



Antimicrobial Stewardship Programs in Inpatient Settings: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

It is estimated that in 2009, more than 3 million kilograms of antimicrobials were administered to human patients in the United States.²⁸ While the life-saving benefits of antimicrobials are indisputable, the consequences of use and misuse must also be considered.²⁹ Unlike any other medication, antimicrobial use influences not only the patient being treated but also the surrounding ecosystem.^{30,31} Major concerns related to the use of antimicrobials are increasing microbial resistance, higher incidence of antimicrobial associated *Clostridium difficile* (*C. difficile*) infection (CDI), other drug related toxicities and increased healthcare costs.²⁹

Over the past decade, the number of bacteria identified as resistant to antimicrobials has increased and commonly prescribed antimicrobial treatments are becoming ineffective.³² A major factor in the emergence of drug-resistant bacteria is bacterial evolution with selective pressure applied via antimicrobial usage including the choice of antimicrobial therapy, the duration of therapy, the route of administration, and the dosage.^{33,34} At the patient level, treatment with an antimicrobial increases the risk that the patient will become colonized or infected with a resistant organism.^{31,34} At the hospital level, increased use of antimicrobials has increased the prevalence of resistant bacteria in hospitals.³¹ Infections due to resistant pathogens, including the epidemic strain of *C. difficile* and Methicillin-resistant *Staphylococcus aureus* (MRSA), are associated with increases in morbidity and mortality.³⁵⁻³⁷

Historically, as new resistance patterns emerged, antimicrobial agents with new targets or new mechanisms of action were developed and became available for use. That approach has slowed dramatically largely due to economic and regulatory factors.²⁸ Among the suggestions for addressing this delay in the “antibiotic pipeline” are new approaches to funding research and development and a modification of the drug approval process to allow clinical superiority trials.²⁸

CDI is concentrated in hospitals and chronic care facilities. The pathogen is widespread in a hospital environment, elderly populations are most vulnerable, and there is high use of fluoroquinolones in those facilities conferring a selective advantage, particularly to the epidemic strain of *C. difficile*.^{33,36} Eighty-five percent or more of patients with *C. difficile* associated disease were exposed to antimicrobials in the 28 days before infection.^{38,39}

Costs associated with antimicrobial use include not only drug costs but costs associated with adverse events and costs associated with antimicrobial resistance.³⁰ Several studies have reported over-prescription of antimicrobials in intensive care units (ICUs). Longer courses without clear evidence of infection or courses extending beyond usual durations have no benefits for patients in infectious disease outcomes but substantial harms including increased length of stay, increased adverse effects, and possibly increased mortality when comparing patients treated for 3 or 4 days to those treated for as long as 20 days.^{40,41} Increased mortality, increased length of hospital stay, and lost productivity must also be considered.²⁹ Additionally, an increased risk of death from cardiovascular causes has been reported in patients taking erythromycin⁴² or azithromycin.⁴³ Of emergency department visits for drug-related adverse events, over 19% were due to antimicrobial use with allergic reactions most common.⁴⁴

Inappropriate use of antimicrobials includes prescription of antimicrobials when they are not needed, continuation of antimicrobials when they are no longer needed, prescription of the wrong dose, use of broad-spectrum agents for bacteria susceptible to narrow-spectrum agents, and choice of wrong antimicrobials for an infection.³¹ Prescribing decisions made by less-experienced staff members (i.e., interns and residents), pressure to decrease hospital length of stay, and increasingly complex clinical presentation are all potential factors in inappropriate prescribing.³⁰

While much of the emphasis is on overuse of antimicrobials, there is evidence of increased mortality associated with inadequate antimicrobial therapy.⁴⁵⁻⁴⁷ Therefore, in an effort to *optimize* the use of antimicrobial agents in hospitalized settings, antimicrobial stewardship programs have been created.

ANTIMICROBIAL STEWARDSHIP PROGRAMS

An antimicrobial stewardship program (ASP) is a focused effort by a healthcare organization or a portion of an organization (i.e., an intensive care unit) to optimize antimicrobial use for the purposes of improving patient outcomes, reducing adverse consequences (toxicity, selection of pathogenic organisms, or emergence of resistance), and delivering cost-effective therapy.^{29,48-50} The emphasis is on appropriate selection, dosing, route, and duration of antimicrobial therapy.^{49,50} Despite recognition of the growing problem of antimicrobial resistance, a 2008 survey estimated that only 48% of hospitals in the US had an antimicrobial stewardship program in place.⁵¹

Proposed strategies for improving antimicrobial stewardship typically involve prospective audit and feedback, formulary restriction, pre-authorization of prescriptions, guidelines for prescribing and/or modifying therapy, and education.^{49,52} A comprehensive ASP may include some or all of the following:^{30,49,52}

- a multidisciplinary team consisting of infectious disease physicians, clinical pharmacists, clinical microbiologists, information system specialists, infection control specialists, and hospital epidemiologists
- collaboration between the ASP team and hospital infection control and pharmacy and therapeutics committees
- support and collaboration of hospital administrators, medical staff leadership, and local providers
- hospital administrative support for computer systems and other resources to improve decision making, measure and track antimicrobial use, track resistance patterns, and identify hospital-based infections and adverse drug events,
- a microbiology laboratory to provide patient-specific data for optimizing treatment, surveillance of resistant organisms, and molecular-level investigation of outbreaks.

PURPOSE AND SCOPE OF REVIEW

The purpose of this review is to synthesize the evidence about the effectiveness of antimicrobial stewardship programs implemented in hospital settings. The report was nominated by Matthew Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, on behalf

of the VA Antimicrobial Stewardship Task Force, and is intended to provide a summary of the evidence on inpatient antimicrobial stewardship programs to guide clinical practice and policy within the Veterans Healthcare System. We focus on adult hospital inpatients and limit our review to randomized controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs), and interrupted time series (ITS) analyses with data for at least 3 time points before and after the intervention. Our main outcomes of interest were patient-centered outcomes. We also report prescribing outcomes, microbial outcomes, costs, harms of stewardship programs, key intervention components, and barriers to implementation, sustainability, and scalability. In particular, as described above, improvements in antimicrobial prescribing and microbial outcomes and costs can be considered meaningful at a patient, hospital and ecosystem level. Therefore, evidence demonstrating a neutral or lack of untoward effect on clinical outcomes may be sufficient for practice policy implementation. We summarize the findings from a prior Cochrane review that included studies published through 2009⁵³ and focus on studies published since the time of that review.

METHODS

TOPIC DEVELOPMENT

Our key questions were developed with input from a technical expert panel.

The final key questions are:

Key Question #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

- a. Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)
- b. Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?

Key Question #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Key Question #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

Key Question #4. What are the harms of inpatient antimicrobial stewardship programs?

Key Question #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

SEARCH STRATEGY

An exploratory search identified a 2005 Cochrane review that partially addressed the key questions but was no longer current (search dates 1980 to 2003).⁵⁴ We used a search strategy similar to that of the Cochrane review to search MEDLINE (Ovid) through June 2013. We limited the search to studies published from 2000 to the present, in English language, and enrolling human subjects. Our search included terms for antimicrobial agents (e.g., anti-bacterial agents, anti-infective agents), infection types, and program implementation (e.g., guideline implementation, practice patterns). The full search strategy is presented in Appendix A. Additional citations were identified from systematic reviews, reference lists of retrieved articles, and suggestions made by our technical expert panel members.

STUDY SELECTION

Titles, abstracts, and articles were reviewed by investigators and research associates trained in the critical analysis of literature. During title and abstract review, we excluded studies for the following reasons and identified for full text review any articles that either did not fall into one of these categories or there was uncertainty about eligibility:

1. Study not published in English language,
2. Study done in nursing home (long-term care) setting. Studies were included if done in a mix of hospital or outpatient and nursing home settings if results were presented separately by site,
3. Study not about antimicrobial stewardship,
4. Study of antimicrobials for medical or surgical prophylaxis,
5. Study of patients with viral or fungal infection or tuberculosis,
6. Pediatric study EXCEPT randomized, controlled trials in pediatric settings,
7. Study not involving an intervention or not involving an intervention of interest; we excluded interventions that were *exclusively* provider education (i.e., interventions designed exclusively for enhancing knowledge such as seminars, memos, grand rounds); patient education programs were included; community/public health campaigns were excluded,
8. Description of an intervention with no assessment of the effect of the intervention,
9. Survey of hospitals to establish range of measures used to control or optimize antibiotic prescribing,
10. Study design OTHER THAN randomized, controlled trial, controlled clinical trial, controlled before/after study, or interrupted time series with at least 3 time points before and after implementation of the intervention,
11. No outcomes of interest; outcomes of interest are a) Clinical (e.g., morbidity, mortality, length of stay), b) Drug (e.g., decision to prescribe, appropriateness of selection, dose, route, etc.), Micro (Microbiological – colonization), Cost, Other (process, sustainability, scalability etc.).

We reviewed full text versions of potentially eligible articles and excluded studies that met any of the criteria outlined in items 1 to 11 above. We also added the following exclusion criterion: study done in setting not relevant to medicine in the United States or involving a population or infectious disease not relevant to United States population.

With the recent update of the Cochrane review,⁵³ we excluded from our review any studies published in the updated version.

DATA ABSTRACTION

From studies identified as eligible after full-text review we extracted the following:

1. Study characteristics – region, intervention, intervention staff (to develop and implement the intervention), resources (i.e., hardware or software used or purchased, staff hired), study design, hospital type, site within hospital (e.g., surgical unit, medical unit, ICU), patients enrolled (number, age), suspected site of infection, suspected organism. We typically categorized ASP interventions using original study author classification. However, we reviewed these classifications with our internal content experts and our Technical Expert Panel Members and stakeholders to ensure general agreement. Within each category we assessed and reportedly separately on specific types of interventions.
2. Patient outcomes – 30-day readmission, mortality, *C. difficile* infection, length of stay, morbidity, adverse effects
3. Antimicrobial prescribing outcomes – timing, use, selection, dose, route, duration

4. Microbial outcomes – institutional resistance and resistance in the study population
5. Costs – healthcare, program, opportunity, drug
6. Harms of stewardship program implementation
7. Other – barriers to implementation, sustainability and scalability of intervention.

From each study, we extracted all data fitting the descriptions of the outcomes in the list above including multiple outcomes, if provided. Our evidence tables (see Appendix), summary tables, and summaries of the evidence report the specific outcome data.

For ITS studies, we report, where provided by study authors, level and trend (or slope) results. Level refers to the change in the value of the outcome measure from pre- to post-intervention. Trend refers to the change between the slope of the line through data points before the intervention and the line through data points after the intervention.

QUALITY ASSESSMENT

We assessed the risk of bias of individual studies using the criteria developed for use in Cochrane Effective Practice and Organization of Care (EPOC) reviews (Appendix B). There are nine criteria for assessing risk of bias for studies with a separate control group (i.e., RCTs, CCTs, and CBA studies) and seven criteria for assessing risk of bias for ITS studies. Each element is scored as high, unclear, or low risk. A study was rated as low risk of bias if each of the individual criteria were scored as low risk, medium risk of bias if one or two criteria were scored as unclear or high risk, and high risk of bias if more than two criteria were scored as unclear or high risk.

Quality of systematic reviews was determined using the measurement tool for assessment of multiple systematic reviews (AMSTAR).⁵⁵

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics and results for all included studies, organized by intervention category. We critically analyzed studies to compare their characteristics, methods, and findings. We created forest plots for outcomes with sufficient data to calculate risk ratios. However, due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting among studies for an intervention, the results cannot be meaningfully pooled. Therefore, we compiled a summary of findings for each key question and drew conclusions based on qualitative synthesis of the findings.

RATING THE BODY OF EVIDENCE

We rated overall strength of evidence for our patient outcomes for each intervention category using methods developed by AHRQ and the Effective Health Care Program.⁵⁶ The strength of the evidence was evaluated based on four domains: 1) risk of bias (whether the studies for a given outcome or comparison have good internal validity); 2) consistency (the degree of similarity in the effect sizes, i.e., same direction of effect, of the included studies); 3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and 4) precision (degree of certainty surrounding an effect estimate of a given outcome).

PEER REVIEW

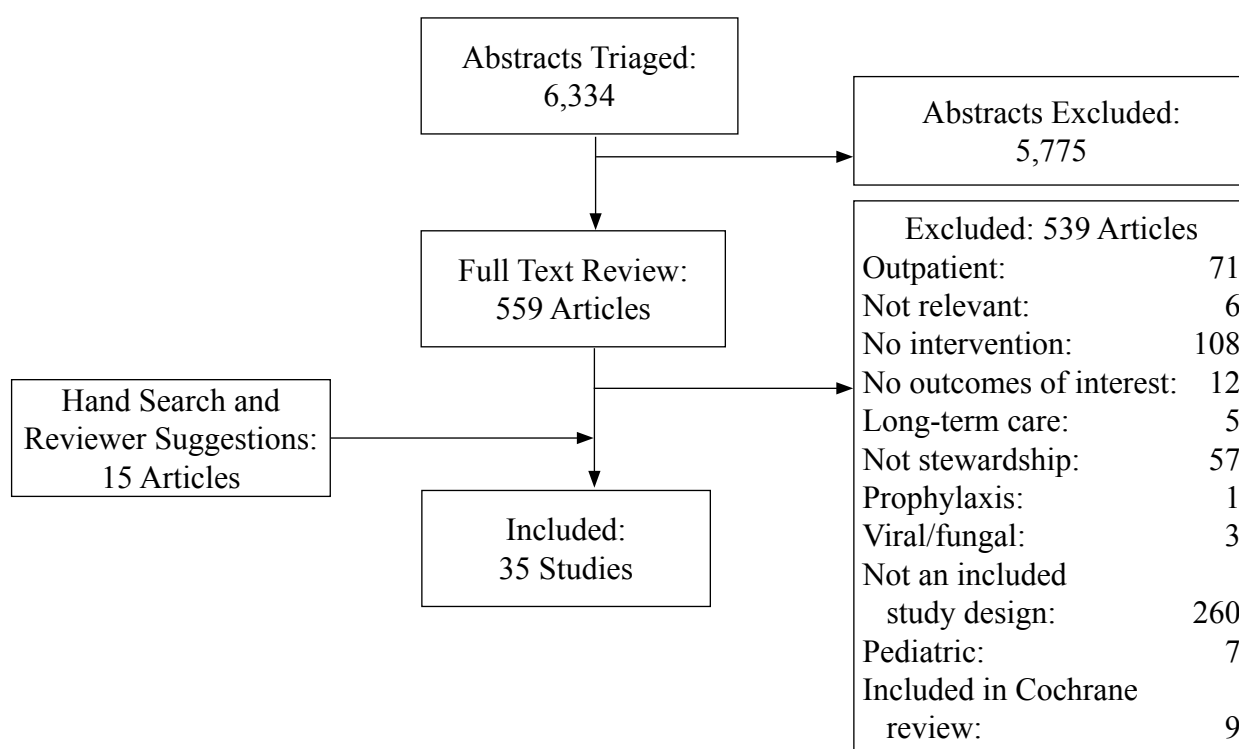
A draft version of this report was reviewed by technical experts as well as clinical leadership. Reviewer comments and our responses are presented in Appendix C.

RESULTS

LITERATURE FLOW

We reviewed 6,334 titles and abstracts from the electronic literature search. After applying inclusion/exclusion criteria at the abstract level, 5,775 references were excluded. We retrieved 559 full-text articles for further review and another 539 references were excluded. An additional 15 references were identified from reference lists of recent relevant systematic reviews or were suggested by peer reviewers for a total of 35 included studies. We grouped the studies by key question, type of intervention, hospital site, and clinical condition. Figure 1 details the exclusion process. We also summarized the results from three recent systematic reviews.

Figure 1. Literature Flow Diagram



KEY QUESTION #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

- a. **Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)**
- b. **Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?**

Existing Systematic Review

A high quality Cochrane review of interventions to improve antimicrobial prescribing for hospital inpatients was originally published in 2005 and included studies published to November 2003.⁵⁴ The review was recently updated to include studies published through December 2006 or listed in the Cochrane Effective Practice and Organization of Care (EPOC) Registry through 2009.⁵³ Interventions were categorized as persuasive, restrictive, or structural. Persuasive interventions focused on education and included distribution of educational materials, educational meetings, local consensus processes, local opinion leaders, verbal, paper, or electronic reminders, audit and feedback and educational outreach (including academic detailing and review and recommend change). Restrictive interventions included order forms, expert approval, removal of restricted antimicrobials, and substitution. Structural interventions included conversion from paper to electronic records, rapid laboratory testing, computerized decision support, and quality monitoring mechanisms. The aim of the intervention was described as either reducing the amount of antimicrobials prescribed where excessive or increasing effective treatment by increasing amount prescribed or improving the timing of antimicrobial administration.

Outcomes reported in the Cochrane review were antimicrobial prescribing (i.e., the decision to prescribe an antimicrobial and the choice of drug, dosage, route, or duration), clinical outcomes (mortality, length of hospital stay), microbial outcomes (colonization or infection with *C. difficile* or antimicrobial-resistant bacteria), and financial outcomes.

The updated review included 89 studies – 25 RCTs, 3 CCTs, 5 CBAs, and 56 ITS studies. The interventions were classified as persuasive in 44 studies, restrictive in 22 studies, both persuasive and restrictive in 15 studies, structural in 2 studies, and both structural and persuasive in 6 studies. There were 95 interventions in the 89 studies, 79 of which were categorized as intended to decrease unnecessary antimicrobial prescribing, 11 categorized as intended to increase effective antimicrobial prescribing, and 5 categorized as intended to reduce inappropriate prescribing but unclear whether the aim was to reduce excessive prescribing or reduce ineffective prescribing. The studies were conducted in North America (52 studies), Europe (29), the Far East (3), South America (3), and Australia (2). Seven studies were based in neonatal or pediatric settings and eight studies were focused on prophylactic antimicrobials. Meta-analyses were performed for selected pre-identified comparisons. However, the number of studies reporting individual outcomes was often limited (for example only 13 of 25 RCTs reported on mortality and only 5 reported on hospital readmissions) or the exact outcome within each category may have varied (e.g., antimicrobial prescribing outcome could include changes in decision to initiate or stop, dose or route of antimicrobial). The review authors did not state how they identified the single outcome selected from each study for analysis but our independent review suggests that only the primary outcome, identified by the original study author, was included. There was no verification or explanation of whether results would be consistent if the review authors included other outcomes within a category (i.e., clinical, prescribing, microbial, costs). Therefore, summary results for outcomes are based on findings from few studies often in different settings and with variable interventions. Selective outcome reporting bias and selective analysis reporting bias have not been adequately addressed.

Primary Outcomes – Clinical

Several clinical outcomes were analyzed using meta-analysis (Table 1). ITS studies were not included in the meta-analyses due to anticipated high heterogeneity versus the RCT, CCT, and CBA studies.

Table 1. Clinical Outcomes by Intervention Aim (from Davey et al., 2013)⁵³

Intervention Aim	Outcome	Risk Ratio [95% Confidence Interval] except as noted	I ²	Study designs, number of participants (n)
Increase effective prescribing	Mortality	0.92 [0.69, 1.22]	72%	2 RCTs, 1 CCT, n=1,484
Increase guideline compliance (CAP)	Mortality	0.89 [0.82, 0.97]	0%	1 RCT, 3 CBAs; n=22,526
Decrease excessive prescribing	Mortality	0.92 [0.81, 1.06]	0%	7 RCTs, 3 cluster RCTs, 1 cluster CCT; n=9,817
Decrease excessive prescribing	Length of stay	Mean difference (days) -0.04 [-0.34, 0.25]	63%	4 RCTs, 2 cluster RCTs; n=8,071
Decrease excessive prescribing	Readmission (all-cause or infection-related)	1.26 [1.02, 1.57]	9%	4 RCTs, 1 cluster RCT; n=5,856

I² = test for heterogeneity; RCT = randomized controlled trial; CBA = controlled before and after trial; CCT = controlled clinical trial

Interventions intended to increase effective prescribing did not significantly affect mortality (RR=0.92 [95% CI 0.69, 1.22]; k=3). One trial was a persuasive intervention for blood stream infections; two involved rapid laboratory tests for multiple infection sites. Each study was conducted in a single hospital.

Interventions intended to increase effective prescribing by increasing guideline compliance in patients with pneumonia reduced mortality (RR=0.89 [95% CI 0.82, 0.97]; k=4). The number of participants was high primarily due to the large control group of one trial. All interventions were persuasive. One study was conducted in multiple nursing homes, the remaining three studies were conducted in multiple hospitals.

Based on meta-analysis of 10 RCTs and 1 CCT, interventions intended to decrease excessive prescribing did not affect mortality (RR=0.92 [95% CI 0.81, 1.06]). Each of the trials included a persuasive component; three trials also involved a structural intervention. One study was conducted in neonatal wards. Of the remaining 10 studies, 5 enrolled patients with respiratory infections and 5 did not specify an infection site. Eight studies were conducted in a single hospital.

Six of the studies reported length of stay and found no significant difference (mean difference -0.04 [95% CI -0.34, 0.25] days). The analysis included the three trials with structural and persuasive components. Four trials enrolled patients with respiratory infections, and five trials were conducted in a single hospital. Five studies reported readmission. One study reported total readmissions (RR=3.00 [95% CI 1.18, 7.64]) while 4 studies reported infection-related readmissions (RR=1.33 [95% CI 0.31, 5.66]). The combined result was a significant increase in overall readmissions (RR=1.26 [95% CI 1.02, 1.57]). Two of the five studies enrolled patients with respiratory infections; three of the five studies were conducted in a single hospital.

Five ITS studies reported on CDI. The four studies reporting incidence data at one month post-intervention reported reductions in incidence ranging from 15% to 65%. Three of the studies also reported data at twelve months with reductions in incidence ranging from 77% to 85% in absolute terms. The fifth study reported prevalence with a reduction of 52% at 12 months post-intervention.

Secondary Outcomes – Prescribing, Microbial, Costs, Harms

Effect sizes were calculated to allow determination of a median effect encompassing the different prescribing outcomes reported (i.e., “any prescribing outcome” included decreased antimicrobial use, decreased frequency, increased appropriate use, etc.). It was not stated if other prescribing outcomes were reported by the original study authors, if review of original results varied by outcome definition, or what justification original authors had for using different outcomes as their primary outcome. It is not possible to assess the pooled effect on individual prescribing outcomes or which specific outcome is dominating the results. With those limitations in mind we describe the findings below. Positive numbers represent a percent change in the intended direction and are considered an absolute pooled percentage difference of the individuals achieving such an outcome in the intervention group minus the control. Median changes were calculated by intervention type and by study design (Table 2). The authors noted that clinical heterogeneity was high due to variations in the clinical outcomes, patient and provider populations, study methodologies, the features of the interventions, and the different settings in which the interventions were applied. Many of the studies included more than one intervention component.

Table 2. Median Change* in Antimicrobial Prescribing by Intervention Type and Study Design (from Davey et al., 2013)⁵³

Intervention Type	RCT	CRCT	CBA	ITS	CITS
Persuasive	24.7%	3.5%	17.7%	42.3%	31.6%
Dissemination of educational materials		-3.1% (k=1) [#]	16.1% (k=2)	10.6% (k=2)	42.5% (k=1)
Reminders	27.4% (k=3) [#]			20.0% (k=5) [#]	
Audit and feedback		3.5% (k=1) [#]	7.5% (k=2)	32.7% (k=4) ^{#^}	24.3% (k=2)
Educational outreach [‡]	25.0% (k=10 including 1 CRCT) [†]		20% (k=1) [#]	46.3% (k=10)	
Restrictive	40.5%		17.1%	34.7%	
Compulsory order forms				7.3% (k=5) [#]	
Expert approval [‡]			-2.8% (k=1)	24.1% (k=7)	
Removal by restriction			37.0% (k=1)	60.7% (k=7) ^{#^}	
Review and make change	40.5% (k=2)			94.3% (k=2)	
Structural	13.3% (k=6) [^]	23.6% (k=2)			

RCT = randomized controlled trial; CRCT = cluster randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after study; ITS = interrupted time series; CITS = controlled interrupted time series; k = number of studies

*Positive change is a change in the direction of the intended change

[#]Includes at least 1 trial of prophylactic antimicrobials

[^]Includes at least 1 trial from neonatal or pediatric setting

[‡]One additional study of this intervention type was not included in calculation of median change

[†]Includes one study from nursing home setting

A subsequent meta-regression included only studies that were purely persuasive or purely restrictive. All were ITS studies. Thirty-eight studies reported prescribing outcomes. Persuasive and restrictive interventions had a similar effect on “any prescribing outcome” at 6, 12, and 24 months post-intervention.

Effect sizes were also determined for “any microbial outcome” (reported in 21 studies). Nine studies (7 ITS, 2 CCT) reported colonization (3 studies) or infection (6 studies) with antibiotic-resistant *gram-negative* bacteria. Of the seven ITS studies, five reported incidence at one month post-intervention with reductions ranging from 36% to 92%. Only one of the studies also reported incidence at 12 months with a change in reduction from 36% at one month to 29% at twelve months. Two ITS studies reported prevalence with a reduction in colonization of 23% at one month in one study and a reduction in infection of 41% in the other study. In one cluster CCT from a neonatal intensive care unit, a 68% reduction in days of colonization with resistant bacteria at six month post-intervention was reported. An effect opposite from the intended effect was observed in a CCT from a neonatal intensive care unit (increased incidence of 39.0%). Seven studies (6 ITS, 1 CBA) reported colonization (1 study) or infection (6 studies) with antibiotic-resistant *gram-positive* bacteria. Outcomes varied in the studies. In the ITS studies, one study reported an outcome at 1 month (a 25% effect in the intended direction), two studies reported outcomes at 6 months (21% and 87% effects in the intended direction), three studies reported outcomes at 12 months (a 2% effect in the opposite direction and 38% and 100% effects in the intended direction), and three studies reported outcomes at 24 months (a 10% effect in the opposite direction and 23% and 50% effects in the intended direction). The CBA study reported a 13.2% difference in VRE infection favoring the intervention ($p < 0.001$). A meta-regression of 14 ITS studies that were purely persuasive or purely restrictive found that persuasive and restrictive interventions had a similar effect on microbial outcomes at 12 and 24 months post-intervention.

Data on both intervention costs and financial savings were reported in 10 studies (including 2 studies of prophylactic antimicrobials). In eight of the studies, savings were greater than costs.

Studies from VA Hospitals

The review cited 9 studies (2 RCTs, 7 ITS) conducted at VA hospitals between 1985 and 2006. Seven were assessed as high risk of bias and 2 as medium risk of bias. Three were categorized as persuasive and six as restrictive interventions. One enrolled patients in the ICU with VAP, the others enrolled patients with any infection.

By our definition of outcome categories, the primary outcome was a clinical outcome in three studies (two reporting CDI incidence and one reporting length of stay) although the length of stay data were not provided in the review. Two studies reporting CDI, both ITS studies with restrictive interventions and enrolling all hospitalized patients, found decreased incidence of CDI (-53% [95% CI -3%, -102%] and -65% [95% CI -48%, -81%] at 1 month, -79% [95% CI -34%, -124%] and -77% [95% CI -60%, -94%] at 12 months). One RCT reported a clinical outcome as a secondary outcome finding a non-significant decrease in mortality (13% intervention, 31% control; RR=0.41 [95% CI 0.16, 1.05]).

In three studies, the primary outcome was a prescribing outcome. Results were mixed with one ITS reporting a non-significant decrease in orders for vancomycin that were deemed inappropriate, one RCT reporting a significant decrease in the percentage of patients receiving antimicrobials for more than three days, and one ITS reporting a decrease in slope but not level for use of levofloxacin.

In the remaining three studies, the primary outcome was microbial. A significant decrease

in colonization or infection with gram-negative bacteria at one month post-intervention was reported in one ITS study but the decrease was non-significant by six months. Another ITS study reported a reduction in incidence of ceftazidime-resistant *Klebsiella pneumonia*, MRSA, and cefotaxime-resistant *Acinetobacter* species. A third ITS study reported a significant decrease in MRSA infections at 6 months.

Conclusions

Overall, interventions to increase effective prescribing had no effect on mortality whereas interventions to increase guideline compliance were associated with a reduction in mortality. Interventions to decrease excessive prescribing had no effect on mortality or length of stay but led to an increase in hospital readmissions. Persuasive and restrictive interventions were similarly effective in improving prescribing outcomes based on median effect sizes across “any prescribing” outcome. There was some evidence of a short-term improvement with restrictive interventions but the benefit was not sustained. A similar pattern was observed for microbial outcomes. Multifaceted interventions were common but not necessarily more effective than simpler interventions. The authors commented on the lack of comparative effectiveness research, incomplete outcome reporting, and the high risk of bias associated with many studies.

Recent Evidence

We identified 35 studies that were not included in the updated Cochrane review. Nine were RCTs (including cluster randomized trials), four were CCTs, two were CBAs, and twenty were ITS studies.

We categorized studies initially by primary intervention including 14 studies of audit and feedback programs,^{1-10,57-60} 5 studies of formulary restriction and preauthorization programs,^{11-14,61} 4 studies of guideline implementation with feedback,¹⁵⁻¹⁸ 4 studies of guideline implementation with no feedback,^{19-21,62} 4 studies of computerized decision support,^{22-24,63} and 4 studies of protocol or policy implementation.^{25-27,64} We summarize systematic reviews and recent evidence from studies of the use of laboratory tests to guide prescribing decisions. Within each of our primary intervention categories, we described interventions as intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery (31 studies) or intended to decrease unnecessary or excessive prescribing (4 studies).

Within the framework of the Cochrane review,⁵³ interventions we categorized as audit and feedback, guidelines with feedback, and guidelines without feedback would be considered persuasive interventions, formulary restriction and preauthorization and protocol interventions would be considered restrictive interventions, and computerized decision support and laboratory tests would be considered structural interventions.

Most studies were conducted at university-affiliated or teaching hospitals. Six studies were performed at community hospitals^{6,8,14,18,19,58} and two did not specify the hospital type.^{15,16} One study analyzed data from administrative care databases for a Canadian province.¹³ We also looked at the site of the intervention with 8 studies conducted in intensive care units (ICUs),^{4,6,9,12,20,27,62,63} 7 studies conducted in medical wards,^{2,5,10,16,26,59,60} 12 studies conducted in multiple sites (medical, surgical, ICU),^{1,3,7,8,11,14,18,22,24,57,58,61} and 1 study in acute care.¹⁷ Seven studies did not report the site.^{13,15,19,21,23,25,64}

Seven studies focused on treatment of respiratory illness,^{15,16,21,24,25,26,62} 26 included patients with any type of infection,^{1-11,13,14,17-20,22,23,27,57,58,60,61,63,64} and one study included only bloodstream infections.¹² One study did not report infection site.⁵⁹

We also identified two recent systematic reviews of studies on the use of laboratory testing, specifically procalcitonin, to monitor bacterial infection.^{66,67} We summarize the findings of those reviews and two RCTs published after the systematic reviews^{67,68} under Laboratory Tests, below.

Table 1a provides an overview of the clinical outcomes by intervention category; prescribing outcomes are presented in Table 1b. We constructed forest plots with RCTs or CCTs that reported risk ratios for mortality (Figure 2) or appropriate prescribing (Figure 3), or reported data that allowed us to calculate the risk ratios. Due to heterogeneity of interventions and populations, results were not pooled. Despite the large number of included studies there was limited outcome reporting. For example, of the 14 audit and feedback studies only 10 reported on mortality, 8 reported on length of stay, 3 on readmissions, and 1 on CDI. Furthermore, while we present forest plots for RCTs and CCTs providing sufficient information, much of the reported evidence is from ITS studies (20 of the 35 included studies) and therefore not suitable for inclusion on forest plots. For appropriate prescribing, only 4 of 12 included RCTs and CCTs provided data in a fashion that permitted creation of forest plots. Because selective outcome reporting and presentation can result in misleading and biased findings we urge caution in drawing definitive conclusions based on reliance of data presented only in a forest plot or even some of the outcomes provided in tables.

Table 3a. Overview of Clinical Outcomes – Antimicrobial Stewardship Interventions for Inpatients

ASP Intervention (# studies)	Mortality	Length of Stay	Readmission	CDI	Summary
Prospective Audit and Feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	+ 1 study ≈ 9 studies	≈ 9 studies	+ 1 study ≈ 2 studies	p=NR, 1 study	Audit and feedback showed no association with clinical outcomes.
Formulary Restriction and Preauthorization (1 RCT, 4 ITS)	≈ 3 studies	≈ 2 studies	NR	+ 1 study	Mortality and length of stay were unchanged with formulary restriction and preauthorization. CDI was decreased.
Guidelines with Feedback (2 RCT, 2 ITS)	≈ 3 studies	≈ 3 studies	NR	+ 2 studies	Mortality and length of stay were unchanged. CDI was decreased in two studies following guidelines with feedback intervention.
Guidelines without Feedback (1 CCT, 1 CBA, 2 ITS)	+ 1 study ≈ 1 study - 1 study	+ 1 study ≈ 1 study - 1 study	≈ 1 study	NR	Inconsistent findings from 3 studies of guidelines implemented without feedback assessing mortality or length of stay. No difference in readmissions.
Computerized Decision Support (1 RCT, 1 CCT, 2 ITS)	≈ 3 studies	+ 1 study ≈ 2 studies	≈ 1 study	+ 1 study ≈ 1 study	No differences in mortality or readmissions with computerized decision support versus controls. Mixed results for length of stay and CDI.
Protocols (2 RCT, 2 ITS)	+ 1 study ≈ 2 studies	+ 2 studies ≈ 1 study	≈ 1 study	NR	For protocols, results were mixed for mortality and length of stay. No difference in readmissions.

ASP = antimicrobial stewardship; NR = not reported; CDI = incidence of *C. difficile* infection

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

Table 3b. Overview of Prescribing Outcomes – Antimicrobial Stewardship Interventions for Inpatients

ASP Intervention (# studies)	Use	Selection	Timing	Duration	Summary
Prospective Audit and Feedback (3 RCT, 2 CCT, 1 CBA, 8 ITS)	Decreased: + 8 studies Appropriate: + 1 study ≈ 1 study	+ 1 study ≈ 1 study	NR	+ 5 studies	Prospective audit and feedback showed improvement in prescribing outcomes
Formulary Restriction and Preauthorization (1 RCT, 4 ITS)	Decreased: + 4 studies	NR	NR	+ 1 study	Formulary restriction and preauthorization were associated with improvement in prescribing outcomes.
Guidelines with Feedback (2 RCT, 2 ITS)	Decreased: + 1 study Compliant/appropriate: + 2 studies	≈ 1 study	+ 1 study	≈ 2 studies	Mixed results were observed for prescribing outcomes with 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: + 1 study Compliant/appropriate: + 2 studies ≈ 1 study	NR	- 1 study	+ 1 study ≈ 1 study	Improvement in prescribing use but not timing or duration with guidelines implemented without feedback.
Computerized Decision Support (1 RCT, 1 CCT, 2 ITS)	Decreased: + 1 study ≈ 1 study	NR	NR	NR	Two studies reported mixed results for antimicrobial use with computerized decision support.
Protocols (2 RCT, 2 ITS)	Appropriate: ≈ 1 study	NR	≈ 1 study	+ 2 studies	No difference in appropriate use or timing but reduced duration of use in studies of ASP protocols.

ASP = antimicrobial stewardship; NR = not reported;

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

Figure 2. Mortality Outcome Reported in Randomized or Controlled Clinical Trials (k=12)
 (NB Our review included 20 ITS studies that did not present data in a format suitable for inclusion on a forest plot. Therefore the figure below provides only a subset of all included data.)

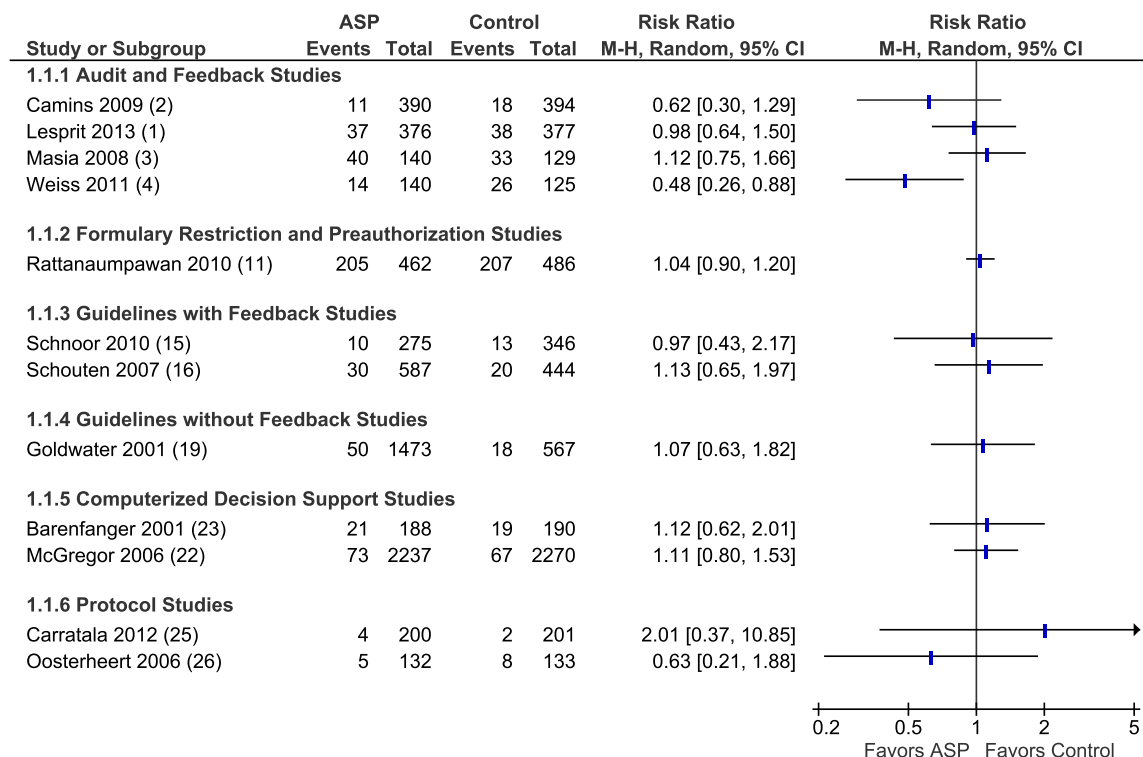
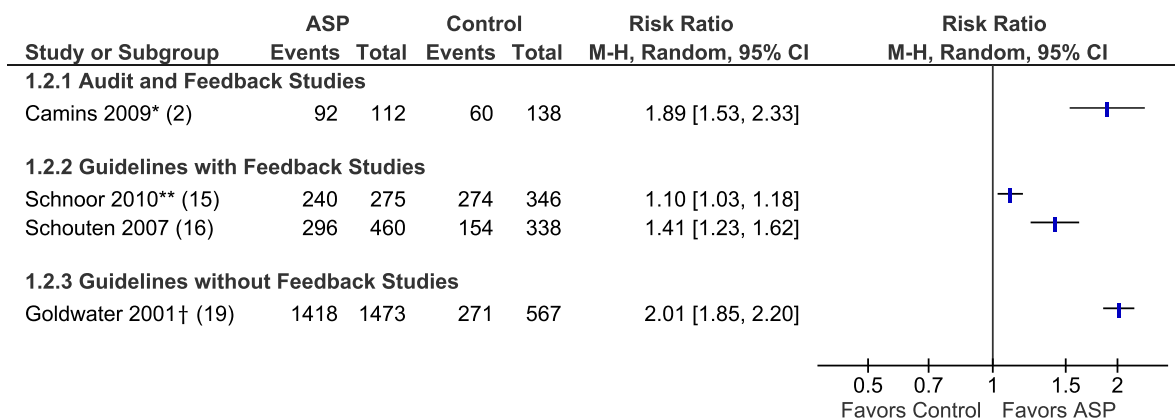


Figure 3. Appropriate Antimicrobial Use Outcome Reported in Randomized or Controlled Clinical Trials (k=4)
 (NB Many RCTs/CCTs did not report on appropriate antimicrobial use, definitions of use varied across and within studies, and some studies did not provide sufficient information to create forest plots. Furthermore, our review included 20 ITS studies that did not present data in a format suitable for inclusion on a forest plot. Therefore the figure below is a subset of all included data.)



* Definitive use

** Estimated from odds ratio (adjusted)

† Replacement of ciprofloxacin with levofloxacin (number of patients)

Audit and Feedback (k=14)

Key Findings

- **Patient Outcomes:** Mortality was reported in ten studies with no differences observed between intervention and control groups or pre- to post-intervention in nine studies. No differences were reported for length of stay (reported in nine studies) or 30-day readmission (reported in two studies); 60-day readmission for relapsing infection was reduced in one study. One study reported fewer *C. difficile* infections following the intervention. Two studies reported adverse events, specifically the need to re-initiate intravenous (IV) antimicrobials in a small number of subjects.
- **Prescribing Outcomes:** Audit and feedback programs were found to decrease use of targeted antimicrobials (reported in seven studies) and decrease excessive use (measured in one study). Results for increasing appropriate use (reported in two studies) were mixed. Five studies reported improvement in duration of therapy (including duration of inappropriate therapy, time to modification of therapy, duration of targeted therapy, and hours of IV therapy) following the intervention. One study reported improvements in antimicrobial selection post-intervention while one study reported mixed results for targeted antimicrobials.
- **Microbial Outcomes:** Two studies reported decreased rates of selected antimicrobial-resistant bacteria following implementation of an antimicrobial stewardship program, but in one of these the incidence of another antimicrobial-resistant organism increased. In another study, no differences in antimicrobial resistance trends were reported for five pathogens but the measure is unclear. One study reported increased gram-negative susceptibility to one antimicrobial but no change in susceptibility to five others. Another study reported no difference between intervention and control groups in secondary infections or colonization.
- **Cost Outcomes:** Nine reported cost outcomes with all reporting decreased drug costs or decreased costs to patients and/or insurers.
- **Limitations:** There were substantial threats to validity, including the possibility of secular trends, opportunities for contamination within study sites, opportunities for bias in assessment, and the potential for unmeasured or unreported changes in use of antimicrobials not targeted by the interventions. Studies were not designed with adequate power to measure impacts of the interventions on patient outcomes.

Characteristics of Studies

We categorized interventions as audit and feedback if, following review of the prescription, feedback on an individual patient basis was provided within 24 hours of the review and was provided directly to the prescriber (either written or verbally). Fourteen studies met inclusion criteria. Eight were ITS studies,^{6-9,57-60} three were RCTs,¹⁻³ two were CCTs,^{4,5} and one was a CBA.¹⁰ Four studies were conducted in North America,^{2,4,6,7} one in the United Kingdom,⁵⁸ five in Europe,^{1,3,5,9,10} three in the Asia Pacific region,^{8,57,60} and one in South America.⁵⁹

One study was low risk of bias⁶⁰ and four were medium risk of bias.^{1,3,6,58} The remaining nine studies were considered to be high risk of bias.

In 13 studies, the aim of the intervention was to alter antimicrobial timing, drug selection, tailoring, and route of delivery.^{1-6,8-10,57-60} In one study, the aim was to decrease unnecessary or excessive prescribing.⁷

All studies were audit and feedback^{30,49} involving a pharmacist or physician who reviewed the management of individual cases in real time and provided advice to clinicians during a course of antimicrobial therapy. Audit and feedback was performed by some combination of clinical pharmacists and physicians in seven studies;^{2,3,6-8,57,59} a clinical pharmacist, physician, and clinical microbiologist in one study;⁶⁰ clinical pharmacists in one study;¹⁰ a clinical microbiologist in one study;⁵⁸ an infectious disease physician alone in three studies;^{1,5,9} and a resident physician in one study.⁴ Most studies involved multifaceted interventions. In nine studies, the providers had access to institutional guidelines on antimicrobial use.^{1,2,3,7,8,10,57,58,60} In three studies, provider education was offered.^{1,9,58} In one study, the targeted antimicrobials would only be provided after approval by the infectious disease service.⁷ In another study, providers were asked to run through a daily checklist which included a statement about adjustments to antimicrobial use.⁴

Thirteen of the fourteen studies were conducted in urban hospitals, most of which were University-affiliated teaching hospitals. The sole exception was conducted in a rural community hospital.⁵⁸ In six studies, the interventions were carried out on general medical wards, or a mixture of medical, surgical, and step-down (telemetry) wards.^{1-3,5,8,10} In three studies,^{4,6,9} the intervention was implemented in an Intensive Care Unit (ICU), whereas in three studies,^{7,57,58} it was implemented in both ICUs and general medical wards. One study was implemented in a medical oncology unit,⁶⁰ one in general surgery, renal medicine, and endocrinology departments,⁸ and another was implemented on the medical wards of a cardiology hospital.⁵⁹

The unit of analysis differed among included studies. Seven used aggregate data from the entire study population.^{6,7,8,57-60} Seven used data on individual patients or antimicrobial prescriptions.^{1-5,9,10} One study specified that since the unit of analysis was the prescription, individual subjects could be enrolled multiple times.³ However, since this study randomly assigned prescription courses to intervention versus control, it is not clear how they dealt with situations in which the same subject was associated with prescriptions in both the intervention and control groups.

Thirteen studies included patients with all sites of infection; two did not report site. Six studies reported specific sites with respiratory tract, urinary tract, gastrointestinal, and skin/soft tissue infections the most common.^{1-4,9,10} In six studies that reported patient characteristics, mean or median age ranged from 54 to 69 years and between 45% and 65% were male.^{2-5,10,57}

Reported outcomes are depicted in Table 4. Detailed results are presented in Appendix D, Tables 1 to 8.

Table 4. Audit and Feedback Interventions: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Cairns 2013 ⁵⁷		X			
Lesprit 2013 ¹	X	X	X	X	
Elligsen 2012 ⁶	X	X	X	X	
Magedanz 2012 ⁵⁹		X	X	X	
Standiford 2012 ⁷	X	X		X	
Teo 2012 ⁸	X	X		X	
Weiss 2011 ⁴	X				
Yeo 2012 ⁶⁰	X	X	X	X	X
Bornard 2011 ⁹	X	X			
Dunn 2011 ¹⁰	X	X		X	
Manuel 2010 ⁵	X	X		X	
Camins 2009 ²	X	X			
Liebowitz 2008 ⁵⁸		X	X		
Masia 2008 ³	X	X		X	X

Patient Outcomes

Of the 13 studies that aimed to alter antimicrobial timing, drug selection, tailoring, or route of delivery, 10 reported patient-specific outcomes. Nine included mortality data^{1-6,8-10} with only one study reporting a significant difference in mortality between intervention and control groups or pre- and post-intervention periods. This study was a CCT of prompting during daily rounds. ICU physicians were prompted to consider six parameters of care, one of which was empirical antimicrobial utilization.⁴ This intervention was associated with reduced risk-adjusted odds of death (OR=0.48 [95% CI 0.26, 0.88]) in the intervention group compared with the control (no prompting) group. A subsequent exploratory analysis including all patients who received empiric antimicrobials also found reduced mortality in the prompting group (OR=0.41 [95% CI 0.18 to 0.92]). When empiric antimicrobial duration was added to mortality models, the adjusted OR for the intervention was attenuated from 0.41 to 0.50, suggesting that shorter duration of empiric antimicrobials explained 15.2% of the overall benefit of prompting.⁶⁹

Nine studies reported length of stay with no significant differences between intervention and control groups or pre- and post-intervention periods.^{1-6,8-10}

Two studies reported 30-day readmission with no difference between intervention and control groups in a randomized trial (21% intervention, 15% control, p=0.22)³ and no difference between whether the intervention was accepted or rejected during the post-intervention phase of an interrupted time series (33% vs. 25%, p=0.10).⁸ A third study, a randomized trial, reported a significant difference in 60-day readmission for relapsing infection (3.4% intervention, 7.9% control, p=0.01).¹

One study reported a 31% decrease in *C. difficile* infections post intervention.⁶ By comparison, a 33% increase was noted in non-study wards at the same hospital.

Adverse events were reported in two studies. In the ITS study conducted on the oncology wards, it was reported that following acceptance of the antimicrobial stewardship recommendations, there were 32/580 cases (5.5%) in which patients deteriorated. In 24 of those cases, deterioration was wholly or partially attributed to progression of malignancy. Two patients were subsequently placed back on broad-spectrum antimicrobials despite negative bacterial cultures and improved to the point of discharge. Four patients deteriorated despite escalation of antimicrobial therapy, and two patients deteriorated due to new-onset fungal infection.⁶⁰ In the CBA study of application of criteria for switching from IV to oral therapy, during the intervention phase, one patient each in both the intervention and control groups required reinstatement of IV therapy.¹⁰

In the study that aimed to reduce ineffective or excessive treatment, no differences in mortality, length of stay, or 30-day readmissions were observed across the 10 year study period.⁷ CDI rates and adverse events were not reported.

Results for individual studies and strength of evidence for patient outcomes across all audit and feedback studies regardless of the intended purpose of the intervention are presented in Table 5.

Table 5. Strength of Evidence for Audit and Feedback Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Lesprit 2013 ¹	RCT	Improve quality of antimicrobial use	Medium	Mortality	NS, RR 0.98 [0.64, 1.50]	Low for Mortality
Camins 2009 ²	RCT	Improve appropriateness	High	Mortality	NS, RR 0.62 [0.30, 1.29]	
Masia 2008 ³	RCT	Decrease targeted antimicrobials	Medium	Mortality	NS, RR 1.12 [0.75, 1.66]	
Weiss 2011 ⁴	CCT	Improve mortality	High	Mortality	Reduced, OR 0.48 [0.26, 0.88]	
Manuel 2010 ⁵	CCT	Improve appropriateness	High	Mortality	NS	
Elligsen 2012 ⁶	ITS	Decrease targeted antimicrobials	Medium	Mortality	NS, 13% pre, 14% post	
Standiford 2012 ⁷	ITS	Decrease ineffective/excessive	High	Mortality	NS	
Teo 2012 ⁸	ITS	Improve appropriateness	High	Mortality	NS, 0.44 deaths/100 inpatient days (pre and post)	
Bornard 2011 ⁹	ITS	Improve quality of antimicrobial use	High	Mortality	NS, RR 0.84 [0.05, 12.99]	
Dunn 2011 ¹⁰	CBA	Increase switch rate from IV to oral	High	Mortality	NS	
Lesprit 2013 ¹	RCT	Improve quality of antimicrobial use	Medium	Length of stay	NS, 15 days (median) (both groups)	Low for Length of Stay
Camins 2009 ²	RCT	Improve appropriateness	High	Length of stay	NS, 7 days intervention, 8 days control (medians)	
Masia 2008 ³	RCT	Decrease targeted antimicrobials	High	Length of stay	NS, 14 days (median) (both groups)	
Weiss 2011 ⁴	CCT	Improve mortality	High	Length of stay (ICU)	NS, 4 days intervention, 5 days control, p=0.07	
Manuel 2010 ⁵	CCT	Improve appropriateness	High	Length of stay	NS	
Elligsen 2012 ⁶	ITS	Decrease targeted antimicrobials	Medium	Length of stay	NS, 6.9 days (pre and post)	
Standiford 2012 ⁷	ITS	Decrease ineffective/excessive	High	Length of stay	NS	
Bornard 2011 ⁹	ITS	Improve quality of antimicrobial use	High	Length of stay	NS, 18 days pre, 19 days post	
Dunn 2011 ¹⁰	CBA	Increase switch rate from IV to oral	High	Length of stay	NS	
Lesprit 2013 ¹	RCT	Improve quality of antimicrobial use	Medium	Readmission*	Reduced, RR 0.43 [0.23, 0.82]	
Masia 2008 ³	RCT	Decrease targeted antimicrobials	High	Readmission	NS, RR 1.40 [0.84, 2.33]	
Standiford 2012 ⁷	ITS	Decrease ineffective/excessive	High	Readmission	NS	
Elligsen 2012 ⁶	ITS	Decrease targeted antimicrobials	Medium	Incidence of CDI	Significance not reported; 16 cases pre, 11 cases post	Low for Incidence of CDI

RCT = randomized controlled trial; CCT = controlled clinical trial; ITS = interrupted time series; CBA = controlled before and after study; NS = not statistically significant; RR = rate ratio [95% confidence interval]; OR = odds ratio [95% confidence interval]; IV = intravenous

*This study reported 60 day readmission for relapsing infection; other studies report 30 day readmission for any cause

Prescribing Outcomes

Antimicrobial Use

Among the 13 studies of interventions intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery, 9 reported antimicrobial use outcomes. One randomized study found a significant increase in initial (less than 72 hours) use that was considered “appropriate” in the intervention arm versus control (78% vs. 58%, RR=1.35 [1.22, 1.49], $p<0.001$). A significant increase in appropriate end antimicrobial use (the final choice of antimicrobial regimen) was also noted in the intervention arm (94% vs. 70%, RR=1.34 [1.25, 1.43], $p<0.001$).² However, an interrupted time series reported that changes in level and trend for appropriate therapies were non-significant.⁹

Three studies, all interrupted time series with the focus of the stewardship program on specific antimicrobials, found evidence of a substantial decrease in use of audited antimicrobials associated with the intervention. In one recent study there was a significant decrease in the level of consumption of audited antimicrobials but no change in the level of total antimicrobials. The change in the trend for use of targeted antimicrobials was not significant.⁸ In another study, the mean amounts of antimicrobials prescribed increased between the pre-evaluation and intervention periods, but the trend for prescriptions decreased during the intervention period, moving from stable to a significant decrease ($p=0.001$).⁶⁰ The third study reported a decrease in mean monthly consumption from 48.9 DDD/100 patient-days during the baseline period to 36.9 DDD/100 patient-days during the full implementation of the stewardship program ($p=0.001$).⁵⁹

Several studies were focused on reducing use of broad-spectrum antimicrobials. A randomized trial of an intervention to decrease use of specific antimicrobials by comparing antimicrobial use to institutional guidelines for selected conditions, found median total consumption of targeted antimicrobials was 8 DDD per patient in the intervention group and 10 DDD per patient in the control group ($p=0.04$).³ However, there was a corresponding increase in antimicrobials that were not a focus of their intervention, and overall antimicrobial use and the costs of antimicrobials dispensed were similar in intervention and control groups.³ The authors concluded that the impact of the intervention was “limited.” Two interrupted time series reported significant decreases in use (level) of broad-spectrum antimicrobials both in the ICU^{6,57} and general wards.⁵⁷ Changes in trend were less consistent with one study reporting a significant change in trend in the ICU but not in the general wards⁵⁷ and the other study reporting a non-significant trend in the ICU.⁶

Dunn reported an increase in the percentage of courses switched from IV to oral antimicrobial therapy on the appropriate day after the intervention (72% vs. 51%, $p=0.02$).¹⁰

In the study that aimed to decrease unnecessary or excessive prescribing, total antimicrobial use decreased from 1,512 DDD/1000 patient-days in 2004 to 1,073 DDD/1000 patient-days in 2008 (29%, $p=0.14$).⁷ The antimicrobial stewardship program began in 2002 but defined daily dose data were not available until 2004. Significant decreases from 2004 to 2008 were also observed for use of antibacterial, antifungal, and antiviral agents.

Duration

Each of the five studies that reported on duration of antimicrobial therapy^{1-3,5,10} observed a significant decrease associated with the intervention.

One study required that a single infectious disease physician review all prescriptions for any of the 15 selected intermediate or broad spectrum antimicrobials. Median days of total antimicrobial, broad-spectrum, and IV use decreased post-intervention while oral consumption increased.¹ Another study, evaluating the use of an antimicrobial utilization team to improve appropriate prescribing, reported shorter days of inappropriate antimicrobial use in the intervention group (median of 2 days vs. 5 days, $p < 0.001$).² A study of reassessment of IV therapy after 3 days reported shorter time to therapy modification in the intervention group (3.9 days vs. 5.0 days, $p = 0.007$).⁵ Masia reported median days receiving three targeted antimicrobials was significantly shorter in the intervention group (4 vs. 6 days, $p = 0.002$).³ An intervention to encourage IV to oral switch reported fewer hours of IV treatment (median of 72 hours in the intervention group vs. 96 hours in the control group, $p = 0.02$).¹⁰

Selection

Two studies assessed the effect of the intervention on drug selection. In one study, overall antimicrobial use decreased during the intervention phase.⁵⁹ There was a significant increase in the use of drugs that were encouraged (i.e., penicillins: $p = 0.03$ for level, $p = 0.007$ for trend), whereas the use of drugs that were discouraged significantly decreased (i.e., fluoroquinolones: $p = 0.004$ for level and for trend).

In the second study, following implementation of an intervention discouraging use of ciprofloxacin and second- and third-generation cephalosporins, third-generation cephalosporin use decreased both hospital-wide (36 DDD/1000 occupied bed-days to 9 DDD/1000 occupied bed-days) and in the intensive care unit (29 DDD/1000 occupied bed-days to 1 DDD/1000 occupied bed-days).⁵⁸ For ITS regression analysis, the change in level was significant both hospital wide ($p < 0.001$) and in the ICU ($p < 0.001$) while the change in trend was significant only for the hospital-wide data ($p = 0.003$). Ciprofloxacin use hospital-wide decreased (12 DDD/1000 occupied bed-days to 1 DDD/1000 occupied bed-days) but the changes in level ($p = 0.09$) and trend were not significant ($p = 0.14$). Ciprofloxacin use decreased in intensive care units (57 DDD/1000 occupied bed-days to 8 DDD/1000 occupied bed-days) with a significant change in level ($p = 0.014$) but not trend ($p = 0.95$).

Microbial Outcomes

Five studies reported microbial outcomes. All were studies that aimed to alter antimicrobial timing, selection, tailoring, or route of delivery.

In a recent randomized, controlled trial focused on improving quality of antimicrobial use, an infectious disease physician reviewed and made recommendations, if appropriate, for new prescriptions for any of 15 targeted intermediate or broad spectrum antimicrobials ordered for patients in the intervention group.¹ Rates of secondary infection or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or extended spectrum B-lactamase-producing Enterobacteriaceae (ESBLE) did not differ significantly between the intervention or control

groups during the 6 months following randomization (MRSA 2.9% intervention, 2.6% control, $p=0.82$; ESBL 3.2% intervention, 4.5% control, $p=0.34$).

In another study, the focus was on decreasing the incidence of infections caused by MRSA.⁵⁸ The intervention involved a clinical microbiologist rounding with inpatient teams. A major goal of the study was to decrease use of broad-spectrum cephalosporins and ciprofloxacin. The rate of MRSA bacteremia decreased by 63% ($p<0.001$) after the intervention was implemented. There was no significant change in the methicillin-susceptible *S. aureus* (MSSA) bacteremia rate or the rate of MRSA colonization.

A third study looked at resistance trends before and after implementation of a multidisciplinary stewardship program.⁶⁰ The analysis included the five most commonly cultured nosocomial pathogens identified in area hospitals. Data were reported as incidence density per 1000 inpatient days but no further information was provided on the measure. No significant differences were noted for trends over the study period. There was a significant decrease ($p=0.017$) in the mean incidence-density for MRSA during the intervention period but differences in the means for the other four pathogens were not significant.

The focus of the fourth study was on appropriate prescribing of targeted antimicrobials but infection rates were reported for several antimicrobial-resistant bacteria.⁵⁹ The study included three phases: 1) baseline, 2) audit and feedback by an infectious disease physician, and 3) audit and feedback by both the physician and a clinical pharmacist. The authors did not provide a definition for the reported rates (e.g., rates of isolates identified in the microbiology laboratory, or rates of resistant bacteria associated with infectious diseases in patients). However, there were significant increases in ceftazidime-resistant *Klebsiella* spp. (from 12% and 16% in stages 1 and 2, to 42% in stage 3; $p<0.001$) and ceftazidime-resistant *Pseudomonas* spp. (4% and 3% in stages 1 and 2, and 14% in stage 3; $p=0.005$). The rate of carbapenem-resistant *Pseudomonas* spp. decreased from 6% and 7% in stages 2 and 3, to 1% in stage 3 ($p=0.01$). The rate of ceftazidime-resistant *Klebsiella* spp. was significantly correlated with the increase in total cephalosporin use ($r=0.239$; $p=0.04$).

The final study, an interrupted time series study targeting broad spectrum antimicrobial use in the ICU, involved review of prescriptions by an antimicrobial stewardship pharmacist, an infectious disease pharmacist, and an infectious disease physician.⁶ The authors reported a significant increase in gram-negative susceptibility to meropenem during the post-intervention phase (83.4% vs. 78.2% prior to the intervention, $p=0.03$). There was no change in susceptibility to ceftriaxone, piperacillin-tazobactam, ciprofloxacin, or ceftazidime.

Costs

Eight studies were intended to alter antimicrobial timing, drug selection, tailoring, or route of delivery reported cost data.^{1,3,5,6,8,10,59,60} All found that their interventions were associated with decreased costs. The magnitude of the cost-savings varied.

Most reported drug costs. In a randomized trial, drug costs for the study period (24 weeks) were €4,670 lower in the intervention group.¹ Another trial reported a €6.41 per patient decrease in antimicrobial costs in the intervention group versus a €1.69 reduction in the control group (p value not reported).¹⁰ A third trial reported a difference in antimicrobial cost of €2,657 per 1,000

patient days between intervention and control groups (IRR=0.87 [0.87, 0.88]).⁵ Another trial reported a small but not significant reduction in median drug costs in the intervention group (€100 vs. €118.5).³

Among the interrupted time series studies, Magedanz reported that mean monthly hospital antimicrobial costs in their hospital dropped from \$30,728 to \$9,624 from stage 1 to 3 of their intervention.⁵⁹ Another study reported a \$95,000 per year decrease in antimicrobial costs.⁶ A third study reported a savings of \$198,575 due to decreased consumption of audited antimicrobials.⁸ The authors noted that savings to patients were \$91,194. Another study reported in the Discussion section that aggregate costs to patients and/or insurers averaged \$3,758 less per month, but details of the analysis were lacking.⁶⁰

One study reported program costs. The estimated cost of the intervention was €2,147 over 24 weeks (including review of antimicrobial prescriptions and ward visits by the infectious disease physician).¹

One study that was intended to decrease unnecessary or excessive prescribing reported that switching from IV to oral therapy, where appropriate, resulted in a cost savings of \$179,285 during the first year of the program. The total reduction in antimicrobial cost during the first year of the program was \$1,284,357.⁷ The authors also reported a significant reduction in total antimicrobial costs per 1,000 patient days over the duration of the stewardship program (from \$44,181 to \$23,933, $p=0.04$), which translated to a savings of \$2,949,705 during the first 3 years of the program.

Formulary Restriction and Preauthorization (k=5)

Key Findings

- **Patient Outcomes:** Formulary restriction and preauthorization interventions were associated with no change in mortality or length of stay. In one study, CDI incidence was reduced post-intervention.
- **Prescribing Outcomes:** Four studies reported decreased use post-intervention. Dose and duration of antimicrobial treatment were lower in the intervention group in one study.
- **Microbial Outcomes:** One study of ciprofloxacin restriction reported decreases in the percentage and rate of carbapenem- and ciprofloxacin-resistant *P. aeruginosa* isolates.
- **Cost Outcomes:** One study reported cost outcomes with lower drug costs in the intervention group.

Characteristics of Studies

We identified five studies assessing formulary restriction or restricted authorization to prescribe antimicrobials.^{11-14,61} One was an RCT¹¹ and the remainder were ITS studies. Three studies focused on altering antimicrobial timing, drug selection, tailoring, or route of delivery^{13,14,61} while two were aimed at reducing unnecessary or excessive prescribing.^{11,12} The risk of bias was high for the RCT¹¹ and two of the ITS studies,^{14,61} medium for one of the ITS studies,¹² and low for the remaining ITS study.¹³ Two of the studies were conducted in North America,^{13,61} two in Europe or the United Kingdom,^{12,14} and one in the Pacific region.¹¹ One study was conducted in the ICU of a university-affiliated hospital and enrolled patients with bloodstream infections.¹²

Three studies enrolled patients with any infection from either all wards (including ICU wards)^{14,61} or medical/surgical wards.¹¹ Two studies were conducted at university-affiliated or teaching hospitals^{11,61} and one at a community hospital.¹⁴ One study analyzed data from administrative healthcare databases covering individuals age 65 and older who were hospitalized.¹³ Of the studies done in hospital settings, one involved an antimicrobial stewardship team,¹⁴ two involved physicians and pharmacists,^{11,61} and one involved physicians only.¹² The interventions typically involved multiple stewardship components. Three studies incorporated elements of case review with feedback^{11,14,61} and two reported increased availability of either infectious disease physician consultation or pharmacy services.^{12,14}

Two studies reported patient characteristics. Mean ages ranged from 57 to 63 years^{11,12} and 53% were male.¹¹

Reported outcomes are depicted in Table 6. Detailed findings are presented in Appendix D, Tables 9 to 16.

Table 6. Formulary Restriction and Preauthorization Interventions: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Aldeyab 2012 ¹⁴	X	X			
Lewis 2012 ⁶¹		X	X		
Peto 2008 ¹²	X	X			
Mamdani 2007 ¹³	X	X			
Rattanaumpawan 2010 ¹¹	X	X		X	

Patient Outcomes

Four of the studies reported patient outcomes.¹¹⁻¹⁴ The formulary restriction ITS study reported no significant difference in mortality rates following implementation of a fluoroquinolone restriction policy (values not reported, $p=0.62$).¹³ The restricted authorization ITS study found no significant differences in ICU mortality (64.3 deaths per 1000 patients after implementation versus 66.2 deaths per 1000 patients before implementation) or mean length of stay (2.4 days after implementation versus 2.6 days before implementation).¹² The single-site RCT found no significant difference between the authorization and no-authorization groups in the number of deaths occurring during hospitalization (44% vs. 43%, $p=0.58$), mean length of hospital stay (30.4 vs. 30.7 days, $p=0.80$), or death due to infection (29% vs. 35%, $p=0.05$).¹¹ In addition, there were no significant differences in the incidence of adverse events, including antimicrobial allergy (2% vs. 7%, $p=0.10$) and antimicrobial-associated diarrhea (25% vs. 18%, $p=0.21$).¹¹ The ITS study of an intervention to reduce high-risk antimicrobial use reported a significant trend for reduced CDI post-intervention.¹⁴

Strength of evidence for the patient outcomes is presented in Table 7.

Table 7. Strength of Evidence for Formulary Restriction and Preauthorization Interventions, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Rattanaumpawan 2010 ¹¹	RCT	Preauthorization	High	Mortality	NS, RR 1.04 [0.90, 1.20]	Low for Mortality
Peto 2008 ¹²	ITS	Preauthorization	Medium	Mortality	NS, 64.3/1000 pts (after) vs. 66.2/1000 pts (before) (p=0.44)	
Mamdani 2007 ¹³	ITS	Formulary restriction	Low	Mortality	NS (p=0.62)	
Rattanaumpawan 2010 ¹¹	RCT	Preauthorization	High	Length of stay	NS (p=0.80)	Low for Length of Stay
Peto 2008 ¹²	ITS	Preauthorization	Medium	Length of stay	NS, 2.4 days (after) vs. 2.6 days (before) (p=0.44)	
Aldeyab 2012 ¹⁴	ITS	Restriction	High	Incidence of CDI	Reduced trend (p=0.008) NS change in level	Low for Incidence of CDI

RCT = randomized controlled trial; ITS = interrupted time series; NS = not statistically significant; RR = rate ratio [95% confidence interval]

Prescribing Outcomes

Antimicrobial Use

Four studies reported antimicrobial use with each study finding decreased use following the intervention.^{12-14,61} The ITS analysis of bloodstream infections reported that estimated mean antimicrobial consumption decreased from 162.9 DDD per 100 patient-days to 101.3 DDD per 100 patient-days. Prior to the intervention, the prescription rate had been rising (slope=1.31). After the intervention, not only did the level decrease (an estimated drop of 84.6 DDD per 100 patient-days) but the post-intervention slope was -0.18 (an estimated mean change in the slope of -1.5 (95% CI -0.16 to -2.83) DDD per 100 patient-days). The decrease was associated with a significant reduction in the use of fluoroquinolones, aminoglycosides, metronidazole, and carbapenems.¹²

One ITS study reported decreased level of use of high-risk antimicrobials as well as total antimicrobials with a restrictive intervention supplemented time guidelines and weekly audit and feedback.¹⁴ Another restrictive study (also supplemented with audit and feedback) found decreased trend in use of ciprofloxacin).⁶¹

The large Canadian, population-based ITS analysis found a significant decrease in overall fluoroquinolone prescription rates following implementation of a fluoroquinolone restriction policy, with an immediate drop to approximately 70 percent of the expected rate ($p<0.01$).¹³ Within one year of implementation, the fluoroquinolone prescription rate began to rise again but the changes were not statistically significant. Specifically, ciprofloxacin use decreased to approximately 40% of the expected use rate in the months following implementation and remained significantly lower than expected during the one-year follow-up period. The actual use rate was 17.1 prescriptions per 1000 elderly persons per quarter compared with a predicted 43.6 prescriptions per 1000 elderly persons per quarter ($p<0.01$). Increased norfloxacin use was observed after implementation of the restriction policy ($p<0.01$). No significant changes in use were observed for cephalosporins, macrolides, penicillins, or tetracyclines. Use of sulfonamides and urinary anti-infectives (mainly nitrofurantoin and trimethoprim) was significantly higher within one year of the implementation of the restriction policy (all $p\leq 0.01$). Authors did not report for what conditions fluoroquinolones were prescribed prior to the intervention. The restriction policy did restrict ciprofloxacin and ofloxacin to “limited use” for urinary tract infection. Hospitalization for urinary tract infections increased in the year after policy implementation (approximately 8% higher than predicted; $p<0.01$) while overall, infection-related hospitalizations were unchanged.

Dose

The RCT from Thailand reported that antimicrobial authorization significantly reduced doses of the targeted antimicrobials (piperacillin/tazobactam, imipenem, and meropenem) when compared with the no-authorization group (p values not reported).¹¹ The DDDs of all antimicrobials and targeted antimicrobials per episode were 21.0 and 5.8, respectively, in the authorization group compared with 26.2 and 7.2 in the no-authorization group. The investigators noted that 22% of prescriptions in the authorization group were changed to other antimicrobials (not recommended by the infectious diseases physicians).

Duration

The RCT from Thailand reported that treatment durations with all antimicrobials and treatment targeted antimicrobials were significantly shorter in the intervention group.¹¹

Microbial Outcomes

Lewis reported significant decreases in the percentage and rate of carbapenem- and ciprofloxacin-resistant *P. aeruginosa* isolates following an intervention to restrict ciprofloxacin.⁶¹ Although carbapenem use increased, no changes were observed in the susceptibilities of nosocomial Enterobacteriaceae or *A. baumannii* to carbapenems.

Costs

Rattanaumpawan estimated that the annual antimicrobial cost savings from drug use evaluation and authorization for all prescriptions of the targeted antimicrobials would be \$862,704.¹¹

Guidelines Implemented with Feedback (k=4)

Key Findings

- **Patient Outcomes:** Mortality and length of stay were unchanged following implementation of guidelines for management of respiratory illnesses (2 studies) or to reduce broad-spectrum antimicrobial prescribing (1 study). Incidence of CDI was significantly reduced following the intervention (2 studies).
- **Prescribing Outcomes:** Implementation of guidelines with feedback was found to significantly decrease use, improve appropriate/compliant prescribing, improve selection, and improve timing. Duration of antimicrobial use was unchanged.
- **Microbial Outcomes:** No studies reported microbial outcomes.
- **Cost Outcomes:** No studies reported cost outcomes.

Characteristics of Studies

Four studies implemented guidelines and provided feedback for guideline users. All reported interventions to alter antimicrobial timing, drug selection, tailoring, or route of delivery. Studies included an RCT evaluating a guideline for treatment of adults with CAP,¹⁵ a cluster RCT evaluating a guideline on antimicrobial use for patients with lower respiratory tract infection,¹⁶ and two ITS studies of guidelines to encourage narrow spectrum antimicrobial use for any infection site.^{17,18} All studies were done in Europe^{15,16} or the UK.^{17,18} Two studies were rated as high risk of bias^{15,16} and two were rated as medium risk.^{17,18} The two studies of patients with respiratory infections were conducted at multiple hospital sites.^{15,16} In one study, the intervention involved a “local organizing committee” consisting of physicians, pharmacists, microbiologists, pulmonologists, and quality improvement officers.¹⁶ The second study did not provide detail on the intervention staff.¹⁵ The two studies of interventions to reduce the risks from broad spectrum antimicrobials were each conducted in one hospital.^{17,18} One reported involvement of a “team” (microbiologist and pharmacist)¹⁸ while the other did not provide information about intervention staffing.¹⁸ Three studies incorporated provider education in the intervention^{15,16,18} and one included ward rounds by the antimicrobial stewardship team.¹⁸

One study enrolled patients who were 80 years and older.¹⁷ Two studies reported patient characteristics with mean ages ranging from 56 to 70 years and between 46% and 53% male.^{15,16}

Reported outcomes are depicted in Table 8. Detailed findings are presented in Appendix D, Tables 17 to 22.

Table 8. Guidelines with Feedback Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Talpaert 2011 ¹⁸	X	X			
Schnoor 2010 ¹⁵	X	X			
Schouten 2007 ¹⁶	X	X			
Fowler 2007 ¹⁷	X	X			

Patient Outcomes

In the RCT of an intervention to improve quality of care for patients with CAP, no significant differences were observed in length of hospital stay or all-cause and CAP-related mortality between intervention and control sites but results were not reported by initial treatment location (inpatient or outpatient) and p values were not reported for post-intervention differences.¹⁵ Overall, post-intervention length of stay was approximately 10 days in the intervention group and 11 days in the control group; thirty-day overall mortality was 3.6% in the intervention group and 3.8% in the control group; and CAP-related mortality was 2.9% in the intervention group and 0.5% in the control group. None of the differences was significant.

In the cluster RCT of an intervention to improve quality of antimicrobial use for lower respiratory tract infections, post-intervention hospital mortality did not differ whether the patients were treated in intervention or control hospitals for either CAP (7.2% intervention vs. 8.7% control, $p=0.58$) or acute exacerbation of chronic bronchitis/chronic obstructive pulmonary disease (AECB/COPD) (4.3% intervention vs. 2.6% control, $p=0.35$). Hospital length of stay also did not differ (CAP: 8.0 days intervention vs. 10.0 days control, $p=0.47$; AECB/COPD: 11.5 days intervention vs. 11.4 days control, $p=0.89$).¹⁶

In an ITS study evaluating a guideline emphasizing narrow-spectrum antimicrobials, there was a significant decrease in monthly counts of CDI (IRR=0.35 [0.17, 0.73], $p=0.0009$) following the intervention but not in new cases of MRSA (IRR=0.79 [0.49, 1.28], $p=0.32$).¹⁷ MRSA count data were collected as a control outcome since levels were not expected to change as a result of the intervention. Mortality and length of stay were reported to “fluctuate randomly” (range 4.7% to 21.0%). Pre- and post-intervention means were reported to be unchanged although it is unclear whether ITS analysis methods were used.

In the second ITS study, the only reported clinical outcome was CDI. Following introduction of a guideline to reduce use of broad-spectrum antimicrobials, there was a decreased incidence of CDI (IRR=0.34 [0.20, 0.58]).¹⁸

Strength of evidence for these outcomes is presented in Table 9.

Table 9. Strength of Evidence for Guidelines with Feedback Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Schnoor 2010 ¹⁵	RCT	Improve adherence to pneumonia guidelines	High	Mortality	NS, RR 0.97 [0.43, 2.17]	Low for Mortality
Schouten 2007 ¹⁶	RCT	Appropriate use	High	Mortality	CAP: NS, RR 0.87 [0.45, 1.66] COPD: NS, RR 1.76 [0.61, 5.08]	
Fowler 2007 ¹⁷	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Mortality	Rates reported only	
Schnoor 2010 ¹⁵	RCT	Improve adherence to pneumonia guidelines	High	Length of stay	NS	Low for Length of Stay
Schouten 2007 ¹⁶	RCT	Appropriate use	High	Length of stay	NS, p=0.89	
Fowler 2007 ¹⁷	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Length of stay	Significance not reported	
Talpaert 2011 ¹⁸	ITS	Reduce broad-spectrum antimicrobial use	Medium	Incidence of CDI	Decreased, IRR 0.34 [0.20, 0.58]	Low for Incidence of CDI
Fowler 2007 ¹⁷	ITS	Reinforce narrow-spectrum antimicrobial policy	Medium	Incidence of CDI	Decreased, IRR 0.35 [0.17, 0.73]	

RCT = randomized controlled trial; ITS = interrupted time series; NS = not statistically significant; RR = rate ratio [95% confidence interval]; CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; CDI = *C. difficile* infection; IRR = incidence rate ratio

Prescribing Outcomes

Antimicrobial Use

The RCT reported adherence to guidelines for management of inpatients with CAP. Adherence to recommendations for initial treatment increased at the intervention sites (5.6%) and decreased at the control sites (-5.5%). Post-intervention, the difference between sites was significant (66% intervention vs. 53% control, $p=0.016$). The adjusted odds of patients receiving appropriate antimicrobial treatment in the intervention group was 1.8 [95% CI 1.1, 2.8].¹⁵

In the cluster RCT, guideline concordance for treatment of CAP, AECB, or COPD improved in intervention hospitals more than in control hospitals (OR=2.63 [1.57, 4.42], $p=0.0003$).¹⁶ For patients with either CAP, AECB, or COPD, there was no difference in the change in switching from IV to oral therapy in accordance with existing criteria from before to after in the intervention or control sites (OR=1.20 [0.02, 76.51], $p=0.931$).

In the ITS, for the antimicrobials targeted for decreased use (cephalosporins and amoxicillin/clavulanate), significant reductions in use were observed as indicated by significant changes in level ($p=0.015$ for sudden change in level) and trend ($p=0.03$ for long term linear trend).¹⁷ Results were less consistent for narrow-spectrum antimicrobials targeted for increased use. There was a significant change in the level of amoxicillin use post-intervention ($p=0.001$ for sudden change in level) and a significant change in trend for benzyl penicillin ($p=0.012$ for long term linear trend). No significant differences in level or trend were observed for trimethoprim or other (untargeted) antimicrobials.

Timing

In the cluster RCT, patients with CAP were significantly more likely to receive timely antimicrobials in intervention sites than at control sites antimicrobial (OR=3.59 [1.02, 12.6], $p=0.046$).¹⁶

Selection

In the cluster RCT, among patients with CAP, AECB, or COPD, no significant difference was observed in “streamlining” (i.e., changing from broad-spectrum therapy to pathogen-directed therapy) (OR=1.94 [0.34, 11.03], $p=0.456$) although few patients were eligible.¹⁶

Duration

The RCT reported adherence to recommendations for duration of treatment of CAP for inpatients increased at the intervention sites (from 47% to 52%) and decreased at the control sites (from 57% to 54%) but the difference between sites post-intervention was not significant.¹⁵

In the cluster RCT, for patients with either AECB or COPD, there was no difference in the change in patients receiving optimal duration of antimicrobial therapy (5 to 7 days) (OR=2.22 [0.96, 5.12], $p=0.62$). The odds ratio was adjusted for clustering of patients relative to providers and hospitals.¹⁶

Microbial Outcomes

No studies reported microbial outcomes.

Costs

No studies reported cost outcomes.

Guidelines Implemented without Feedback (k=4)

Key Findings

- **Patient Outcomes:** Three studies of guideline implementation without feedback yielded inconsistent results for mortality and length of stay. One study in a neurosurgical ICU reported higher ICU mortality in the intervention group while two non-ICU studies reported either no difference or reduced mortality in the intervention group. One study in community and rehabilitation hospitals reported longer length of stay for patients in the intervention group while the ICU study reported no difference and a non-ICU study reported shorter length of stay post-intervention.
- **Prescribing Outcomes:** Improvements in use and/or appropriate use and compliance were noted in three of the four studies with no difference in the fourth study. Treatment duration was shorter in one study and unchanged in a second study. One study reported on timing with significantly fewer patients receiving antimicrobials within 8 hours in the intervention group.
- **Microbial Outcomes:** One study reported a decrease in the MRSA resistance proportion post-intervention.
- **Cost Outcomes:** Two studies reported significantly lower drug costs following the intervention.

Characteristics of Studies

Four studies reported on development and implementation of guidelines. Two focused on interventions to alter antimicrobial timing, drug selection, tailoring, or route of delivery^{21,62} and two were interventions to decrease unnecessary or excessive prescribing.^{19,20} Two studies were considered high risk of bias^{19,21} and two medium risk of bias.^{20,62} Two studies were conducted in the United States^{19,62} and two in Europe.^{20,21}

All but one of the studies¹⁹ was conducted in a university-affiliated hospital. Two enrolled patients in the ICU;^{20,62} the other two studies were either unclear or did not report the site of the intervention. An antimicrobial team was involved in both of the ICU studies.^{20,62} In one study, a physician and pharmacist were involved¹⁹ while the fourth study did not specify. Three studies reported patient characteristics with mean age of participants ranging from 58 to 71 years and between 43% and 65% male.^{19,20,62}

Table 10 shows outcomes reported in studies of guidelines without feedback. Detailed results are presented in Appendix D, Tables 23 to 30.

Table 10. Guidelines without Feedback Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Mangino 2011 ⁶²		X			
Meyer 2007 ²⁰	X	X	X	X	
Capelastegui 2004 ²¹	X	X			
Goldwater 2001 ¹⁹	X	X		X	

Patient Outcomes

The CBA study of guidelines for conversion from IV to oral therapy reported patient outcomes. Post-intervention adjusted mortality was significantly higher in the control cohort (OR=1.8 [1.1, 2.9]) than in the intervention cohort. The analysis was adjusted for pneumonia severity, multilobar involvement, COPD, and antimicrobial administration before hospital admission.²¹ Readmission did not differ between groups. The post-intervention adjusted length of stay in the intervention cohort (4.7 days) was significantly shorter than in control cohort (7.6 days) ($p<0.001$).²¹

The ITS aimed at reducing duration of treatment reported an *increased* number of deaths in the ICU after the intervention (6.9% vs. 4.1%, $p<0.001$).²⁰ Length of stay did not differ (mean of 3.1 days both before and after the intervention). It was noted that these findings are based on a before-after analysis rather than an ITS analysis. There was some evidence (notably increased use of ventilators, central venous catheters, and urinary catheters) to suggest that the severity of disease increased from the pre-intervention to the post-intervention period.

The study comparing guidelines for therapeutic interchange with standard education found no significant difference in mortality (3.4% therapeutic interchange vs. 3.2% educational tools; p value not reported) or total adverse events (0.7% therapeutic interchange, 1.6% standard educational tools).¹⁹ However, length of hospital stay was significantly *longer* in the therapeutic interchange hospitals (12.1 days vs. 10.5 days, p value not reported) which the authors suggested may be due to the long-term rehabilitation beds at one of the therapeutic interchange hospitals. Total adverse events did not differ between hospital groups.

Table 11 presents strength of evidence for these outcomes.

Table 11. Strength of Evidence for Guidelines without Feedback Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Goldwater 2001 ¹⁹	CCT	Reducing costs without sacrificing patient care	High	Mortality	NS, RR 1.07 [0.63, 1.82]	Low for Mortality
Meyer 2007 ²⁰	ITS	Reduce duration	Medium	Mortality	Increased, p<0.05	
Capelastegui 2004 ²¹	CBA	Appropriateness, timing, duration	High	Mortality	Reduced, OR 1.8 [1.1, 2.9]*	
Goldwater 2001 ¹⁹	CCT	Reducing costs without sacrificing patient care	High	Length of stay	Increased, p<0.05	Low for Length of Stay
Meyer 2007 ²⁰	ITS	Reduce duration	Medium	Length of stay	NS	
Capelastegui 2004 ²¹	CBA	Appropriateness, timing, duration	High	Length of stay	Reduced, p<0.001	
Capelastegui 2004 ²¹	CBA	Appropriateness, timing, duration	High	Readmission	NS, OR=0.8 [0.3, 2.0]**	Low for Readmission

CCT = controlled clinical trial; ITS = interrupted time series; CBA = controlled before and after study; NS = not statistically significant; RR = rate ratio [95% confidence interval; OR = odds ratio

*In this study, the post-intervention cohort was the reference group; ORs are for the control hospital cohort versus the intervention hospital cohort

Prescribing Outcomes

Use

In the ITS study of management of patients with HAP, VAP, and HCAP, from pre-implementation to post-implementation of locally-customized treatment guidelines, there were no differences in compliance with de-escalation of therapy after 3 days of therapy where clinically appropriate (56/173 [32%] vs. 36/96 [38%], $p=0.40$). Use of empiric antimicrobials was more likely to be compliant with ATS/IDSA guidelines during the post-implementation period (79/257 [31%] vs. 66/151 [44%], $p=0.01$), an effect that was sustained over 3 quarterly intervals ($p=0.0008$).⁶²

In the CBA study of conversion from IV to oral therapy, there was no significant difference in receipt of appropriate antimicrobial therapy between the post-intervention group and the post-intervention control group (OR=1.1 [0.7, 1.7]). There was a significant improvement from pre- to post-intervention at the intervention site.²¹

An ITS study of a guideline focused on reducing duration of antimicrobial therapy for ICU patients with pneumonia reported a significant decrease in total antimicrobial use. The DDD/1000 pd decreased from 949.8 to 626.7, a change of 323.1 DDD/1000 pd (95% CI -444.5, -201.6).²⁰ Significant decreases in use were observed for second-generation cephalosporins, imidazoles, penicillins with B-lactamase inhibitor, and glycopeptides.

In the CCT comparing therapeutic interchange to standard educational tools for the purpose of switching from ciprofloxacin to levofloxacin, use of levofloxacin was higher in the therapeutic interchange hospitals with 97% of patients receiving levofloxacin compared with 48% in the standard educational tools hospitals ($p<0.001$).¹⁹

Duration

The CBA study of guidelines for conversion from IV to oral therapy reported a significant reduction in duration of IV therapy with an adjusted mean of 2.6 days in the post-intervention cohort, 3.9 days in the pre-intervention cohort ($p<0.001$), 5.2 days in the pre-intervention control cohort, and 5.3 days in the post-intervention control cohort. Similar differences were observed for overall duration of antimicrobial therapy.²¹

In a study of therapeutic interchange versus standard educational tools to encourage a change in prescribing pattern, the duration of fluoroquinolone use did not differ significantly between the hospital sites.¹⁹

Timing

In the controlled before and after study of guidelines for conversion from IV to oral therapy in patients with CAP, patients in the intervention cohort were significantly less likely than those in the pre- or post-intervention control cohorts to receive antimicrobials within 8 hours after presentation. There was a significant improvement from pre- to post-intervention at the intervention site.²¹

Microbial Outcomes

The ITS study of the effects of a guideline on reducing duration of therapy reported a significant decrease in the antimicrobial resistance proportion of MRSA from the ICU following the intervention (8.4% to 2.9%, $p < 0.05$).²⁰ Changes for other pathogens were not significant.

Costs

Goldwater reported cost outcomes in the study comparing therapeutic interchange with standard educational tools.¹⁹ Mean drug costs per patient were significantly lower in the therapeutic interchange hospitals (\$79.80 vs. \$114.50, $p < 0.001$). The cost savings associated with replacement of ciprofloxacin with levofloxacin were \$60.10 per patient in the therapeutic interchange hospitals and \$37.30 per patient in the educational tools hospitals.

Implementation of a guideline aimed at reducing duration of antimicrobial therapy in ICU patients with pneumonia significantly reduced total antimicrobial costs per 1000 patient days.²⁰ The change in level was -5.86 €/pd (95% CI -8.66, -3.05).

Computerized Decision Support ($k=4$)

Key Findings

- **Patient Outcomes:** Three studies of computerized systems to identify cases for possible intervention or link susceptibility test results to pharmacy orders found no significant effect on mortality. One study of a system linking laboratory results and pharmacy orders found a shorter length of stay in the intervention group but two studies of systems for case identification found no differences. Readmission rates were unchanged following implementation of a system to identify cases for intervention. Incidence of CDI was decreased in one study of a computerized case identification system but unchanged in a second study.
- **Prescribing Outcomes:** Two studies of systems to identify cases for possible intervention reported decreased use of broad-spectrum antimicrobials with no change in recommended antimicrobials.
- **Microbial Outcomes:** A computerized decision support system aimed at reducing broad-spectrum antimicrobial use improved susceptibility of ICU Gram-negative isolates.
- **Cost Outcomes:** Computerized systems to identify cases were found to reduce costs although only one of three studies reported a significant change.

Characteristics of Studies

Four studies implemented computerized support systems.^{22-24,63} All of the interventions were designed to alter antimicrobial timing, drug selection, tailoring, or route of delivery. Three studies were of high risk of bias²²⁻²⁴ and one of medium risk of bias.⁶ The studies were conducted in university-affiliated hospitals in the United States,^{22,23} a community teaching hospital in the United States,²⁴ or the ICU of a teaching hospital in Australia⁶³ and generally enrolled all inpatients. Two of the four studies reported multifaceted interventions including education, guidelines, and microbiologist consults.^{23,24}

In one RCT, the goal was to optimize patient therapy and minimize inappropriate or inadequate use.²² All patients received the control (standard care) protocol in which the pharmacist manually

created a list of patients receiving one of 23 restricted antimicrobials over the past 24 to 48 hours. The antimicrobial team reviewed the charts of those patients and recommended changes to therapy, if necessary. In the intervention group, a Web-based clinical decision support system generated alerts based on a patient's antimicrobial use and laboratory results. The antimicrobial team would access the alerts, review the patient's information (laboratory results, medications, and admission, discharge, and transfer data), and enter recommendations for change, if needed. Alerts were generated for control patients but the antimicrobial team was blinded from receiving them. Patients and treating physicians were not aware of which group the patient was randomized to. Data were reported for 4,507 patients (2,237 intervention, 2,270 control). Mean age was 50 years and 53% were female. Alerts were generated for 570 (26%) of the intervention arm patients; the team intervened on 359 (16%) patients. The team intervened on 180 (8%) of the patients in the control arm.

A CCT was designed to study the effect of a computerized system for linking microbiological data to pharmacies and alerting pharmacists to potential interventions to prevent inappropriate antimicrobial therapy.²³ The trial was discontinued early due to the observed benefits of the computerized system. In the control group, a pharmacist manually retrieved results of all antimicrobial susceptibility testing (AST) from the microbiology department, reviewed a patient's antimicrobial regimen and test results, and intervened, if necessary, by either written or verbal communication with the treating physician. In the study group, a computer program linked test results and pharmacy information and alerted pharmacists to potential treatment changes. In this group, pharmacists also received education about microbiologic topics and it is not possible to determine whether outcomes were due to the computerized support or the education session.

An ITS study was designed to assess the clinical and economic effects of reports generated by "data-mining software."²⁴ The study included patients with either pneumonia or intraabdominal sepsis. The reports included patient demographics, laboratory values, medications, and selected medical history gathered from the electronic medical record. The reports also provided recommendations for choice of antimicrobial therapy and de-escalation of therapy. Reports were reviewed by an antimicrobial stewardship pharmacist. If a patient was considered to be receiving inappropriate treatment, the case was reviewed with an infectious disease physician and written recommendations were provided. It was noted that the hospital already had in place a provider education program, antimicrobial prescribing pathways, a protocol for conversion from IV to oral therapy, dose adjustment based on renal function, and pre-authorization for use of formulary-restricted antimicrobials. During the 6 year study period (3 years before and 3 years after implementation), over 2400 charts were reviewed (over 2100 from patient with pneumonia). The mean age of the patients was 62 years.

A similar intervention was evaluated in a second ITS analysis.⁶³ The focus of the study was on changes in resistance patterns of common Gram-negative organisms after a computerized decision support system for antimicrobial prescribing was implemented. The computer program was developed specifically for the ICU setting and provided prescribing recommendations based on local antimicrobial susceptibility profiles of bacteria and patient-specific information (clinical information and allergies). The overall goal of the intervention was to reduce use of broad-spectrum antimicrobials. No patient demographic data were reported.

The outcomes reported in studies of computerized decision support are presented in Table 12. Results are reported in Appendix D, Tables 31 to 38.

Table 12. Computerized Decision Support Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Nowak 2012 ²⁴	X	X		X	
Yong 2010 ⁶³	X	X	X		
McGregor 2006 ²²	X			X	
Barenfanger 2001 ²³	X			X	

Patient Outcomes

The RCT comparing computerized alerts to standard care review of antimicrobial treatment reported no significant difference in in-hospital mortality (3.3% intervention arm vs. 3.0% control arm, $p=0.55$) or length of stay (3.8 days intervention arm vs. 4.0 days control arm, $p=0.38$). Findings were similar when the analysis included only patients who received system alerts. There was no significant difference in the percentage of patients experiencing diarrhea as a side effect (*C. difficile* testing; 5.7% intervention arm vs. 6.6% control arm, $p=0.21$).²²

In the CCT, in the analysis of the total study sample, mortality did not differ significantly (11% in the study group vs. 10% in the control group, $p=0.74$) but length of stay was significantly shorter in the study group (11 days vs. 14 days, $p=0.035$).²³

An ITS study reported non-significant differences in mortality, length of stay, and 30-day readmission for both patient groups (intra-abdominal sepsis, pneumonia) pre- to post-intervention.²⁴ These findings were based on an analysis of mean data (i.e., time series methods were not used). Incidence of CDI was analyzed with time series methods and significant differences in quarterly changes in rate of CDI were observed from pre- to post-intervention.

The other ITS study reported length of stay over the 7 year study period.⁶³ Average length of ICU stay was 4.2 days with yearly values decreasing from 4.4 days during the first year of the study to 4.0 days during the final year of the study. No statistical analysis was performed on length of stay.

Strength of evidence for these outcomes is presented in Table 13.

Table 13. Strength of Evidence for Computerized Decision Support Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
McGregor 2006 ²²	RCT	Appropriateness	High	Mortality	NS, RR 1.11 [0.80, 1.53]	Low for Mortality
Barenfanger 2001 ²³	CCT	Lower mortality, cost, and duration	High	Mortality	NS, RR 1.12 [0.62, 2.01]	
Nowak 2012 ²⁴	ITS	Appropriateness, cost	High	Mortality	NS Sepsis: RR 0.50 [0.18, 1.38] Pneumonia: RR 0.96 [0.63, 1.47]	
McGregor 2006 ²²	RCT	Appropriateness	High	Length of stay	NS, 3.8 days intervention, 4.0 days control (medians)	Low for Length of Stay
Barenfanger 2001 ²³	CCT	Lower mortality, cost, and duration	High	Length of stay	Reduced, p=0.035	
Nowak 2012 ²⁴	ITS	Appropriateness, cost	High	Length of stay	NS Sepsis: 7.2 (pre), 7.4 (post) Pneumonia: 5.9 (pre), 5.5 (post)	
Nowak 2012 ²⁴	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 ²⁴	ITS	Appropriateness, cost	High	Incidence of CDI	Decreased, p=0.018	Low for Incidence of CDI
McGregor 2006 ²²	RCT	Appropriateness	High	Incidence of CDI	NS, p=0.49	

RCT = randomized controlled trial; CCT = controlled clinical trial; ITS = interrupted time series; NS = not statistically significant; RR = rate ratio [95% confidence interval]

Prescribing Outcomes

Two ITS analyses reported antimicrobial consumption.^{24,63} In one study, decreased use of quinolones, vancomycin, carbapenems, and piperacillin-tazobactam followed the intervention with little change in use of first line antimicrobials.²⁴ In the second study, use of 3rd and 4th generation cephalosporins, carbapenems, extended-spectrum penicillins, aminoglycosides, and fluoroquinolones (measured as DDD/1000 bed days) did not differ over the study period.⁶³

Microbial Outcomes

Changes in antimicrobial resistance patterns of common Gram-negative organisms were evaluated in one ITS study.⁶³ Analyses were based on clinical microbiology isolates from all ICU patients admitted during the study period. An intervention to reduce broad-spectrum antimicrobial use was associated with reductions in the rates of resistance to key antimicrobials in several Gram-negative bacteria, notably *Pseudomonas* and inducible Enterobacteriaceae groups. For *Pseudomonas aeruginosa*, gentamicin susceptibility decreased prior to the intervention but then increased post-intervention with a significant difference between the pre- and post- intervention phases (change from pre-intervention trend reported as mean percent change per year: 11.6 [1.8, 21.5], p=0.02). A similar pattern was observed for imipenem with a significant difference between pre- and post-intervention (mean percent change per year: 18.3 [4.9, 31.6], p=0.009). Non-significant differences were observed for ceftazidime and ciprofloxacin susceptibility. Enterobacteriaceae with potentially inducible beta-lactamases were grouped. Significant increases in gentamicin (mean percent change 6.5 [2.7, 10.2], p=0.002) and ciprofloxacin (mean percent change 3.5 [1.3, 5.7], p=0.003) susceptibility were observed with no change in imipenem susceptibility. For *E. coli*, *Klebsiella*, and *Acinetobacter* no changes in susceptibility from pre- to post-intervention were noted. There was no adjustment for the large number of comparisons.

Costs

In the RCT by McGregor, total antimicrobial costs during the 3 month study period were \$285,812 for patients in the intervention arm versus \$370,006 for patients in the control arm (23% savings). Average saving per patient was \$37.64.²²

The CCT reported average total cost, average variable cost (i.e., costs associated directly with patient care), and pharmacy costs.²³ In the analysis that included the total study sample, average total costs and average variable costs were significantly lower in the study group (both p=0.008). Pharmacy costs did not differ significantly (p=0.104).

An ITS study reported that the slope of antimicrobial dollars per patient day (ADPD) differed significantly from pre- to post-intervention (p=0.009). The authors estimated that if costs would continue to increase at the pre-intervention pace, more than \$1.7 million dollars was saved over the 4 years of the intervention.²⁴

Protocols (k=4)

Key Findings

- **Patient Outcomes:** In clinically stable adults with CAP, protocols for switching from IV to oral antimicrobials did not have an effect on mortality; hospital length of stay was significantly shorter in the early switch groups. Systematic reassessment at 72 hours was associated with reduced mortality and no change in length of stay.

- **Prescribing Outcomes:** Protocols for switching patients with CAP from IV to oral therapy reduced the duration of IV therapy. Systematic reassessment was not associated with improved appropriateness of prescribing.
- **Microbial Outcomes:** Susceptibility of *P. aeruginosa* to imipenem increased following introduction of ertapenem.
- **Cost Outcomes:** No studies reported cost outcomes.

Characteristics of Studies

Four studies described the implementation of protocols.^{25-27,64} All were intended to alter antimicrobial timing, drug selection, tailoring, and route of delivery. Risk of bias was medium for all four studies. Three studies were conducted in Europe²⁵⁻²⁷ and one in the United States.⁶⁴ Two studies reported the inclusion of additional stewardship components with order form and weekly audit and feedback in one study²⁷ and guidelines in the other.²⁶

Two RCTs were designed to compare protocols for early switch from IV to oral antimicrobials to usual care.^{25,26} Neither study provided details about how the criteria for switching therapies were developed or who was responsible for administering the protocol. In one study, the protocol also included early mobilization and use of predefined criteria for hospital discharge.²⁵ Usual care was defined as treatment according to the practices of individual attending physicians. In the other study, usual care was seven days of IV treatment.²⁶ Both studies enrolled patients with CAP but one study was limited to patients with severe CAP.²⁶ In that study, more than 80% of patients were in pneumonia severity class IV or V. In the other study, more than 60% were in class IV or V. Both studies were conducted at more than one hospital. Patient characteristics were similar (mean ages 69 and 71 years, 65% and 66% male).

Another study, an ITS analysis,²⁷ looked at the effect of systematic reassessment of the antimicrobial prescription after approximately 3 days of treatment on the quality (i.e., appropriateness) of antimicrobial prescriptions. The study was conducted in the medical ICU of an urban university teaching hospital. Sixty two patients were studied during a 3 month period before the intervention and 52 were studied during a 4 month period after the intervention. The mean age was 62 years and 62% were male. The majority of infections were in the lungs (64%). Baseline characteristics were similar for the two study periods.²⁷

The fourth study, also an ITS study, involved a policy for autosubstitution of ertapenem for ampicillin-sulbactam.⁶⁴ The study was conducted in a community teaching hospital; no details were provided regarding the administration of the policy. No patient characteristics were reported. The focus was on the susceptibility of antimicrobial agents against *Pseudomonas aeruginosa*.

Outcomes reported are presented in Table 14 with detailed results reported in Appendix D, Tables 39 to 45.

Table 14. Protocol Studies: Reported Outcomes

Author year	Patient	Prescribing	Microbial	Cost	Harms
Carratala 2012 ²⁵	X	X			
Pulcini 2011 ²⁷	X	X			
Goldstein 2009 ⁶⁴		X	X		
Oosterheert 2006 ²⁶	X	X			

Patient Outcomes

In the two RCTs of switching from IV to oral therapy, mortality did not differ significantly between intervention and control groups though hospital length of stay was significantly reduced.^{25,26} In one study, mortality from day 4 through a 28 day follow-up was 4% (5/132) in the intervention group and 6% (8/133) in the control group (RR=0.63 [0.21, 1.88]).²⁶ In the other study, 30-day mortality was 2% (4/200) in the intervention group and 1% (2/201) in the control group (RR=2.01 [0.37, 10.85]).²⁵ Mean lengths of hospital stay were 9.6 days (intervention) and 11.5 days (control) ($p<0.05$) in one study;²⁶ median lengths of stay were 3.9 days (intervention) and 6.0 days (control) ($p<0.001$) in the other.²⁵ One study reported 30-day readmission with no significant difference between groups (9.1% intervention, 7.5% control; RR=1.21 [0.63, 2.33]).²⁵ Clinical deterioration, reported in one study, did not differ between groups (6% intervention, 5% control, $p>0.05$).²⁶ Another study reported a significant difference in drug reactions (4.5% intervention vs. 15.9% control, $p<0.001$) but no difference in medical complications (20.0% intervention vs. 24.4% control, $p=0.34$).²⁵

The systematic reassessment study also reported mortality and length of stay. There was a significant reduction in mortality post-intervention (8% post-intervention vs. 23% pre-intervention; $p=0.03$) although it is unclear whether this was ICU mortality or hospital mortality.²⁷ Length of stay did not differ (13.8 days both pre- and post-intervention).

None of the protocol studies reported incidence of CDI. Strength of evidence for patient outcomes is presented in Table 13.

Prescribing Outcomes

Both studies of protocols for switching from IV to oral therapy reported decreased length of IV treatment. In one study, the mean duration of IV therapy was significantly shorter in the intervention group versus the control group (3.6 days vs. 7.0 days, $p<0.05$).²⁶ In the second study, the median duration was significantly shorter in the intervention group (2.0 days vs. 4.0 days, $p<0.001$).²⁵ One of the studies reported mean length of overall antimicrobial treatment with no significant difference between the intervention and control groups (10.1 and 9.3 days, respectively; mean difference 0.8 days, [-0.6, 2.0]).²⁶ The other study reported median time to antimicrobial therapy with no significant difference between groups (3.3 days intervention vs. 4.0 days control, $p=0.45$).²⁵

In the systematic reassessment time series study, a trend analysis revealed no change in level (-0.14 [-0.30, 0.02], $p=0.72$) or trend (-0.0004 [-0.04, 0.03], $p=0.59$) of appropriateness of antimicrobial therapy after the intervention. The prevalence of inappropriate therapies also did not decrease (a change from 43% to 38%, $p=0.86$).²⁷

The ITS study of autosubstitution looked at use of ertapenem during three time periods: prior to the introduction of ertapenem, after ertapenem was added to the formulary, and after the autosubstitution policy was implemented.⁶⁴ Median DDDs for ertapenem were 0, 8, and 44 during the three time periods. No statistical analysis was reported. The change in slope for imipenem use from the first time period to the second was significant (change=-4.46, $p<0.001$). Use of other antimicrobials (levofloxacin, cefepime, ceftazidime, and piperacillin-tazobactam) was unchanged during the study period.

Microbial Outcomes

In the study of an autosubstitution protocol, susceptibility of *P. aeruginosa* to imipenem increased following introduction of ertapenem to the formulary (slope for trend=1.74, $p<0.001$) and the trend was unchanged following the addition of the autosubstitution policy (slope=0.02; $p=0.85$). The decreased use of imipenem that accompanied the increased use of ertapenem was significantly related to the improved susceptibility of *P. aeruginosa* to imipenem.⁶⁴

Costs

None of the studies reported costs.

Table 15. Strength of Evidence for Protocol Studies, by Clinical Outcome

Study, year	Study design	Purpose	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
Carratalà 2012 ²⁵	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR 2.01 [0.37, 10.85]	Low for Mortality
Oosterheert 2006 ²⁶	RCT	Evaluate effectiveness of early switch	Medium	Mortality	NS, RR 0.63 [0.21, 1.88]	
Pulcini 2011 ²⁷	ITS	Appropriateness	Medium	Mortality	Reduced, p=0.03	
Carratalà 2012 ²⁵	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 ²⁶	RCT	Evaluate effectiveness of early switch	Medium	Length of stay	Reduced, WMD 1.9 [0.6, 3.2]	
Pulcini 2011 ²⁷	ITS	Appropriateness	Medium	Length of stay	NS, p=0.99	
Carratalà 2012 ²⁵	RCT	Evaluate effectiveness of early switch	Medium	Readmission	NS, RR 1.21 [0.63, 2.33]	Low for Readmission

ITS = interrupted time series; RCT = randomized controlled trial; NS = not statistically significant; RR = rate ratio [95% confidence interval]; WMD = weighted mean difference

Laboratory Tests (Findings from Systematic Reviews and Recent Trials)

Key Findings

- **Patient Outcomes:** Procalcitonin to guide initiation or duration of antimicrobial therapy for adults with acute respiratory infection or in the ICU with any infection had no effect on mortality. One study reported an increase in ICU length of stay and increased need for mechanical ventilation in the procalcitonin group.
- **Prescribing Outcomes:** Systematic reviews reported reductions in antimicrobial use with procalcitonin testing while recent RCTs reported no differences.
- **Microbial Outcomes:** Microbial outcomes were not reported.
- **Cost Outcomes:** Cost outcomes were not reported.

Procalcitonin, the prohormone of calcitonin, has been identified as a marker for the diagnosis of bacterial infections. Procalcitonin levels increase in response to bacterial infection but not viral infection. Levels decrease when the infection is resolved.

A recent high quality Cochrane systematic review and meta-analysis of individual patient data looked at studies of procalcitonin monitoring in patients with acute respiratory infections (ARIs).⁶⁵ The review included studies from both inpatient and outpatient settings. A second recent review by Agarwal and Schwartz, of moderate to high quality, included the studies conducted in the ICU that were cited in the Cochrane review but reported data from patients with any type of infection.⁶⁶

Characteristics of Studies Included in Systematic Reviews

Both reviews included prospective RCTs in which procalcitonin cut-off ranges were used to guide initiation and discontinuation of antimicrobial therapy in one study group. The Cochrane review provided more details about the studies.⁶⁵ Studies were eligible for inclusion if the control group received antimicrobials without use of procalcitonin levels. Therapy for patients in the control group may have been directed by guidelines but studies in which providers had access to other biomarkers were excluded. The Cochrane review included studies of adults with an acute respiratory infection; the primary diagnoses were upper respiratory tract infection (13% of patients enrolled) or lower respiratory tract infection (87% of patients enrolled including 48% with community-acquired pneumonia). Of 14 studies eligible for the review, 2 were done in primary care settings, 2 enrolled outpatients treated in the emergency room, 5 enrolled patients admitted via the emergency department, and 5 enrolled ICU patients. Approximately 24% of the total patient enrollment was from primary care, 62% from emergency department, and 14% from ICU settings.⁶⁵ The second review included the five studies that enrolled ICU patients and a study reported only in abstract form.⁶⁶

Seven of the studies in the Cochrane review were conducted in Switzerland (one of these studies included a hospital in the United States), three in Germany, two in China, and one each in France and Denmark.⁶⁵ The five ICU studies were from Switzerland (k=2), Germany (k=2), and France (k=1). The additional study included in the Agarwal review was from Belgium.⁶⁶ Primary outcomes of interest in the Cochrane review were all-cause mortality (up to 30 day follow-up) and setting-specific treatment failure.⁶⁵ The primary outcome in the Agarwal review was duration or intensity of antimicrobial therapy.⁶⁶ Both reviews reported length of stay.

Studies Published After the Systematic Reviews

We identified 2 RCTs published after the systematic reviews.^{67,68} The study by Jensen was conducted in nine medical/surgical ICUs in Denmark.⁶⁷ Unlike many studies, this was a drug escalation intervention. Daily procalcitonin measurements were taken and elevated levels prompted additional cultures, acute diagnostic imaging, and expanded spectrum of antimicrobial therapy. The trial included 1200 patients; median age was 67 years and 55% were male. Nearly 70% of the patients were experiencing respiratory failure and 43% had circulatory failure.

The second study enrolled patients from eight ICUs in France.⁶⁸ Procalcitonin levels were evaluated at 6 hours and on days 3 and 5. Results were used to guide initiation and discontinuation of antimicrobials. The trial was terminated early due to low enrollment. Baseline data were reported for 58 of 62 patients randomized (4 patients withdrew consent) with median age of 57 years and 74% male gender.

Patient Outcomes

In the Cochrane review, overall mortality was 5.7% (118/2085) in the procalcitonin group and 6.3% (134/2126) in the control group.⁶⁵ The adjusted odds ratio was 0.94 (95% CI 0.71, 1.23). Among patients treated in the emergency department, there were no differences in the outcomes of mortality (4.7% procalcitonin vs. 4.5% control; $p=0.90$), a combination of mortality or ICU admission (9.8% procalcitonin vs. 11.2% control, $p=0.16$), or length of hospital stay (median of 8 days for both groups, $p=0.28$). For patients treated in the ICU, there were no significant differences between treatment groups for mortality (19.9% procalcitonin vs. 23.8% control, $p=0.44$), length of ICU stay (median of 12 days in both groups, $p=0.39$), or length of hospital stay (21 days for procalcitonin group vs. 24 days for control group, $p=0.39$).

The Cochrane review also reported outcomes by diagnosis.⁶⁵ Mortality did not differ between treatment groups for any of the diagnoses. Among patients with community-acquired pneumonia, mortality was 9.2% in the procalcitonin group and 10.8% in the control group ($p=0.47$). Among patients with ventilator-associated pneumonia, the corresponding rates were 6.3% and 10.3% ($p=0.49$).

In the Agarwal review, studies were not pooled.⁶⁶ Five of the six studies of ICU patients with any infection reported mortality with no significant differences observed between the procalcitonin and control groups. Six studies reported ICU length of stay with significantly shorter lengths of stay in the procalcitonin groups in two of the six studies. Three studies reported hospital length of stay with no differences between groups in any of the studies.

Of the recent studies, Jensen reported 28 day mortality was 31.5% (190/604) in the procalcitonin group and 32.0% (191/596) in the control group (Hazard Ratio=0.98 [0.83, 1.16]).⁶⁷ ICU length of stay was longer (6 days vs. 5 days, $p=0.004$) and ICU days with mechanical ventilation were greater (3,569 days vs. 2,861 days, $p<0.001$) in the procalcitonin group. There was also evidence of increased organ failure in the procalcitonin group in an analysis based on “all admitted days in hospitals” rather than ICU days.

The second study reported mortality data for the 62 patients randomized.⁶⁸ No significant differences were reported between groups at day 5 (10% in each group), at ICU discharge (23% in the procalcitonin group, 33% in the control group, $p=0.40$), or at hospital discharge (same

as ICU discharge). ICU length of stay (22 days for the procalcitonin group vs. 23 days for the control group, $p=0.58$) and hospital length of stay (27 days and 33 days, respectively, $p=0.22$) did not differ significantly.

Prescribing Outcomes

In the Cochrane review, initiation of antimicrobials was significantly lower in the procalcitonin group (64% vs. 84%, $p<0.001$).⁶⁵ Duration of antimicrobial use in those receiving antimicrobials (median of 7 days vs. 10 days, $p<0.001$) and total exposure of antimicrobials (considering all randomized patients) (median of 4 days vs. 8 days, $p<0.001$) were also significantly lower in the procalcitonin group. These differences were maintained among patients treated in the emergency department and the intensive care unit with the exception that 100% of patients in both groups received antimicrobials in the intensive care unit.

By disease category (upper acute respiratory infection, community-acquired pneumonia, and ventilator-associated pneumonia), the initiation of antimicrobials, duration of antimicrobials, and total exposure of antimicrobials were significantly less among patients in the procalcitonin group with the exception of those with ventilator-associated pneumonia (all of whom were treated with antimicrobials).⁶⁵

Agarwal reported duration of antimicrobial therapy.⁶⁶ Each of the included studies reported duration outcomes although definitions varied among the studies. Five of the six studies reported decreased duration of antimicrobial therapy.

Among the recent studies, no difference in time to appropriate prescribing for patients with infections other than bloodstream infections was reported in one trial (0.2 days for the procalcitonin group vs. 0.4 days for the control group, $p=0.61$).⁶⁷ For blood stream infection, there was a significantly shorter time to appropriate therapy in the procalcitonin group (-0.1 days vs. 0.8 days, $p=0.02$). In the second study, the median time on antimicrobial therapy was the same for the two study groups (5 days).⁶⁸ At 5 days after randomization, among 27 survivors in the procalcitonin group 18 (67%) were taking antimicrobials compared with 21 of 26 survivors (81%) in the control group (RR=0.83 [0.60, 1.14]).

KEY QUESTION #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Key Findings

- Six studies provided information on intervention components associated with effective antimicrobial stewardship. Consistent and persistent effort from qualified personnel employing effective communication skills and often supported by electronic medical records or computerized decision support systems were central themes through these studies.

Six studies included in our review provided additional information on intervention components associated with effective antimicrobial stewardship. We summarize those studies below.

Goldwater provided insights into successful implementation of programs to influence prescribing.¹⁹ The study compared a therapeutic interchange protocol with standard educational tools for modify fluoroquinolone prescribing. The therapeutic interchange protocol was presented and approved at medical staff department and medical executive committee meetings. It was noted that “consistent and persistent effort” was needed to maintain changes in prescribing patterns and “qualified personnel” are needed to track compliance with prescribing guidelines. Effective communication was also mentioned including newsletters, direct mailings, notes or stickers in medical records, and direct conversations.

The need to tailor antimicrobial stewardship to individual wards or ICUs was also noted by Meyer et al.²⁰ The authors cited potential differences in prescribing practices and resistance patterns across facilities or units within a single facility. The study focused on changes in antimicrobial use following implementation of a guideline to reduce duration of antimicrobial therapy for patients in a neurosurgical ICU. The leadership of an “experienced intensive care physician who was responsible for educating the rotating neurosurgeons” was also noted as a factor in the success of the intervention.

Barenfanger reported on an intervention that used a commercially available software program that linked laboratory susceptibility testing results to the pharmacy and notified pharmacists of potential problems with the patient’s treatment regimen.²³ The intervention also included pharmacist education focused on microbiologic topics. Shorter lengths of stay and cost savings were noted for the intervention group; mortality was unchanged. The authors reported that physicians in the intervention group accepted the intervention because the electronic antimicrobial susceptibility report offered information that was not previously available to physicians. Pharmacists were able to provide physicians with recommendations for antimicrobials that would be more appropriate for a particular patient based on the susceptibility report. Physicians in the control group (usual hospital practice) were less likely to welcome the pharmacists’ suggestions. In that group, pharmacists obtained paper copies of the susceptibility reports for patients tested the previous day. The reports were correlated with the patients’ current therapy and, unless the changes needed were urgent and needed to be communicated by telephone, notes were placed in the patients’ charts. Pharmacists received information that was already available to physicians and therefore there were more likely to be disagreements about therapy.

McGregor commented on the time savings associated with use of a computerized clinical decision support system.²² The commercially available system was designed to generate alerts for the antimicrobial management team when treatment was inappropriate or inadequate. The management team then communicated with the physician. The comparator was manual chart review and recommendations for changes to patient therapy. It was reported the antimicrobial management team spent 4.1 person-hours per day making interventions on the control arm and 3.2 person-hours per day on the intervention arm. The primary advantage of the computer system was in identifying patients that needed interventions.

In a trial to reduce the use of broad-spectrum antimicrobials among ICU patients, the timing of the intervention was considered important.⁶ Patients who received 3 days of therapy with the targeted antimicrobials were enrolled. Cases were reviewed at day 3 and at day 10. The authors

commented that by day 3, microbiologic data and the early “clinical trajectory” of the patient could be incorporated into the recommendation.

A study conducted in three departments of a general hospital in Singapore discussed features of their program.⁸ It was noted that audit with non-immediate feedback and formulary restriction policies were already in place with limited effectiveness (i.e., approximately 40% of prescriptions were considered sub-optimal). The program was modified to enable a “whole-system” approach. Components included one-page antimicrobial guidelines for infections of major organs, an algorithm for IV to oral conversion, and a 2-stage audit of prescriptions with immediate concurrent feedback. The goal was to maintain physician autonomy while nurturing optimal prescribing. A computerized system was used to identify patients prescribed the audited antimicrobials. Clinical pharmacist compiled and reviewed the patient information. Complicated cases were subsequently reviewed and evaluated by an infectious disease physician, microbiologist, and pharmacist. If the prescription was determined to be inappropriate, verbal and/or written information was conveyed to the prescribing physician. All prescribing information was compiled for quarterly updates to departments including the appropriateness of prescriptions, the acceptance rate of interventions, and recommended areas for improvement.

KEY QUESTION #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

Key Findings

- **Hospital Setting:** None of the studies identified in our search for recent evidence were conducted at VA medical centers. Nearly all were conducted in university-affiliated teaching hospitals with only six studies conducted in community hospitals. Nine studies were conducted in ICUs. Because intervention components, study design, patient populations, and targeted infection or antimicrobial use differed across studies with no study directly attempting to replicate previous findings we caution against inferring that any outcome variation was due to hospital setting or unit.
- **Suspected Patient Condition:** Lung infections were the most frequently reported specific patient condition (seven studies). Results appeared qualitatively similar in these studies compared with the overall findings. Due to limited information and variability in study design, intervention and patient characteristics we urge caution in trying to assess whether effectiveness varies by suspected patient condition.

Hospital Type

None of the studies included in our review was conducted at a VA medical center. Most studies were conducted in university-affiliated or teaching hospitals. The exceptions were four studies conducted in general or community hospitals,^{6,8,14,58} three conducted in multiple hospitals,^{19,25,26} two of which included community hospitals,^{19,25} and two that did not specify hospital setting.^{15,16} One study used healthcare administrative databases from Ontario, Canada.¹³

With few studies conducted in community hospitals it is difficult to reach any conclusions about differences in effectiveness. Three ITS studies of audit and feedback interventions were carried out in community hospitals. In one study, the aim was to reduce use of broad-spectrum

antimicrobials. Data from over 4,600 patients treated in three ICUs of a single community hospital were included.⁶ An antimicrobial stewardship pharmacist reviewed records of patients who had received 3 days of therapy with one of the targeted antimicrobials and, if it appeared that therapy could be optimized, consulted with a senior infectious disease pharmacist and an infectious diseases physician. Suggested changes were entered in a database, a note was placed in the patient chart, and the pharmacist verbally communicated with members of the care team. A similar review was completed on the tenth day of therapy. No changes in mortality, length of stay, or CDI were observed following introduction of the stewardship program. A significant decrease in use of broad-spectrum antimicrobials was reported.

A second study piloted a stewardship intervention in three departments of a community hospital.⁸ An antimicrobial stewardship team developed guidelines for treatment of infections and an audit and feedback program was implemented. Clinical pharmacists reviewed patient records and made recommendations for changes to therapy. Complex cases were discussed with an infectious disease physician. The focus was on broad-spectrum and high cost antimicrobials. Over 1,500 prescriptions were reviewed. Mortality was unchanged following the intervention. There was a decreased level of targeted antimicrobials post-intervention but the change in trend was not significant. There was no change in the level of overall antimicrobial use but a significant increasing trend.

The third study was designed to discourage the use of quinolones and third-generation cephalosporins.⁵⁸ The study site was a 480-bed hospital serving a population of approximately 230,000. The focus was on microbial outcomes and antimicrobial usage in the ICU and hospital-wide. The guidelines used in the study were approved by the Antimicrobial Stewardship Committee (details of the Committee membership were not reported). A senior microbiologist attended ward rounds and provided prescribing advice. Post-intervention there were significant reductions in the use of third-generation cephalosporins both hospital-wide and in the ICU while use of ciprofloxacin was reduced only in the ICU. There was a significant change in the level of MRSA hospital-wide.

One study used a restrictive intervention.¹⁴ The ITS study took place in a 233-bed community hospital. Antimicrobials were classified as high-, medium-, or low-risk with restrictions on the use of the high-risk group. Weekly audit and feedback were used to encourage adherence to the policy. Mortality, length of stay, and readmission were not reported. There was a significant change in trend for CDI post-intervention; change in level was not significant. There were significant decreases in level of use for both high-risk and overall antimicrobials but no changes in trend.

A CCT of implementation of a guideline to change prescribing habits (replacement of ciprofloxacin with levofloxacin) was conducted in four hospitals.¹⁹ At a 151-bed community hospital and a 656-bed tertiary facility, a therapeutic interchange program was put in place with pharmacists intervening when a non-preferred fluoroquinolone was prescribed. At a 232-bed community and rehabilitation hospital and a 339-bed community hospital, standard educational tools were used to encourage prescribing of the preferred antimicrobial. Pharmacists at the standard educational tools hospitals were more involved in patient rounds. No information was provided about availability of infectious diseases specialists or clinical microbiologists. It

was noted that therapeutic interchange had been effectively used at one of the study hospitals for approximately three years prior to the study. The authors found a significantly higher rate of prescription of the preferred agent at the therapeutic interchange hospitals (96% of patients compared with 48% of patients at the standard educational tools hospitals, $p < 0.001$). There were differences in the sites of infection between the two intervention groups with more abdominal infections treated with fluoroquinolones at the standard educational tools sites and more blood infections and prophylactic use of fluoroquinolones at the therapeutic interchange sites.

An RCT of a protocol to reduce the duration of IV therapy and length of stay for patients with CAP enrolled patients at a 900-bed university hospital and a 300-bed private hospital.²⁵ Randomization of patients was stratified by hospital. The intervention consisted of a printed checklist placed in the charts of intervention group patients to remind their providers about the protocol. Length of stay was reported by hospital site. At the university hospital, mean length of stay was 4.0 days in the intervention group and 6.0 days in the usual care group (difference = -2.0 [-2.7, -1.3]; $p < 0.001$). At the community hospital, mean length of stay was 3.7 days in the intervention group and 6.3 days in the usual care group (difference = -2.6 days [-3.2, -1.7]; $p < 0.001$). The authors did not comment on differences between the hospital sites.

In their narrative review, MacDougall and Polk commented on differences between teaching and non-teaching hospitals.⁴⁸ They noted that surveys of hospitals or physician members of infectious diseases societies have typically found that larger hospitals and teaching hospitals were more likely to have antimicrobial restriction programs than smaller hospitals or non-teaching hospitals. The authors suggested that the increased likelihood of finding of antimicrobial control programs at teaching hospitals might be due to greater perceived need for control of antimicrobial prescribing, greater availability of resources and staff to oversee the program, or lesser need to allow for physician autonomy.

Hospital Unit

We also looked at effectiveness by unit within the hospital. Our review of recent evidence identified eight studies conducted in an ICU, seven in medical wards, fifteen in mixed medical/surgical/ICU, two in acute care, and eight that didn't report the hospital unit. Mortality, length of stay, and antimicrobial outcomes from the eight ICU studies and one multi-site study that reported ICU findings are presented in Table 16. Additional data on ICU studies may be found in the section on Laboratory Tests.

Overall, the findings from ICU studies were similar to findings from all eligible studies.

Five studies reported mortality. A CCT of audit and feedback enrolling patients with any infection found decreased mortality in the intervention group.⁴ An ITS study enrolling patients with CAP found significantly higher mortality following guideline implementation.²⁰ The other three studies found no significant difference in mortality before and after an intervention.^{5,9,27}

Four studies reported length of stay finding no differences before and after an intervention.^{6,9,20,27} The goal of one study was to reduce duration of treatment in patients with respiratory infections.²⁰

Antimicrobial prescribing outcomes were reported in eight studies. Significant decreases in consumption were reported in four studies^{6,12,20,57} with no difference in a third study.⁶³

Compliance with guideline recommended therapy was reported in one study with significant improvement following the intervention.⁶² However, in two studies, quality of therapy was not different post-intervention.^{9,27}

Table 16. Studies Conducted in Intensive Care Units

Author, year	Study design	Intervention type	Goal	Infection site	Mortality	Length of Stay	Antimicrobial Prescribing
Cairns 2013 ⁵⁷	ITS	Audit and Feedback	Reduction in broad-spectrum antimicrobials	Any	NR	NR	<i>Broad-spectrum use</i> decreased level and increased rate of change (both $p < 0.001$)
Elligsen 2012 ⁶	ITS	Audit and Feedback	Reduction in broad-spectrum antimicrobials	Any	Before: 13.1% After: 14.4% $p = 0.20$	Before: 6.9 days After: 6.9 days $p = 0.92$	<i>Broad-spectrum use (monthly)</i> Before: 644 days of therapy per 1000 pd After: 503 days of therapy per 1000 pds ($p < 0.0001$)
Weiss 2011 ⁴	CCT	Audit and Feedback	Reduce mortality (exploratory analysis)	Any	With prompting: OR=0.48, 95% CI 0.26-0.88 $p = 0.014$	NR	NR
Bornard 2011 ⁹	ITS	Audit and Feedback	Improve quality of prescriptions	Any	Before: 3.0% After: 3.0% $p = 1.0$	Before: 8 days After: 19 days $p = 0.72$	<i>Appropriate therapies</i> Change in level $p = 0.67$ Change in trend $p = 0.055$
Peto 2008 ¹²	ITS	Formulary Restriction or Pre-authorization	Avoid unnecessary antimicrobial usage	Blood	NR	NR	<i>Mean antimicrobial consumption</i> Before: 162.9 DDD/100 pd After: 101.3 DDD/100 pd "significant"
Mangino 2011 ⁶²	ITS	Guideline without Feedback	Improve adherence to clinical pathway	CAP HAP HCAP	NR	NR	<i>Compliant empiric therapy</i> Pre-intervention: 79/257 (30.7%) Post: 66/151 (43.7%) $p = 0.01$
Meyer 2007 ²⁰	ITS	Guideline without Feedback	Reduce duration of antimicrobial treatment	CAP	ICU Before: 80/1964 (4.1%) After: 162/2354 (6.9%) $p < 0.001$	Before: 3.1 days After: 3.1 days $p = ns$	<i>Antimicrobial use density</i> Before: 949.8 DDD/1000 pd After: 626.7 DDD/1000 pd "significant"

Author, year	Study design	Intervention type	Goal	Infection site	Mortality	Length of Stay	Antimicrobial Prescribing
Yong 2010 ⁶³	ITS	Computer Decision Support	Reduction in broad-spectrum antimicrobials to improve local resistance patterns	Any	NR	NR	Trend analysis: use of antimicrobials to cover Gram-negative bacteria was stable during study period Observed improved susceptibility of Gram-negative isolates
Pulcini 2011 ²⁷	ITS	Protocol	Improve quality of prescriptions	Any	Day 7 Pre-intervention: 3/62 (5%) Post: 2/52 (4%) p=0.18	Pre-intervention: 13.8 days Post: 13.8 days	<i>Quality of therapy (day 3)</i> Pre-intervention: Appropriate 27/62 (43) Inappropriate 21/62 (34) Unnecessary 14/62 (23) Post-Appropriate 20/52 (38) Inappropriate 19/52 (37) Unnecessary 13/52 (25) p=ns

DDD = defined daily dose; pd = patient days; NR = not reported; ns = not significant; RCT = randomized controlled trial; CCT = controlled clinical trial; ITS = interrupted time series; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

Suspected Patient Condition

Our review included six studies of inpatients with CAP and other respiratory tract infections,^{15,16,21,25,26,62} one of patients with either lung or abdominal infections,²⁴ and one of patients with bloodstream infections.¹² The remaining studies either included patients with any type of infection or did not report the infection site.

The ITS study of patients with bloodstream infections found mean antimicrobial consumption was significantly reduced following a stewardship intervention.¹² The intervention restricted authorization allowing only ICU consultants to prescribe antimicrobials. ICU consultants or infectious diseases specialists were available for bedside consultation five days per week and provided 24 hour telephone support seven days per week. No other outcomes of interest were reported in this study.

A summary of the seven studies enrolling patients with respiratory infections is presented in Table 17. The findings for patients with respiratory infections did not differ from the overall findings of this review.

Mortality was reported in six studies with five finding no difference in mortality either between intervention and control groups or before and after implementation of the intervention.^{15,16,24-26} The exception was a CBA study that reported increased mortality in the intervention cohort compared with the control post-intervention cohort.²¹

For length of stay, an RCT of a protocol for reducing duration of IV therapy and length of stay²⁵ and a CBA study of guidelines for improving appropriate timing and duration of treatment²¹ reported significant reductions in the intervention groups.

Six of the studies reported antimicrobial prescribing outcomes. Five reported on appropriate antimicrobial prescribing. Three studies found improved appropriate initial prescribing in the intervention group or following the intervention^{15,16,62} while one found no difference.²¹ Two studies reported on treatment within four or eight hours of presentation with both finding improvements in this outcome associated with the intervention.^{16,21} Two RCTs reported on treatment duration with one reporting shorter duration of IV therapy in the intervention group²⁵ and one finding no difference between intervention and control.²⁶

Table 17. Studies Enrolling Patients with Respiratory Infections (CAP, VAP, HAP, HCAP)

Author, year	Study design	Intervention type	Goal	Mortality	Length of Stay	Antimicrobial Prescribing
Schouten 2007 ¹⁶	CCT	Guideline with Feedback	Increase quality of antimicrobial use	<i>Intervention</i> CAP patients 20/318 (7.2) p=0.58 COPD/CB patients 10/269 (4.3) p=0.35 <i>Control</i> CAP patients 15/207(8.7) COPD/CB patients 5/237 (2.6)	<i>Intervention</i> CAP patients 8.0 days (median) p=0.47 COPD/CB patients 11.5 days (median) p=0.89 <i>Control</i> CAP patients 10.0 days (median) COPD/CB patients 11.4 days (median)	<i>Empirical regimen - correct indication, compliant with guidelines</i> OR=2.63 (95% CI 1.57 to 4.42) <i>Initiation of antimicrobial within 4 hrs of presentation, CAP patients</i> OR=3.59 (95% CI 1.02 to 12.6)
Schnoor 2010 ¹⁵	RCT	Guideline with Feedback	Improve quality of care	<i>30 day overall mortality</i> Intervention: 3.6% Control: 3.8% p=ns	Intervention: 10.0 days Control: 10.9 days p=ns	Adj odds of inpatients receiving appropriate treatment – intervention relative to control (OR=1.8, 95% CI 1.1 to 2.8)
Mangino 2011 ⁶²	ITS	Guideline without Feedback	Improve adherence to clinical pathway	NR	NR	<i>Compliant empiric therapy</i> Pre-intervention: 79/257 (30.7%) Post: 66/151 (43.7%) p=0.01
Capelastegui 2004 ²¹	CBA	Guideline without Feedback	Improve process of care and final outcome	<i>30 day</i> Adj OR=1.8 (1.1 to 2.9) versus control (cohort 2) group	Significant reductions in adjusted mean duration - intervention vs. all other groups p<0.001	<i>Appropriate use</i> Adj OR=1.1 (0.7 to 1.7) versus control (cohort 2) group <i>Antimicrobials within 8 hrs of presentation</i> Adj OR 2.3 (1.7 to 3.0) versus control (cohort 2) group

Author, year	Study design	Intervention type	Goal	Mortality	Length of Stay	Antimicrobial Prescribing
Nowak 2012 ²⁴	ITS	Computerized Decision Support	Effectiveness of data mining program	<i>Pre</i> 45/1163 (4.0%) <i>Post</i> 38/1023 (3.7%) p>0.05	<i>Pre</i> 5.9 (4.9) days <i>Post</i> 5.5 (7.8) days p>0.05	NR
Carratalà 2012 ²⁵	RCT	Protocol	Reduce duration of IV therapy and length of stay	<i>Intervention</i> 4/200 (2.0%) <i>Control</i> 2/201 (1.0%) Difference 1.0 (95% CI -1.4 to 3.4%)	<i>Intervention</i> 3.9 days (median) <i>Control</i> 6.0 days (median) Difference -2.1 (95% CI -2.7 to -1.7)	<i>Duration of IV treatment</i> <i>Intervention</i> 2.0 days (median) <i>Control</i> 4.0 days (median) Difference -2.0 (95% CI -2.0 to -1.0)
Oosterheert 2006 ²⁶	RCT	Protocol	Effectiveness of early switch from IV to oral therapy	<i>Intervention</i> 5/132 (4%) <i>Control</i> 8/133 (6%) Difference 2% (95% CI -3% to 8%)	<i>Intervention</i> 9.6 (5.0) days <i>Control</i> 11.5 (4.9) days Difference 1.9 (95% CI 0.6 to 3.2)	<i>Overall antimicrobial treatment</i> <i>Intervention</i> 10.1 days <i>Control</i> 9.3 days p=ns

DDD = defined daily dose; pd = patient days; NR = not reported; ns = not significant; IV = intravenous; RCT = randomized controlled trial; CCT = controlled clinical trial; CBA = controlled before and after; ITS = interrupted time series; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia

KEY QUESTION #4. What are the harms of inpatient antimicrobial stewardship programs?

Key Findings

- Only two studies reported *possible* harms associated with antimicrobial stewardship programs. Other “harms” could include significant increases in adverse patient, microbial, or prescribing outcomes due to the ASP intervention although this was rarely reported.

Of the studies included in our review, harms were rarely reported. Only two studies reported *possible* harms associated with antimicrobial stewardship programs. Both were studies with audit and feedback as the primary intervention. One study that aimed to alter prescribing *anecdotally* suggested that two patients may have been inappropriately switched to a narrower-spectrum antimicrobial. A chart review at one week after acceptance of the ASP recommendation revealed that the patients’ condition had deteriorated. When subsequently switched back to broad-spectrum antimicrobials, the patients improved.⁶⁰ However, no evidence was presented that the intervention led to inappropriate discontinuation of antimicrobials. A study that aimed to reduce unnecessary treatment reported that the intervention was terminated.⁷ One reason provided was that prescribing physicians were not happy with restrictions although a formal survey was not reported. Other “harms” could include statistically significant adverse increases in patient, microbial, or prescribing outcomes due to the ASP intervention as reported for Key Questions #1. Low quality evidence across ASP programs showed that this rarely occurred.

KEY QUESTION #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

Key Findings

- **Barriers to Implementation:** Four studies described implementation barriers; two included provider surveys. Suggestions for improving adherence to ASPs included involvement of stakeholders and opinion leaders in guideline and program development, addition of quality improvement cycles, understanding the prescribing culture, and collaboration between physicians and pharmacists. Eight studies provided data on resources required to implement an ASP program. Included were composition of an antimicrobial stewardship team, physician and pharmacist workloads, and equipment costs.
- **Sustainability:** Most reviewed studies were one year or less and did not comment on sustainability.
- **Scalability:** None of the studies included in our review reported on scalability.

Barriers to Implementation

Provider Adherence or Acceptance

Our review included a study of implementation of guidelines to increase the quality of antimicrobial use for patients with lower respiratory tract infection.¹⁶ The authors described a qualitative study of barriers to appropriate antimicrobial use conducted prior to the intervention study.⁷⁰ In the qualitative study, interviews were conducted with 11 residents, 6 consultants, 2 microbiologists, 2 emergency department nurses, 2 pulmonary ward nurses, and 1 clinical pharmacist. The interview questions were open-ended and focused on a clinical case (a patient with CAP) with questions about barriers to appropriate use of antimicrobials as outlined in six key recommendations for care: 1) prescription of a guideline-adherent empirical antimicrobial regimen, 2) timely initiation of therapy, 3) adjustment of regimen to accommodate decreased renal function, 4) switching from IV to oral therapy based on existing criteria, 5) streamlining empirical therapy into pathogen-directed therapy based on culture results, and 6) culturing blood samples, and culturing and Gram-staining sputum samples. Responses identified barriers to adherence related to *knowledge* (lack of familiarity or experience, lack of awareness or insight), *attitude* (lack of agreement with the guideline including applicability to patient, lack of confidence in guideline developer, and disagreement about interpretation of the evidence; lack of outcome expectancy; inertia of existing practice), and *external barriers* (guideline unclear; presence of conflicting guidelines; social pressure; lack of communication between professionals; organizational constraints such as lack of time or resources, antimicrobials not present, or lack of provider continuity on wards). The authors recommended development of evidence-based guidelines with involvement from representatives of all relevant clinical specialties, journal-club sessions for discussion of controversies in the literature, and feedback/tutorial sessions.¹⁶ In the intervention study, they included a key lecture by an opinion leader, feedback at the hospital level, and consensus critical-care pathways. A second phase allowed for adjustment of intervention components based on individual hospital baseline results.¹⁶

Schnoor reported low provider attendance at educational sessions.¹⁵ The study involved multiple hospitals and multiple sentinel practices (the total number of providers was not reported) but only 12 practitioners attended the first educational session and only 4 attended the second session. The authors suggested that adding audits or a continuous quality improvement cycle to the intervention might increase physician compliance but noted high cost as a barrier. A questionnaire sent to study physicians following the implementation phase found that physicians viewed guidelines as “helpful to improve the quality of care” (n=13), as “good educational tools” (n=10), and as a “helpful guide in decision making” (n=16) with fewer describing guidelines as “cookbook” (n=4) or “oversimplified” (n=5). The most commonly reported reason for non-adherence to guidelines was “related to the patient.” It was also reported that “inadequate care at home” led to low-risk patients being hospitalized. Additional reasons for non-adherence were failure of the symptom assessment index included in the guideline to include underlying diseases, dissenting opinions of patients, and difficulty changing one’s behavior. When the 17 “sentinel practices” involved in the study were asked which version of the guideline they used “frequently” for supporting treatment decisions, 3 reported using an interactive electronic (compact disk) version of the guideline, 7 reported using the guideline posters, and 15 reported using the short printed version of the guideline. The response rate for the questionnaire was not reported.

The authors of an audit and feedback study suggested several factors that may have contributed to the successful implementation of their stewardship program.⁸ Understanding the local prescribing culture, providing a working environment conducive to prudent prescribing, obtaining support from management and buy-in from providers, and offering a non-restrictive policy that allowed for prescriber autonomy were considered key elements of the program.

A study of a data-mining program to identify cases and make recommendations concluded that the success of the stewardship program was due to collaboration between the pharmacist and the infectious disease physician.²⁴ Earlier attempts (using only passive interventions such as formulary restriction or guidelines) were not successful in reducing costs or improving rates of infection.

Several studies, primarily of audit and feedback interventions, reported acceptance of the intervention recommendations.^{1,3,6,8,24,57} Teo reported an overall acceptance rate of 70%.⁸ Recommendations were made by the antimicrobial stewardship team (infectious disease physician, microbiologist, clinical pharmacists). The most frequent recommendations were for discontinuation of therapy or narrowing or broadening therapy. Another study reported an acceptance rate of 74%.⁵⁷ Recommendations came from the stewardship team (stewardship pharmacist and infectious disease registrar and/or physician). Modifications to prescriptions for restricted broad-spectrum antimicrobials were most common followed by recommendations to discontinue therapy. In the study by Elligsen, an antimicrobial stewardship pharmacist, in consultation with a senior infectious disease pharmacist, reviewed the records of all ICU patients prescribed one of the targeted broad-spectrum antimicrobials. If it appeared that a modification of therapy was appropriate, an infectious disease physician reviewed the case. The acceptance rate was 82%.⁶ The most frequent recommendations regarded discontinuation of therapy and change to an alternate antimicrobial. Lesprit reported that over 90% of recommendations made by a single infectious disease physician were adopted by the treating physicians.¹ The most

frequent modifications recommended were switching from IV to oral therapy, de-escalation of therapy, shortening duration of therapy, and stopping therapy. In another study, all prescriptions for levofloxacin, vancomycin, and carbapenems were reviewed by an infectious disease physician. Approximately 50% of attending physicians complied with recommendations to discontinue or modify the initial prescription. Compliance varied somewhat for the three targeted antimicrobials: levofloxacin 40%, carbapenems 70%, and vancomycin 88%.³

One study of computerized decision support also reported acceptance. Following implementation of a stewardship program that involved computer-generated reports and recommendations which were subsequently reviewed by pharmacists and infectious disease physicians, it was reported that 80% of recommendations were accepted by prescribers within 48 hours.²⁴ Recommendations most frequently related to appropriateness of empiric therapy, de-escalation of therapy once laboratory results were available, discontinuation of therapy if infection was not clearly documented, and changes to duration of therapy.

Resources

Several studies reported on resources required. For an audit and feedback program in which an antimicrobial monitoring team provided real-time review of orders for restricted antimicrobials with intervention as needed, the team included an infectious diseases physician at 50% effort, a clinical pharmacist with infectious diseases training at 80% effort, and a data analyst at 5% effort. Direction of the stewardship program was considered part of the infection control program and no additional resources were required. The program was implemented at a single large (admissions per year ranging from over 28,000 the first year of the program to over 38,000 in the final year), tertiary care teaching medical center.⁷

An audit and feedback program in the medical and surgical wards (650 beds) of a hospital involved post-prescription review by one infectious disease physician followed by verbal or written communication with the prescribing physician, if needed.¹ For prescriptions not requiring further intervention, the median time for review was 6 minutes. For prescription requiring screening, data review, and interaction with the prescribing physician, the median time for review was 15 minutes (with a range of 10 to 60 minutes). The mean daily time required was 2.5 hours. Over a 24-week period, the study enrolled 376 patients in the intervention group. The estimated cost of the intervention (including ward visits by the infectious disease physician) was €2,147.

In another audit and feedback program, it was estimated that the weekly workload for the infectious disease physician was approximately three hours.⁹ The infectious disease physician visited the 10-bed ICU three times per week to provide feedback to prescribers and conducted approximately 2 training sessions per month. A bacteriologist spent approximately one hour per week on stewardship, meeting five days per week with the intensivists to discuss laboratory results.

An audit and feedback program at a single 430-bed hospital and involving week-day antimicrobial stewardship rounds (a stewardship pharmacist and an infectious disease specialist) was reported to require a full-time pharmacist and 8 to 10 hours per week of infectious disease physician time.⁵⁷ The program was implemented in both the ICU and the general wards.

Staffing for an antimicrobial stewardship program was reported in a study of guidelines implemented with feedback.¹⁸ The study was conducted at one hospital. The Antimicrobial

Management Team included one full- and one part-time microbiology consultant, three infection control nurses, and one antimicrobial pharmacist who was on-site and did ward rounds three days per week. After the introduction of a narrow-spectrum antimicrobial policy, the antimicrobial pharmacist was on-site and performing ward rounds five days per week (week days only). The change was made to promote adherence to the revised guideline.

Another study described the time required for different phases of their intervention.⁶² The authors noted the importance of leaders to champion the project, active involvement of stakeholders, and benchmarking. Designated as a performance improvement project, the intervention included development of a consensus pathway (based on existing national-level guidelines), identification of quality performance indicators for assessing guideline compliance, and creation of a form for data collection and a repository for data storage. This phase required three months. Each of the four participating academic care centers then customized the pathway based on local epidemiology and hospital formulary and developed educational tools to facilitate implementation. This phase required approximately six months. Educational efforts included slide sets for presentations at grand rounds and other lectures and printed materials. With monthly rotations by house staff, educational programs were needed throughout the implementation.

The cost of purchasing commercially available computer software that could link susceptibility test results to pharmacy data and identify patients receiving potentially inappropriate therapy was reviewed by Barenfanger.²³ It was estimated that implementation of the intervention would save \$2,932,000 at the study hospital (a 450-bed community teaching hospital). The list price of the software was \$44,500 so even after the software purchase, the savings were substantial.

Nowak reported that the data-mining software used for the antimicrobial stewardship intervention was already being used for other clinical needs.²⁴ Implementation costs, therefore, were limited to the time required to modify the software to generate the reports for stewardship. It was also noted that existing pharmacists were able to perform the stewardship components that were already in place before the software was introduced (i.e., conversion from IV to oral therapy and dosage adjustments) and infectious disease physicians were able to review cases and write recommendations. A new antimicrobial stewardship pharmacist was added to review the computer generated reports and augment them with additional information from the medical record. It was estimated that the antimicrobial stewardship pharmacist spent 3 to 4 hours per day compiling the reports and the infectious disease physician spent 30 to 60 minutes per day reviewing them.

Sustainability

One study reported on sustainability. An audit and feedback antimicrobial stewardship program was put in place in 2001 and continued to 2008.⁷ Other components of the program were preauthorization for use of certain antimicrobial agents and guidelines for ordering. Defined daily dose data were reported for the final five years of the program and for two years following program termination. The DDD/1000 patient-days increased by 5.2% ($p=0.014$) during the 2 years after the program. No change was noted for length of stay, mortality, or readmissions. The drug-related group case mix index was also unchanged. It was noted that the program was discontinued so that the funding could be used to provide additional infectious diseases

physicians for consultation. There was also some dissatisfaction with the requirement for preauthorization. Given that costs increased after the program while patient outcomes (i.e., mortality, length of stay, readmission) were unchanged, the stewardship program was modified and restarted.

Scalability

None of the studies included in our review reported on scalability. Most were conducted in a single hospital or included additional hospitals as comparator sites. Within a single hospital, many studies were conducted in either the ICU or general medical wards. No study that implemented a stewardship program in multiple sites (i.e., medical and surgical wards) provided information about factors associated with implementing the program in different wards.

SUMMARY AND DISCUSSION

SUMMARY OF FINDINGS BY KEY QUESTION

Key Question #1. What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

- a. **Primary Outcome: Patient centered outcomes (30 day readmission, mortality, *Clostridium difficile* infection, length of stay, adverse effects)**
- b. **Secondary Outcomes: 1) Antimicrobial prescribing (timing, use, selection, dose, route, duration); 2) Microbial outcomes (institutional resistance, resistance in study population); 3) Costs (healthcare, program, opportunity, drug)?**

Our systematic review of studies evaluating antimicrobial stewardship, found multiple studies that provide low level evidence that ASP programs may be associated with an improvement in antimicrobial prescribing practices and costs without negative effects on patient outcomes such as mortality, length of hospital stay, CDI, and readmissions. We caution readers in over-interpretation of findings. Despite identifying numerous studies and additional systematic reviews, the quality of the available evidence is low, prescribing improvements often not sustained, and generalizability to settings, patients or health conditions beyond those specifically studied, difficult. Few studies were randomized controlled trials. The ability to control for secular trends or other confounding variables was limited. Thus most of our findings indicate “associations” of outcomes with interventions rather than cause and effect.

Among the recent studies, the greatest body of evidence of effectiveness is for decreasing inappropriate antimicrobial use or increasing appropriate antimicrobial use, especially for prospective audit and feedback interventions. There is also some evidence of the effectiveness of audit and feedback interventions on decreasing duration of antimicrobial use. There is limited evidence of effectiveness based on antimicrobial selection or timing.

New findings included in our report are generally in agreement to conclusions from a recently updated Cochrane review that characterized interventions in a slightly different fashion.⁵³ Although this review included 89 studies, reported findings are based on few studies with only one prescribing outcome captured per study. As noted previously, we have concerns about selective outcome reporting bias and selective analysis reporting bias in the review.

Key Question #2. What are the key intervention components associated with effective inpatient antimicrobial stewardship (e.g., persuasive, restrictive, structural, or combination intervention; personnel mix; level of support)?

Six studies provided information on intervention components associated with effective antimicrobial stewardship. Key components identified included: consistent and persistent effort from qualified personnel, effective communication skills, support from electronic medical records or computerized decision support systems.

Key Question #3. Does effectiveness vary by a) hospital setting (rural, urban, academic, VA, non-VA) or b) suspected patient condition?

None of the 35 studies identified in our search for recent evidence were conducted at VA medical centers. Nearly all were conducted in university-affiliated teaching hospitals. However, the recent Cochrane review included nine studies from VA hospitals noting improvement in CDI (k=2) and microbial outcomes (k=3) with mixed results for prescribing outcomes (k=3) and no change in mortality (k=1). Nine studies were conducted in ICUs and findings were similar to the overall findings.

Lung infections were the most frequently reported specific patient condition (seven studies). Results appeared qualitatively similar in these studies compared with the overall findings.

Key Question #4. What are the harms of inpatient antimicrobial stewardship programs?

Only two studies included in this review reported *possible* harms associated with antimicrobial stewardship programs and both provided only anecdotal evidence. Other “harms” could include significant increases in adverse patient, microbial, or prescribing outcomes due to the ASP intervention although few studies reported these outcomes.

Key Question #5. Within the included studies, what are the barriers to implementation, sustainability, and scalability of inpatient antimicrobial stewardship programs?

Four of the thirty-five studies identified for our review described barriers to implementation. Suggestions for improving adherence to ASPs included involvement of stakeholders and opinion leaders in guideline and program development, addition of quality improvement cycles, understanding the prescribing culture, and collaboration between physicians and pharmacists. We identified one study that addressed sustainability finding that antimicrobial costs continued to decrease over the seven years the program was in place while costs increased during the two years after program termination. A similar trend was observed for defined daily doses per 1000 patient-days. None of the studies included in our review reported on scalability.

LIMITATIONS

We noted wide variation in populations enrolled, specific interventions utilized (even in our broad program categorization), country, hospital and unit setting and conditions and objectives assessed. There was no replication of findings from one study to another and individual studies were typically relatively small in size and short in follow-up duration. Furthermore, the studies were done in many different nations with disparate health systems, hospital organizations, staffing patterns, methods of paying for antimicrobials and for healthcare in general, formularies, systems of care, etc. Because of differences across studies and no study directly attempting to replicate previous findings we caution against inferring that any outcome variation was due to hospital setting or unit or whether effectiveness varies by suspected patient condition.

Few eligible studies were high methodological quality (randomized, controlled, double blinded trial). It would be difficult to blind investigators or participants in a trial of antimicrobial stewardship. Nearly all the studies were done in single centers and there were substantial controlled and uncontrolled influences on outcomes. 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 like this are more practical than large, well powered, externally funded randomized trials, but the results are also less reliable. Indeed, we are unaware of funding opportunities that are likely to support high quality, large, randomized trials of antimicrobial stewardship.

Since few studies of antimicrobial stewardship are randomized controlled trials, studies are unlikely to be entered in a registry before they are done. There is a substantial risk of reporting and publication bias—that outcomes showing a benefit of some kind are more likely to be described and studies with positive outcomes more likely to be published than studies showing no benefit or harms.

Furthermore, studies of antimicrobial stewardship with the incidence of CDI as an outcome are often initiated in response to an increase in or relatively high incidence of CDI. Many report a decrease in CDI incidence after an intervention is introduced. Unless the study is a randomized controlled trial, it is difficult to know if the decreased incidence reflects an effect of the intervention, termination of an outbreak, or regression to the mean.

Effective interventions may have been effective because of uncharacterized or unreported characteristics of the setting. These interventions may not be effective in different settings.

A number of studies present aggregate data on antimicrobial use from the entire study population rather than data on individual cases for which the intervention was applied. There are advantages associated with use of aggregate data in terms of the total hospital antimicrobial costs, but use of aggregate data does not adequately account for changes in use for cases with interventions or other defined patient groups.

DISCUSSION

Most studies demonstrated an effect on at least one of the studied outcomes, and in nearly all these cases the effect favored the stewardship intervention. Most of the significant findings involved secondary prescribing, microbial, or cost outcomes rather than a significant change in the patient-centered outcomes we considered. Studies were not designed to adequately assess impact on mortality or other clinical outcomes. It is reassuring however, that reported improvements in prescribing and costs were not accompanied by deleterious effects on patient outcomes of mortality, length of stay, hospital readmission, and CDI. Furthermore, because a growing body of literature supports the assertion that antimicrobial use contributes to antimicrobial resistance, costs, adverse events, and other important clinical outcomes, the finding that multiple stewardship strategies can decrease antimicrobial use is encouraging. Thus evidence provided in this review suggests that there are several strategies available to clinicians that can decrease antimicrobial prescribing and limit costs, without any apparent harms.

One of the goals of stewardship is to reduce the amount of inappropriate antimicrobial use, which estimates place at 30-60% of all antimicrobial use. Only a handful of the included studies specified that the reductions in antimicrobial use came through reducing inappropriate use; possibly, some of the reductions in use involved appropriately prescribed antimicrobials. However, since most studies involved providing guidance, feedback, or opportunities to re-evaluate antimicrobial use, versus outright cessation of such use, it seems unlikely that necessary antimicrobials were discontinued at an increased rate when compared with usual clinical care. It is also possible that as use of targeted antimicrobials decreased, physicians may have used other drugs instead, a phenomenon referred to as “squeezing the balloon.”⁷¹ Future studies of antimicrobial stewardship should attempt to systematically assess changes in use of all antimicrobials, since cessation of potentially life-saving antimicrobials is one of the main hypothetical harms of antimicrobial stewardship.

Unfortunately there are few data on sustainability, scalability or specific components of interventions most likely to be effective. Suggestions for improving adherence to ASPs included involvement of stakeholders and opinion leaders in guideline and program development, addition of quality improvement cycles, understanding the prescribing culture, and collaboration between physicians and pharmacists. Studies that described ASPs noted that the composition of antimicrobial stewardship teams varied but often included a physician, pharmacist, and microbiologist. Most reviewed studies were one year or less and did not comment on sustainability. The Cochrane review found that effects were often not sustained beyond six months but with limited data on long-term effects the authors recommended future studies assess effects at one year or longer.⁵³ None of the studies included in our review reported on scalability.

No study directly compared one intervention with another. This is unsatisfying in one sense, in that policy-makers looking for the most effective strategy for antimicrobial stewardship are left without an answer. However, the converse of this is that multiple strategies have been associated with reductions in antimicrobial use and costs, without any signal of associated harm. Accordingly, if antimicrobial stewardship is something that an organization decides to undertake, the decision as to which strategy to adopt can be tailored to fit the available resources. Given our previous concerns about the quality and applicability of data we urge that implementation be prospectively reevaluated based on ongoing evaluation of effectiveness, harms, costs and sustainability.

Although the recent Cochrane review⁵³ included nine studies conducted in VA hospitals, we found no recent studies meeting eligibility criteria that were conducted in VA healthcare settings. One recently completed VA study that did not meet our inclusion criteria was a survey of 152 VA Medical Centers.⁷² Responses were received from 140 centers (response rate of 92%) and 130 of those had inpatient services. Forty-nine facilities with inpatient services (38%) reported that they had an antimicrobial stewardship team. Of those with teams, 45 of 49 (92%) had involvement of infectious disease physicians, 39 of 49 (80%) had involvement of pharmacists, and 37 of 49 (76%) had involvement of a clinical microbiology laboratory director. Fifty-five percent interfaced with the infection control committee, 31% interfaced with information technology support staff, and 29% interfaced with hospital administration. In addition, results should soon be available from a recently completed controlled before and after trial at two VA hospitals involving an audit and feedback intervention for increasing guideline concordant care for patients with catheter-associated urinary tract infection.⁷³

Most of the published studies come from urban academic medical centers. This may reflect where the preponderance of stewardship efforts take place or, more likely, it may reflect where people involved in stewardship efforts have the resources and time to evaluate their interventions and write and submit manuscripts. As a result, it is difficult to draw conclusions about whether effectiveness varies by hospital setting.

We found substantial variability of the hospital settings of the published stewardship interventions, from entire hospitals, to specific wards, to ICUs. No article compared efforts in two or more settings. There were nine articles on interventions in ICUs and six were effective in some way. ICUs are typically smaller units with a relatively small group of prescribers, and ICUs often operate with protocols for common, high stakes conditions. Antimicrobial use is common, and often empirical. Antimicrobial resistance is common in patients in ICUs. Without precise comparative data, we are left with the impression that an intervention targeting antimicrobial use in a hospital's ICUs might be a logical place to start and might be more likely to yield valuable results than interventions in other settings or hospital wide.

No study was designed specifically to identify harms of stewardship interventions, and few studies reported on harms. Studies not meeting eligibility criteria have reported on harms of stewardship interventions. Nicks et al. reported on a survey of emergency room physician level of understanding of the Center for Medicare and Medicaid Services (CMS) guidelines for community-acquired pneumonia.⁷⁴ Many hospitals track adherence to the core measures related to the CMS guidelines. More than half of the respondents (55%; 95% CI = 47% to 70%) reported prescribing antimicrobials to patients they did not believe had pneumonia in an effort to comply with the CMS guidelines, and 42% (95% CI = 34% to 50%) of these stated that they did so more than three times per month. Only 40% (95% CI = 32% to 48%) of respondents indicated a belief that the guidelines improve patient care.

Some stewardship interventions have been perceived by providers as barriers to efficient workflow, however, we did not find high quality clinical trials documenting barriers to implementation of stewardship programs. A number of articles discussed anecdotal experience with barriers. The major types of barriers were cost of the intervention, provider resistance, and lack of adequate information systems to support stewardship efforts or evaluation of the efforts. One study that did not meet eligibility criteria reported evidence that providers alter their prescribing behavior to circumvent restrictions.⁷⁵ The intervention was a requirement for prior approval of certain antimicrobial agents that was in place between 8am and 10pm. The authors observed a disproportionate number of orders for restricted drugs between 10pm and 11pm which suggested that providers wanting to order these drugs and not obtain prior approval simply waited until after the restriction was in place to order them.

RECOMMENDATIONS FOR FUTURE RESEARCH

A typical antimicrobial course is complex, involving several decisions over hours to days or even weeks. There are many clinical, imaging, and laboratory inputs to monitor, and courses are often given to complex, heterogeneous patients. These characteristics make it difficult to conduct well-designed trials to accurately assess most outcomes.

Direct comparisons of different stewardship strategies have inherent appeal, but since there are multiple such strategies, larger comparative-effectiveness studies may need to wait until further research winnows the field down to a more manageable number of strategies for such studies. It is not easy to judge whether interventions in which authorship, review, and dissemination of guidelines occurred on a local level and/or interventions which accommodated local epidemiology were associated with better outcomes than other studies but these factors are worth consideration for future studies.

Hospitals and healthcare systems in the United States and many other countries have recognized the need for antimicrobial stewardship. The Veterans Health Administration, the Joint Committee on Accreditation, and many other organizations now expect that hospitals will take steps to increase the quality of, and diminish unnecessary, antimicrobial use. Several strategies for antimicrobial use have been proposed,⁴⁹ but there is little high quality evidence on comparative effectiveness. Future research is sorely needed to clarify the benefits, potential harms, barriers, sustainability, and costs of antimicrobial stewardship programs. Generous funding for comparative effectiveness trials would be ideal. Large healthcare organizations should recognize that units within them will likely be conducting one or more stewardship activities. These organizations should strongly consider organizing these activities in a way that provides useful information on comparative effectiveness. Healthcare payers should recognize that large amounts of money will be spent on antimicrobial stewardship and that these expenditures can be more efficiently utilized if comparative research is done to identify the most effective approaches and strategies. Given that it may be hard to avoid cross-over or contamination in studies randomized at the subject level, cluster RCTs may be the most feasible way to provide high-quality evidence. Large healthcare organizations could play a role since they could provide the multiple sites—but shared data—that would make such a study feasible.

CLINICAL CONSIDERATIONS

Until high quality comparative effectiveness research becomes available, hospitals and healthcare systems will feel pressure to do something. There is currently no definitive blueprint for how to improve antimicrobial use most effectively. However, the literature on stewardship and implementation science provides a tentative roadmap that will allow hospitals to move forward. The following reflects our synthesis of this literature.

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. Data on antimicrobial use by clinical unit, type of patients, provider groups, and by individual providers should be gathered and analyzed locally wherever possible. Usage should be compared with available national guidelines or benchmarks.⁷⁶ For example, a hospital might want to analyze antimicrobial therapy for a common, important disease like community acquired pneumonia to determine how often antimicrobial therapy is consistent with guidelines,⁷⁷ how often therapy is timely, how often cases with syndromes that are not likely to represent community acquired pneumonia are in fact treated as if they were, how often therapy is adjusted appropriately as clinical circumstances evolve, and how often the route and duration of therapy fit with guidelines. 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 necessary for many stewardship activities. Among these are infection prevention programs, microbiology laboratories, pharmacy services, infectious disease physicians, electronic medical record systems, continuous improvement programs, and staff or trainee education and certification programs. All of these can contribute to stewardship activities, and all should be part of planning and implementation efforts to identify areas of improvement and design strategies to improve use. It is important to inform hospital and healthcare system leaders of the need for stewardship based on local conditions and anticipated benefits and seek their support in the form of policies, procedures, and financial support.

Formative evaluation should be integral to any stewardship activity. The formative evaluation component can be built upon the information that is gathered to identify the need for the intervention in the first place. Formative evaluation will inform the participants and hospital administrators whether the program is effective. If not, the program can be strengthened, or another approach can be taken. If an intervention is effective, formative evaluation can help determine if the intervention should be continued. If a problem with antimicrobial use has been solved, it may be possible to redirect efforts and resources to solve another problem. Antimicrobial therapy is a continuously evolving area of medicine. New drugs are developed and marketed, antimicrobial susceptibilities change over time, 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.

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