Antimicrobial Stewardship Programs: Effects on Clinical and Economic Outcomes and Future Directions

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ABSTRACT

- *Objective:* To review the evidence evaluating inpatient antimicrobial stewardship programs (ASPs) with a focus on clinical and economic outcomes.
- *Methods:* Pubmed/MEDLINE and the Cochrane Database of Systematic Reviews were used to identify systematic reviews, meta-analyses, randomized controlled trials, and other relevant literature evaluating the clinical and economic impact of ASP interventions.
- *Results:* A total of 5 meta-analyses, 3 systematic reviews, and 10 clinical studies (2 randomized controlled, 5 observational, and 3 quasi-experimental studies) were identified for analysis. ASPs were associated with a reduction in antimicrobial consumption and use. However, due to the heterogeneity of outcomes measured among studies, the effectiveness of ASPs varied with the measures used. There are data supporting the cost savings associated with ASPs, but these studies are more sparse. Most of the available evidence supporting ASPs is of low quality, and intervention strategies vary widely among available studies.
- *Conclusion:* Much of the evidence reviewed supports the assertion that ASPs result in a more judicious use of antimicrobials and lead to better patient care in the inpatient setting. While clinical outcomes vary between programs, there are ubiquitous positive benefits associated with ASPs in terms of antimicrobial consumption, *C. difficile* infection rates, and resistance, with few adverse effects. To date, economic outcomes have been difficult to uniformly quantify, but there are data supporting the economic benefits of ASPs. As the number of ASPs continues to grow, it is imperative that standardized metrics are considered in order to accurately measure the benefits of these essential programs.

Key words: *Antimicrobial stewardship; antimicrobial consumption; resistance.*

Antimicrobial resistance is a public health concern that has been escalating over the years and is now identified as a global crisis [1–3]. This is partly due to the widespread use of the same antibiotics that have existed for decades, combined with a lack of sufficient novel antibiotic discovery and development [4]. Bacteria that are resistant to our last-line-of-defense medications have recently emerged, and these resistant organisms may spread to treatment-naive patients [5]. Multidrug-resistant organisms are often found, treated, and likely originate within the hospital practice setting, where antimicrobials can be prescribed by any licensed provider [6]. Upwards of 50% of antibiotics administered are unnecessary and contribute to the problem of increasing resistance [7]. The seriousness of this situation is increasingly apparent; in 2014 the World Health Organization (WHO), President Obama, and Prime Minister Cameron issued statements urging solutions to the resistance crisis [8].

While the urgency of the situation is recognized today, efforts aimed at a more judicious use of antibiotics to curb resistance began as early as the 1960s and led to the first antimicrobial stewardship programs (ASPs) [9–11]. ASPs have since been defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of

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administration" [1]. The primary objectives of these types of programs are to avoid or reduce adverse events (eg, *Clostridium difficile* infection) and resistance driven by a shift in minimum inhibitory concentrations (MICs) and to reverse the unnecessary economic burden caused by the inappropriate prescribing of these agents [1].

This article examines the evidence evaluating the reported effectiveness of inpatient ASPs, examining both clinical and economic outcomes. In addition, we touch on ASP history, current status, and future directions in light of current trends. While ASPs are expanding into the outpatient and nursing home settings, we will limit our review here to the inpatient setting.

Historical Background

Modern antibiotics date back to the late 1930s when penicillin and sulfonamides were introduced to the medical market, and resistance to these drug classes was reported just a few years after their introduction. The same bacterial resistance mechanisms that neutralized their efficacy then exist today, and these mechanisms continue to confer resistance among those classes [5].

While "stewardship" was not described as such until the late 1990s [12], institutions have historically been proactive in creating standards around antimicrobial utilization to encourage judicious use of these agents. The earliest form of tracking antibiotic use was in the form of paper charts as "antibiotic logs" [9] and "punch cards" [10] in the 1960s. The idea of a team approach to stewardship dates back to the 1970s, with the example of Hartford Hospital in Hartford, Connecticut, which employed an antimicrobial standards model run by an infectious disease (ID) physician and clinical pharmacists [11]. In 1977, the Infectious Diseases Society of America (IDSA) released a statement that clinical pharmacists may have a substantial impact on patient care, including in ID, contributing to the idea that a team of physicians collaborating with pharmacists presents the best way to combat inappropriate medication use. Pharmacist involvement has since been shown to restrict broad overutilized antimicrobial agents and reduce the rate of *C. difficile* infection by a significant amount [13].

In 1997 the IDSA and the Society for Healthcare Epidemiology of America (SHEA) published guidelines to assist in the prevention of the growing issue of resistance, mentioning the importance of antimicrobial stewardship [14]. A decade later they released joint guidelines for ASP implementation [15], and the Pediatric Infectious Disease Society (PIDS) joined them in 2012 to publish a joint statement acknowledging and endorsing stewardship [16]. In 2014, the Centers of Disease Control and Prevention (CDC) recommended that every hospital should have an ASP. As of 1 January 2017, the Joint Commission requires an ASP as a standard for accreditation at hospitals, critical access hospitals, and nursing care [17]. Guidelines for implementation of an ASP are currently available through the IDSA and SHEA [1,16].

ASP Interventions

There are 2 main strategies that ASPs have to combat inappropriate antimicrobial use, and each has its own set of systematic interventions. These strategies are referred to as "prospective audit with intervention and feedback" and "prior authorization" [6]. Although most ASPs will incorporate these main strategies, each institution typically creates its own strategies and regulations independently.

Prospective audit with intervention and feedback describes the process of providing recommendations after reviewing utilization and trends of antimicrobial use. This is sometimes referred to as the "back-end" intervention, in which decisions are made after antibiotics have been administered. Interventions that are commonly used under this strategy include discontinuation of antibiotics due to culture data, de-escalation to drugs with narrower spectra, IV to oral conversions, and cessation of surgical prophylaxis [6].

Prior authorization, also referred to as a "front-end" intervention, is the process of approving medications before they are used. Interventions include a restricted formulary for antimicrobials that can be managed through a paging system or a built-in computer restriction program, as well as other guidelines and protocols for dosing and duration of therapy. Restrictions typically focus on broad spectrum antibiotics as well as the more costly drugs on formularies. These solutions reduce the need for manual intervention as technology makes it possible to create automated restriction-based services that prevent inappropriate prescribing [6].

Aside from these main techniques, other strategies are taken to achieve the goal of attaining optimal clinical outcomes while limiting further antimicrobial resistance and adverse effects. Different clinical settings have different needs, and ASPs are customized to each setting's resources, prescribing habits, and other local specificities

[1]. These differences present difficulty with interpreting diverse datasets, but certain themes arise in the literature: commonly assessed clinical outcomes of inpatient ASPs include hospital length of stay (LOS) and readmission, reinfection, mortality, and resistance rates. These outcomes are putatively driven by the more prudent use of antimicrobials, particularly by decreased rates of antimicrobial consumption.

ASP Team Members

While ASPs may differ between institutions, the staff members involved are typically the same, and leadership is always an important aspect of a program. The CDC recommends that ASP leadership consist of a program leader (an ID physician) and a pharmacy leader, who co-lead the team [18]. In addition, the Joint Commission recommends that the multidisciplinary team should include an infection preventionist (ie, infection control and hospital epidemiologist) and practitioner [17]; these specialists have a role in prevention, awareness, and policy [19]. The integration of infection control with stewardship yields the best results [15], as infection control aims to prevent antibiotic use altogether, while stewardship increases the quality of antibiotic regimens that are being prescribed [20].

It is also beneficial to incorporate a microbiologist as an integral part of the team, responsible for performing and interpreting laboratory data (ie, cultures). Nurses should be integrated into ASPs due to the overlap of their routine activities with ASP interventions [21]; other clinicians (regardless of their infectious disease clinical background), quality control, information technology, and environmental services should all collaborate in the hospital-wide systems related to the program where appropriate [18].

Evidence Review

To assess the effectiveness of inpatient ASPs, we performed a literature search using Pubmed, Cochrane Database of Systematic Reviews, and MEDLINE/OVIDSp up to 1 September 2016. The search terms used are listed in the **Table**. Included in this review were studies evaluating clinical or economic outcomes related to inpatient ASPs; excluded were editorials, opinion pieces, articles not containing original clinical or economic ASP outcome data, ASPs not performed in the inpatient setting, and studies that were included in identified systematic reviews or meta-analyses. Also excluded from this review were studies that reviewed ASPs performed in niche settings or for applications in which ASPs were not yet prevalent, as assessed by the authors. The search initially yielded 182 articles. After removing duplicates and excluded articles, 18 articles were identified for review: 8 meta-analyses and systematic reviews and 10 additional clinical studies (2 randomized controlled, 5 observational, and 3 quasi-experimental studies) evaluating clinical and economic outcomes not contained in the identified aggregated studies. Systematic reviews, meta-analyses, and other studies were screened to identify any other relevant literature not captured in the original search. The articles included in this review are summarized in 2 Tables, which may be accessed at www.turner-white.com/pdf/jcom_jul17_antimicrobial_appendix.pdf.

Table. Literature Search Strategy

Pubmed
("antibiotic stewardship") OR ("antimicrobial stewardship") OR ("antibiotic management") OR ("antimicrobial management")
("antibiotic stewardship") OR ("antimicrobial stewardship") OR ("antibiotic management") OR ("antimicrobial management") AND (history OR historical)
("antibiotic stewardship") OR ("antimicrobial stewardship") OR ("antibiotic management") OR ("antimicrobial management") AND outcomes
"antibiotic stewardship" AND (economics OR financial)
("[antibiotic OR antimicrobial OR antibacterial] AND [stewardship]") AND (economics OR financial OR cost)
("antibiotic stewardship" AND "allergy")
("[antibiotic OR antimicrobial] stewardship" AND future)
MEDLINE/OVID
Search terms: (financial or cost or economics). mp. (+antibiotic and +stewardship) .m_titl. (+antimicrobial and +stewardship) .m_titl. ("antibiotic stewardship" and evolution).mp ("[antibiotic OR antimicrobial] AND stewardship" and evolution).mp. (antibiotic or antimicrobial) and +resistance).mp. ([antibiotic or antimicrobial] and +resistance).m_titl.
MeSH terms: Anti-Bacterial Agents/ or *Drug Resistance, Bacterial/ or *Infection Control/ or *Bacterial Infections, *Drug Utilization/ or *Anti-Bacterial Agents/ or *Bacterial Infections
Cochrane Review
("antibiotic stewardship") OR ("antimicrobial stewardship") OR ("antibiotic management") OR ("antimicrobial management")

Results

Antimicrobial Usage

The most widely studied aspect of ASPs in the current review was the effect of ASP interventions on antimicrobial consumption and use. Three systematic reviews [22–24] showed improved antibiotic prescribing practices and reduced consumption rates overall, as did several studies inside and outside the intensive care unit (ICU) [25–31]. One study found an insignificant declining usage trend [32]. An important underlying facet of this observation is that even as total antibiotic consumption decreases, certain antibiotic and antibiotic class consumption may increase. This is evident in several studies, which showed that as aminoglycoside, carbapenem, and β-lactam-β-lactamase inhibitor use increased, clindamycin (1 case), glycopeptide, fluoroquinolone, and macrolide use decreased [27,28,30]. A potential confounding factor relating to decreased glycopeptide use in Bevilacqua et al [30] was that there was an epidemic of glycopeptide-resistant enterococci during the study period, potentially causing prescribers to naturally avoid it. In any case, since the aim of ASPs is to encourage a more judicious usage of antimicrobials, the observed decreases in consumption of those restricted medications is intuitive. These observations about antimicrobial consumption related to ASPs are relevant because they putatively drive improvements in clinical outcomes, especially those related to reduced adverse events associated with these agents, such as the risk of *C. difficile* infection with certain drugs (eg, fluoroquinolones, clindamycin, and broad-spectrum antibiotics) and prolonged antibiotic usage [33–35]. There is evidence that these benefits are not limited to antibiotics but extend to antifungal agents and possibly antivirals [22,27,36].

Utilization, Mortality, and Infection Rates

ASPs typically intend to improve patient-focused clinical parameters such as hospital LOS, hospital readmissions, mortality, and incidence of infections acquired secondary to antibiotic usage during a hospital stay, especially *C. difficile* infection. Most of the reviewed evidence indicates that there has been no significant LOS benefit due to stewardship interventions [24–26,32,37], and one meta-analysis noted that when overall hospital LOS was significantly reduced, ICU-specific LOS was not [22]. Generally, there was also not a significant change in hospital readmission rates [24,26,32]. However, 2 retrospective observational studies found mixed results for both LOS and readmission rates relative to ASP interventions; while both noted a significantly reduced LOS, one study [38] showed an all-cause readmission benefit in a fairly healthy patient population (but no benefit for readmissions due to the specific infections of interest), and the another [29] showed a benefit for readmissions due to infections but an increased rate of readmissions in the intervention group overall. In this latter study, hospitalizations within the previous 3 months were significantly higher at baseline for the intervention group (55% vs. 46%, $P = 0.042$), suggesting sicker patients and possibly providing an explanation for this unique observation. Even so, a meta-analysis of 5 studies found a significantly elevated risk of readmission associated with ASP interventions (RR 1.26, 95% CI 1.02–1.57; $P = 0.03$); the authors noted that non–infection-related readmissions accounted for 61% of readmissions, but this was not significantly different between intervention and non-intervention arms [37].

With regard to mortality, most studies found no significant reductions related to stewardship interventions [22,24,26,29,32]. In a prospective randomized controlled trial, all reported deaths (7/160, 4.4%) were in the ASP intervention arm, but these were attributed to the severities of infection or an underlying, chronic disease [25]. One meta-analysis, however, found that there were significant mortality reductions related to stewardship guidelines for empirical antibiotic treatment (OR 0.65, 95% CI 0.54–0.80, $P < 0.001$; $I^2 = 65\%$) and to de-escalation of therapy based on culture results (RR 0.44, 95% CI 0.30–0.66, $P < 0.001$; $I^2 = 59\%$), based on 40 and 25 studies, respectively [39]; but both results exhibited substantial heterogeneity (defined as $I^2 = 50\%–90\%$ [40]) among the relevant studies. Another meta-analysis found that there was no significant change in mortality related to stewardship interventions intending to improve antibiotic appropriateness (RR 0.92, 95% CI 0.69–1.2, $P = 0.56$; $I^2 = 72\%$) or intending to reduce excessive prescribing (RR 0.92, 95% CI 0.81–1.06, $P = 0.25$; $I^2 = 0\%$), but that there was a significant mortality benefit associated with interventions aimed at increasing guideline compliance for pneumonia diagnoses (RR 0.89, 95% CI 0.82–0.97, $P = 0.005$; $I^2 = 0\%$) [37]. In the case of Schuts et al [39], search criteria specifically sought studies that assessed clinical outcomes (eg, mortality), whereas the search of Davey et al [37] focused on studies whose aim was to improve antibiotic prescribing, with a main comparison being between restrictive and persuasive interventions; while the difference may seem

subtle, the body of data compiled from these searches may characterize the ASP effect of mortality differently. No significant evidence was found to suggest that reduced antimicrobial consumption increases mortality.

Improving the use of antimicrobial agents should limit collateral damage associated with their use (eg, damage to normal flora and increased resistance), and ideally infections should be better managed. As previously mentioned, one of the concerns with antibiotic usage (particularly fluoroquinolones, macrolides, and broad-spectrum agents) is that collateral damage could lead to increased rates of *C. difficile* infection. One meta-analysis showed no significant reduction in the rate of *C. difficile* infection (as well as overall infection rate) relative to ASPs [22]; however, this finding was based on only 3 of the 26 studies analyzed, and only 1 of those 3 studies utilized restrictions for flouroquinolones and cephalosporins. An interrupted time series (ITS) study similarly found no significant reduction in *C. difficile* infection rate [32]; however, this study was conducted in a hospital with low baseline antibiotic prescribing (it was ranked second-to-last in terms of antibiotic usage among its peer institutions), inherently limiting the risk of *C. difficile* infection among patients in the pre-ASP setting. In contrast to these findings, a meta-analysis specifically designed to assess the incidence of *C. difficile* infection relative to stewardship programs found a significantly reduced risk of infection based on 16 studies (RR 0.48, 95% CI 0.38–0.62, $P < 0.001$; $I^2 = 76\%$) [41], and the systematic review conducted by Filice et al [24] found a significant benefit with regard to the *C. difficile* infection rate in 4 of 6 studies. These results are consistent with those presented as evidence for the impact of stewardship on *C. difficile* infection by the CDC [42]. Aside from *C. difficile* infection, one retrospective observational study found that the 14-day reinfection rate (ie, reinfection with the same infection at the same anatomical location) was significantly reduced following stewardship intervention (0% vs. 10%, $P = 0.009$) [29]. This finding, combined with the *C. difficile* infection examples, provide evidence for better infection management of ASPs.

While the general trend seems to suggest mixed or no significant benefit for several clinical outcomes, it is important to note that variation in outcomes could be due to differences in the types of ASP interventions and intervention study periods across differing programs. Davey et al [37] found variation in prescribing outcomes based on whether restrictive (ie, restrict prescriber freedom with antimicrobials) or persuasive (ie, suggest changes to prescriber) interventions were used, and on the timeframe in which they were used. At one month into an ASP, restrictive interventions resulted in better prescribing practices relative to persuasive interventions based on 27 studies (effect size 32.0%, 95% CI 2.5%–61.4%), but by 6 months the 2 were not statistically different (effect size 10.1%, 95% CI –47.5% to 66.0%). At 12 and 24 months, persuasive interventions demonstrated greater effects on prescribing outcomes, but these were not significant. These findings provide evidence that different study timeframes can impact ASP practices differently (and these already vary widely in the literature). Considering the variety of ASP interventions employed across the different studies, these factors almost certainly impact the reported antimicrobial consumption rates and outcomes to different degrees as a consequence. A high degree of heterogeneity among an analyzed dataset could itself be the reason for net non-significance within single systematic reviews and meta-analyses.

Resistance

Another goal of ASPs is the prevention of antimicrobial resistance, an area where the evidence generally suggests benefit associated with ASP interventions. Resistance rates to common troublesome organisms, such as methicillin-resistant *S. aureus* (MRSA), imipenem-resistant *P. aeruginosa*, and extended-spectrum β-lactamase (ESBL)–producing *Klebsiella spp* were significantly reduced in a meta-analysis; ESBL-producing *E. coli* infections were not, however [22]. An ITS study found significantly reduced MRSA resistance, as well as reduced Pseudomonal resistance to imipenem-cilastin and levofloxacin (all $P < 0.001$), but no significant changes with respect to piperacillin/tazobactam, cefepime, or amikacin resistance [32]. This study also noted increased *E. coli* resistance to levofloxacin and ceftriaxone (both $P < 0.001$). No significant changes in resistance were noted for vancomycin-resistant enterococci. It may be a reasonable expectation that decreasing inappropriate antimicrobial use may decrease long-term antimicrobial resistance; but as most studies only span a few years, only the minute changes in resistance are understood [23]. Longer duration studies are needed to better understand resistance outcomes.

Of note is a phenomenon known as the "squeezing

the balloon" effect. This can be associated with ASPs, potentially resulting in paradoxically increased resistance [43]. That is, when usage restrictions are placed on certain antibiotics, the use of other non-restricted antibiotics may increase, possibly leading to increased resistance of those non-restricted antibiotics [22] ("constraining one end [of a balloon] causes the other end to bulge … limiting the use of one class of compounds may be counteracted by corresponding changes in prescribing and drug resistance that are even more ominous" [43]). Karanika et al [22] took this phenomonen into consideration, and assessed restricted and non-restricted antimicrobial consumption separately. They found a reduction in consumption for both restricted and non-restricted antibiotics, which included "high potential resistance" antibiotics, specifically carbapenems and glycopeptides. In the study conducted by Cairns et al [28], a similar effect was observed; while the use of other classes of antibiotics decreased (eg, cephalosporins and aminoglycosides), the use of β–lactam–β–lactamase inhibitor combinations actually increased by 48% (change in use: +48.2% [95% CI 21.8%–47.9%]). Hohn et al [26] noted an increased usage rate of carbapenems, even though several other classes of antibiotics had reduced usage. Unfortunately, neither study reported resistance rates, so the impact of these findings is unknown. Finally, Jenkins et al [32] assessed trends in antimicrobial use as changes in rates of consumption. Among the various antibiotics assessed in this study, the rate of flouroquinolone use decreased both before and after the intervention period, although the rate of decreased usage slowed post-ASP (the change in rate post-ASP was +2.2% [95% CI 1.4%–3.1%], $P < 0.001$). They observed a small (but significant) increase in resistance of *E. coli* to levofloxacin pre- vs. post-intervention (11.0% vs. 13.9%, $P < 0.001$); in contrast, a significant decrease in resistance of *P. aeruginosa* was observed (30.5% vs. 21.4%, $P < 0.001$). While these examples help illustrate the concept of changes in antibiotic usage patterns associated with an ASP, at best they approximate the "squeezing the balloon" effect since these studies present data for antibiotics that were either restricted or for which restriction was not clearly specified. The "squeezing the balloon" effect is most relevant for the unintended, potentially increased usage of non-restricted drugs secondary to ASP restrictions. Higher resistance rates among certain drug classes observed in the context of this effect would constitute a drawback to an ASP program.

Adverse Effects

Reduced toxicities and adverse effects are expected with reduced usage of antimicrobials. The systematic review conducted by Filice et al [24] examined the incidence of adverse effects related to antibiotic usage, and their findings suggest, at the least, that stewardship programs generally do not cause harm, as only 2 of the studies they examined reported adverse events. Following stewardship interventions, 5.5% of the patients deteriorated; and of those, the large majority (75%) deteriorated due to progression of oncological malignancies. To further illustrate the effect of stewardship interventions on toxicities and side effects of antimicrobials, Schuts et al demonstrated that the risk of nephrotoxicity while on antimicrobial therapy was reduced based on 14 studies of moderate heterogeneity as a result of an ASP (OR 0.46, 95% CI 0.28–0.77, $P = 0.003$; $I^2 = 34\%$) [39,44]. It is intuitive that reduced drug exposure results in reduced adverse effects, as such these results are expected.

Economic Outcomes

Although the focus of ASPs is often to improve clinical outcomes, economic outcomes are an important component of ASPs; these programs bring associated economic value that should be highlighted and further detailed [22,45,46]. Since clinical outcomes are often the main objective of ASPs, most available studies have been clinical effect studies (rather than economic analyses), in which economic assessments are often a secondary consideration, if included.

As a result, cost evaluations are conducted on direct cost reductions whereas indirect cost reductions are often not critically evaluated. ASPs reduce hospital expenditures by limiting hospital-acquired infections and the associated medical costs where they are effective at decreasing consumption of antimicrobials [22,45], and by reducing antibiotic misuse, iatrogenic infections, and the rates of antibiotic-resistant organisms [47]. In one retrospective observational study, annual costs of antibiotics dropped by 33% with re-implementation of an ASP, mirrored by an overall decrease in antibiotic consumption of about 10%, over the course of the intervention study period [30]. Of note is that at 1 year post-ASP re-implementation, antibiotic consumption actually increased (by 5.4%); however, because antibiotic usage had changed to more appropriate and cost-effective therapies, cost expenditures associated with antibiotics were still reduced by 13% for that year relative to pre-ASP

re-implementation. Aside from economic evaluations centered on consumption rates, there is the potential to further evaluate economic benefits associated with stewardship when looking at other outcomes, including hospital LOS [22], as well as indirect costs such as morbidity and mortality, societal, and operational costs [46]. Currently, these detailed analyses are lacking. In conjunction with more standardized clinical metrics, these assessments are needed to better delineate the full cost effectiveness of ASPs.

Evidence Summary

The evidence for inpatient ASP effectiveness is promising but mixed. Much of the evidence is low-level, based on observational studies that are retrospective in nature, and systematic reviews and meta-analyses are based on these types of studies. Studies have been conducted over a range of years, and the duration of intervention periods often vary widely between studies; it is difficult to capture and account for all of the infection, prescribing, and drug availability patterns (as well as the intervention differences or new drug approvals) throughout these time periods. To complicate the matter, both the quality of data as well as the quality of the ASPs are highly variable.

As such, the findings across pooled studies for ASPs are hard to amalgamate and draw concrete conclusions from. This difficulty is due to the inherent heterogeneity when comparing smaller individual studies in systematic reviews and meta-analyses. Currently, there are numerous ways to implement an ASP, but there is not a standardized system of specific interventions or metrics. Until we can directly compare similar ASPs and interventions among various institutions, it will be challenging to generalize positive benefits from systematic reviews and meta-analyses. Currently, the CDC is involved in a new initiative in which data from various hospitals are compiled to create a surveillance database [48]. Although this is a step in the right direction for standardized metrics for stewardship, for the current review the lack of standard metrics leads to conflicting results of heterogenic studies, making it difficult to show clear benefits in clinical outcomes.

Despite the vast array of ASPs, their differences, and a range of clinical measures—many with conflicting evidence—there is a noticeable trend toward a more prudent use of antimicrobials. Based on the review of available evidence, inpatient ASPs improve patient care and preserve an important health care resource—antibiotics. As has been presented, this is demonstrated by the alterations in consumption of these agents, has ramifications for secondary outcomes such as reduced instances of *C. difficile* infections, resistance, and adverse effects, and overall translates into better patient care and reduced costs. But while we can conclude that the direct interventions of stewardship in reducing and restricting antibiotic use have been effective, we cannot clearly state the overall magnitude of benefit, the effectiveness of various ASP structures and components on clinical outcomes (such as LOS, mortality, etc.), and the cost savings due to the heterogeneity of the available evidence.

Future Directions

Moving forward, the future of ASPs encompasses several potential developments. First and foremost, as technological advancements continue to develop, there is a need to integrate and utilize developments in information technology (IT). Baysari et al conducted a review on the value of utilizing IT interventions, focusing mainly on decision support (stand-alone or as a component of other hospital procedures), approval, and surveillance systems [49]. There was benefit associated with these IT interventions in terms of the improvement in the appropriate use of antimicrobials (RR 1.49, 95% CI, 1.07–2.08, $P < 0.05$; $I^2 = 93\%$), but there was no demonstrated benefit in terms of patient mortality or hospital LOS. Aside from this study, broad evidence is still lacking to support the use of IT systems in ASPs because meaningful comparisons amongst the interventions have not been made due to widespread variability in study design and outcome measures. However, it is generally agreed that ASPs must integrate with IT systems as the widespread use of technology within the healthcare field continues to grow. Evidence needs to be provided in the form of higher quality studies centered on similar outcomes to show appropriate approaches for ASPs to leverage IT systems. At a minimum, the integration of IT into ASPs should not hinder clinical outcomes. An important consideration is the variation in practice settings where antibiotic stewardship is to be implemented; eg, a small community hospital will be less equipped to incorporate and support technological tools compared to a large tertiary teaching hospital. Therefore, any antibiotic stewardship IT intervention must be customized to meet local needs, prescriber behaviors, minimize barriers to implementation, and utilize available resources.

Another area of focus for future ASPs is the use of rapid diagnostics. Currently, when patients present with signs and symptoms of an infection, an empiric antimicrobial regimen is started that is then de-escalated as necessary; rapid testing will help to initiate appropriate therapy more quickly and increase antimicrobial effectiveness. Rapid tests range from rapid polymerase chain reaction (PCR)-based screening [50], to Verigene gram-positive blood culture (BC-GP) tests [51], next-generation sequencing methods, and matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) [52]. Rapid diagnostic tools should be viewed as aides to assist ASPs in decreasing antibiotic consumption and improving patient outcomes; these various tools have been shown to improve clinical outcomes when integrated into ASPs, but offer little value addressing the goals of ASPs when used outside of stewardship programs and their sensitive timeframes [53].

In terms of future ASP expansion, stewardship implementation can become more unified and broad in scope. ASPs should expand to include antifungal interventions, an area which is showing progress [36]. ASPs can also be implemented in new areas throughout the hospital (eg, pediatrics and emergency room), as well as areas outside of the hospital setting, including long-term care facilities, dialysis centers, and other institutions [54–56]. A prospective randomized control study was conducted in 30 nursing homes to evaluate the use of a novel resident antimicrobial management plan (RAMP) for improved use of antimicrobials [57]. This study found that the RAMP had no associated adverse effects and suggests that ASP is an important tool in nursing homes. In addition, the general outpatient and pediatric settings show promise for ASPs [56,58,59], but more research is needed to support expansion and to identify how ASP interventions should be applied in these various practice settings. The antimicrobial stewardship interventions that will be utilized will need to be carefully delineated to consider the scale, underlying need, and potential challenges in those settings.

While the future of antibiotic stewardship is unclear, there is certainty that it will continue to develop in both scope and depth to encompass new areas of focus, new settings to improve outcomes, and employ new tools to refine approaches. An important first step for the continued development of ASPs is alignment and standardization, since without alignment it will continue to be difficult to compare outcomes. This issue is currently being addressed by a number of different organizations. With current support from the Joint Commission, the CDC, as well as the President's Council of Advisors on Science and Technology (PCAST) [8], regulatory requirements for ASPs are well underway, and these drivers will appropriately position ASPs for further advancements. By reducing variability amongst ASPs and delineating implementation of ASPs, there can be a clear identification of both economic and clinical benefits associated with specific interventions.

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References

1. Barlam TF, Cosgrove SE, Abbo AM, et al. Implementing an antimicrobial stewardship program: guidelines by the Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51–77.
2. Hughes D. Selection and evolution of resistance to antimicrobial drugs. IUBMB Life 2014;66:521–9.
3. World Health Organzation. The evolving threat of antimicrobial resistance – options for action. Geneva: WHO Press; 2012.
4. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence 2013;4:185–91.
5. Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 2010;74:417–33.
6. Owens RC Jr. Antimicrobial stewardship: concepts and strategies in the 21st century. Diagn Microbiol Infect Dis 2008;61:110–28.
7. Antibiotic resistance threats in the United States, 2013 [Internet]. Centers for Disease Control and Prevention. Available at www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
8. Nathan C, Cars O. Antibiotic resistance – problems, progress, prospects. N Engl J Med 2014;371:1761–3.
9. McGoldrick, M. Antimicrobial stewardship. Home Healthc Nurse 2014;32:559–60.
10. Ruedy J. A method of determining patterns of use of antibacterial drugs. Can Med Assoc J 1966;95:807–12.
11. Briceland LL, Nightingdale CH, Quintiliani R, et al. Antibiotic streamlining from combination therapy to monotherapy utilizing an interdisciplinary approach. Arch Inter Med 1988;148:2019–22.
12. McGowan JE Jr, Gerding DN. Does antibiotic restriction prevent resistance? New Horiz 1996;4: 370–6.
13. Cappelletty D, Jacobs D. Evaluating the impact of a pharmacist's absence from an antimicrobial stewardship team. Am J Health Syst Pharm 2013;70:1065–69.
14. Shales DM, Gerding DN, John JF Jr, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the prevention of an-

timicrobial resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Infect Control Hosp Epidemiol 1997;18:275–91.
15. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159–77.
16. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Ctrl Hosp Epidemiol 2012;33:322–7.
17. The Joint Commission. Approved: New antimicrobial stewardship standard. Joint Commission Perspectives 2016;36:1–8.
18. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis 2014;59(Suppl 3):S97–100.
19. Moody J. Infection preventionists have a role in accelerating progress toward preventing the emergence and cross-transmission of MDROs. Prevention Strategist 2012 Summer:52–6.
20. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. N Engl J Med 2013;368:299–302.
21. Olans RN, Olans RD, Demaria A. The critical role of the staff nurse in antimicrobial stewardship--unrecognized, but already there. Clin Infect Dis 2016;62:84–9.
22. Karanika S, Paudel S, Grigoras C, et al. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother 2016;60:4840–52.
23. Wagner B, Filice GA, Drekonja D, et al. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. Infect Control Hosp Epidemiol 2014;35:1209–28.
24. Filice G, Drekonja D, Greer N, et al. Antimicrobial stewardship programs in inpatient settings: a systematic review. VA-ESP Project #09-009; 2013.
25. Cairns KA, Doyle JS, Trevillyan JM, et al. The impact of a multidisciplinary antimicrobial stewardship team on the timeliness of antimicrobial therapy in patients with positive blood cultures: a randomized controlled trial. J Antimicrob Chemother 2016;71:3276–83.
26. Hohn A, Heising B, Hertel S, et al. Antibiotic consumption after implementation of a procalcitonin-guided antimicrobial stewardship programme in surgical patients admitted to an intensive care unit: a retrospective before-and-after analysis. Infection 2015;43:405–12.
27. Singh S, Zhang YZ, Chalkley S, et al. A three-point time series study of antibiotic usage on an intensive care unit, following an antibiotic stewardship programme, after an outbreak of multi-resistant Acinetobacter baumannii. Eur J Clin Microbiol Infect Dis 2015;34:1893–900.
28. Cairns KA, Jenney AW, Abbott IJ, et al. Prescribing trends before and after implementation of an antimicrobial stewardship program. Med J Aust 2013;198:262–6.
29. Liew YX, Lee W, Loh JC, et al. Impact of an antimicrobial stewardship programme on patient safety in Singapore General Hospital. Int J Antimicrob Agents 2012;40:55–60.
30. Bevilacqua S, Demoré B, Boschetti E, et al. 15 years of antibiotic stewardship policy in the Nancy Teaching Hospital. Med Mal Infect 2011;41:532–9.
31. Danaher PJ, Milazzo NA, Kerr KJ, et al. The antibiotic support team--a successful educational approach to antibiotic stewardship. Mil Med 2009;174:201–5.
32. Jenkins TC, Knepper BC, Shihadeh K, et al. Long-term outcomes of an antimicrobial stewardship program implemented in a hospital with low baseline antibiotic use. Infect Control Hosp Epidemiol 2015;36:664–72.
33. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother 2013;57:2326–32.
34. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother 2013;68:1951–61.
35. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. J Antimicrob Chemother 2014;69:881–91.
36. Antworth A, Collins CD, Kunapuli A, et al. Impact of an antimicrobial stewardship program comprehensive care bundle on management of candidemia. Pharmacotherapy 2013;33:137–43.
37. Davey P, Brown E, Charani E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2013;4:CD003543.
38. Pasquale TR, Trienski TL, Olexia DE, et al. Impact of an antimicrobial stewardship program on patients with acute bacterial skin and skin structure infections. Am J Health Syst Pharm 2014;71:1136–9.
39. Schuts EC, Hulscher ME, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847–56.
40. Higgins JPT, Green S, editors. Identifying and measuring heterogeneity. Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. [Internet]. The Cochrane Collaboration, March 2011. Available at http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm.
41. Feazel LM, Malhotra A, Perencevich EN, et al. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:1748–54.
42. Impact of antibiotic stewardship programs on Clostridium difficile (C. diff) infections [Internet]. Centers for Disease Control and Prevention. [Updated 2016 May 13; cited 2016 Oct 11]. Available at www.cdc.gov/getsmart/healthcare/evidence/asp-int-cdiff.html.
43. Burke JP. Antibiotic resistance – squeezing the balloon? JAMA 1998;280:1270–1.
44. This nephrotoxicity result is corrected from the originally published result; communicated by Jan M Prins on behalf of the authors for reference [39]. Prins, JM (Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Centre, Amsterdam, Netherlands). Email communication with Joseph Eckart (Pharmacy Practice & Administration, Ernest Mario School of Pharmacy, Rutgers University, Piscat-

away, NJ). 2016 Oct 9.
45. Coulter S, Merollini K, Roberts JA, et al. The need for cost-effectiveness analyses of antimicrobial stewardship programmes: a structured review. Int J Antimicrob Agents 2015;46:140–9.
46. Dik J, Vemer P, Friedrich A, et al. Financial evaluations of antibiotic stewardship programs—a systematic review. Frontiers Microbiol 2015;6:317.
47. Campbell KA, Stein S, Looze C, Bosco JA. Antibiotic stewardship in orthopaedic surgery: principles and practice. J Am Acad Orthop Surg 2014;22:772–81.
48. Surveillance for antimicrobial use and antimicrobial resistance options, 2015 [Internet]. Centers for Disease Control and Prevention. [Updated 2016 May 3; cited 2016 Nov 22]. Available at www.cdc.gov/nhsn/acute-care-hospital/aur/index.html.
49. Baysari MT, Lehnbom EC, Li L, Hargreaves A, et al. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: a systematic review and meta-analysis. Int J Med Inform. 2016;92:15-34.
50. Bauer KA, West JE, Balada-llasat JM, et al. An antimicrobial stewardship program's impact with rapid polymerase chain reaction methicillin-resistant Staphylococcus aureus/S. aureus blood culture test in patients with S. aureus bacteremia. Clin Infect Dis 2010;51:1074–80.
51. Sango A, Mccarter YS, Johnson D, et al. Stewardship approach for optimizing antimicrobial therapy through use of a rapid microarray assay on blood cultures positive for Enterococcus species. J Clin Microbiol 2013;51:4008–11.
52. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect 2014;69:216–25.
53. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis 2014;59 Suppl 3:S134–145.
54. Dyar OJ, Pagani L, Pulcini C. Strategies and challenges of antimicrobial stewardship in long-term care facilities. Clin Microbiol Infect 2015;21:10–9.
55. D'Agata EM. Antimicrobial use and stewardship programs among dialysis centers. Semin Dial 2013;26:457–64.
56. Smith MJ, Gerber JS, Hersh AL. Inpatient antimicrobial stewardship in pediatrics: a systematic review. J Pediatric Infect Dis Soc 2015;4:e127–135.
57. Fleet E, Gopal Rao G, Patel B, et al. Impact of implementation of a novel antimicrobial stewardship tool on antibiotic use in nursing homes: a prospective cluster randomized control pilot study. J Antimicrob Chemother 2014;69:2265–73.
58. Drekonja DM, Filice GA, Greer N, et al. Antimicrobial stewardship in outpatient settings: a systematic review. Infect Control Hosp Epidemiol 2015;36:142–52.
59. Drekonja D, Filice G, Greer N, et al. Antimicrobial stewardship programs in outpatient settings: a systematic review. VA-ESP Project #09-009; 2014.
60. Zhang YZ, Singh S. Antibiotic stewardship programmes in intensive care units: why, how, and where are they leading us. World J Crit Care Med 2015;4:13–28. (referenced in online Table)