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Antimicrobial Stewardship Programs in Inpatient Settings: A Systematic Review

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Prepared by:
Evidence-based Synthesis Program (ESP) Center
Minneapolis VA Medical Center
Minneapolis, MN
Timothy J. Wilt, M.D., M.P.H., Director

Investigators:
Principal Investigators:
Gregory Filice, M.D.
Dimitri Drekonja, M.D., M.S.

Co-Investigators:
Timothy J. Wilt, M.D., M.P.H.
Nancy Greer, Ph.D.
Mary Butler, Ph.D.
Brittin Wagner, Ph.D.

Research Associates:
Roderick MacDonald, M.S.
Maureen Carlyle, M.P.H.
Indulis Rutks, B.S.

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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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EXECUTIVE SUMMARY

BACKGROUND

It is estimated that in 2009, more than 3 million kilograms of antimicrobials were administered to human patients in the United States. While the life-saving benefits of antimicrobials are indisputable, the consequences of use and misuse must also be considered. Major concerns related to the use of antimicrobials are increasing resistance, higher incidence of *Clostridium difficile (C. difficile)* infection (CDI) and increased healthcare costs (including costs related to adverse events associated with antimicrobial use).

While much of the discussion focuses on overuse, there is also evidence of adverse outcomes associated with inadequate antimicrobial therapy. Antimicrobial stewardship programs (ASPs) are a focused effort by a health care system, a hospital, or a portion of a hospital (e.g., an intensive care unit) to *optimize* the use of antimicrobial agents. The goals of an ASP are to improve patient outcomes, reduce adverse consequences, reduce or prevent an increase in antimicrobial resistance, and deliver cost-effective therapy. The emphasis is on appropriate selection, dosing, route, and duration of antimicrobial therapy.

The purpose of this review is to synthesize the evidence about the effectiveness of antimicrobial stewardship programs implemented in hospital settings. We focus on ASPs including one or more of the following components: prospective audit and feedback, formulary restriction, pre-authorization of prescriptions, guidelines for prescribing and/or modifying therapy, computerized decision support, or laboratory testing. The topic 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 developed the following key questions with input from a technical expert panel.

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?

METHODS

An exploratory search identified a 2005 Cochrane review that partially addressed the key questions but was no longer current (search dates 1980 to 2003). 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. 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. Full text versions of potentially eligible articles were retrieved for review. We excluded studies done in settings or enrolling patient populations not relevant to the United States; studies not involving an intervention or not involving an intervention of interest (e.g., studies of interventions involving only education were excluded); studies describing an intervention with no assessment of the effects of the intervention; studies not reporting either patient outcomes, prescribing outcomes, microbial outcomes, costs, or harms; studies of antimicrobials for medical or surgical prophylaxis; studies of patients with viral or fungal infection, or tuberculosis; and studies other than randomized controlled trials (RCTs), controlled clinical trials (CCTs), controlled before/after trials (CBAs), or interrupted times series (ITS) with at least three data points before and after implementation of the intervention.

An updated version of the 2005 Cochrane review was released in April 2013 and included studies published through 2009. To avoid duplication, we included in our review only studies meeting the eligibility criteria described above and not included in the most recent version of the Cochrane review.

Data Abstraction

From studies identified as eligible after full-text review, we extracted study characteristics, patient outcomes, prescribing outcomes, microbial outcomes, costs, and harms. We also extracted information on barriers to implementation, sustainability and scalability.

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). 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.

Data Synthesis

We constructed evidence tables showing the study characteristics and results for all included studies, organized by intervention category. We created forest plots for outcomes with sufficient data to calculate risk ratios. Due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting among studies for each intervention, we were not able to pool results. We compiled a summary of findings 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 Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program. The strength of the evidence was evaluated based on four domains: 1) risk of bias, 2) consistency, 3) directness, and 4) precision.

Peer Review

A draft version of this report was reviewed by technical experts as well as clinical leadership. Reviewer comments (Appendix C) were addressed and our responses were incorporated in the final report.

RESULTS

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. Nine were RCTs (including cluster randomized trials), four were CCTs, two were CBAs, and twenty were ITS studies. We also summarized three systematic reviews relevant to this topic.

We categorized studies initially by primary intervention including 14 studies of audit and feedback programs, 5 studies of formulary restriction and preauthorization programs, 4 studies of guideline implementation with feedback, 4 studies of guideline implementation with no feedback, 4 studies of computerized decision support, and 4 studies of protocol or policy implementation. Within each intervention category, we further 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).

Most studies were conducted at university affiliated or teaching hospitals. Four studies were performed at community hospitals, three at mixed sites, and two did not specify the hospital type. One study analyzed data from administrative care databases for a Canadian province. We also looked at the site of the intervention with 8 studies conducted in intensive care units (ICUs), 7 studies conducted in medical wards, 12 studies conducted in multiple sites (medical, surgical, ICU), and 1 study in acute care. Seven studies did not report the site.

Seven studies focused on treatment of respiratory illness, 26 included patients with any type of infection, and 1 study included only bloodstream infections. One study did not report infection site.

We also identified two recent systematic reviews and two trials published after those reviews that focused on use of procalcitonin monitoring to guide antimicrobial therapy. All of the individual trials of procalcitonin monitoring that were identified in our original literature search were included in the systematic reviews so we summarized the findings from the existing reviews.

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)?**

Findings from an Existing Systematic Review

The recently updated high quality Cochrane systematic review of 89 studies identified through 2009 (25 RCTs, 3 CCTs, 5 CBAs, and 56 ITS studies) assessed this question focusing mainly on prescribing outcomes. The 56 ITS studies were not included in meta-analyses for outcomes of readmission, mortality, or length of stay due to anticipated high study design heterogeneity versus the RCTs, CCTs and CBAs. Despite the large number of studies included, most did not report on all outcomes (e.g., 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., the antimicrobial prescribing outcome could include changes in decision to initiate or stop dose or route of antimicrobial; readmissions were reported as "all-cause" in 1 study and "infection related" in 4 others). 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.

Primary Outcomes

Interventions to increase effective prescribing in patients with any infection had no effect on mortality (k=3) whereas interventions to increase guideline compliance in patients with community acquired pneumonia (k=4) were associated with reduced mortality. Interventions to decrease excessive prescribing had no effect on mortality (k=11) or length of stay (k=6) and were associated with increased hospital readmissions (k=5 with 1 study reporting all-cause readmission and 4 studies reporting infection-related readmission). Five ITS studies (4 with restrictive interventions, 1 with a persuasive intervention) reported on CDI with a median effect of 68.0% reduction in infection.

Secondary Outcomes

Persuasive (k=44) and restrictive (k=25) interventions were associated with improved prescribing outcomes based on median outcome effect sizes (i.e., the percent subjects with an

improvement or change in the antimicrobial selection, dose, route, or duration versus control). In addition, interventions were typically associated with effect size changes in microbial outcomes in the direction of the intended effect. Meta-regression analyses comparing prescribing (k=38) and microbial (k=14) outcomes from studies that were purely persuasive or purely restrictive showed some evidence of a short-term improvement with restrictive interventions that was not sustained. The outcome measures used to assess effectiveness varied across studies. Multifaceted interventions were common but not necessarily more effective than simpler interventions.

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 at VA Hospitals

The review included 9 studies conducted at VA hospitals and published between 1985 and 2006. Reduced incidence of CDI associated with the stewardship intervention was reported (2 studies). Findings for prescribing and microbial outcomes were mixed. Few clinical outcomes were reported.

Findings from Recent Evidence

The existing systematic review reported mixed results for clinical outcomes and overall improvement in prescribing and microbial outcomes. We focused our review on studies published after 2000 and not included in the prior systematic review or published after the 2009 search date of that review. We summarize findings (Executive Summary Tables 1a and 1b) and report strength of evidence for clinical outcomes (Executive Summary Table 2) according to type of antimicrobial stewardship intervention. Due to small numbers of studies of an intervention reporting each outcome, inconsistency across studies, and overall medium to high risk of bias in included studies, the strength of evidence for all clinical outcomes was rated as low.

Audit and Feedback (k=14)

Among the fourteen studies assessing audit and feedback as the primary stewardship strategy, we found substantial differences in study design, location, and population. Only three were randomized, controlled trials, and the studies were dispersed geographically including Europe, the United Kingdom, Asia, and North and South America.

There were substantial threats to validity, including the possibility of secular trends, 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.

Few studies reported significant differences in patient-related outcomes, although those that did reported differences that favored the intervention. However, several studies demonstrated reduced antimicrobial use associated with the intervention, whether they targeted specific antimicrobials, or all antimicrobials. In one study usage of the targeted antimicrobials decreased, but overall use was not significantly changed.

Executive Summary Table 1a. 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 ≈ 1study - 1 study**	**+ 1 study ≈ 1study - 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

Executive Summary Table 1b. 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

Executive Summary Table 2. Strength of Evidence for Inpatient Antimicrobial Stewardship Studies, by Clinical Outcome

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
A. Audit and Feedback Studies (k=14)						
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]	Low for Readmission
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

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
B. Formulary Restriction and Preauthorization Studies (k=5)						
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, 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, p=0.21	
Aldeyab 2012[14]	ITS	Restriction	High	Incidence of CDI	Reduced *trend* (p=0.008) NS change in *level*	Low for Incidence of CDI
C. Guidelines Implemented with Feedback Studies (k=4)						
Schnoor 2010[15]	RCT	Improve adherence to pneumonia guidelines	High	Mortality	NS	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, RR 0.97 [0.43, 2.17]	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]	
D. Guidelines Implemented without Feedback Studies (k=4)						
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 (ICU)	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

Study, year	Study design	Purpose of intervention	Risk of bias	Outcome	Finding versus control or prior to implementation	Strength of evidence, by outcome
E. Computerized Decision Support Studies (k=4)						
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	
F. Miscellaneous (Protocol) Studies (k=4)						
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

RCT = randomized controlled trial; ITS = interrupted time series; CCT = controlled clinical trial; CBA = controlled before and after study; NS = not statistically significant; OR = odds ratio [95% confidence interval]; RR = rate ratio [95% confidence interval]; IRR = incidence rate ratio [95% confidence interval]; HR = hazard ratio [95% confidence interval]; WMD = weighted mean difference; IV = intravenous; CDI = *C. difficile* infection; CAP = community acquired pneumonia; COPD = chronic obstructive pulmonary disease

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

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

Most studies reported information on costs, though data presentation varied markedly from study to study. No study reported on whether the intervention was cost saving, that is whether saving in antimicrobial use and other savings were greater than program costs.

Little information on potential harms of stewardship programs were reported, although among the limited microbiological results reported, there was an increase in one of the assessed antimicrobial-resistant organisms. Furthermore, we found no evidence that clinical outcomes such as mortality, hospital length of stay, or readmissions were increased.

Formulary Restriction and Preauthorization (k=5)

We identified five studies that evaluated restrictive interventions for ASP, three evaluated preauthorization, and two assessed the impact of formulary restriction (i.e., requiring prescribers to provide a reason for fluoroquinolones designated as limited use drugs). The restrictive interventions did not significantly impact overall mortality (three studies) or hospital length of stay (two studies). All four studies reporting antimicrobial use found reductions in use or inappropriate use that favored the restrictive antimicrobial stewardship intervention. In the RCT, antimicrobial costs were lower in the ASP intervention arm but the significance of the difference was not reported.

Guidelines Implemented with Feedback (k=4)

None of the three studies reporting mortality and length of stay found that guidelines implemented with feedback impacted these outcomes in patients with respiratory illnesses or unspecified conditions. Two studies, one enrolling elderly patients in acute care wards, noted decreased CDI when a narrow-spectrum antimicrobial policy was implemented. Three of four studies reported improved antimicrobial use outcomes (adherence to guideline recommended treatment and decreased prescribing of antimicrobials targeted for decreased use). One study reporting antimicrobial timing outcomes reported improvements in the intervention group as did one study reporting selection outcomes. No differences were found in antimicrobial duration. One study reported microbial outcomes and one reported intervention implementation costs.

Guidelines Implemented without Feedback (k=4)

Across studies of guidelines created and implemented for different purposes (conversion from intravenous (IV) to oral therapy, increasing concordant therapy, etc.), results were moderately consistent in finding few differences in mortality or length of hospital stay. Compliance with initiation of recommended treatment typically increased, duration of therapy was 2 to 3 days shorter following the intervention, and costs were significantly reduced.

Computerized Decision Support (k=4)

An RCT comparing computerized alerts to manual review found reduced costs and no difference in mortality, diarrhea, or length of hospital stay. Alerts were directed to the antimicrobial management team rather than treating physicians. With the computerized alerts, the team spent one hour less each day with the greatest time saving in identifying patients who might need an intervention. A CCT comparing a computerized system linking susceptibility testing to pharmacy information to a manual review of test results found no differences in mortality but decreased length of stay, lower total costs, and lower patient care costs with the computerized system. Following introduction of a computerized decision support system to reduce prescribing

of broad-spectrum antimicrobials, susceptibility of *Pseudomonas* to imipenem improved. The addition of software to search medical records and generate reports did not reduce mortality, length of stay, or readmission but reduced CDI. Other changes noted were less clinically significant and, given the large number of comparisons, results should be interpreted with great caution.

Protocols (k=4)

Implementation of protocols for switching from IV to oral therapy, reassessing therapy after three days, or autosubstitution of antimicrobials resulted in mixed findings for mortality (two studies found no difference and one small study reported reduced mortality) and length of stay. Two studies reported shorter length of IV treatment. Another reported no change in the prevalence of inappropriate therapies. The autosubstitution study found improved microbial outcomes as a result of the autosubstitution of ertapenem for ampicillin-sulbactam.

Laboratory Tests (2 systematic reviews, 2 recent RCTs)

Both of the recent systematic reviews found that compared with standard care, the use of procalcitonin to guide antimicrobial therapy (initiation and duration) for patients with acute respiratory infection or ICU patients with any infection significantly reduced antimicrobial use with no change in mortality, length of stay, or treatment failure. Recent trials reported no differences in mortality, mixed results for ICU length of stay, and non-significant findings for prescribing outcomes.

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. 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. One study noted that a computerized clinical decision support system was time saving compared with manual chart review and recommendations.

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

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. Only six studies were conducted in community hospitals and nine in ICUs. Many studies had different focuses, making it difficult to reach any conclusions about differences in effectiveness according to hospital setting or unit (ICU or other unit). Furthermore, 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.

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.

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

Only two studies reported *possible* harms associated with implementation of antimicrobial stewardship programs. Both were studies with audit and feedback as the primary intervention and reporting of harms was anecdotal. Other "harms" could include statistically significant adverse increases in patient, microbial, or prescribing outcomes due to the ASP intervention. However, reports of possible harms were rare and evidence was of low quality.

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

We identified four studies that described implementation barriers. Based on a single survey, barriers to adherence were identified as knowledge, attitude, and external barriers. The authors recommended development of evidence-based guidelines with involvement from representatives from relevant clinical services and opportunity for iterative feedback. Provider attendance at educational sessions was poor and adding audits or continuous quality improvement cycles to the intervention may increase physician compliance. Other suggestions to improve implementation included gaining a better understanding of the local prescribing culture, fostering an environment of appropriate prescribing, and increasing collaboration between infectious diseases physicians and pharmacists.

Several studies reported on resources required. The makeup of an antimicrobial stewardship team, physician and pharmacist time and workload monitoring patients and reviewing prescriptions to make recommendations, frequency of staff training sessions, and costs of personnel and/or equipment were reviewed.

Most reviewed studies were one year or less and did not comment on sustainability. Over a seven year period an audit and feedback program assessed the impact of a preauthorization for use of antimicrobial agents and guidelines for ordering. After study termination, antimicrobial prescriptions increased by 5.2%. The program was discontinued to permit funding for hiring of additional infectious disease physicians. Authors also noted dissatisfaction amongst providers with the preauthorization requirements. No studies commented on scalability.

CONCLUSIONS

Key Findings

- There is low quality evidence that ASPs can improve prescribing and microbial outcomes with reduced costs without significant adverse impact on patient outcomes.
- In the recent literature, the greatest body of evidence is from audit and feedback studies but a systematic review of earlier studies provided evidence of comparable effects for persuasive and restrictive interventions.

- Studies varied in design (with few randomized, controlled trials), population enrolled, hospital setting, intent of the stewardship program, components of the stewardship program, outcomes assessed and length of follow-up making definitive conclusions about successful program elements, type and sustainability difficult. Most studies were done at a single site, often a university-affiliated hospital, limiting conclusions about scalability.
- Although high quality evidence on comparative effectiveness of ASPs would allow for more definitive conclusions and implementation recommendations, the availability of resources to conduct such studies is limited. Because generalizability to other settings is difficult we urge ongoing evaluation and communication with antimicrobial stewardship program leaders to assess whether implementation of these findings results in desired effects at individual institutions or across national healthcare systems.

We found multiple studies providing low quality evidence that ASPs are associated with improvement in antimicrobial prescribing patterns and reductions in antimicrobial resistance and costs without significant negative impact on mortality, hospital length of stay, or 30 day readmission. These conclusions are based on an updated and comprehensive search of the evidence that includes a wide range of study types, populations, interventions, and outcomes.

Improving hospital antimicrobial prescribing in adults through antimicrobial stewardship programs is an important healthcare need. In addition to improving direct clinical outcomes for individual patients (i.e., mortality, length of stay and hospital readmissions), improving hospital antimicrobial prescribing can be considered successful if it has other positive effects that include lower drug and personnel costs and reduced development of hospital antimicrobial resistance even in the absence of measured clinical outcome improvements. Therefore, the use of these "intermediate" measures (prescribing and microbial outcomes) to assess effectiveness may be appropriate in terms of study design and health policy implementation if data provides reasonable reassurance that ASP interventions intended to alter antimicrobial prescribing patterns do not unintentionally result in clinical harms.

We categorized ASP interventions as audit and feedback, formulary restriction and preauthorization, guideline implementation with feedback, guideline implementation without feedback, computerized decision support, protocol or policy, or laboratory testing. These categorizations are consistent with previous research and conceptual frameworks in this area. We recognize that many of these interventions are multifaceted and contain elements of other intervention categories making classification difficult and somewhat subject to interpretation.

Studies were typically low in methodological quality and varied considerably in the study design, populations enrolled, hospital setting, condition or intent of the ASP program, composition and implementation of the intervention, comparison group, and outcomes assessed. This variability along with limited outcome reporting hampers definitive conclusions or recommendations for policy implementation. Furthermore, many programs are multifaceted and results may be unique to a particular intervention component, population, clinical condition or hospital type, unit or setting. Thus generalizability to other settings is difficult. We urge ongoing evaluation to assess whether implementation of these findings results in desired effects at individual institutions or across national healthcare systems.

Our results are generally consistent with a Cochrane review that included studies through 2009

and categorized and analyzed results in a slightly different fashion. Based on our identification of new literature and feedback from our Technical Expert Panel members antimicrobial stewardship is a rapidly developing field with abundant new evidence emerging. Thus ongoing review and assessment is likely needed to provide up-to-date information for practitioners, policymakers, and researchers.

It is not possible based on the evidence to determine if one type of ASP program is more successful than another or whether targeting a program for a specific ASP intent is superior to another approach. Among the recent studies, the greatest body of evidence of effectiveness is for decreasing inappropriate antimicrobial use or increasing appropriate antimicrobial use (Executive Summary Table 1b), 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. The Cochrane review reported that the median change in antibiotic prescribing for persuasive interventions included in their review ranged from 3.5% for cluster-RCTs to 42% for interrupted time series (with positive changes in the direction of the intended effect). For restrictive interventions, the range was 17% for CBA studies to 41% for RCTs.

We found very limited data on components of ASPs contributing to success, barriers to implementation, scalability or sustainability or whether results vary by hospital setting (academic, urban, rural) or unit. Reproducibility of specific studies was not done and applicability of reported findings is likely low and requiring replication. Some key components are likely to vary by hospital settings, resources, and needs. Future research is needed to identify the most cost-effective and sustainable programs for individual hospitals and broader health care systems. We recommend ongoing evaluation of any program that is implemented to permit adequate evaluation of effectiveness and harms, assessment and removal of barriers to success, determination of sustainability and cost-effectiveness, and if necessary modification.

ABBREVIATIONS

Abbreviation	Definition
AECB	acute exacerbations of chronic bronchitis
ASP	antimicrobial stewardship program
CAP	community-acquired pneumonia
CBA	controlled before and after study
CCT	controlled clinical trial
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRCT	cluster randomized controlled trial
DDD	defined daily dose
EPOC	Effective Practice and Organization of Care
HAP	hospital-acquired pneumonia
HCAP	healthcare-associated pneumonia

ICU	intensive care unit
ITS	interrupted time series
IV	intravenous
LOS	length of stay
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
OR	odds ratio
PD	patient-days
RCT	randomized controlled trial
RR	risk ratio
VA	Department of Veterans Affairs
VAP	ventilator-associated pneumonia
€	euro, currency used by the Institutions of the European Union
£	pound sterling, currency of the United Kingdom