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# A Baker's Dozen of Top Antimicrobial Stewardship Publications in 2016

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Abbreviated Title: Top Stewardship Papers in 2016

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**Abstract**

Antimicrobial stewardship efforts are an emphasis among many institutions around the world to combat inappropriate antimicrobial utilization, rising healthcare costs and emerging antimicrobial resistance. Implementation of new innovative strategies may be challenging for many institutions with limited or constrained resources. Using proven effective methods as evidenced by other institutions in the peer-reviewed literature may offer an opportunity to evaluate institution-specific practices, which may be implemented locally. A structured examination and survey of the peer-reviewed, stewardship literature by an expert group of clinicians, scholars and educators determined the most influential publications from 2016. Herein, the top thirteen manuscripts are reviewed to aid clinicians identify potential stewardship opportunities and serve as an educational tool for trainees and others.

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## Introduction

Antimicrobial stewardship programs (ASPs) have been established as a primary mechanism to combat growing concerns of inappropriate antimicrobial use, antimicrobial-associated adverse events and emergence of antimicrobial resistance.[1, 2] The Centers for Disease Control and Prevention (CDC) estimates that 1 out of every 3 outpatient prescriptions for antibiotics is inappropriate with nearly half of outpatient antibiotics being prescribed for upper respiratory tract infections (RTIs).[3,4] From 2010 to 2015, approximately $56 billion was attributed to antibiotic expenditures with greater than half of these costs being associated with the outpatient setting.[5] Following *The National Action Plan for Combating Antibiotic-Resistant Bacteria* in 2015, federal agencies and accrediting bodies quickly adopted requirements for antimicrobial stewardship programs to be in place or to receive payment in acute care facilities.[6-8] Mandates have also expanded to the outpatient services and long-term care facilities.[9] The potential for movement to quality based payment service by Centers for Medicare and Medicaid Services (CMS) will likely further highlight the need for evidence-based antimicrobial practices.[10] Physicians, pharmacists, microbiologists, nurses and other healthcare practitioners offer unique perspectives and skill sets for development, implementation, and continuation of successful antimicrobial stewardship programs.[1, 11, 12] In addition, information technology also plays a critical role in successful implementation of a functional antimicrobial stewardship.[13]

Building a “war chest” of key articles in a practice discipline is essential for any clinician and educator. Keeping up with the medical literature continues to prove difficult as nearly 900,000 citations were indexed in MEDLINE® alone in 2016.[14] From 2007 with the first antimicrobial stewardship guidelines from the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) to December 2016, there has been an average

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annual growth of 250% annually in indexed articles with the MeSH term "antimicrobial stewardship" in MEDLINE.

Subscriptions to table of contents, local journal clubs and attendance at professional meetings are all valuable mechanisms to stay atop the literature; however, a more thorough evaluation includes interpretation and local application.[15-17] Outside of infectious diseases specialty training programs, which are limited in number or potential interest, and antimicrobial stewardship certificate programs (eg MAD-ID, SIDP), education on stewardship and antimicrobials is insufficient in the medical and pharmacy school curricula.[18,19] This leads to self-directed learning and guidance through critical evaluation of the literature by experienced clinicians. Guidelines are also an appropriate place to initiate a working knowledge of antimicrobial stewardship.[1,11] While there is tremendous value in clinical practice guidelines, the level of evidence for many intervention-based recommendations in the newly updated stewardship guidelines are low to moderate or based on expert opinion only.[1,20]

Other expert groups have provided summary articles of "top publications" in a particular topical area to assist readers in building a library of key articles in order to build and maintain an updated, evidence based approach.[21] This paper, using a structured methodology, provides a detailed summary and application recommendation for the top articles published in calendar year 2016 that evaluate antimicrobial stewardship intervention(s). Potential gaps in the literature and critical needs for future stewardship-related research are also briefly discussed.

## Methods

The Southeastern Research Group Endeavor (SERGE-45) network is a 60-member research group composed of infectious diseases pharmacists and physicians who are educators,

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researchers and clinicians. Twelve members were identified as manuscript contributors to serve as the primary authorship team. Following two planning teleconferences, the co-authors agreed eligible papers would meet the following inclusion criteria: (1) any manuscript published in 2016 including electronic publications later in print in 2017 and (2) the manuscript must include a stewardship intervention considered to be "actionable" that readers could implement it at their own institution. Based on the above criteria, SERGE-45 members were asked to "nominate" publications from the 2016 calendar year which were considered to be significant contributions to the antimicrobial stewardship literature. A total of 49 unique publications were nominated. A PubMed search ("antimicrobial" or "antibiotic" "stewardship) was simultaneously conducted and validated by 3 contributors (P.B.B, D.C. and C.B.). Results revealed 887 publications in 2016 which were individually reviewed and evaluated for possible inclusion. Only one additional manuscript was added to the initial pool of nominations, bringing the total to 50 publications. A follow-up teleconference among contributors to discuss submissions reduced the total of possible publications to 25 following exclusions, primarily being the publication did not have an intervention piece related to antimicrobial stewardship. Potential manuscripts (n=25) for final inclusion were then distributed to all SERGE-45 network members and individually ranked via SurveyMonkey (www.surveymonkey.com, San Mateo, CA) based on perceived contribution and strength of contribution to the stewardship literature . The survey had a response rate of approximately 48.3%. Prior to dissemination of the survey results for review, three contributors (D.C., P.B.B. and C.B.) reconvened via teleconference to adjudicate survey results to ensure inclusion of the most impactful manuscripts based on network member opinion. The top 13 manuscripts were finalized and distributed to manuscript co-authors for individual summary.

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The contributors also discussed the need for a summary table of key guidelines and references that did not meet study inclusion but are valuable references for emerging or established stewards. These publications are summarized in Table 1.

**Antibiotic Stewardship Intervention: Pre-Prescription Authorization versus Post-Prescription Review with Feedback**

Many strategies for antimicrobial stewardship exist with pre-prescription authorization (PPA) and/or post-prescription review with feedback (PPRF) outlined as core components in the 2016 IDSA guidelines for implementing an ASP.[1] The guidelines provide a "strong recommendation, moderate-quality evident" for implementing either one or both strategies. Following an overview of the data supporting each strategy in isolation, the guideline authors note that data comparing the strategies is limited.

In an attempt to fill this data gap, Tamma and colleagues[22] conducted a quasi-experimental, crossover trial in adult general medicine patients at a large academic hospital comparing these two strategies. The primary outcome was days of antibiotic therapy (DOT) per 1000 patient-days, including days of antibiotics prescribed upon discharge. Secondary outcomes included length of therapy (LOT), incidence of *Clostridium difficile* infection (CDI) within 60 days, length of hospital stay after start of antibiotics, and in-hospital mortality. Four general medicine teams were divided into two groups, one group started with PPA for months 1-4 followed by a month long washout then months 6-9 with the PPRF. The second group began with PPRF and ended with PPA after the month long washout period. Housestaff taking care of subjects in the PPA group were required to contact a clinical pharmacist or ID fellow for restricted antibiotic approval prior to initiation. It is noteworthy that on day 1 of therapy, there were more patients on

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hospital guideline compliant therapy in the PPA arm versus the PPRF arm (34% vs 41%, p<0.1). This translated into less patients in the PPA arm being on antimicrobials by day 3; however, fewer of these patients had an indication for antibiotic continuation at that time compared to the PPRF arm (36% vs 24%, p = 0.03). Median DOT and LOT had statistically significant reductions in the PPRF arm compared to the PPA arm. There was no difference in other secondary outcomes including CDI, length of hospital stay, and in-hospital mortality.

The findings from Tamma and colleagues provide comparative analysis of two core stewardship strategies recommended in the IDSA guidelines. This data could assist both programs in development and established programs that may be reevaluating current core activities. However, the single-center design and short time interval for each strategy limit broad generalizability. Future studies on this subject are needed to provide a definitive answer.

**Antimicrobial Stewardship Methods for Streamlining Antimicrobial Agents in Patients with Bloodstream Infection**

Antimicrobial stewardship aims to optimize antimicrobial utilization with a goal of improving patient outcomes. Many stewardship approaches have evidence to support effectiveness, including the aforementioned prior authorization of antimicrobials and prospective audit and feedback. There is little evidence available that compares stewardship approaches, especially from within the same institution, which could help control for inherent differences in practices among institutions.

Bushen and colleagues[23] at the Hospital of the University of Pennsylvania have a well-established antimicrobial stewardship program that started with a prior authorization program in 1993. In 2009 they removed most of the antimicrobial restrictions and moved their ASP to using

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prospective audit and feedback. This provided the opportunity to conduct a comparison of the two stewardship approaches. This study included patients with bloodstream infection (BSI), and the study groups were time based. Patients with BSI between May 2008 and May 2009 were included in the prior authorization group, and July 2009 through June 2011 composed the prospective audit and feedback group. The primary outcome evaluated was frequency of streamlining within 72 hours of availability of susceptibilities, defined as changing an antibiotic to one at least one step narrower than what was selected for empiric therapy, or a change to definitive therapy if the organism was resistant to empiric therapy. The secondary endpoint was time to streamlining. There was no difference in streamlining observed between the prior authorization group and the prospective audit and feedback group for all BSI (60.7% vs. 53.2%; $p = 0.123$). There was also no difference in the time to streamlining, with both groups reporting a median time to streamlining of approximately 22 hours after availability of susceptibilities. One notable finding in the prospective audit period was an increase in opportunities to streamline antibiotics for patients with gram-negative BSI. This institution observed an increase in empiric use of broad spectrum antibiotics against gram-negative organisms during the prospective audit period and thus had more opportunities to narrow antibiotics when a gram-negative organism was isolated (51.4% vs. 35.6%; odds ratio (95% CI) 1.85 (1.06-3.25). It appears that both prior authorization and prospective audit and feedback are similarly effective for streamlining antibiotics for patients with BSI. However, when broad spectrum gram-negative antibiotics are not restricted, streamlining efforts may be more useful when directed at patients with gram-negative BSI.

The generalizability is limited by the single-center nature of the study in addition to having a dedicated ASP where some centers may lack such resources. The study also used antimicrobial

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susceptibility as an opportunity for de-escalation without consideration of patient specific factors which may have influenced initial drug selection. Finally, the study did not examine the impact of the streamlining on treatment outcome. Despite these limitations, this study provides useful data comparing commonly employed stewardship strategies.

**Rapid Review and Intervention Compared with Standard of Care in Patients with Positive Blood Cultures**

Bloodstream infections are a major cause of morbidity and mortality, however initial positive culture results, Gram stain and morphology, are frequently communicated to treating physicians without treatment recommendations. Antimicrobial stewardship teams can play an important role in assisting with the optimization of antimicrobial therapy for BSI by coupling microbiology data with pertinent clinical recommendations at the time of culture results.

Cairns and colleagues[24] designed a prospective, randomized controlled trial to determine if rapid review of positive blood cultures by the ASP improved timeliness of appropriate antimicrobial therapy on the general inpatient wards in two Australian hospitals. ASP members included an infectious diseases physician and a senior pharmacist. The intervention arm, which included a medical record and culture review, and necessary recommendations communicated by the ASP, was compared to the standard of care (SOC) of the laboratory communicating Gram stain results to the treating physician. The primary outcome of timeliness of treatment was assessed in three ways: time from blood culture draw until start of active treatment, time from blood culture draw until start of appropriate treatment and time to cessation of antimicrobials when pathogens were deemed contaminants. Outcome assessment was performed by two blinded infectious diseases

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physicians and disagreements resolved by discussion and a third physician opinion. Compared with the SOC arm (n=81), the intervention arm (n=79) was eight times more likely to be started on active antimicrobials (HR 8.02, 95% CI: 2.15-29.91) and 1.9 times more likely to be started on appropriate antimicrobials (HR 1.95, 95% CI: 1.13-3.38) earlier. The median time to appropriate therapy was 20 hours less in the intervention arm. There were no significant differences in the time to treatment cessation in the setting of contamination. The secondary outcome of all-cause mortality was statistically higher in the intervention group; however only one of the seven patients died secondary to infectious complications. While the findings of this study could provide a framework for future opportunities in some centers, several limitations impact the external validity of this study including: low gram-negative resistance rates, low enrollment secondary to the exclusion of high risk services due to preexisting infectious disease involvement (intensive care unit, hematology, burn and lung transplantation) and low number of contaminated samples.

**Clinical Decision Support Impact on Antimicrobial Use and Length of Stay**

Many stewardship interventions today involve some layer of clinical decision support. Use of clinical decision support (eg EPIC, TheraDoc) can also assist in determining impact of stewardship initiatives on several important metrics including hospital length of stay, antimicrobial consumption and cost savings associated with interventions.

Nault and colleagues[25] conducted a quasi-experimental retrospective study from August 2008-August 2013 to determine the longitudinal impact of a clinical decision-support system (Antimicrobial Prescription Surveillance System, APSS) on antimicrobial use and length of stay when integrated into a prospective audit and feedback strategy. Similar to other software, APSS

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monitors clinical information and identifies opportunities for intervention such as drug-drug interactions, drug-bug mismatches and dosing optimization. The study was conducted at a 677-bed hospital system in Quebec, Canada which did not conduct any systematic stewardship initiatives prior to July 2010 and thus data was analyzed in a pre and post-intervention analysis. The outcomes assessed included average hospital length of stay, antimicrobial consumption in defined daily doses (DDD) per 1000 patient days (DDDs/1000 PDs), DOT per 1000 inpatient days (DOTs/1000 PDs), antimicrobial spending using fixed prices, and percentage of inappropriate prescribing or non-concordance with guidelines. The study revealed a 91% intervention acceptance rate in the post-intervention period. The length of stay also declined post-intervention with a continued trend over the following 3 years. Similarly, antimicrobial consumption (DDDs and DOT) demonstrated an immediate and sustained impact. Using a segmented regression analysis of interrupted time series, the study found a decrease in DOT from baseline (-28, P=0.01; intercept 301 DOT/1000 PDs). Pharmacy expenditures also significantly decreased (annual direct savings of $350,000). The study extrapolated their findings to indirect savings of $2085 per hospitalization. The study also found a decrease in inappropriate prescribing practices albeit not statistically significant. The findings are limited by the single-center nature of the study, inherent differences in intervention receptiveness at other facilities and the possibility of residual confounding.

The findings of this study illustrate the utility of clinical decision support software in facilitating stewardship initiatives and measuring the respective sustainable impact. While there are costs associated with purchasing software, the findings of this study demonstrate an overall return on investment for both patients and clinicians. The study points out that many centers may not have physicians or pharmacists with infectious diseases training; however, the use of support software

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may lessen the time burden associated with a prospective audit and feedback strategy. The study also indirectly highlights associated behavioral changes given that use of antimicrobials was being closely monitored and evaluated.

**Syndrome-Specific Antibiotic Stewardship Intervention: Community-acquired Pneumonia**

Community acquired pneumonia (CAP) is one of the most common reasons for antibiotic therapy in the hospital setting and is responsible for over 1 million admissions annually in the United States.[26] IDSA/SHEA antimicrobial stewardship guidelines have recommended syndrome specific antibiotic stewardship interventions however this is a weak recommendation based on low-quality evidence.[1] Due to the high incidence, and potential for optimization of both antibiotic selection and duration, CAP may be an excellent target for many antimicrobial stewardship programs.

Haas and colleagues[27] implemented an intervention focusing on improving the management of CAP. A clinical practice guideline and orderset for CAP management of adult, non-ICU inpatients was created and implemented with collaboration from Infectious Diseases, Hospital Medicine, Pulmonary and Critical Care, Internal Medicine, Emergency Medicine, Pathology, Pharmacy and Microbiology. The primary outcome was the difference in duration of antibiotic therapy during the baseline and intervention phases. Secondary outcomes included change in utilization of levofloxacin, unnecessary use of computed tomography (CT) scans of the chest and sputum culture collection. Two hundred fifty patients were included (166 from baseline group and 84 from intervention period).

Median duration of therapy was decreased from 10 days to 7 days ($p<0.0001$). Levofloxacin prescribing at discharge decreased from 60% to 27% of cases ($p<0.0001$). The utilization of

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chest CT scans and sputum cultures were also decreased. No difference was found in clinical failure rate (7% and 10%, p=0.53) between the baseline and intervention groups; however, more frequent rehospitalization was noted during the intervention phase. The authors noted that this finding deserves further exploration but was not likely attributable to shorter course therapy. This study while limited to a single-center and a relatively small sample size, showcases the impact of a systematic hospital wide approach to antimicrobial stewardship. In institutions where a daily prospective audit and feedback stewardship approach is not feasible, multidisciplinary collaboration to create guidelines and ordersets may have a significant impact on antimicrobial utilization within a particular syndrome or disease state.

**Syndrome-Specific Antibiotic Stewardship Intervention: *Clostridium difficile* infection**

CDI continues to be a significant cause of health care-associated infections and an area of focus for many ASPs. Areas of focus for stewardship programs include: optimization of *C. difficile* testing and therapy, reduction of inappropriate concomitant antimicrobial utilization and reduction of unnecessary H2-antagonist/proton pump inhibitor therapies.[28] The majority of studies to date have focused on reduction of CDI through stewardship measures.[29] However, the utilization of ASP to improve the care of patients with CDI has not been well studied.

Welch and colleagues[30] conducted a single-center quasi experimental study within the University of Michigan Health System evaluating patients before and after implementation of an ASP directed CDI bundle. The primary outcome was a composite of attributable 30-day mortality, intensive care unit (ICU) admission within 30 days of diagnosis, need for colectomy or ileostomy for complicated CDI within 30 days or CDI recurrence. CDI recurrence was defined as a second occurrence of CDI 2 to 8 weeks after the date of the index case. The ASP review and

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interventions were conducted by an ASP pharmacist Monday-Friday between 8AM-5PM. Recommendations were classified into four types: prescribing guideline concordant CDI therapy, discontinuation or de-escalation of non-CDI antibiotics, minimization of acid-suppressive therapy, and recommendation for ID or surgical consultation. Change in process measures such as vancomycin treatment for severe CDI, time to initiation of vancomycin, discontinuation of unnecessary PPIs and rate of ID consultation for severe CDI was also evaluated.

No difference was found in the primary composite outcome between the intervention and pre-intervention groups (12.3% vs 14.7% p=0.40). ASP intervention was shown to improve process measures including PPI discontinuation and ID consultation for severe CDI. The lack of difference in the composite endpoint was hypothesized to be due to low baseline rates of the individual components of the composite outcome. Limitations of this study include single-center study design, one ASP review per patient and lack of evaluation of alternative treatment modalities such as fidaxomicin or fecal microbiota transplant. Further research is warranted in institutions with higher recurrence and/or complication rates.

**Selective Antimicrobial Susceptibility Reporting**

Selective reporting is an antimicrobial stewardship technique that attempts to steer prescribers to narrower spectrum antibiotics. Broad spectrum antibiotic susceptibilities are only published when the organism tested is resistant to narrow spectrum agents. Fluoroquinolones are an attractive target for selective reporting. They are broad spectrum agents that are effective for a wide range of infections and have high bioavailability, all characteristics that make these agents appealing first-line options for prescribers and increase the potential for overuse. With

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significant risks of adverse effects and increasing resistance associated with fluoroquinolone use, stewardship initiatives to decrease utilization are of interest.

Langford and colleagues[31] reported on their experience with selective ciprofloxacin reporting at a 400 bed hospital in Toronto that notably experienced two outbreaks of CDI in 2010 and 2011. They developed a selective reporting policy for Enterobacteriaceae that were isolated from any site of infection. If the isolate was susceptible to all other agents on the gram-negative panel (excluding ampicillin) the ciprofloxacin susceptibility would not be reported. This institution had antibiotic utilization data and isolate susceptibility data for each month between April 2008 and March 2015. They conducted an interrupted time series analysis with segmented regression to evaluate a primary outcome of change in inpatient ciprofloxacin utilization as measured in DDD. Secondary outcomes included *Escherichia coli* and *Pseudomonas aeruginosa* susceptibility to ciprofloxacin. They found that selective ciprofloxacin reporting decreased inpatient ciprofloxacin utilization from 87 DDD to 39 DDD ($p<0.001$). There was no statistically significant difference in *P. aeruginosa* susceptibility to ciprofloxacin, but selective ciprofloxacin reporting appeared to slow the decrease in ciprofloxacin susceptibility in *E. coli* as predicted by their regression model. The *E. coli* ciprofloxacin susceptibility was statistically higher than predicted 12 and 24 months after the intervention was implemented. They did observe an increase in amoxicillin/clavulanate use after the ciprofloxacin intervention. Selective reporting may be an effective approach to decrease use of a targeted antibiotic or class, and may also be beneficial for antimicrobial resistance. It is important to monitor for a potential compensatory increase in utilization of alternative antibiotics when an intervention specifically targets one antibiotic or class of antibiotics. Whereas this intervention appears attractive for institutions with equally high fluoroquinolone utilization, its value cannot be generalized to

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hospitals with low or moderate fluoroquinolone use. In addition, it is logical to suppress fluoroquinolone susceptibilities in patients with minor infections (cystitis, skin and soft tissue, etc.) to encourage the use of narrower spectrum agents in these settings. However, this approach may be questionable in patients with serious infections such as bloodstream infections (BSI) since fluoroquinolones offer the highest bioavailability and lowest treatment failure rates among all available oral options.[32] Finally, without measurements of antimicrobial utilization in the community, it is not possible to attribute the perceived change in susceptibilities of *E. coli* isolates which are predominantly community-acquired to a decline in fluoroquinolone use in the hospital. An improvement in susceptibilities of *P. aeruginosa* isolates, which are predominantly hospital-acquired, would have been more conceivable as a result of this intervention.

**Antimicrobial Stewardship and Rapid Diagnostics: Blood Culture PCR**

Knowledge in rapid diagnostic technologies (RDTs) among pharmacists engaged in antimicrobial stewardship activities is variable and overall low.[33] Conventional microbiology culture and susceptibility reporting requires 48 to 72 hours to produce final results, leading to a delay in judicious and appropriate use of antimicrobials, which negatively impact patient outcomes in an era of escalating antimicrobial resistance. The use of rapid organism identification techniques in addition to ASPs has been shown to decrease the time from culture collection to organism identification and consequently the time to effective antimicrobial therapy and de-escalation, which may positively impact patient outcomes.

MacVane and colleagues[34] sought to examine the impact of a polymerase chain reaction (PCR)-based blood culture identification panel combined with a real-time ASP on antimicrobial use and patient outcomes. This was a retrospective study conducted at Medical University of South

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Carolina with relatively low antimicrobial resistance rates. The primary outcome was the comparison of times to effective therapy and initial antimicrobial use with the blood culture identification panel versus conventional methods with and without antimicrobial stewardship. The unique aspect of the study were the comparisons across three arms to account for the incremental contribution of each individual intervention to study endpoints: conventional organism identification arm (control), conventional organism identification with antimicrobial stewardship arm (ASP), and blood culture identification panel with antimicrobial stewardship arm (BCID). Clinical and economic endpoints were also compared between arms and included hospital length of stay, in-hospital mortality, infection-related mortality, 30-day all-cause readmission, microbiological clearance, and hospital costs. There were 783 patients with positive blood cultures identified and screened during the study periods. Out of these 783 patients, only 364 met the inclusion criteria: 115 in the control arm, 104 in the ASP arm, and 145 in the BCID arm. Many cultures were excluded because they were deemed contaminants or they were not on the blood culture identification panel. The blood culture isolates of the included patients were similar in prevalence between the three arms and included 41.6% gram-positive bacteria, 50.5% gram-negative bacteria, and 7.9% *Candida* spp. However, the source of BSI was more frequently intra-abdominal in the control arm than in other arms. Time to organism identification was significantly shorter in the BCID arm (17.2 hours; $P < 0.001$) than in the control arm (57.4 hours) or the ASP arm (53.9 hours). Time to effective therapy was also significantly shorter in the BCID arm (4.9 hours; $P < 0.001$) than in the control arm (15.0 hours) or the ASP arm (13.0 hours). Rates of antimicrobial de-escalation were significantly shorter in the BCID arm and the ASP arm (76% and 59%, respectively; $P = 0.001$) than in the control arm (39%). Time to first antimicrobial de-escalation was significantly shorter in the BCID arm (48.1 hours; $P = 0.03$) than

in the ASP arm (60.5 hours) or the control arm (63.0 hours). There were no statistically significant differences with regards to hospital length of stay, in-hospital mortality, infection-related mortality, 30-day all-cause readmission, microbiological clearance, or hospital costs between the three arms.

This study showed that ASPs improved antimicrobial utilization in the early course of BSI and the addition of rapid organism identification techniques to ASPs resulted in a more rapidly effective therapy and more judicious utilization of antimicrobials. Limitations include the retrospective design, lack of randomization, and stewardship interventions occurring only during working hours. Findings of this study support the use of rapid organism identification techniques in addition to ASPs in the management of bloodstream infections to further enhance antimicrobial utilization.

**Antimicrobial Stewardship and Rapid Diagnostics: MALDI-TOF**

Rapid diagnostics within microbiology have revolutionized the way microbiology labs identify pathogens; however, the additional cost of implementing these techniques can be difficult to justify. A number of studies have shown that many benefits of rapid diagnostics are only fully realized when coupled with interventions by an ASP.[35-38] Previous studies have reported cost savings of implementing rapid diagnostic identification in conjunction with ASP intervention, but these studies either evaluated a limited population or did not take into account the costs of additional pharmacist time requirements to make interventions.[37, 39, 40]

Patel and colleagues [41] evaluated the total hospital costs 3-months before and after implementation of Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry (MALDI-TOF) with ASP interventions on bloodstream infections (BSI) at the

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University of Michigan Health System. The primary outcome was total hospital cost from the date of positive index blood culture to the date of discharge or death in adult patients with BSI. During the pre-intervention period, medical teams were alerted of Gram stain results for blood cultures, but no real-time alerts were made for identification or susceptibility. In the intervention period, real-time alerts to medical teams on Gram stain results continued, but real-time alerts for Gram stain, identification, and susceptibilities were also reported to the ASP. The total hospital cost per BSI decreased by $2,439 per BSI ($42,580 versus $45,019), which accounted for a net annual cost savings of approximately $2.34 million at this large institution. This cost savings accounts for increased pharmacist time spent on interventions and the cost of the technology, but does not include the potential increased revenue from back filling hospital beds due to decreased length of stay. The largest driver of the overall reduction was in decreased ICU costs per BSI ($10,833 versus $13,727). Beyond the cost savings seen, the reduction in thirty-day mortality was significantly improved in the intervention group (12% versus 21%, $P< 0.01$). The results of this study show that implementing rapid diagnostics with ASP intervention can improve patient outcomes while also decreasing overall healthcare costs. However, it remains difficult to justify an undertaking of this size when many institutions still look at costs as budget silos without taking into account how other budgets are offset. Furthermore, the costs associated with implementing MALDI-TOF are likely to vary by institution. The single-center quasi-experimental design should also be considering when extrapolating these results to other respective institutions. This study provides further evidence that ASP focusing on quality of care can improve outcomes while also improving overall hospital costs.

**Antimicrobial Stewardship in the Emergency Department (ED)**

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One of the aforementioned National Action Plan's goals is to establish ASP in healthcare facilities.[6] While inpatient ASP has been the first target for many healthcare organizations, the ED is another area ripe for intervention despite many unique challenges. These challenges include: high censuses, rapid patient turnover rates, lack of standardized follow-up procedures and heightened emphasis on patient satisfaction surveys which likely have reimbursement implications for the facility. Patients are often prescribed antibiotics in the ED after positive urine analyses (UA) result and are discharged on multiple days of therapy with a presumed urinary tract infection (UTI) regardless of clinical symptoms.

Zhang and colleagues[42] developed a quality improvement project to assess antibiotic prescribing practices during a 4-month period for UTI at a community hospital emergency department through a prospective cohort study (chart review with audit and feedback approach). Data was collected for ED encounters in which a urine culture was ordered during the ED visit. The primary endpoint was potential days of antimicrobial therapy avoided if antibiotic discontinuation or change was recommended by an ED clinical pharmacist (EPh) for non-pregnant patients without urinary symptoms. Discontinuation of antimicrobial therapy resulted in 113 antibiotic days saved (27% of all days) and changes in therapy resulted in 9 antibiotic days saved (2% of all days) which resulted in a total of 112/426 (29%) of prescribed days saved. The secondary endpoints included correlation of antimicrobial usage with various UA components and percentage of EPh recommendations accepted. Factors found to significantly increase the odds of antibiotic prescribing included the presence of the following in the UA: leukocyte esterase (OR 4.5; 95% CI: 1.2-17.2; p=0.03) or nitrites (OR 10.8, 95% CI: 1/7-68.1; p=0.01). Age ≥75 years old was also significantly associated with increased risk of antibiotic prescribing (OR3.5, 95% CI: 1.2-9.6; p=0.02). For patients who were discharged on antibiotics, 97% of

actionable recommendations by the EPh were accepted by the reviewing midlevel provider (n=35). This study is limited to the data provided in the electronic medical health record in which the EPh was reviewing to assess symptoms of UTI compared to UA result and final UC results. The study did not specify whether UA was the result of a urine dipstick and/or microscopy for pyuria. The study highlights the importance of educating providers that bacteriuria and pyuria do not necessarily signify UTI in the absence of symptoms. Inappropriate prescribing of antibiotics for abnormal urine analyses results and asymptomatic bacteriuria remains a target for improvement in ambulatory settings, hospitals and skilled nursing facilities.

**Behavioral Interventions and Inappropriate Antibiotic Prescribing**

Outpatient antimicrobial stewardship is desperately needed; however, at present is virtually non-existent throughout most of the United States. The ramifications of this continue to burden the healthcare system as most antibiotics prescribed in the outpatient setting are for conditions which often do not warrant antimicrobial therapy. Moreover, the ecologic consequence of excessive antibiotic use on the community has resulted in change in epidemiology of antimicrobial resistance and increase in the burden of difficult to treat infections in the community. For example, infections due to extended-spectrum ß-lactamase (ESBL)-producing *Enterobacteriaceae* are now predominantly community-borne.[43-45] Many outpatient stewardship interventions take place at the level of the patient where the prescriber has selected a therapy. Meeker and colleagues[46] sought to examine the effects of behavioral intervention at the point of care through a multisite cluster randomized clinical trial which took place in two major metropolitan cities. The primary outcome was inappropriate antibiotic prescribing rate for acute RTI and thus the efficacy of the interventions was assessed based on reductions in this practice.

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A baseline for current prescribing practices was established for 18 months prior to the intervention implementation. Three intervention types were implemented including suggested non-prescription alternatives via an electronic order set, required justification for antimicrobial therapy entered into the patient electronic health record and peer comparison of prescribing rates. The latter two interventions were strengthened by the effect of social norms on prescribing behaviors. Clinics were randomly assigned to no intervention (control), one, two or all three of the interventions and followed for 18 months. The study demonstrated a statistically significant difference using accountable justification (absolute difference, −18.1%; $p < .001$) and peer comparison (absolute difference, −16.3%; $p < .001$) as behavioral interventions; however, it is worth noting the rate of return visits with a possible bacterial infection was higher in the justification plus peer comparison groups compared to the control group (1.4% vs. 0.4%). The findings of the study could be limited by factors impacting external validity including type of practice, heterogeneity of clinician practice and electronic health record software. Changing clinician behavior is perhaps the most difficult strategy as it pertains to appropriate prescribing regardless of setting, this study provides some framework for where to start.

**Personalized Prescription Feedback in Primary Care**

Recent literature has revealed the breadth of antimicrobial consumption in the primary care setting.[47] Core elements have been published by the CDC in an attempt to begin implementing strategies the decrease overuse in the community setting.[48] Studies documenting prescription feedback as a stewardship intervention have been recently published.

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In this publication Hemkens and colleagues[49] describe the rationale and design of their trial, which aims to assess the effect of personalized prescription feedback on antibiotic prescribing practices of primary care providers (PCPs).

The researchers utilized national reimbursement claims data to identify 2900 PCPs in Switzerland with high antibiotic prescription rates. This sample was subdivided into an intervention group and a control group. The intervention group received postal and online evidence based guidelines initially plus quarterly data for 24-months comparing them to peers regarding their antibiotic prescribing practices. Guidelines provided were on the 7 most frequent reasons for antibiotics in primary care (acute unspecified URIs, sore throat/acute tonsillitis/pharyngitis, acute rhinosinusitis, acute otitis media, acute bronchitis, CAP, and uncomplicated UTI. The control group received no information. The primary endpoint was antibiotics prescribed to any patient in a one-year period was as measured by DDD per 100 consultations within the intent to treat population. Secondary outcomes included assessments by age group, sex, and antibiotic type.

Of the 2689 PCPs included in the intent-to-treat analysis (211 providers in the intervention group opted out), there was no difference in prescribing rates between the intervention and control group for either year evaluated. Great seasonal variation occurred in prescribing rates throughout the study period. Less prescribing by the intervention group to patients 6 to 18 years was identified but not sustained for both years. Less prescribing by the intervention group to patients 19 to 65 years was only seen in the second year.  No differences were seen when analyzed by antibiotic type.

The failure of this intervention to meet the primary outcome serves to support existing notions that (1) ASP personnel face substantial challenges towards impacting prescribing practices of

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PCPs, and (2) much work is left to be done towards directing interventions geared at modifying the antibiotic prescribing practices of PCPs. The publication is noteworthy because while provider-specific feedback in the inpatient setting is well known to produce favorable practice changes, limited data on this intervention type exists in the outpatient arena. This work does provide a pragmatic framework that may help direct the design of future studies, but is somewhat limited by the use of aggregate data.

**Antimicrobial Prescribing Strategies in the Outpatient Setting**

Inappropriate antimicrobial prescribing for uncomplicated RTIs remains a primary antimicrobial stewardship target. The majority of these infections are viral in etiology requiring no antibiotic therapy; however approximately 60-70% of patients with a sore throat or acute bronchitis are prescribed antibiotics. Two primary factors driving prescribing include fear of secondary complications from the infection as well as pressure from patients to receive antibiotic therapy. Delayed antimicrobial prescribing may represent a bridge to decrease the overall use of antimicrobials; however, data are limited in its overall effectiveness.

de la Poza Abad and colleagues[50] undertook a randomized, open-label study to evaluate 4 different antibiotic prescription strategies in the management of uncomplicated RTIs in Spain. These included a delayed patient-led approach (patient received antibiotic at clinic appointment), a delayed antibiotic prescription approach where patient was required to return for the prescription, an immediate prescription approach (antibiotics were started same day as visit), and no antibiotic approach. Patients were instructed to consider returning to for care if no improvement after 5 days for pharyngitis or 10 days for all other infections. The primary outcomes were duration and severity of symptoms based on a 6-point Likert scale (Scores 3 and

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4 were moderate; 5 or 6 were severe). Secondary outcomes included antibiotic use, patient satisfaction scores, and self-reported patient belief in the overall effectiveness of the antibiotic course. The majority of patients were female with a mean age of 45 and no underlying respiratory comorbidities. Nearly 75% of patients in the study had pharyngitis or acute bronchitis. Duration of severe symptom was 3.6 days in patients receiving an immediate prescription, which was significantly shorter than patient-led approach (5.1; $p<0.05$), delayed prescription approach (4.0; $p<0.05$), and no prescription approach (5.1, 4.0 and 4.7 days, respectively; $p<0.05$ for all). Patients receiving an immediate prescription also had a significant decrease in duration of moderate symptom (4.7 days) compared to patient led-approach, delayed prescription approach, and no prescription approach (6.0, 5.3 and 6.5 days, respectively; $p<0.05$ for all). While statistically significant, the clinical significance of these findings are minimal considering there were no differences between groups regarding complications, adverse effects, or need for unscheduled care. General health status assessed at 30 days also revealed no differences. Importantly, only 12% of patients in the no prescription group received antibiotics. Moreover, 33% and 23% respectively of patient-led and delayed prescription groups ultimately took antibiotic therapy demonstrating the value of a delayed-prescribing approach on antibiotic usage. The findings of this study are limited by sample size, predominance of limited disease states, and study design. This data helps confirm other recent data showing benefits of delayed-prescribing on uncomplicated URIs.[51,52] However, more data are needed especially in patients with lower educational levels (approximately 75% of patients in this study had secondary education or higher).

**Discussion/Conclusion**

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While a large number of important articles have been published in recent years related to antimicrobial stewardship, few articles have been focused specifically on both behavioral and clinical interventions. Practitioners are seeking sound, scientifically validated stewardship interventions that will provide benefit while minimizing harm. Guidance which enhances efforts at facilities based on factors such as target population, local epidemiology, resource availability, and type of practice site (community vs. academic) is critical. It is important to publish all data related to stewardship interventions, both positive and negative, to help guide practitioners in the development of their specific ASPs. For example, an important "negative" paper published demonstrated that providing rapid diagnostic testing for staphylococci is not effective without active notification or antimicrobial stewardship intervention.[53] Therefore ASPs that choose to implement rapid diagnostic testing should have a dedicated stewardship advocate for this technology for clinical and cost effectiveness.

The IDSA/SHEA ASP implementation guidelines note a number of core interventions that are of low quality evidence leading to a weak recommendation.[1] Some of these areas include use of didactic education, implementing facility specific clinical practice guidelines for common infectious diseases, implementation of pharmacokinetic monitoring and adjustment programs for vancomycin, allergy assessment initiatives, and microbiology cascade reporting. While some of the articles included in this review should help strengthen these core recommendations, more data are needed in these areas to strengthen support for these interventions.

There are also a number of areas with significant data limitations mentioned in the guidelines such as implementation research. While requirements have been instituted by organizations such as Joint Commission, true implementation of stewardship programs remains sparse at around 40% of hospitals in the United States (CDC) with a goal of 100% by 2020. Continued research

with a focus on clinical interventions will help give interested stakeholders the tools to help implement ASPs nationwide.

Evaluation of the vast amounts of stewardship literature is challenging for both the stewardship novice and the experienced stewardship practitioner. At a time when regulatory bodies are increasing requirements for stewardship programs both in the inpatient and outpatient settings, many pharmacists as well as other healthcare practitioners without formal training or experience are participating in or heading these programs. It is imperative in the era of increasing antimicrobial resistance and paucity of currently available agents for multidrug resistant infections to maximize research focusing specifically on stewardship interventions.

In this antimicrobial stewardship review that is primarily focused on interventional studies, SERGE-45 investigators chose a variety of papers from North America, Europe and Oceana. Antimicrobial stewardship is a global topic and studies from the rest of the world are highly anticipated in next year's version of this review. In an era of increasing antimicrobial resistance rates, it is conceivable that most of the aforementioned interventions were designed to reduce antimicrobial consumption. Moreover, it is empowering to see some of the reviewed interventions primarily focused on optimizing antimicrobial therapy in patients with serious infections. This emphasizes the important role of ASP in improving the quality of patient care, which is the ultimate goal of all healthcare providers. Notably, it seems overly optimistic that many of these quality interventions examine mortality or hospital length of stay as their primary end point. First, most antimicrobial stewardship interventions are underpowered to achieve either goal. Second, the association between appropriate empirical antimicrobial therapy and improved outcomes (reduced mortality and hospital length of stay) has been repeatedly demonstrated in patients with serious infections such as sepsis and BSI.[54-58] It is critical for our specialty to move

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away from the pressure of reinventing the wheel in every single study. The use of appropriateness of antimicrobial therapy as the primary end point in quality antimicrobial stewardship interventions is not only more practical, it is logical and supported by the literature. After all, mortality and hospital length of stay are subject to many clinical variables (acute severity of illness, host comorbidities, etc.), but the only one that is modifiable by ASP is antimicrobial therapy.

Whereas the majority of reviewed articles examined hospital-based antimicrobial stewardship interventions, at least 4 targeted antimicrobial prescription in ambulatory settings, including emergency departments. These community-based antimicrobial stewardship interventions are of vast importance given the rapid increase in antimicrobial resistance rates in the community and the emergence of multi-drug resistant (MDR) bacteria such as methicillin-resistant *Staphylococcus aureus* and ESBL-producing *Enterobacteriaceae* as community-onset pathogens.[44,45] Many reviewed interventions focused on reducing fluoroquinolone utilization in hospitals. However, it appears more intuitive to extend these interventions to target fluoroquinolone use in the community as recently published data has begun to evaluate.[59] First, a large proportion of fluoroquinolone use in the community is for self-limiting URTI and uncomplicated cystitis where the use of narrower spectrum antimicrobial agents is more appropriate. Second, fluoroquinolone use has already declined in U.S. hospitals over the past decade either due to increasing antimicrobial resistance rates and understandably loss of providers' faith in fluoroquinolones as empirical agents for hospitalized patients with serious infections or existing institutional antimicrobial stewardship efforts.[60] For this reason, fluoroquinolone resistance rates in the community have exceeded those in many hospitals particularly in southeastern USA.[61,62] The emergence of *E. coli* sequence type 131 at the turn of

606 the century as the dominant MDR strain in the community and skilled nursing facilities is now a
607 major public health threat.[63] Further efforts to combat excessive and inappropriate antimicrobial
608 use in the community are highly welcomed. We hope this review of relevant stewardship
609 intervention research will help stewardship practitioners apply this data to their particular
610 practice.
611
612
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626
627
628 **References**

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| **Table 1. General Guideline, Policy and Antibiotic Metric References for Antimicrobial Stewardship Programs** | |
|---|---|
| **Title** | **Citation** |
| **Guidelines** | |
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| CDC Antibiotic Use in Nursing Homes | Available at: http://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html |
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