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Antimicrobial Stewardship as Part of the Infection Prevention Effort

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Abstract Antimicrobial stewardship programs (ASPs) optimize antimicrobial use to decrease the incidence of infection with multidrug-resistant organisms (MDRO) and the emergence of drug resistance, to improve patient outcomes and safety, and to decrease hospital costs. ASPs achieve these goals through several types of interventions that can occur before or after the antimicrobial has been prescribed; interventions can also be "active" or "passive." We believe that active post-prescription interventions such as post-prescription audit and feedback have the most supportive evidence and most promise. Stewardship activities must be integrated into already established efforts for infection prevention. We believe it is critical that antimicrobial stewardship, infection control, pharmacy, information technology, and clinical microbiology work collaboratively in order to decrease the incidence of infection due to MDRO.

Keywords Antimicrobial stewardship · Multidrug resistant · Infection prevention · Infection control · Antimicrobial utilization · Antimicrobial pressure · Antimicrobial resistance · Inappropriate antibiotic · Prospective audit and feedback · Preauthorization

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Introduction

Antimicrobial drug resistance is a serious problem that continues to worsen. Health-care organizations worldwide now recognize that antimicrobial resistance is a burgeoning threat that impacts health-care across geographic borders and the spectrum of medical care [1, 2]. Patients who develop drug-resistant infections are at higher risk of mortality, morbid outcomes, prolonged hospitalization, complexity of care, and toxicity as a result of limited treatment options [3, 4]. To make matters worse, the antimicrobial pipeline for new drugs is running dry, especially for gram-negative multidrug-resistant pathogens [5].

A major risk factor for acquired drug resistance is previous exposure to antimicrobials. It is estimated that 30–50 % of antimicrobial prescriptions are inappropriate [3, 6, 7]. Therefore, the potential for reducing inappropriate use of this critical and dwindling resource is great. In addition to driving drug resistance, inappropriate use of antimicrobials is considered the reason for increases in hospital-acquired infections (HAI) such as *Clostridium difficile* infection (CDI), higher health-care costs, and adverse patient safety events.

In response to the problems above, antimicrobial stewardship programs (ASPs) assist practicing clinicians in appropriate decision-making regarding antimicrobial use. A successful ASP utilizes a multifaceted, multidisciplinary approach to support prescriber decision-making, education, and prescription systems infrastructure. The main goal of antimicrobial stewardship is to optimize the therapeutic use of antimicrobials, including appropriate selection, dosing, route, and duration of therapy in order to improve patient outcomes. Secondary goals are to decrease the emergence of antimicrobial resistance, decrease the selection of pathogenic organisms, and improve patient safety. Tertiary goals include reduction in health-care costs and satisfaction of regulatory requirements (Table 1).

ASP activities combat drug resistance and acquisition of HAI at a level that is farther upstream in the causal pathway

Table 1 Goals of an Antibiotic Stewardship Program

Level	Goal
Primary	Optimize the therapeutic use of antimicrobials
Secondary	Decrease the emergence of antimicrobial resistance and the selection of pathogenic organisms
	Improve patient outcomes and patient safety
Tertiary	Decrease the cost of healthcare
	Satisfy regulatory requirements

than most traditional infection control interventions. Thus, the effect of AS may be difficult to prove outside of highly controlled research settings due to the multifaceted nature of multidrug-resistant organism (MDRO) acquisition. Therefore, it is critical that AS, infection control, pharmacy, information technology, and clinical microbiology work collaboratively toward the goal of infection prevention [8]. AS is an essential component in these overall efforts.

A growing body of literature provides evidence that ASPs are clinically successful at preventing infection and are cost-effective. We describe a myriad of programmatic interventions to achieve AS goals. Finally, we predict future directions for research and regulatory oversight of ASP.

Structure of Antibiotic Stewardship Programs

The general structure of an ASP is described in the guidelines of the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) [3]. Each program must be tailored to local needs, resistance, antimicrobial use patterns, institutional culture, and resources [9]. Typically the ASP is led by both a physician and a pharmacist, with experience in the treatment of infectious diseases (ID). Ideally the ASP also involves members from multidisciplinary backgrounds (e.g. adult and pediatric medicine, microbiology, infection control, and surgery). Resources designated for IT support are particularly important for two reasons: (1) to provide feasible methods for collecting accurate data regarding antimicrobial use and resistance, and (2) to provide a route for directed interventions on a systems level. The administrative structure surrounding an ASP varies between institutions. Typically the ASP will require reporting to leaders of the medical staff as well as the pharmacy and therapeutics (P&T) committee [3, 9].

Stewardship Leads to Improved Patient Outcomes

Below we discuss the evidence that ASPs can prevent selection of antimicrobial resistant bacterial strains, prevent HAI such as CDI, lead to improved patient safety and outcomes, and decrease hospital costs.

Drug-Resistance and Infection Prevention

Antibiotics facilitate the emergence and spread of MDROs through several mechanisms. Thus, it is logical that programs that decrease antimicrobial utilization should lead to decreased antimicrobial resistance. This direct effect has been difficult to prove given the numerous other factors involved in the development of bacterial resistance, including patient case mix and demographics, changes in prevalence of organisms, emergence and introduction of new resistance mechanisms, and effects of concomitant infection control measures [10•]. In addition, the effects of an ASP may take years to materialize [11]. As a result, few studies have demonstrated that implementation of an ASP leads to short-term reductions in antimicrobial resistance and fewer, if any, have demonstrated long-term reductions [12].

Several studies have demonstrated an association between decreased use of an antimicrobial agent or class of agents and decreased incidence of a specific MDRO, including fluoroquinolone use and methicillin-resistant *Staphylococcus aureus* (MRSA) [13] and resistant *Pseudomonas* [14]; vancomycin and third-generation cephalosporins and resistant enterococci [15]; aztreonam and cephalosporin use and resistant Enterobacteriaceae [16–18]; and carbapenem use and carbapenem-resistant *Acinetobacter*, *Pseudomonas*, and Enterobacteriaceae [19, 20]. In almost all instances, decreases in MDROs occurred after antibiotic efforts were coupled with enhanced infection control practices. In addition, restriction of one antibiotic often leads to increased use of others, thereby increasing the risk of other types of resistance [20, 21]. Thus, antibiotic restriction alone may not be sufficient to control an MDRO outbreak or decrease endemic levels of MDROs.

Many studies have also demonstrated that implementation of an ASP can lead to decreased incidence of CDI. Unfortunately, methodologic limitations in these studies impair their generalizability. More specifically, interventions occur in the setting of an epidemic, are typically studied in a quasiexperimental approach at a single hospital, and are typically coupled with other interventions. Nevertheless, a few studies show the impact of ASPs on CDI.

Aldeyab et al. studied an outbreak of 318 cases of CDI due to NAP1/027 in three hospitals in Northern Ireland [22]. Hospitals implemented strict infection control practices, improved environmental hygiene, and restricted fluoroquinolone use. Restriction of fluoroquinolones was the only factor associated with significant reduction in CDI based on a time-series analysis. Similarly, the incidence of CDI decreased by 60 % during an outbreak in Quebec after implementation of a non-restrictive ASP to guide antimicrobial use [23].

Implentation of an ASP also decreased the incidence of CDI in endemic and non-tertiary-care settings. A hospital in London implemented revised guidelines for antibiotic use that steered prescribers from "high-risk" broad-spectrum antibiotics to "low-risk" antibiotics [24]. Implementation of these guidelines led to a 70 % decrease in CDI. Carling et al. implemented an ASP with prospective audit and feedback in a community hospital and demonstrated a significant reduction in antibiotic use and CDI over a 7-year period despite increasing patient acuity within the hospital [25]. The Scottish Antimicrobial Prescribing Group, a national stewardship program in Scotland, developed guidelines to optimize antibiotic prescribing in hospitals and primary care settings and introduced measures to improve infection control practices which led to decreased country-wide rates of CDI [26]. Finally, an ASP that targeted interventions in three intensive care units over a 2-year period decreased antibiotic use and significantly lowered rates of CDI [27].

Improved Safety and Outcomes

In addition to decreasing the risk and incidence of infection due to MDRO and *C. difficile*, ASPs improve patient safety, decrease length of stay, and lead to better clinical outcomes. Hospitals with an ASP in place have fewer adverse drug reactions to antibiotics [28]. Similarly, implementation of an ASP leads to improved patient safety and quality of care by increasing the likelihood that a patient will receive an effective antibiotic. Inappropriate antibiotic therapy has be clearly linked with mortality risk in septic patients [29–32]. An ASP can also decrease length of stay of selected patients [33]. After implementing a rapid microbiologic test for blood cultures among ICU patients, Stevenson et al. demonstrated a decreased time to appropriate therapy and a 6-day reduction in length of stay [34]. Finally, the implentation of an ASP with prospective audit leads to an increase in clinical cure rate for complicated infections by almost twofold [35].

Hospital Costs

Most ASPs save money for hospitals. Numerous studies have demonstrated that implementation of an ASP will lead to pharmacy cost savings of between $200,000 and $2 million per year compared to pharmacy costs prior to implementation [3, 36]. Standiford et al. recently investigated pharmacy costs at a large tertiary care hospital before, during, and, most notably, after implementation of an ASP. The ASP saved the hospital approximately $3 million during its first 3 years and kept costs essentially stable during the subsequent 4 years. The ASP was then discontinued and antibiotic costs increased by $2 million during the following 2 years [37].

Despite the above, it remains unclear just how cost-effective ASPs are when the costs of the program are appropriately considered. In fact, some experts remain concerned that costs of ASPs and interventions are only marginally offset by cost savings [38]. The above articles, however, are likely too narrow in their evaluation of "cost savings." For example, appropriate treatment of some infections may actually increase direct pharmacy costs. Similarly, these articles do not take into account cost savings from improvement in patient-specific outcomes such as decreased length of stay, relapse rates, and infections due to MDROs and *C. difficile*. For example, Scheetz et al. described a decision analysis model to examine the costs associated with bacteremia. Patients who received a consultation in the context of an ASP had higher pharmacy costs than patients who did not, but gained 0.08 quality-adjusted life-years (QALYs). After considering the improved QALYs, the authors concluded that the ASP was cost-effective [39]. Similarly, Stevenson et al. evaluated a novel ASP intervention among bacteremic ICU patients, and demonstrated cost savings of more than $21,000 per patient among those who received the intervention, mainly from consideration of decreased length of stay [34].

Basic ASP Interventions and Evidence of Effect

ASPs can improve patient care through several types of intervention. Conceptually, these interventions can occur before or after the antimicrobial has been prescribed; similarly, interventions can also be "active," requiring interaction with or action by a prescriber, or "passive" and simply available if the prescriber chooses to consider them (Fig. 1). Importantly, some degree of overlap and interconnectedness among these four categories will occur. Passive interventions may be more acceptable to front-line providers and produce less direct conflict. These passive interventions, however, will have minimal effect unless they are followed by active interventions that directly address provider decision-making.

Passive Interventions in the Pre-Prescription Period

Institution-specific Treatment Guidelines. Although national clinical practice guidelines exist for many types of infection, successful clinical practice involves careful consideration of local epidemiology, local formulary, and clinical and epidemiologic features of the individual patient. Additionally, clinical decision-making must sometimes occur in the face of absent or ambiguous national guidelines. Therefore, institution-specific recommendations for commonly encountered, high-priority clinical syndromes can be an especially valuable resource provided by an ASP. Institution-specific guidelines assist in streamlining and standardizing antibiotic decision-making and

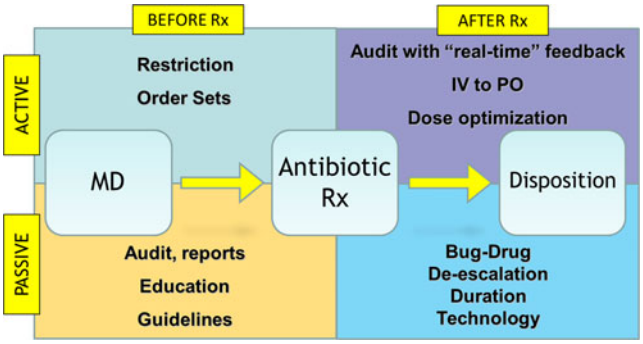

Fig. 1 Conceptual framework for AS interventions that are categorized into interventions made before and after antimicrobial prescription, and passive versus active engagement with the prescriber (*Rx* prescription, *IV* intravenous, *PO* oral, *MD* physician)

provide a basic resource for decision algorithms, one-to-one education, and discussion between AS team members and front-line providers. Example topic areas for institution-specific guidelines that may be targeted by an ASP include surgical prophylaxis, community-acquired pneumonia, urinary tract infection, and asymptomatic bacteriuria.

Education. Education efforts targeting large groups, such as presentations at medical or surgical grand rounds, effectively reach a large number of prescribers in a short period of time. These presentations increase visibility, awareness, and the basic fund of knowledge among prescribers, and communicate the rationale for AS interventions. Unit-specific and institution-wide antimicrobial utilization can be presented formally in this manner. Unfortunately, prescribers may have short memories or minor misunderstandings that go unresolved. Education alone, without any active intervention, has been minimally effective and does not produce sustained behavioral change [3, 11].

Targeted Susceptibility Reporting. Microbiology laboratories can influence prescriber behavior by selecting specific drug susceptibility tests to report on clinical specimens while censoring others in order to promote the prescription of conventional, clinically appropriate, or cost-effective antimicrobials. Clinicians may be frustrated by the apparent "hiding" of information or may inaccurately assume susceptibility if the higher "tier" drug is not listed. Therefore, carefully selected reporting must be based on the clinical scenario. Objective data to suggest that this practice ultimately improves antibiotic utilization is lacking, and most of the few studies available have targeted outpatient practice settings [40, 41].

Antimicrobial Utilization Data Feedback. Antimicrobial utilization is essential data for ASP leaders to use to target specific areas for intervention, including particular drug classes or agents, units, clinical services, or patient populations. Directed data feedback to front-line providers has been previously utilized as a motivator for behavioral change in a variety of settings, including surveillance of HAIs [42, 43]. A similar data feedback approach may be applied to antimicrobial utilization, especially as a directed response to educational efforts or specific problem areas [44]. However, front-line providers may need assistance in interpreting these data, as the science of benchmarking antimicrobial utilization is still emerging [45].

Active Interventions Before Antimicrobial Prescription

Formulary Restriction and Preauthorization. Hospital P&T committees rely on ASP leaders to review antimicrobial drugs and provide expertise on formulary decisions. Consideration for inclusion in the formulary requires a thorough review of therapeutic efficacy, safety, and cost. In addition, ASP leaders must evaluate the formulary for redundancy, clinical niche, and the potential for driving resistance or overuse.

If a drug is felt to be necessary to include in the formulary due to clinical need but at high risk of improper use or toxicity, the drug may be approved contingent on obtaining preauthorization or requiring formal ID consultation. The preauthorization component requires one-to-one discussion between front-line providers and an ASP representative prior to dispensing the drug, typically by phone. This one-to-one interaction provides an opportunity for education and discussion leading to a joint understanding of what is clinically appropriate.

Potential problems may arise. Some prescribers view preauthorization as intrusive. Thus, this approach may not be acceptable at all medical centers due to the institutional culture [3, 11]. Mutual respect between the provider and the ASP representative is essential for the discussion to be productive and beneficial. For example, one study suggests that preauthorization calls taken by attending level physicians or ID trained pharmacists are more effective than those taken by trainees [46]. In addition, callers frequently (39 %) include inaccuracies in discussion of patient-specific information which can then lead to inappropriate antimicrobial recommendations [46, 47]. Other considerations are the potential for delay in administration of important therapies for sick patients, as well as the need for an "on-call" preauthorization pager at all hours. These fears, conflicts, and logistical hurdles have led some programs to allow an unrestricted single dose of a drug, instituting the authorization requirement at the second dose or the following morning. More recent studies have utilized internet-based or electronic approval systems and have demonstrated decreases in antibiotic use [48, 49].

Formulary restriction and preauthorization is considered a core strategy in the IDSA/SHEA guidelines [3]. As discussed above, this approach has proven successful in reducing pharmacy cost and tempering the use of antimicrobials in several studies [25, 36, 37, 50], but improvements in

organism susceptibilities have been difficult to consistently demonstrate [10•, 51]. The guidelines recommend that restrictive policies be followed by close monitoring of overall utilization and resistance to detect any unintended shifts [3].

Treatment Pathways and Decision Support. Institutions can also create treatment pathways and algorithms to assist front-line clinicians with antimicrobial selection, dosing, and duration for scenarios targeted by institution-specific guidelines. Empiric antibiotic choices for commonly encountered diagnoses, such as community-acquired pneumonia [52], are especially amenable to this type of intervention [53, 54]. Some computerized physician order entry systems provide link-out capabilities for AS decision support materials. Order entry itself can also incorporate specific elements, such as a predetermined stop date [55]. IT delivery systems provide an exciting area for growth and innovation in AS clinical decision support [56]. Personal digital assistant or smartphone applications and web-based systems create outlets for disseminating AS guidelines or local antibiograms in convenient, real-time media.

Passive Interventions After Antimicrobial Prescription

Clinical Decision Support. As in the period before the antimicrobial has been prescribed, electronic systems can be developed to prompt providers with treatment recommendations in the period after prescription based on local patient and microbiologic data [55, 57]. Validated decision support systems have often led to improved compliance with practice guidelines, fewer adverse antimicrobial-related reactions, and improved antimicrobial choice and dosing [21, 58]. For example, in a cluster-randomized study of 2,326 patients, patients in wards randomized to an antibiotic decision support system were more likely to receive appropriate empiric therapy and had lower hospital costs and length of stay than patients in wards randomized to control [59]. ASPs can provide several different types of clinical decision support for clinicians, including protocols for de-escalation and recommendations for length of therapy.

Protocols for De-Escalation of Therapy. An important intervention to improve antimicrobial use is narrowing coverage based on culture and susceptibility results (i.e., 48–72 h after antimicrobial therapy has been initiated and cultures have been obtained). Antimicrobial de-escalation can decrease unnecessary antibiotic use [27] and hospital costs [33, 60], and decrease the incidence of CDI [27]. In ICU patients with ventilator-associated pneumonia, de-escalation strategies decrease overall antibiotic use, while mortality and length of stay are unaffected [61, 62].

Length of Therapy. Antibiotic discontinuation strategies are a key component of ASPs [63•]. For example, a recent quasiexperimental study demonstrated that feedback about duration of antibiotic therapy in patients admitted to a medical ICU who received antibiotics for >14 days led to decreased antibiotic utilization and lower rates of *Acinetobacter* and *Klebsiella* infections [64].

Electronic Reminders and Alerts. Several types of automated reminders can be generated to motivate clinicians. For example, electronic order entry systems can remind providers about antibiotic overuse scenarios in the post-prescription period, including use of multiple of antibiotics for a prolonged period of time, use of antibiotics without positive culture results, or antibiotic use that exceeds recommended duration of therapy. While education may increase the use and uptake of these reminders, it is unclear if passive reminders will produce real behavioral change or simply "pop-up fatigue."

Some clinical reminders can identify key high-risk scenarios. In particular, alerts should be generated when a patient receives antimicrobial therapy against which the infecting organism is demonstrated to have in vitro resistance. This phenomenon, also known as "bug-drug mismatch," occurs more frequently than most clinicians may believe. For example, up to 30 % of patients admitted to the ICU with bacteremia and 30–40 % of patients with MRSA infections have bug-drug mismatch [65, 66].

Rapid Diagnostic Testing. Rapid diagnostic tests can help improve antibiotic utilization but require that clinicians order and interpret them correctly. Biomarkers such as procalcitonin have been used to predict bacterial infection and determine when therapy can be stopped [63•]. Similarly, use of rapid diagnostic tests that, for example, distinguish methicillin-resistant from methicillin-sensitive *S. aureus* in blood can lead to decreased vancomycin use and improved clinical outcomes [33, 34]. Of note, however, rapid diagnostic tests do not always improve antibiotic utilization. Shiley et al. evaluated 196 adult patients with respiratory symptoms and a positive viral PCR multiplex assay [67], Of 131 patients who received antimicrobial therapy, 125 continued to receive therapy even after the positive viral results were available. Eight of these patients eventually developed CDI.

Active Post-Prescription Interventions

Prospective Audit with Feedback. Prospective audit with real-time feedback is a cornerstone of AS [3]. In our opinion, this intervention has the most supportive evidence and the most promise.

The electronic alerts described above can be directed to an AS team member rather than as a simple, passive

reminder to the clinician. In fact, implentation of an ASP that uses clinical decision support systems to identify patients leads to intervention in the management of twice as many patients as implentation of an ASP without clinical decision support systems [68, 69]. An ID-trained physician and/or an ID-trained pharmacist then audits the patient record and provides feedback to the treating clinician regarding antimicrobial management.

Numerous studies have demonstrated that ASPs that utilize strategies for post-prescription audit and real-time feedback lead to a decrease in unnecessary antibiotic use and an improvement in patient outcomes [35]. The following studies are notable for their novel findings, approach, or methods.

Carling et al. implemented an ASP with prospective audit and feedback by an ID physician and an ID-trained pharmacist in a community hospital [25]. The ASP team audited patients prescribed one of four types of antibiotic and provided written recommendations in the patients' charts. The use of aztreonam and ceftazidime decreased significantly over the 7-year period after implementation. Similarly, the rate of infection due to *C. difficile* or MDR Enterobacteriaceae decreased significantly despite an increase in ICU patients and patient complexity.

A randomized controlled trial by Camins et al. evaluated the impact of an antibiotic utilization team that provided prospective audit of patients who received three targeted antibiotics [70•]. Twelve internal medicine teams were randomized to receive prospective audit and feedback or control, which included passive use of indication-specific guidelines. Among 784 patients evaluated during the 10-month study period, patients in the intervention arm were more likely to receive appropriate empiric and definitive antimicrobial therapy than controls. Solomon et al. performed a similar randomized controlled trial among 17 medical teams [71]. Teams randomized to one-on-one post-prescription education had 41 % less use of levofloxacin and ceftazidime than the control teams.

Cosgrove et al. recently performed a prospective quasiexperimental study to evaluate the impact of prospective audit and feedback on the use of six targeted antibiotic classes in five academic hospitals [72•]. Interestingly, the effect of the intervention differed across institutions: use decreased significantly at two hospitals, increased at two hospitals, and remained unchanged at one hospital. The authors noted that the demonstrated benefit occurred in hospitals with well-resourced and well-established ASPs.

Intravenous-to-Oral Conversion. Among antibiotics with good bioavailability, switching from an intravenous to an oral agent can shorten length of stay and decrease costs, particularly among patients with community-acquired pneumonia [73, 74]. This intervention is a simple, safe, cost-effective, and generally well-accepted by treating clinicians.

Future Directions

The urgent need to address antimicrobial resistance will continue to drive more investigation and innovation in AS [8, 10•, 75]. Only through larger and more methodologically rigorous studies can the effects of ASP interventions be evaluated at the level of patient outcomes such as HAI acquisition, length of stay, and mortality, as opposed to at the intermediate level outcome of decreased antibiotic use. AS interventions will also be coupled with infection control interventions as "bundles" to combat MDRO, rather than these two highly related disciplines being separated.

Regulatory agencies are increasingly interested in ASPs and antimicrobial use as targets for future quality metrics and evidence of institutional commitment to addressing antimicrobial resistance and patient safety [75, 76]. The Centers for Medicare and Medicaid Services has released a draft of new surveyor worksheets that contain elements of AS interventions that are not citation-level [76]. The CDC's National Healthcare Safety Network (NHSN) has an optional program for participating hospitals to track and report antimicrobial use and resistance (AUR) [77]. As antimicrobial utilization becomes a target for quality improvement, we believe participation in NHSN AUR will increase and these national data and benchmarks will become more valuable.

Comparing antibiotic utilization among health-care facilities in a fair and meaningful way is a labor-intensive task. Currently, two different utilization metrics are commonly used: defined daily dose and days of therapy. Each metric has advantages and disadvantages [78]. Standardization of a universal utilization metric as well as research into methods for risk adjustment have yet to be fully developed, but important preliminary work has been carried out [45, 79•]. Interfacility comparisons must be informed by the multiple factors that impact clinically appropriate antimicrobial use: patient case mix, hospital size, referral status, presence of specialty services (e.g., transplant surgery), and clinical service types. Other proposed quality indicators for ASP include process measures such as time to administration of appropriate therapy, adverse drug reactions or interactions, regimens with redundant spectra, or regimens that are inadequate or excessive [75]. Finally, as has been echoed throughout this review, ASPs do not live in isolation. Concurrent infection control practices, hand hygiene, and local resistance rates will affect MDRO incidence, and therefore what is clinically appropriate at the institutional level.

Conclusions

The implentation of an ASP improves patient outcomes by decreasing unnecessary antibiotic use, increasing adherence with antimicrobial treatment principles, and improving

antimicrobial dose, timing, and duration. In particular, ASPs decrease the risk of acquiring infection due to MDRO and *C. difficile*. ASPs have many tools to improve antimicrobial use. We believe these interventions can be separated into four categories: passive and active interventions both before and after antimicrobial prescription. While both types of intervention are necessary, we believe that active interventions have a higher impact, are more reliable, and are longer-lasting than passive interventions. In particular, post-prescription audit with real-time feedback offers the best option for ASPs to achieve their goals and prevent emergence and infection due to MDR pathogens.

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