MRSA ($P = .04$) but not MSSA ($P = .55$); MRSA colonization unchanged; MRSA bacteremia rate reduced by 63% ICU: MRSA bacteremia unchanged ($P = .40$); decreased bloodstream infections (4.2 to 0.27 per 1,000 occupied bed-days)
			Resistance in study population	NS decrease in colonization
Formulary restriction and preauthorization interventions				
Lewis 2012[36]	ITS	Restriction	Institutional resistance	13.2% decrease in carbapenem-resistant *Pseudomonas aeruginosa* isolates after intervention (decrease of 3.8% per year, $P = .035$), percentage stable prior to intervention; 13.7% decrease in ciprofloxacin-resistant isolates over study period (3.9% per year, $P = .002$), decrease in slope consistent before and after intervention; NS downward trend for cefepime-resistant isolates; NS increased trend for piperacillin-tazobactam–resistant isolates; decreasing trend in rates of carbapenem-resistant (2.1 cases/10,000 patient-days per year), ciprofloxacin-resistant, and cefepime-resistant (1.8 cases/10,000 patient-days per year) *P. aeruginosa* infections (all $P < .001$); increasing trend in rate of piperacillin-tazobactam–resistant isolates; NS effect on susceptibilities of other isolates

Guidelines without feedback studies				
Meyer 2007[42]	ITS	Reduce duration	Institutional resistance	Two-year resistance proportions of selected pathogens showed a significant decrease in the MRSA proportion after the intervention: of 167 *Staphylococcus aureus* isolates, 8.4% were resistant during 2002–2003, and of 208 *S. aureus* isolates, only 2.9% were resistant during 2004–2005
Computerized decision support studies				
Yong 2010[48]	ITS	Reduce use broad-spectrum antimicrobials	Institutional resistance	*P. aeruginosa*, (1) gentamicin susceptibility decreased before the intervention but then increased postintervention with a significant difference between the pre- and postintervention phases (change from preintervention trend reported as mean percentage change per year: 11.6% (95% CI, 1.8% to 21.5%), P = .02); (2) imipenem with a significant difference between pre- and postintervention (mean percentage change per year, 18.4% [95% CI, 4.9% to 31.6%], *P* = .009); NS for ceftazidime (3.2 (95% CI, −13.0 to 6.6); *P* = .51) and ciprofloxacin (−4.9 [95% CI, −14.1 to 4.2], *P* = .28) susceptibility; *Escherichia coli,* no imipenem-resistant isolates were observed and >98% of all isolates were susceptible to third-generation cephalosporins, gentamicin, and ciprofloxacin with no changes over the study period (mean percentage changes of −0.6% to 0.3%, *P* values from .54 to .73); NS changes over the study period were noted for *Klebsiella* species susceptibility (mean percentage changes of 0.3% to 3.0%, *P* values .10 to .88); *Acinetobacter* species, NS changes in susceptibility to imipenem, gentamicin, or ciprofloxacin were observed over the study period (mean percentage changes of 0.3% to 14.0%, *P* values from .11 to .93); Enterobacteriaceae with potentially inducible β-lactamases were grouped; significant increases in gentamicin (mean percentage change, 6.5% (95% CI, 2.7%–10.2%); *P* = .002) and ciprofloxacin (mean percentage change, 3.5% (95% CI, 1.3–5.7), *P* = .003) susceptibility were observed with no change in imipenem susceptibility
Protocol studies				
Goldstein 2009[52]	ITS	Evaluate effect of antimicrobial substitution	Institutional resistance	Susceptibility of *P. aeruginosa* to imipenem (median %): pre (0–9 months), 69%; formulary (10–19 months), 75% (slope = 1.74, *P* < .001); substitution (20–48 months), 88% (slope = 0.02, *P* = .85); for every unit decrease in monthly DDD of imipenem, there was an increase of 0.38% (*P* = .008) in susceptibility of *P. aeruginosa* to imipenem in the same month; susceptibility of *P. aeruginosa* to other antimicrobials: levofloxacin, increased (slope = 0.53, *P* = .021); cefepime: increased (slope = 0.54, *P* < .001); piperacillin-tazobactram: increased (slope = 0.14, *P* = .04)

NOTE. CI, confidence interval; ESBLE, extended spectrum B-lactamase-producing enterobacteriacae; ITS, interrupted time series; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus*; NS, not statistically significant; RCT, randomized controlled trial.

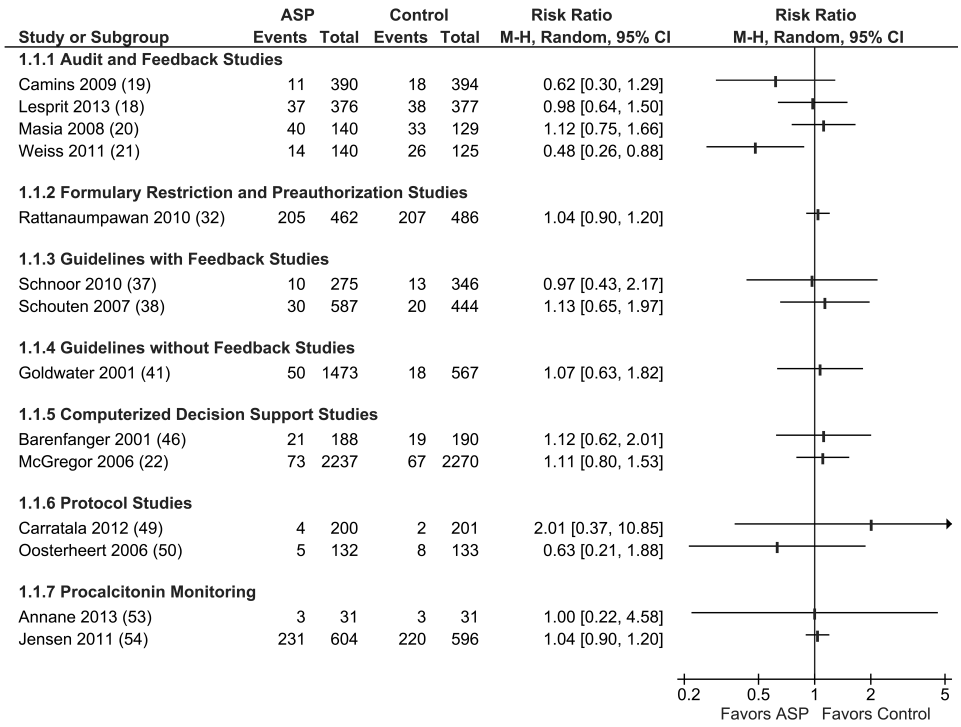

FIGURE 2. Risk ratios for mortality from randomized controlled trials. ASP, antimicrobial stewardship program; CI, confidence interval; M-H, Mantel-Haenszel.

patient outcomes. However, there was only limited evidence for the effects of ASPs on patient outcomes, and most of the evidence was of low quality (Table 3). In the absence of measured improvements in patient outcomes, it is reassuring that reported improvements in prescribing (typically reduced antimicrobial use) were not accompanied by obvious deleterious effects on mortality, length of stay, hospital readmission, and CDI.

Antimicrobial use contributes to antimicrobial resistance, healthcare costs, and adverse events. One might reasonably expect that decreased antimicrobial use resulting from antimicrobial stewardship might decrease antimicrobial resistance over the long run. However, this expectation is not testable within the time frame of nearly all studies of the impacts of ASPs.

Our results are consistent with and provide updated information to a Cochrane review that included studies through 2009.[14] Although the Cochrane review included 89 studies, each of the reported patient outcomes were based on few studies, and the prescribing outcome was a composite of a single prescribing outcome captured from each study.

Methodological limitations well-described in the Cochrane review[14] continue to hamper the evidence base. We found substantial threats to validity, including the possibility of secular trends, contamination within study sites, opportunities for biased assessments, and the potential for unmeasured or unreported changes in use of antimicrobials not targeted or studied by the interventions. Individual studies were generally small with short follow-up durations. The typical study was done by infectious disease pharmacists or infectious disease physicians who tried to influence antimicrobial therapy and performed formative evaluation to assess the impact of their intervention(s). Studies were often done within an existing system with available resources and measured conveniently available variables. Studies of the impact of an ASP on CDI rates were often done in response to an outbreak or increase in CDI incidence. Many reported decreased CDI rates after the intervention, but decreases may have been due to regression to the mean.

As with many quality improvement programs, most ASPs are multifaceted. No study directly compared one intervention or specific element with another. The available evidence was from studies covering a wide range of study types, health systems, populations, staffing patterns, formularies, goals of the stewardship programs, intervention components, lengths of intervention and follow-up periods, and outcome measures, making it difficult to reach definitive conclusions about successful program elements. We were unable to determine specific elements contributing to program success. Few studies addressed program sustainability, and because most were done at a single site, often a university-affiliated hospital, there is limited information about generalizability to other settings. We urge ongoing evaluation to assess whether ASPs are associated with desired effects at individual institutions

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or across national healthcare systems and more detailed reporting of program elements.

Antimicrobial stewardship is a rapidly developing field. Ongoing review and assessment is needed to provide up-to-date information for practitioners, policymakers, and researchers. However, there is no definitive blueprint for how to most effectively improve antimicrobial use or where such efforts should focus. Considerable evidence suggests that stewardship can decrease antimicrobial use without detectable harms. To go beyond these findings and detect effects on patient outcomes will require larger studies, likely involving the coordination of multiple facilities. In the absence of high-quality comparative effectiveness research, the literature on stewardship and implementation science provides a tentative roadmap that will allow hospitals to move forward.

The first step should be to use existing information or gather new information to determine where antimicrobial use might be less than ideal or is in need of improvement. Although the data show that antimicrobial use can nearly always be improved, urinary tract infections and respiratory tract infections are large drivers of antimicrobial use and are often treated inappropriately, suggesting potential high-yield clinical conditions for intervention.[57] Data on antimicrobial use by clinical unit, type of patients, provider groups, and individual providers should be analyzed locally and compared with available national guidelines or benchmarks.[58] If there is substantial room for improvement, an intervention designed to effect that improvement would then be designed.

Hospitals and healthcare systems typically have many of the components in place to implement stewardship activities. Among these are infection prevention programs, microbiology laboratories, pharmacy services, infectious disease physicians, electronic medical records, continuous improvement programs, and staff education and certification programs. Individuals representing each of these areas should be part of planning and implementation stewardship efforts. Support from hospital and healthcare system leaders is also critical.

Formative evaluation is integral to assessing the effectiveness of any stewardship activity. The formative evaluation component can begin with the information gathered to identify the need for the intervention in the first place. If a subsequent intervention is not effective, the program can be strengthened or another approach can be taken. If the intervention is effective, formative evaluation can help determine whether the intervention should be continued or whether efforts and resources can be redirected to solve another problem. Antimicrobial therapy is a continuously evolving area of medicine. As new drugs are developed and marketed, antimicrobial susceptibilities and disease patterns change. Change and local variation are constants in antimicrobial therapy, and formative evaluation can help an organization ensure that it is ahead of the curve rather than behind it.

CONCLUSIONS

Research to date has established that ASPs including audit and feedback, guideline implementation, and decision support improve prescribing and microbial outcomes without significant adverse impact on patient outcomes. Comparative effectiveness, sustainability, and scalability of different approaches are not known. Future research should include multicenter studies across large healthcare systems to advance knowledge beyond the existing evidence base from small, often single-site, studies that have focused on antimicrobial outcomes. Nevertheless, the current state of knowledge is sufficient to make stewardship implementation a priority in all hospitals, especially given the emerging threat of resistance.

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APPENDIX

SEARCH STRATEGY

Database: Ovid MEDLINE(R)

1. 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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