

# Evidence-based Synthesis Program (ESP)

## Antimicrobial Stewardship Programs in Inpatient Settings

### A Systematic Review of the Evidence

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# Evidence-based Synthesis Program (ESP)

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# Evidence-based Synthesis Program (ESP)

## Disclosure

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# Evidence-based Synthesis Program (ESP)

## VA Evidence-based Synthesis (ESP) Program Overview

- Sponsored by VA Office of R&D and Quality Enhancement Research Initiative (QUERI).
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:
  - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

# Evidence-based Synthesis Program (ESP)

- **Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:**
  - develop clinical policies informed by evidence,
  - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
  - guide the direction for future research to address gaps in clinical knowledge.
- **Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:**

<http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm>

# Evidence-based Synthesis Program (ESP)

- **Steering Committee** representing research and operations (PCS, OQP, ONS, and VISN) provides oversight and guides program direction.
- **Technical Expert Panel (TEP)**
  - Recruited for each topic to provide content expertise.
  - Guides topic development; refines the key questions.
  - Reviews data/draft report.
- **External Peer Reviewers & Policy Partners**
  - Reviews and comments on draft report
- **Final reports posted on VA HSR&D website and disseminated widely through the VA.**

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

# Evidence-based Synthesis Program (ESP)

## Current Report

### Antimicrobial Stewardship Programs in Inpatient Settings

### A Systematic Review of the Evidence (September, 2013)

Full-length report available on ESP website (VA INTRANET only):

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

# Evidence-based Synthesis Program (ESP)

## Background

- **More than 3 million kilograms of antimicrobials administered to human patients in the United States in 2009 (Spellberg 2013)**
- **Antimicrobial use influences the patient being treated AND the surrounding ecosystem (Fleming 1945, Avorn 2000, CDC 2010)**

# Evidence-based Synthesis Program (ESP)

## Background

- **Inappropriate/excessive antimicrobial use associated with:**
  - **Increasing microbial resistance**
  - **Higher incidence of antimicrobial associated *Clostridium difficile* infection (CDI)**
  - **Other drug related toxicities and increased healthcare costs (Jacob 2010)**
- **Inadequate antimicrobial use associated with increased mortality (Kollef 1999, Ibrahim 2000, Micek 2010)**

# Evidence-based Synthesis Program (ESP)

## Background

- **Antimicrobial Stewardship Programs**
  - Effort to *optimize* antimicrobial use
    - selection, dose, route, duration
  - **Goals:**
    - Improve patient outcomes
    - Prevent/reduce antimicrobial resistance
    - Reduce adverse antimicrobial effects
    - Deliver cost-effective therapy

(Avorn 2000, Fishman 2006, Dellit 2007, Jacob 2010, Ohi 2011)

# Evidence-based Synthesis Program (ESP)

## Background

- **Antimicrobial Stewardship Programs may involve:**
  - **Multidisciplinary teams (infectious disease physicians, clinical pharmacists, clinical microbiologists, infection control specialists, epidemiologists)**
  - **Support and collaboration of hospital leadership and administration**
  - **Computer systems for decision making and tracking antimicrobial use, infections, adverse drug events**

(Avorn 2000, Fishman 2006, Dellit 2007, Jacob 2010, Ohi 2011)

# Evidence-based Synthesis Program (ESP)

## Background

- **Intervention types include:**
  - **Prospective audit with feedback**
  - **Formulary restriction and preauthorization**
  - **Education**
  - **Guidelines and clinical pathways**
  - **Antimicrobial cycling**
  - **Order forms**
  - **Streamlining or de-escalation of therapy**
  - **Dose optimization**
  - **Parenteral to oral conversion**

(Dellit 2007)

# Evidence-based Synthesis Program (ESP)

## Purpose of Review

**Synthesize evidence about effectiveness & harms of antimicrobial stewardship programs implemented in adult inpatient settings**

# Evidence-based Synthesis Program (ESP)

## Key Questions

- **Key Question #1**

What is the effectiveness of inpatient antimicrobial stewardship programs on the following:

- a. **Primary Outcome: Patient centered outcomes (mortality, readmission, CDI, length of stay)**
- b. **Secondary Outcomes:**
  - 1) **Antimicrobial prescribing**
  - 2) **Microbial outcomes**
  - 3) **Costs**

# Evidence-based Synthesis Program (ESP)

## Key Questions

- **Key Question #2**

What are the key intervention components associated with effective inpatient antimicrobial stewardship?

- **Key Question #3**

Does effectiveness vary by:

- a) hospital setting
- b) suspected patient condition?

# Evidence-based Synthesis Program (ESP)

## Key Questions

- **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?

# Evidence-based Synthesis Program (ESP)

## Methods

- **Cochrane review (Davey 2005) with search to 2003 partially addressed key questions**
- **MEDLINE search 2000 to June 2013, based on Cochrane search strategy, limited to English language**
- **Additional citations from systematic reviews, reference lists of retrieved articles, and suggestions from technical expert panel and peer reviewers**
- **During our review process, Cochrane review updated (Davey 2013) with search to 2009**
  - we included only studies not in this review

# Evidence-based Synthesis Program (ESP)

## Methods

- **Excluded**
  - Conducted in nursing homes or long-term care facilities
  - Pediatric population
  - Antimicrobials for medical or surgical prophylaxis
  - Viral or fungal infections, tuberculosis
  - Provider education only or community/public health campaigns
  - Descriptions of interventions with no outcome assessment
  - Design other than randomized controlled trial, controlled clinical trial, controlled before and after study, or interrupted time series
  - Setting not relevant to medicine in the US (e.g., antimicrobials available without prescription) or involving a population or infectious disease not relevant to US population
  - Did not report outcomes of interest

# Evidence-based Synthesis Program (ESP)

## Methods

- Standard methods for data extraction
- Assessed risk of bias of individual studies (Cochrane Effective Practice and Organization of Care method) and strength of evidence for patient-centered outcomes
- Categorized studies by intervention type
  - Difficult for some studies - multiple interventions, hybrid interventions
- Unable to pool data due to heterogeneity of interventions, study designs, patient populations, and outcomes reporting

# Evidence-based Synthesis Program (ESP)

## Literature Flow

Abstracts Triaged: 6,334



Full Text Review: 559 Articles

Excluded: 539 Articles

Not an included study design: 260

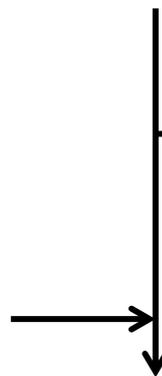
No intervention: 108

Outpatient setting: 71

Not stewardship: 57

Other: 43

Hand Search: 15 Articles



Included: 35 Studies

# Evidence-based Synthesis Program (ESP)

## Results

- **Existing Cochrane Review (Davey 2013)**
  - Included 89 studies published through 2009
  - Focused on prescribing outcomes
  - Categorized interventions as:
    - Persuasive (education, reminders, audit and feedback)
    - Restrictive (order forms, formulary restriction)
    - Structural (EMR, decision support systems)

# Evidence-based Synthesis Program (ESP)

## Results (Davey 2013)

- **Patient-Centered Outcomes - Mortality**
  - Interventions to *increase guideline compliance* for patients with community acquired pneumonia reduced mortality:
    - (4 studies, RR 0.89 [0.82, 0.97])
  - Interventions to *increase effective prescribing* (3 studies) and interventions to *decrease excessive prescribing* (11 studies) were not significantly associated with mortality

# Evidence-based Synthesis Program (ESP)

## Results (Davey 2013)

- **Patient-Centered Outcomes - Other**
  - **Interventions to *decrease excessive prescribing* :**
    - **No effect length of stay**
      - (6 studies, mean difference, -0.04 days [-0.34, 0.25])
    - **Associated with increased hospital readmissions**
      - (5 studies, 1.26 [1.02, 1.57])
    - **Reduction in *C. difficile* infection:**
      - 15% to 65% at one month post-intervention
      - 4 interrupted time series studies

# Evidence-based Synthesis Program (ESP)

## Results (Davey 2013)

- **Prescribing Outcomes**
  - Calculated median effect size with all prescribing outcomes; positive sign = change in intended direction
  - **Persuasive, restrictive, and structural interventions:**
    - Associated with improved prescribing
      - Median change in prescribing ranged from 4% to 46% across intervention types and study design types

# Evidence-based Synthesis Program (ESP)

## Results

- **VA-ESP Evidence**
  - 9 RCTs, 4 CCTs, 2 CBAs, 20 ITS studies
  - Categorized studies by intervention type:
    - 14 audit and feedback
    - 5 formulary restriction and preauthorization
    - 4 guideline implementation with feedback
    - 4 guideline implementation with no feedback
    - 4 computerized decision support
    - 4 protocol or policy implementation

# Evidence-based Synthesis Program (ESP)

## KQ1 – Program Effectiveness: Clinical Outcomes

ASP Intervention (# studies)	Mortality	Length of Stay	Readmission	CDI
Prospective Audit and Feedback (14)	+ 1 study ≈ 9 studies	≈ 9 studies	+ 1 study ≈ 2 studies	p=NR, 1 study
Formulary Restriction and Preauthorization (5)	≈ 3 studies	≈ 2 studies	NR	+ 1 study
Guidelines with Feedback (4)	≈ 3 studies	≈ 3 studies	NR	+ 2 studies
Guidelines without Feedback (4)	+ 1 study ≈ 1study - 1 study	+ 1 study ≈ 1study - 1 study	≈ 1 study	NR
Computerized Decision Support (4)	≈ 3 studies	+ 1 study ≈ 2 studies	≈ 1 study	+ 1 study ≈ 1 study
Protocols (4)	+ 1 study ≈ 2 studies	+ 2 studies ≈ 1 study	≈ 1 study	NR

# Evidence-based Synthesis Program (ESP)

## KQ1 – Program Effectiveness: Prescribing Outcomes

ASP Intervention (# studies)	Use	Selection	Timing	Duration
Prospective Audit and Feedback (14)	Decreased: + 8 studies Appropriate: + 1 study, ≈ 1 study	+ 1 study ≈ 1 study	NR	+ 5 studies
Formulary Restriction and Preauthorization (5)	Decreased: + 4 studies	NR	NR	+ 1 study
Guidelines with Feedback (4)	Decreased: + 1 study Compliant/appropriate: + 2 studies	≈ 1 study	+ 1 study	≈ 2 studies
Guidelines without Feedback (4)	Decreased: + 1 study Compliant/ appropriate: + 2 studies, ≈ 1 study	NR	- 1 study	+ 1 study ≈ 1 study
Computerized Decision Support (4)	Decreased: + 1 study, ≈ 1 study	NR	NR	NR
Protocols (4)	Appropriate: ≈ 1 study	NR	≈ 1 study	+ 2 studies

# Evidence-based Synthesis Program (ESP)

## KQ1 - Program Effectiveness

- **Microbial Outcomes (9 studies)**
  - **6 reported improvement**
    - **decreased infection or resistance**
  - **3 reported no differences**
- **Cost Outcomes (5 studies)**
  - **4 reported decreased costs**
  - **1 reported no difference**

# Evidence-based Synthesis Program (ESP)

## KQ2 Results – Key Implementation Components

- **All author opinion (6 studies)**
  - **Consistent and persistent effort from qualified personnel**
  - **Effective communication skills**
  - **Support from electronic medical records or computerized decision support systems**

# Evidence-based Synthesis Program (ESP)

## KQ3 Results – Effectiveness in Different Settings or Different Suspected Conditions

- **Davey 2013 review**
  - 9 from VA Medical Centers
  - Similar results (unchanged mortality [1], decreased CDI [2], mixed results prescribing [3], decreased infection [3])
- **No recent studies from VA eligible**
- **Most studies from University-affiliated hospitals**

# Evidence-based Synthesis Program (ESP)

## KQ3 Results – Effectiveness in Different Settings or Different Suspected Conditions

- **ICU programs (9 studies)**
  - Similar to overall results
- **Most studies included “any suspected infection”**
- **Respiratory infection (7 studies)**
  - Similar to overall results

# Evidence-based Synthesis Program (ESP)

## KQ4 Results – Harms of Programs

- 2 studies reported *possible* harms (other than patient, prescribing, and microbial harms from KQ1)
  - Anecdotal evidence of inappropriate switch to narrow-spectrum antimicrobial
  - Termination of program speculated to be due to provider dissatisfaction with prescribing restrictions

# Evidence-based Synthesis Program (ESP)

## KQ5 Results – Barriers to Implementation, Sustainability, Scalability

- **Barriers (4 studies; 2 with interview/survey data)**
  - Lack of familiarity, experience, awareness
  - Disagreement with guidelines/conflicting guidelines
  - Lack of communication between professionals
  - Organizational constraints
- **Sustainability (1 study)**
  - Use and costs decreased over 5 years of study and increased when study was terminated
- **Scalability (No studies)**

# Evidence-based Synthesis Program (ESP)

## Discussion

- **Antimicrobial stewardship strategies can decrease antimicrobial prescribing and limit costs, without substantial harms**
- **Greatest body of recent evidence is from audit and feedback programs**
- **Systematic review of earlier studies provided evidence of comparable effects for persuasive and restrictive interventions**
- **Evidence base for KQ1 was substantial; much less substantial for KQ2-5**

# Evidence-based Synthesis Program (ESP)

## Discussion

- **Studies not designed to adequately assess impact on mortality or other clinical outcomes**
- **Suggestions for improving adherence to ASPs:**
  - **Involvement of stakeholders and opinion leaders in guideline and program development**
  - **Addition of quality improvement cycles**
  - **Understanding the prescribing culture**
  - **Collaboration between physicians and pharmacists (mostly opinion rather than evidence-based)**

# Evidence-based Synthesis Program (ESP)

## Discussion

- **Limitations:**
  - **Quality of evidence: Low**
  - **Few randomized controlled trials**
  - **Limited ability to control for secular trends or other confounding variables**
  - **Possibility of regression to the mean in *C. difficile* rates**
  - **Findings for specific interventions have not been replicated**

# Evidence-based Synthesis Program (ESP)

## Discussion

- **Limitations (continued):**
  - **Prescribing improvements often not sustained or long-term follow-up not reported**
  - **Most studies done in academic medical centers; generalizability to other settings is difficult.**

# Evidence-based Synthesis Program (ESP)

## Discussion

- **Limitations (continued):**
  - **Within academic centers, substantial variation in settings, structures, patient bases, culture**
    - **Strength: stewardship has impact in diverse settings**
    - **Weakness: Hard to be sure that each specific intervention works across all settings**
  - **Few studies reported on harms of stewardship interventions; most not designed to identify harms, and most would not have been adequately powered to recognize them**

# Evidence-based Synthesis Program (ESP)

## Future Research Needs

- **Given the complexity of antimicrobial prescribing, conducting well-designed studies is difficult**
- **Large healthcare organizations should consider organizing stewardship activities (that are likely on-going within the organization) to provide useful information on comparative effectiveness of different intervention types**

# Evidence-based Synthesis Program (ESP)

## Overall Conclusions

- **Despite these many shortcomings, the overall evidence suggests that antimicrobial stewardship interventions are associated with improved intended outcomes, mostly antimicrobial usage, over short time periods (1-3 years)**
- **The literature supports hospital and healthcare system implementation of sensible, practical antimicrobial stewardship interventions to improve outcomes**

# Evidence-based Synthesis Program (ESP)

## Recommendations

- **Data on antimicrobial use by clinical unit, type of patients, provider groups, and by individual providers should be gathered to determine where antimicrobial use might be less than ideal or is in need of improvement**

# Evidence-based Synthesis Program (ESP)

## Recommendations

- Existing 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 should be utilized to contribute to stewardship activities
- Leadership should also be informed and involved in planning; leadership support is essential

# Evidence-based Synthesis Program (ESP)

## Recommendations

- **Formative evaluation should be used to identify effective stewardship programs and programs in need of modification**

# Evidence-based Synthesis Program (ESP)

## Questions?

**If you have further questions,  
feel free to contact:**

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The full report and cyberseminar presentation is available on the ESP website  
(Intranet Only):

<http://www.hsrd.research.va.gov/publications/esp/>