The Evolving Role of Antimicrobial Stewardship in Management of Multidrug Resistant Infections

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KEYWORDS

• Antimicrobial stewardship • Antimicrobial resistance • Antibiotics

KEY POINTS

- It is crucial that antimicrobial stewardship programs (ASPs) be put into practice now to provide for optimal patient outcomes and preserve antimicrobials for future use.
- Strategies for improving antibiotic use and evidence for best practices in antibiotic stewardship will continue to evolve.
- The specific types of interventions implemented by institutions will depend on local circumstances and capabilities.
- It is vital that health care settings have ASPs so that patients, both present and future, will continue to have the benefit of life-saving antimicrobials.

INTRODUCTION

The discovery of potent antimicrobial agents was one of the greatest contributions to medicine in the 20th century. When introduced, they had an immediate and dramatic impact on the outcomes of infectious diseases (ID), making once lethal infections readily curable. Unfortunately, the emergence of antimicrobial-resistant pathogens now threatens these advances. Antimicrobial resistance is a serious health threat

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that affects the clinical outcome of patients as well as results in higher rates of adverse events and health care costs. The seriousness of the health impact of antimicrobial resistance is a major public health crisis.[1] Unfortunately, there are already patients every day who contract infections who cannot be treated with currently available antimicrobials. Antimicrobial resistance affects everybody and it has no geographic boundaries. As the world learned from the 2014 Ebola epidemic, every deadly pathogen is just a plane ride away.

What can be done to address this crisis? There is no question that antibiotic misuse is the most important modifiable factor that leads to antimicrobial resistance. The good news is that we do have a solution to this problem. Since their inception, antimicrobial stewardship programs (ASP) have proven highly successful in improving antibiotic use. These programs can improve patient outcomes, reduce adverse events (including *Clostridium difficile* infection), reduce readmission rates, and reduce antibiotic resistance.[2–6] The proven benefits of ASPs have led to increasing calls for their implementation in all hospitals.

This article explores the effect of ASPs toward optimizing antimicrobial use and the impact on antimicrobial resistance.

RESISTANCE AND THE NEED FOR ANTIMICROBIAL STEWARDSHIP

The primary goal of ASP is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile* infection), and the emergence of resistance.[7] Thus, the appropriate use of antimicrobials is an essential part of patient safety and deserves careful oversight and guidance. There is a strong association between antimicrobial use and the emergence of resistance. Observational studies associate greater antibiotic prescribing with greater rates of antibiotic resistance.[8,9] Thus, overuse or inappropriate use of antimicrobials is primary drivers for antimicrobial resistance. However, according to the US Centers for Disease Control and Prevention, 20% to 50% of all antibiotics prescribed in US acute care hospitals are either unnecessary or inappropriate.[10,11]

Unlike other medications, the potential for spread of resistant organisms means that the misuse of antibiotics can adversely impact the health of patients who are not even exposed to them. The ability of antimicrobials to cause “collateral damage” is vastly underappreciated. As stated in the White House release dated March, 27, 2015, National Action Plan for Combating Antimicrobial-Resistant Bacteria, “the emergence of drug resistance in bacteria is reversing the gains of the past 80 years, with many important drug choices for the treatment of bacterial infections becoming increasingly limited…. The loss of antibiotics that kill or inhibit the growth of bacteria means that we can no longer take for granted quick and reliable treatment of rare or common bacterial infections, including bacterial pneumonia.”[12] Within the first goal of the Action Plan is the recommendation for implementation of health care policies and ASPs that improve patient outcomes, and efforts to minimize the development of resistance by ensuring that each patient receives the right antibiotic at the right time at the right dose for the right duration. Over the next 5 years, the goals of this Action Plan include reducing the incidence of carbapenem-resistant Enterobacteriaceae (CRE) infections by 60%, *C difficile* infection (CDI) and methicillin-resistant *Staphylococcus aureus* bloodstream infections by 50%, MDR *P aeruginosa* by 35%, and invasive pneumococcal disease by 25%. ASPs are evolving from management of antimicrobial drug therapy to management of ID. Diagnostic accuracy is key for appropriate antimicrobial use. Filice and colleagues[13] found that, when the diagnosis was correct, 62% of

antimicrobial courses were appropriate compared with 5% when the diagnosis was incorrect or indeterminate ($P<.001$) This big picture approach will be necessary to meet the disease based goals of the National Action plan.

ASPs can be implemented effectively in a wide variety of health care facilities; strategies and policies have been reviewed elsewhere.[1,7,14]

COLLABORATE FOR SUCCESS

Control of antimicrobial resistance with an effective stewardship programs requires a multifactorial collaborative effort, including physicians and pharmacists as the core members along with infection control, microbiology, administration, information technology, quality control, and other key stakeholders. Physicians are a key core member of an effective ASP. If available, an ID specialist is most effective in this role; however, smaller facilities may formulate an effective program with other physicians who have a strong knowledge of appropriate antimicrobial use. Hospitalists can be effective physician members of a stewardship program given their presence in inpatient care and their frequent use of antimicrobials.[15] ID specialists optimize treatment in the inpatient setting by recommending appropriate antibiotic choices, duration of therapy, and route of delivery.[16] Existing evidence suggests that, when recommendations by an ID specialist are followed, patients are more often correctly diagnosed, have shorter lengths of stay, receive more appropriate therapies, have fewer complications, and may use fewer antibiotics overall.[17]

Pharmacists, preferably with advanced training in ID, are also essential members of an ASP. The American Society of Health System Pharmacists states that, "Pharmacist have a responsibility to take prominent roles in ASP, in part, from pharmacists' understanding of and influence over antimicrobial use within the health system."[18] One role of the pharmacists is to ensure the optimal use of antimicrobials by assuring the 5 *D*s: right diagnosis, drug, dose, duration, and deescalation. Once appropriate therapy has been initiated, pharmacists can optimize therapy by applying pharmacokinetic pharmacodynamic principles such as extended-infusion β-lactam therapy. As shown in 1 study, patients who received extended-infusion cefepime for the treatment of MDR *P aeruginosa* infections had a lower mortality compared with those who receive standard 30-minute infusions (3% vs 20%; $P = .03$).[19]

Time to effective antimicrobial therapy is important to optimize patient outcomes. Pharmacists play a key role in applying microbiology rapid diagnostic test (RDT) results. One of the first studies to evaluate using a RDT for *S aureus* bacteremia in conjunction with ID pharmacist intervention showed mean time to optimal antimicrobial therapy was 1.7 days shorter ($P = .002$) after RDT implementation.[20] Two collateral benefits were observed; pharmacists were able to advocate and obtain ID consults in many cases and the mean hospital costs were $21,387 less per patient in the post-RDT group.

Ongoing education of the medical staff is another important role. The emergence of new resistance enzymes such as CRE, New Delhi Metallo-β-lactamase, and *Klebsiella pneumoniae* carbapenemases creates an "alphabet soup" of confusion for non-ID physicians. Pharmacists should provide timely education and guidance to health care providers for each new antimicrobial and emerging multidrug-resistant organisms (MDROs). The impact of MDRO on patient care extends beyond optimizing drug therapy. It also impacts infection control.

Even with ASPs, the most effective antimicrobials are of little value if health care providers do not wash their hands and thereby contribute to the spread of infection between patients. The need for meticulous attention to the fundamentals of infection

control should not be understated. This was demonstrated in the 2011 *K pneumoniae* carbapenemase–producing *K pneumoniae* outbreak at the National Institutes for Health.[21] Despite isolation measures implemented at the beginning of hospitalization, silent transmission spawned a cluster that led to infections in 8 patients, 6 of whom died from the infection. Multidisciplinary meetings to keep everyone informed, involved physicians, nurses, pharmacists, infection preventionists, respiratory therapists, housekeepers, nutritionists, hospital administration, patient and environmental safety, and other staff.

As part of the ASP team, infection control preventionists play an important role in preventing the spread of MDRO. One of the most successful examples is the Israel nationwide intervention aimed at containing the spread of CRE. Nosocomial CRE acquisition in acute care declined from a monthly high of 55.5 to an annual low of 4.8 cases per 1000,000 patient-days ($P<.001$).[22]

As MDROs increase in the hospital setting, combination antimicrobial use increases. The collateral damage from exposure to multiple antibiotics is the development of CDI. A recent infection control survey of 571 US hospitals asked questions related to CDI prevention and found the use of ASP to prevent CDI is lacking in 48% of hospitals.[23]

The microbiologist provides essential data for ASPs. Hospital and unit specific antibiograms help to guide appropriate empiric antimicrobial therapy. New RDT are game changing in the management of patients. This new technology allows for the identification of organisms in hours versus 3 to 4 days using traditional methods. Multiple studies have documented the positive impact on patient care when RDT are used in conjunction with ASP.[24] Improvement in time to optimal therapy, shorter length of stay, and lower mortality has been reported.

COST OF RESISTANCE AND IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

Cost is the elephant in the room for ASP. Hospital administration often expects ID physicians to oversee ASP without any financial compensation. Pharmacists who are not ID trained are asked to perform stewardship intervention in addition to their current responsibilities without additional training, mentoring, or compensation. Without buy in from hospital administration and without appropriate financial support for ASP, it is unlikely that hospitals can perform stewardship at a high level. There is hope, however; the President's Council of Advisors on Science and Technology recommended that a regulatory requirement for antibiotic stewardship be in place by the end of 2017.[25]

Required programs that are linked to reimbursement are often what are needed to create change. It has been well-established that MDRO infections are associated with longer lengths of stays and higher costs of care compared with infections with susceptible organisms.[26]

Frequently, ASPs will need to recommend 2 or more antibiotics to treat patients infected with MDROs. New expensive antibiotics are often the most appropriate option, but the silo budget mentality in hospitals place tremendous pressure on the pharmacy department to use the least expensive antimicrobials. This penny wise–pound foolish approach may change with the new Centers for Medicare and Medicaid Services recommendation to document outcomes of antibiotic stewardship activities. Studies have shown delays in time to effective antibiotic therapy leads to increased costs and poor outcomes.[27]

Last, the recent CRE outbreak linked to colonized scopes has resulted in lawsuits from patients who acquired CRE infections after procedures.[28] This can be a

significant financial loss to a hospital in addition to the negative publicity, loss of patient trust, and most important loss of life from a preventable infection.

EVIDENCE OF STEWARDSHIP ON THE IMPACT OF ANTIMICROBIAL RESISTANCE

There are 2 core strategies that provide the foundation for an ASP. These strategies are not mutually exclusive[7]:

1. Prospective audit with intervention and feedback. Prospective audit of antimicrobial use with direct interaction and feedback to the prescriber, performed by either an IDs physician or a clinical pharmacist with ID training, can result in reduced inappropriate use of antimicrobials.
2. Formulary restriction and preauthorization. Formulary restriction and preauthorization requirements can lead to immediate and significant reductions in antimicrobial use and cost and may be beneficial as part of a multifaceted response to a nosocomial outbreak of infection.

Several methods of improving prescribing of antimicrobial agents by ASP have been evaluated and include antimicrobial avoidance when not warranted (eg, avoid antibacterial agents for viral respiratory infections); appropriateness of initial antimicrobial choices and doses, which can be optimized by following existing guidelines; monitoring for drug–bug mismatches (eg, when the pathogen is resistant in vitro to the initially prescribed antimicrobial); reducing unnecessary prolongation of duration; and deescalation to a more narrow antimicrobial regimen from the empirical choice once a culture reveals the pathogen. No single intervention can solve the problem. Data are variable as to the impact each of the strategies have on reducing antimicrobial resistance.

The best strategies for the prevention and containment of antimicrobial resistance have not been established definitively. Often, multiple interventions have been made simultaneously, making it difficult to assess the benefit attributable to any 1 specific intervention. However, a comprehensive program that includes active monitoring of resistance, fostering of appropriate antimicrobial use, and collaboration with an effective infection control program to minimize secondary spread of resistance is considered to be optimal.

A recent Cochrane review evaluated 89 studies from 19 countries to determine effective interventions to improve antimicrobial prescribing practices for hospital inpatients.[29] Most of the interventions (80/95, 84%) targeted the choice of antibiotic prescribed (drug selected, timing of first dose, or route of administration). The remaining 15 interventions aimed to change exposure of patients to antibiotics by changing the decision to treat or the duration of treatment. Twelve studies evaluated antimicrobial resistance as an outcome. Interventions to change antimicrobial prescribing were associated with a decrease in CDI, resistant gram-negative bacteria, methicillin-resistant *S aureus*, and vancomycin-resistant enterococci. The metaanalysis indicated that restrictive interventions tended to have a more immediate effect on decreasing resistance of the restricted agent, but prospective audit and feedback seemed to be more effective for a long-term effect.

The effect of several studies on antimicrobial resistance is listed in **Table 1**. The studies listed assessed various interventions, which include antimicrobial restriction, deescalation, reduction of duration, and various forms of comprehensive antimicrobial stewardship with protocol adherence and audit and feedback. Five of the studies assessed the impact of antimicrobial restriction and subsequent development of antimicrobial resistance.[30–34] There has been robust evidence that reduction of resistance

Table 1
Antimicrobial stewardship interventions: impact on resistance as an outcome

Study/Design	Intervention	Resistance Outcome Assessed	Finding
de Man[30]/cross-over study in 2 neonatal ICUs; same hospital	*Antimicrobial restriction*: During the first 6 mo of the study unit A used an amoxicillin and cefotaxime regimen while unit B used a penicillin and tobramycin regimen. During the second 6 mo the units switched antibiotics	Colonization of cefotaxime or tobramycin resistant GNR at 6 mo	68% reduction in days of colonization with resistant bacteria
Lan[31]/Prospective, observational	*Restriction of ceftazidime*	Rate of ESBL *E coli* and *K pneumoniae* in ICU	Decrease in colonization and infection by ESBL-producing *E coli* or *K pneumoniae*
Lewis[32]/interrupted time analysis	*Restriction of ciprofloxacin*	Rate of ciprofloxacin resistant *P aeruginosa*	Significant decreasing trend observed in the percentage and the rate of isolates of *P aeruginosa* that were resistant to antipseudomonal carbapenems and ciprofloxacin.
Medina Presentado[33]/prospective	*Restriction of ciprofloxacin and ceftriaxone*; before/after design	Susceptibility of GNB	Reduction of resistant GNB in the after period—especially *Acinetobacter* spp and *P aeruginosa*
White[34]/observational	*ABX restriction*; before and after implementation of restriction of amikacin, ceftazidime, ciprofloxacin, fluconazole, ofloxacin	Susceptibility of Gram-negative blood isolates	Reduced resistance ($P<.01$)
Singh[46]/RCT	*Duration* and use of monotherapy vs standard duration based on CPIS	Antimicrobial Resistance and superinfection	Less resistance or superinfection with intervention (15% vs 37%; $P = .017$)
Chastre[47]/RCT	*Duration* 7 vs 14 d for VAP	Resistance, mortality, recurrence	Multidrug-resistant pathogens developed less with 8 d therapy ($P = .04$)

Kim[36]/prospective	*Deescalation* RCT for initial therapy of VAP; deescalation based on culture	Development of antimicrobial resistance	Nonsignificant more MRSA in deescalation arm; no difference GNB
Joffe[37]/second analysis of RCT of VAP invasive bronchitis vs endobronchial culture	*Deescalation* based on culture	Development of antimicrobial resistance	No difference observed
Leone[38]/prospective RCT	*Deescalation* of patients with sepsis	Development of superinfection	Increased superinfection in deescalation arm but no mention of resistance effect
Carling[39]/prospective	*Multidisciplinary* antimicrobial management program; before and after assessment	*C difficile* rates and resistance of Enterobacteriaceae	Significant reduction in both
Dortch[40]/prospective, observational	*Antimicrobial stewardship protocols*; observed effect	Rate of MDR gram-negative bacilli during implementation	MDR GNB decreased from 37.4% to 8.5%
Yong[41]/prospective, observational	*Antimicrobial Stewardship* intervention	Susceptibility of *Pseudomonas* before and after intervention	Reduced resistance of *Pseudomonas* to imipenem and gentamicin
Nowak[42]/observational, pre–post analysis	*Antimicrobial Stewardship Intervention*	Rates of infections owing to common nosocomial pathogens caused by resistant pathogens	Rates of MRSA and *C difficile* decreased
DiazGranados[43]/prospective audit	*Audit for AS in ICU;* baseline compared with intervention	ID physician and ID Pharmacist-recommendations and rounds	Lower rates of resistance ($P = .033$). audit and feedback were independently associated with appropriate antimicrobial selection and prevention of resistance

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Study/Design	Intervention	Resistance Outcome Assessed	Finding
Niwa[44]/retrospective before/after intervention	*Assessment of comprehensive ASP* outcomes of extensive implementation of antimicrobial stewardship were evaluated from the standpoint of antimicrobial use density, treatment duration, duration of hospital stay	Occurrence of antimicrobial-resistant bacteria and medical expenses	Significant reduction in the antimicrobial consumption was observed in the second-generation cephalosporins, carbapenems, aminoglycosides, leading to a reduction in the cost of antibiotics by 11.7%. The appearance of MRSA and the proportion of MDR Gram-negative bacteria decreased significantly
Trienski[45]/observational evaluation	*Assessment of comprehensive ASP* prospective audit with intervention and feedback model with the clinical pharmacist and ID physician making formal rounds on selected patients in both critical care and medical/surgical units; interventions included deescalation, bug–drug mismatch, dose optimization, duration (refer to text)	Observation of resistance rates on basis of antibiograms	Observed a decrease in antimicrobial resistance rates of GNB in ICU

Abbreviations: ABX, antibiotics; ASP, antimicrobial stewardship program; CPIS, Clinical Pulmonary Infection Score; ESBL, extended spectrum beta-lactamase; GNB, gram-negative bacilli; ICU, intensive care unit; ID, infectious disease; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomized clinical trial; VAP, ventilator-associated pneumonia.

to a restricted antimicrobial has been observed when that agent is restricted for use; however, an unintended consequence may be development of resistance of alternative agents that replace the restricted agents—squeezing the balloon.[35]

Three studies assessed deescalation and observed no effect on antimicrobial resistance within the time frame of the investigation.[36–38] Although there is a general perception that "deescalation" is appropriate and a primary principle of antimicrobial stewardship and while prior national guidelines and numerous papers contend that deescalation is beneficial for patients and the health system (eg, reduction of cost and resistance), there is very little high-level evidence to support this. As stated in a recent Cochrane review of antimicrobial deescalation for adults with sepsis, "There is no adequate or direct evidence on whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis…. Appropriate studies are needed to investigate the potential benefits proposed by de-escalation treatment."[29] Subsequent to this Cochrane Review, Leone and colleagues[38] reported the first randomized, controlled trial to specifically assess deescalation, defined as narrowing the spectrum of the initial antimicrobial therapy, in patients with sepsis in the intensive care unit. Of 116 patients included in the analysis, 59 were assigned randomly to the deescalation group and 57 to the continuation of appropriate antimicrobial therapy group (pneumonia was the cause of infection in 58% and 40% patients in the deescalation and continuation arms, respectively; $P = .06$). Deescalation was associated with an increased number of antimicrobial days (the primary study outcome) as well as risk of superinfection; but there was no mention of an effect on resistance. The authors concluded that deescalation was not noninferior to the continuation of appropriate empirical antimicrobial therapy. There was no impact on mortality or length of intensive care stay. Despite the randomized, controlled trial design, there were several limitations of the study, including nonblinding, a misbalance of type of infection (more lung infections in the deescalation arm), nonreporting the number of healthcare-associated pneumonia versus ventilator-associated pneumonia, and nonreporting of the appropriateness of the initial antimicrobial therapy. Furthermore, in a post hoc analysis of the 56 patients with pneumonia there was no difference in outcomes measured. In light of the absence of mortality difference and the presence 'serious' flaws of this randomized, controlled trial, we believe deescalation should remain recommended for the potential benefits to reduce antimicrobial use and resistance.

Most of the remaining studies assessed a comprehensive ASP often with audit and feedback and specific antibiotic stewardship protocols.[39–45] Many of the programs described in these studies combined some form of restriction (eg, reserved specific antimicrobials for ID or intensive care use) with a prospective audit and feedback process. Several studies used computer systems to identify various bug–drug relationships or for implementation of specific protocols for a particular syndrome (eg, pneumonia or urinary tract infection). At Summa Health System, patients are prospectively evaluated daily (5 days a week) by an ID physician and a dedicated ID-trained doctor of pharmacy using a software program to identify patients on various aspects and courses of antimicrobial agents.[45] Stewardship rounds on the general wards and intensive care units are conducted and various recommendations concerning antimicrobial therapy are communicated to the prescribing service. The goal of ASP is to limit antimicrobial use by optimizing the antimicrobial selection, dosing, route, and duration of therapy. The most common interventions recommended are deescalation, change of regimen based on microbiology results (especially for drug–bug mismatches), dosing adjustments including dose optimization on the basis of a minimum inhibitory concentration, discontinuation of antimicrobials, and ID consult. In addition to showing a reduction in antimicrobial use and cost, we have observed a

reduction of 30-day readmission rates (from 16.7% to 6.5% for all cause readmissions; $P = .05$) and antimicrobial resistance to most Gram-negative bacilli as listed in our yearly antibiograms.[5,45]

Duration of therapy is important; each additional day of unnecessary antibiotics increases a patients' risk of acquiring CDI.[46,47] The appropriate duration of therapy for intraabdominal infections is unclear. Traditionally duration of antimicrobial therapy has been 7 to 14 days. A shorter course could decrease the risk of antimicrobial resistance. A recent study in surgery patients with complicated intraabdominal infection and adequate source control found patient outcomes after short course antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days).[48]

USE OF NEW ANTIMICROBIALS

After an extended period in which few new systemic antibiotics were approved for use in the United States, the last few years have seen an increase in newly approved antimicrobials, and government policies, and professional society advocacy are combining to increase the development of additional agents. In the past year several new approvals have focused on gram-positive infections (dalbavancin, ortivancin, tedizolid) and 2 on gram-negative infections (ceftolozane-tazobactam and ceftazadime-avibactam). Other agents in late stage development include delafloxacin, eravacycline, omadacycline, solithromycin, surotomycin, and plazomicin. The appropriate use of these new agents will be facilitated by effective stewardship. Many clinicians accept at face value the misperception that use of newer agents does not accord with practicing stewardship; this idea represents a false dichotomy. In reality, the concepts of use of new drugs and stewardship can be very compatible. There has been a common perception in the past that as new agents became available, we were going to restrict them and never use them because we wanted to save them. But that may not be best for our patients. We have patients who are at high risk and so are good candidates for use of these new agents as initial therapy. Appropriate selection and timely administration of initial therapy is critically important and has a major impact on outcomes, including risk for death. Given the effectiveness of newer—and sometimes more expensive—agents against pathogens that have developed resistance to established agents, the use of newer agents in appropriately selected patients is compatible with good clinical care and antimicrobial stewardship. Oversight of treatment of newer agents by ASPs can assure appropriate use. As stated in the past by Dennis Maki, MD, "The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patient with finer brandy."[49]

The development of rapid molecular tests able to quickly identify or rule out the presence of MDROs will also have great value in helping clinicians individualize newer antimicrobial therapy to optimal effect.

SUMMARY

In light of the serious threat of emerging antimicrobial-resistant pathogens, it is crucial that ASPs be put into practice now to provide for optimal patient outcomes and preserve antimicrobials for future use. Strategies for improving antibiotic use and evidence for best practices in antibiotic stewardship will continue to evolve. The specific types of interventions implemented by institutions will depend on local circumstances and capabilities. Nevertheless, it is vital that health care settings have ASP so that patients, both present and future, will continue to have the benefit of life-saving antimicrobials.

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