# Antibiotic Resistance

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## Mechanisms and New Antimicrobial Approaches

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# Preface

Resistance to antimicrobials has been described involving all types of infectious agents and continues to be a growing challenge in modern medicine. A common problem in acute care hospitals is the use of potent, broad-spectrum antibiotics, as well as inappropriate or suboptimal therapy, all of which contribute to the development of antibiotic resistance. One of the solutions to this issue, which may prolong the effectiveness of currently available antibiotics is antimicrobial stewardship strategies that encourage the judicious use of these antibiotics. Moreover, the potential of emerging and enabling technologies like nanotechnology should be harnessed to tackle the global problem of multidrug-resistance (MDR). These issues are discussed in this book.

Understanding the fundamental mechanisms of antibiotic resistance is a key step for the discovery of effective methods to cope with the resistance. This book discusses up-to-date knowledge about the mechanisms of antibiotic resistance in different types of bacteria and application of this knowledge into developing new and optimal treatment strategies. In addition, it explores alternative antimicrobial approaches in fighting microbial resistance. Several chapters are devoted to the potential of nanotechnology in combating MDR bacteria, to the role of magnetite-based nanomaterials in developing alternative therapeutic and preventive approaches against pathogens, to different polymer-containing metal nanocomposites as promising antimicrobial agents, and to the role of nanooxides and nitric oxides in fighting antibiotic-resistant bacteria. Alternative natural sources of antimicrobial agents are also discussed in detail, including plant-derived products, such as essential oils (EOs) and plant extracts, bacteriophages, bacteriocin-producing bacteria, marine-derived bacteria, fungi, sponges, algae, corals, mollusks, and other invertebrates.

The potential audience for the book include researchers in microbiology, biotechnology, pharmacology, nanotechnology, and infection control; students of medical, pharmaceutical, and biological faculties; and clinicians dealing with infections in various locations.

CHAPTER

# 1 ANTIMICROBIAL STEWARDSHIP: HOSPITAL STRATEGIES TO CURB ANTIBIOTIC RESISTANCE

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## INTRODUCTION

The discovery of antibiotics may be one of the greatest achievements in medicine. Antibiotic treatments have improved clinical outcomes from infections, leading to the reduction of morbidity and mortality in surgical, transplant, cancer, and critical care patients. With the use of potent broad-spectrum antibiotics, selective pressures have made antibiotic resistance an urgent worldwide concern. Increasing numbers of hospital-acquired infections are now caused by multidrug-resistant pathogens, making treatment progressively difficult and antibiotic choice increasingly limited. The Centers for Disease Control and Prevention (CDC) data showed that in 2010, 55.7% of patients discharged from 325 hospitals received antibiotics during their hospital stay, and 37.2% of those antibiotic prescriptions were unnecessary or could be improved, which is in line with previous studies in the literature on antibiotic utilization in acute care hospitals.[1] Inappropriate antimicrobial use can lead to the selection of resistant pathogens, *Clostridium difficile* infections, antibiotic-induced toxicities, and adverse drug reactions, all of which have a significant negative impact on patient morbidity, mortality, and health-care costs. It has been recognized that reduction of antibiotic use would slow the growth of or alleviate the problem of antibiotic resistance and *C. difficile* infections. In 1997, the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) published guidelines for the prevention of antimicrobial resistance in hospitals, coining the term *antimicrobial stewardship.*[2] In addition to a comprehensive infection control program and surveillance of bacterial resistance, these guidelines advocated for the judicious use of antimicrobials in order to slow or prevent the development of antimicrobial resistance.

Since 2006, the CDC has launched multiple campaigns to target antibiotic resistance and improve health care. In each of these campaigns, the CDC emphasized the need for judicious antibiotic utilization in acute care hospitals. In 2007, the IDSA and SHEA published guidelines for developing antimicrobial stewardship programs (ASPs) at an institutional level.[3] In this document, IDSA and SHEA define the primary goal of ASPs to be the improvement of clinical outcomes while minimizing the unintended consequences of antimicrobial use, including emergence of resistance, toxicity, and selection of pathogenic organisms such as *C. difficile.* SHEA and IDSA, along with the Pediatric Infectious Disease Society (PIDS), issued a policy statement in 2012

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recommending that ASPs be mandated through regulatory channels.[4] Specifically, this policy statement advocated for the Centers for Medicare and Medicaid Services (CMS) to require participating institutions to implement ASPs. This document further detailed the minimum requirements for an effective ASP and made recommendations on expansion of stewardship efforts to the ambulatory setting, education, and research. In 2014, the CDC recommended that all acute care hospitals implement ASPs to combat the worsening problems of antibiotic resistance and *C. difficile* infections and released a document called "Core Elements of Hospital Antibiotic Stewardship Programs" to aid hospitals in this goal.[5]

In the United States, California remains the first and only state to pass legislation on antimicrobial stewardship. In 2008, Senate Bill 739 (SB 739) mandated California acute care hospitals to put processes in place to monitor the judicious use of antibiotics. It was left to each institution to develop its own procedures to comply with this mandate. The regulatory conditions were vague, and hospitals made various efforts to fulfill these requirement. In a web-based survey of 422 California acute care hospitals in 2010−11, 50% of the 223 respondents had a current ASP, and 30% reported planning to implement an ASP.[6] This survey was subject to reporting bias, however, as those hospitals with active ASPs were more likely to respond. It was reported that SB 739 encouraged some of these hospitals to initiate an ASP. Those that did not adopt ASPs were likely to be smaller or rural hospitals, and lack of resources and administrative support were the most frequently cited barriers to doing so. Interestingly, many hospitals that reported not having an official ASP did have some stewardship processes in place, such as formulary restriction and antimicrobial oversight by pharmacists. In Sep. 2014, California Senate Bill 1311 (SB 1311) further required hospitals to implement an official policy on antimicrobial stewardship and to establish a multidisciplinary stewardship committee by Jul. 2015.[7] This bill was much more prescriptive in its requirements than its predecessor, driving home the minimum requirements for an effective stewardship program in acute care hospitals. In Mar. 2015, the White House released the National Action Plan for Combating Antibiotic-Resistant Bacteria. This 63-page action plan aims to guide programs of the US government, public health, health care, and agriculture in a common effort to address the urgent challenge of mounting antibiotic resistance. The plan sets 1-, 3-, and 5-year milestones for each of five goals, the first of which is to slow the emergence of resistant bacteria and prevent the spread of infections. By 2020, the action plan seeks to establish ASPs in all acute care hospitals and improved antibiotic stewardship across all health-care settings, with a reduction of inappropriate antibiotic use by 20% in inpatient settings.[8] This illustrates the commitment of the United States to meet the critical problem of antimicrobial resistance.

Globally, antimicrobial stewardship is gaining momentum as the challenge of antibiotic resistance became an urgent worldwide concern. In a 2012 international survey of 660 hospitals from 67 countries from 6 continents on inpatient antimicrobial stewardship, 58% of respondents had an ASP and 22% planned to implement one.[9] Academic medical centers accounted for almost 50% of respondents. Reducing antimicrobial resistance was the most frequently cited goal for ASPs across all continents. Formulary restriction was practiced in 81% of hospitals, while 64% had postprescription review as part of the stewardship strategy. Two-thirds of hospitals in North America and Europe had ASPs, with 80% of European countries having antimicrobial stewardship standards at the national level. It was noted that ASPs were more established in Sweden (100%), United States (88%), France (81%), and the United Kingdom (77%) than other countries.[10] However, it should be noted since hospitals with active ASPs were more likely to participate in this survey, the results are

subject to selection bias. Progress is being made in the implementation and expansion of stewardship programs across the United States and Europe. The degree of legislative requirements differ significantly among countries, their primary objectives are different as well. In France, the primary goal is to reduce antibiotic resistance. Reduction of health-care-associated infections is the main impetus in the United Kingdom. For the United States, the principal driver is to improve clinical outcomes. The utilization of electronic medical records, physician order entry, and data warehousing as part of antimicrobial stewardship is much more common in the United States than in France or the United Kingdom.

## MOVING FROM COST TO QUALITY AND PATIENT SAFETY

The CDC estimates that at least 2 million patients each year acquire serious infections with drug-resistant bacteria in the United States, accounting for at least 23,000 deaths and significant morbidity and health-care costs.[11] In addition, the CDC estimates that 150,000 cases per year go to US Emergency Departments for antimicrobial-related adverse events.[12] Effective ASPs can improve patient care and be cost effective. They have shown reductions in antimicrobial use with annual savings of $200,000−900,000, making the programs self-supporting.[13,14] Most of the data from the literature measured direct pharmacy acquisition costs. When taken together with the impact on length of stay, readmission rates, and avoidance of potential adverse drug reactions, the financial impact of ASPs is even greater. The cost effectiveness of ASPs is often cited to garner administration support in a climate of cost-conscious medical care. However, the main goal of antimicrobial stewardship should be to improve patient care and optimize clinical outcomes. More and more, antimicrobial stewardship has become the focus of quality and patient safety improvement efforts.

Appropriate antimicrobial utilization is tied to quality patient care. In a cohort study of 500 randomly selected hospitalized patients with an antimicrobial course, Filice et al. found that diagnostic accuracy correlated to optimal antimicrobial use.[15] Diagnostic accuracy in turn was closely tied to the quality of clinical evidence at the time of initial diagnosis. Accuracy was generally poor for the diagnoses of pneumonia and urinary tract infection, which are extremely common in the inpatient setting. In this study, the appropriateness of antibiotics was judged by a group of four infectious disease physicians. It should be noted that each reviewer's responses was compared with those of the other three reviewers, and agreement was 69−72%.

It is generally accepted that routine treatment of asymptomatic bacteriuria is inappropriate.[16] It is a substantial contributor to antibiotic overuse in hospitalized and nursing home patients, particularly among patients with urinary catheters. In a study at two Veterans Affairs health-care systems, Trautner et al. introduced a streamlined diagnostic algorithm for catheter-associated urinary tract infection versus asymptomatic bacteriuria.[17] This intervention significantly decreased the inappropriate ordering of urine cultures, thereby decreasing the inappropriate treatment of asymptomatic bacteriuria. At the same time, the study did not find undertreatment of true catheter-associated urinary tract infections during the intervention period.

Regardless of appropriateness, all antibiotic use exerts selective pressures that contribute to the development of resistance and other unintentional consequences. It is apparent that not only is the choice of antibiotics important, the duration of therapy may be equally important. In a retrospective

cohort study of 7792 hospitalized adult patients who received 2 or more days of antibiotics, dose-dependent increases in the risk of *C. difficile* infection was associated with the cumulative dose, number of antibiotics, and days of antibiotic exposure.[18] These studies illustrate that appropriate and judicious use of antimicrobials is directly tied to quality patient care and clinical outcomes. Hence, a program such as antimicrobial stewardship, which aids clinicians in this goal, has a major impact on quality and patient safety.

## ELEMENTS OF ASPs

### ANTIMICROBIAL STEWARDSHIP TEAM

The core members of the ASP should include a physician leader and a clinical pharmacist, both of whom with training in infectious diseases, antimicrobial stewardship, or both, with the patient at the center. Larger medical centers can employ infectious disease specialists in this role. Hospitalists can also be ideal leaders in this position, given their involvement in inpatient care and quality improvement.[5] Administration and medical staff support are paramount to the success of ASPs. Physician buy-in is essential for compliance with stewardship team recommendations. Collaboration among the staff in infection control, hospital epidemiology, quality improvement, microbiology laboratory, and information technology (IT) is important for a comprehensive and efficient program.

It should be noted that the structure of the ASP should correspond to available resources and the needs of the individual institution. Even in resource-limited settings, reducing inappropriate antibiotic use is an effective way to improve quality and patient safety by decreasing antibiotic-resistant pathogens, *C. difficile* infection, and antibiotic-related adverse events. In a hospital in Utah without an infectious disease physician, a pharmacist-led ASP made substantial decreases in the use of the four most commonly used antimicrobial agents, with statistically significant reduction in length of stay for community-acquired-pneumonia patients and substantial cost savings.[19] In a review of ASPs in community hospitals, Ohl et al. described the benefits of ASPs and illustrated several case studies of various ASP structures and strategies, utilizing an institution's available resources and support.[20] The available evidence indicates that antimicrobial stewardship is a worthwhile and cost-effective endeavor regardless of hospital size or location.

## ANTIMICROBIAL STEWARDSHIP STRATEGIES FOR ACUTE CARE HOSPITALS (TABLE 1.1)

### KEY STEWARDSHIP INTERVENTIONS

Two key interventions were recommended in the IDSA/SHEA guidelines as the cornerstones of an effective ASP: (1) formulary restriction with preauthorization and (2) prospective audits with intervention and feedback.[3] Antimicrobial restriction, either through formulary limitations at the level of the institution's Pharmacy and Therapeutic Committee or requirement for justification of use, has been shown to be effective in reducing the use of targeted antibiotics. Some hospitals require

**Table 1.1 Antimicrobial Stewardship Strategies for Acute Care Hospitals**

| | Patient-Based | Systems-Based |
|---|---|---|
| Key interventions | • Prospective auditing with feedback<br>• 48-h antibiotic time-out | • Formulary restriction |
| **Supplemental interventions** | | |
| Education | • Physician feedback | • Institutionwide conferences<br>• Clinical pathways<br>• Practice guidelines |
| Pharmacy | • Dosing optimization<br>• Intravenous to oral conversion<br>• Prolonged infusion | • Monitor for adverse events |
| Laboratory | • Rapid diagnostics with stewardship intervention | • Cascade reporting<br>• Antibiograms |
| Information technology | • Order sets<br>• Decision support for antibiotic choice<br>• Alert for antibiotic time-outs | • Electronic order forms<br>• Drug–bug mismatch decision support<br>• Monitor antimicrobial utilization |

the physician to fill out the indication at the time of order entry, while others require prior authorization through an approval process. A retrospective study was done at New York-Presbyterian Hospital, a 700-bed academic teaching hospital in New York City, to assess the appropriateness of using Gram-negative antibiotics in a setting of extensive antimicrobial resistance.[21] This hospital had an active ASP in place for 10 years prior to the study, comprising of formulary restriction, hospital-specific guidelines, and institutionwide education, but not postprescription review. Two snapshot dates were reviewed. The majority of the antimicrobials were used as part of an empiric regimen, with one-third of the patients being in the intensive care unit. In this study, 26% of the antibiotics were not optimal; the most common reason for this was that the spectrum of activity was too broad. This study illustrated the importance of deescalation interventions such as prospective auditing.

Prospective auditing with feedback to the prescriber has been demonstrated to improve appropriate antibiotic prescription. The principal function of this intervention is the deescalation of an empiric antimicrobial regimen based on culture results, thereby focusing therapy on the most effective agent for treating the infection. Other recommendations may include dosing optimization, discontinuation of antibiotics, and monitoring for adverse events. The reviews are done by a physician or clinical pharmacist who is not part of the treatment team. In a multicenter study of five tertiary care academic hospitals in the United States, prospective auditing with feedback was shown to reduce antimicrobial use, although the degree varied by institution, with those centers with established ASPs reducing antimicrobial use significantly.[22] It was also noted that the utilization reduction was not sustained in the follow-up period, suggesting that continued prospective auditing and feedback are required to maintain judicious use of antibiotics. It is likely that because this study was conducted in academic centers, the turnover of resident physicians required continued auditing and feedback, as senior residents graduate and new interns entered each year. Various feedback

mechanisms have been described in the research literature, ranging from one-on-one education sessions to placing a feedback sheet at the front of the patient's chart. In a single-center study at a tertiary care teaching hospital comparing distinct modes of communication, there was no statistically significant difference in compliance with stewardship recommendations made by direct telephone calls, notes in the medical record, or text pager messages.[23] Higher acceptance of recommendations was noted with the deescalation of antibiotics than discontinuation of them, suggesting that physicians were more comfortable with changing or focusing therapy than stopping it. This finding is consistent with the pervasive practice of continuing antibiotics "just in case" and the erroneous perception that antibiotics cause no harm.

In addition to the two key interventions recommended by IDSA and SHEA, the CDC recommended antibiotic "time-outs" at 48 h after the initiation of antibiotics by the treating physician.[5] While prospective auditing is done by a member of the ASP team, antibiotic time-outs are performed by the treating team. Antibiotics are often started in an empiric fashion, especially in the critically ill. At 48 h, the treating physician should consider whether antibiotics are still indicated, or whether an alternative diagnosis other than infection has been made. Culture results should be available by this time, allowing the physician to deescalate the antimicrobial regimen based on culture results in order to target the pathogen with the most appropriate therapy for the site of infection. The dose, route of administration, and duration of antibiotics should also be considered. This intervention lies in the hands of the individual prescriber. Each clinician should prescribe antimicrobials in a thoughtful, evidence-based manner.

## SUPPLEMENTAL INTERVENTIONS

### EDUCATION

Education is an important element of ASPs. These include educational conferences, teaching sessions for residents, and written guidelines. The development of evidence-based practice guidelines and clinical pathways that incorporate local resistance patterns can be helpful in influencing prescribing habits. Not only would education influence prescriber behavior, it can lead to buy-in for acceptance of other stewardship strategies, such as prospective auditing with feedback. However, education alone, without the key interventions discussed previously, have been shown to be only minimally effective.[3] In academic centers, where residents order the majority of antibiotics, it is essential to provide education on an ongoing basis, as senior residents graduate and new interns arrive each year. Antimicrobial stewardship should become part of medical education in order to institute a culture of judicious antibiotic use. In addition, as local susceptibility data change, the medical staff should be made aware of these trends in order to select the most appropriate empiric antimicrobial regimen. In a study that analyzed four years of bacterial susceptibility data and prescribing trends from two West London tertiary referral hospitals, their affiliated renal units, and the surrounding community practices served by a single laboratory, the authors found significant differences in antibiotic susceptibility within and between the hospitals, with substantial year-to-year fluctuations among most drug−bug combinations.[24] As one would expect, more resistant organisms were found in the critical care units and renal cohorts than in the medical wards and community cohorts. These trends likely are related to the greater frequency of antibiotic use in critical care

units and renal cohorts. Through education, resistance trends can be communicated to the clinicians. In addition to medical management of infections, education efforts should include emphasis on the dire nature of antibiotic resistance and the impact of inappropriate antimicrobial utilization on quality and patient safety. It should be stressed that antimicrobials are not benign, and its use should be thoughtful and evidence based.

## PHARMACY STRATEGIES

Certain pharmacy-driven strategies can enhance an ASP. Optimization of antimicrobial dosing is an important part of improving clinical outcomes while minimizing toxicity. Consideration of patient attributes (such as age, weight, and renal function), the particular organism and its minimal inhibitory concentration, site of infection, and drug characteristics (pharmacokinetics and pharmacodynamics) are essential to the optimization of antimicrobial therapy. A simple strategy is the automatic conversion from intravenous to oral antibiotics for those drugs with good oral bioavailability. This would improve patient safety by decreasing the incidence of catheter-associated infections and have a positive effect on health-care costs.

Prolonged or extended infusion of intravenous β-lactam antibiotics optimizes the time-dependent bactericidal activity of this class of antimicrobials. Achieving the target serum levels is necessary for treatment success, especially in critically ill patients with difficult-to-treat infections. Several pharmacokinetic–pharmacodynamic studies using Monte Carlo simulation have been done for piperacillin–tazobactam and cefepime.[25] Prolonging the infusion increased the likelihood of reaching optimal target serum levels, while a lower total daily dose of the drug was used. This dosing scheme is likely not necessary to treat highly susceptible pathogens. Robust clinical outcome data related to this dosing strategy are lacking. Those institutions that have implemented routine prolonged infusion of β-lactam antibiotics have been able to demonstrate financial benefits in terms of lower total daily dose and drug acquisition costs. Logistical issues must be considered, including dedicated time through an intravenous line and the stability of certain β-lactam antibiotics. In a critically ill patient with severe sepsis or septic shock, prolonged or extended infusion of antibiotics may not be practical during the resuscitation phase of clinical management.

Another important pharmacy function is the monitoring of antibiotic-related adverse events and toxicities, which directly affects patient safety. The pharmacist on the antimicrobial stewardship team is in an optimal position for adverse event reporting. The US Food and Drug Administration (FDA) MedWatch program (the FDA Adverse Event Reporting System) was introduced in 1993.[26] It is the largest federal voluntary reporting system used to report observed or suspected adverse events, product quality, and therapeutic failures for medications, biologics, and medical devices. Historically, postmarketing surveillance of antimicrobials has discovered adverse events not previously documented in clinical trials, resulting in the withdrawal of several antibiotics.

## INCORPORATING IT

In 2009, the Health Information Technology for Economic and Clinical Health Act was signed to encourage physicians and hospitals to implement electronic health records (EHRs) in the United States.[27] As more and more hospitals adopt EHRs, this element of technology can be used to enhance antimicrobial stewardship efforts. EHRs and add-on clinical decision support systems

(CDSSs) have capabilities to improve patient safety and enhance efficiency. EHR and CDSS platforms differ with customizable features to varying degrees, but most have capabilities that can be utilized in ASPs.[28] EHRs offer the ability to look at patient data from a central remote location and to provide lists of patients on specific antimicrobials, making the reviewing of medical records highly efficient. Electronic order forms can be utilized to require clinical indications for antimicrobial prescriptions, while order sets for certain clinical syndromes can provide decision support to treating physicians and guide antibiotic prescription. At the time of the initial prescription, physicians have the opportunity to start the most effective therapy for the patient.

In a pilot study to incorporate a point-of-prescription tool to improve antibiotic prescribing, four academic medical centers in conjunction with the CDC formed a collaborative to develop a daily rounding flowsheet that incorporated the core principles of antimicrobial stewardship.[29] The study found that they were able to engage unit-based providers in stewardship efforts. Alerts can be incorporated as a reminder for antimicrobial time-outs. Most EHRs and CDSSs provide preprogrammed drug−bug mismatch decision support, utilizing microbiological susceptibility results and inpatient pharmacy data. CDSSs also can track antimicrobial utilization, microbial susceptibility, and generate antibiograms. As more and more hospitals adopt EHRs and CDSSs become more sophisticated, opportunities exist to incorporate technology into antimicrobial stewardship efforts.

## LABORATORY STRATEGIES

Laboratory strategies can be used to supplement antimicrobial stewardship efforts. Current conventional culture-based methods to isolate and identify a pathogen, followed by susceptibility testing, can take 72 h or more. The time that passed before effective antibiotics were used can affect clinical outcomes. This has been shown for Gram-negative septicemia as well as septic shock patients, where the delay in the timely initiation of antibiotics directly correlated with mortality.[30,31] Automated alerts for positive blood cultures coupled with stewardship interventions can ensure that the patient is prescribed effective antibiotics sooner. In a study of three hospitals at the Detroit Medical Center with active ASPs, active alerts were sent to the pharmacist, who then made stewardship interventions as indicated. This decreased the time it took to begin appropriate therapy and had a positive impact on length of stay and mortality.[32]

Direct susceptibility testing by disk diffusion provides antibiotic susceptibility for the whole sample rather than individual pure colonies. These results are generally available 24 h sooner than conventional culture methods. There is research that supports its accuracy and provides physicians with early microbiological results to direct antibiotic therapy. In a study of 123 clinical samples comparing conventional antimicrobial susceptibility testing with direct susceptibility testing, Coorevits et al. showed an overall agreement of over 86%.[33] In 89% of discordant cases, direct susceptibility testing showed a more resistant result than conventional methods, mainly due to the presence of a resistant organism in a mixed culture. It should be noted that direct susceptibility testing by disk diffusion has been criticized by several microbiology societies because the bacterial inoculum is not standardized. Hence, the results should be interpreted with a critical eye, preferably by an infectious disease physician.

Technical advances in the area of microorganism detection have led to the commercial availability of several rapid molecular assays.[34] Multiplex polymerase chain reaction (PCR) uses a fluorescent labeled probe with more than one set of primers to amplify pieces of target DNA, detecting multiple organisms and resistance genes. After implementation of a FilmArray Blood Culture Identification (BCID) panel (BioFire Diagnostics, Salt Lake City, UT) at an academic tertiary care hospital in Omaha, NE, Southern and colleagues compared its performance to conventional culture methods using clinical blood culture isolates during the first 30 days of implementation.[35] This PCR panel identifies 19 pathogens as well as genes for *mecA* (methicillin resistance), *vanA/B* (vancomycin resistance), and $bla_{KPC}$ (carbapenem resistance) directly from positive blood cultures. Overall, the FilmArray BCID showed a sensitivity of 75.7% and a specificity of 100%. When considering only on-panel organisms, the sensitivity increased to 94.3%. The BCID also failed to detect some blood pathogens. In addition, the assay had difficulty with organisms that were not on the panel, in polymicrobial cultures, and in positive blood cultures from patients already on antibiotics. The BCID panel was found to be rapid and relatively reliable, showing promise for clinical practice. Nanosphere's Verigene blood culture Gram-positive (BC-GP) and Gram-negative (BC-GN) assays (Northbrook, IL) use a nanoparticle probe technology. Positive blood cultures undergo nucleic acid extraction and PCR amplification, followed by the hybridization of target DNA to capture oligonucleotides on a microarray. The Verigene BC-GP identifies 12 Gram-positive organisms and 3 resistance genes, while the Verigene BC-GN identifies 9 Gram-negative genuses and species, as well as multiple resistance markers. A multicenter, prepost, quasi-experimental study was conducted at five acute care community hospitals to measure the effect of rapid testing using the Verigene BC-GP in combination with antimicrobial stewardship intervention.[36] The sensitivity and specificity of the Verigene BC-GP was 100% sensitive and specific as opposed to conventional culture methods. Rapid identification with ASP intervention significantly improved the mean time to targeted therapy and lower median length of stay, while mortality rates were unchanged. The Verigene BC-GN was evaluated in a single-center study conducted at an 850-bed tertiary care medical center.[37] The investigators confirmed the diagnostic accuracy of the BC-GN, finding a sensitivity of 97.1% and a specificity of 99.5%. Using a theoretical stewardship intervention design, they found a significant difference in potential times to both effective and optimal antibiotic treatment compared to standard care. However, a significant limitation to this study was that the stewardship interventions were only theoretical, with a presumed 100% acceptance rate, and the results were potential improvements.

In a study of 219 patients with Gram-negative bacteremia, Perez et al. investigated the use of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) combined with direct susceptibility testing on positive blood cultures in conjunction with real-time notification and stewardship intervention. This resulted in a 46-h reduction in time to optimal antibiotic therapy, with a significant reduction on length of stay and hospital costs.[38] In a related study, Perez et al. investigated the clinical effects of rapid identification and direct susceptibility testing on patients with multidrug-resistant Gram-negative bacteremia.[39] The use of MALDI-TOF MS directly on positive blood cultures significantly reduced the mean time to identification by 26 h. The additional use of direct susceptibility testing that was set up at the time of blood culture positivity reduced the average time to final identification and susceptibility from 47 to 29 h. Combining rapid laboratory identification of the pathogen and direct susceptibility data with real-time antimicrobial stewardship interventions, the average time to optimal

antibiotic therapy was reduced from 81 h during the preintervention period to 23 h in the intervention period. These reductions translated to improvements in 30-day mortality and mean hospital length of stay.

It should be noted that this study was done at a 1000-bed quaternary-care academic hospital with a high rate of antibiotic resistance. A total of 69% of study patients were on ineffective therapy at the time of blood culture positivity. In this setting, antibiotic susceptibility is difficult to predict, making the rapid diagnostic techniques more crucial in patient care and likely resulting in higher impact. Interestingly, almost half of the interventions were made based on the identification of the organism alone, before direct susceptibility results were available. It should be emphasized that rapid results are of little value if these results are not acted upon in a timely manner. In these studies, real-time antimicrobial stewardship interventions were used in conjunction with rapid diagnostics to achieve the improved outcomes.

Cascade reporting of antimicrobial susceptibilities can be an effective strategy to influence prescriber habits.[40] In cascade reporting, the antimicrobial agent with the narrowest spectrum within each class is released first. The broader-spectrum antibiotics are released only if the organism is resistant to the narrower-spectrum agents. All the resistant results are released (Fig. 1.1).

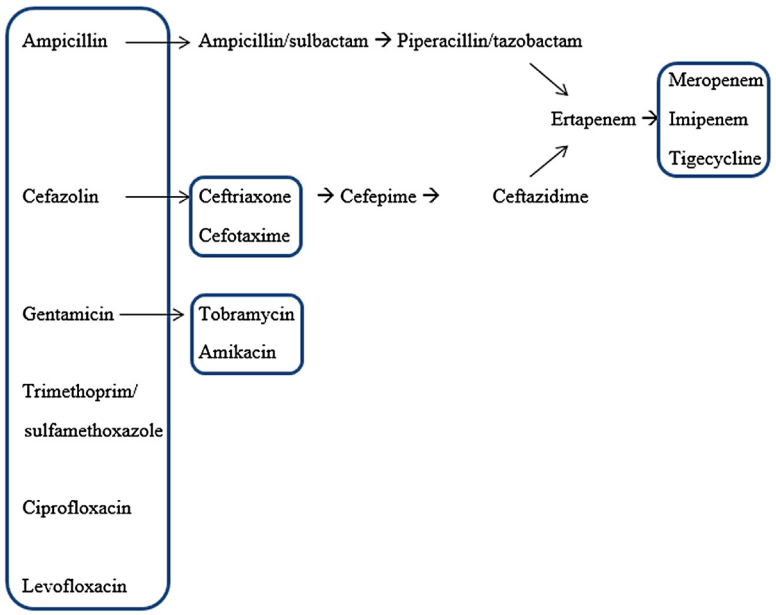


**FIGURE 1.1**

Sample selective reporting cascade of antibiotics for Enterobacteriaceae. The left column of agents are routinely released on susceptibility reports. If the bacterium is resistant to one or more antimicrobial, agents further on the cascade are released per this algorithm. For example, ceftriaxone and cefotaxime are released if the bacterium is resistant to cefazolin. Nonsusceptible agents are released regardless of their location on the cascade.

Clinical judgment remains the most valuable tool when decisions regarding antibiotic use are made. However, clinical presentations of infection are often nonspecific; it is often difficult to distinguish between bacterial causes of infection (when antibiotics are indicated), viral etiology, or noninfectious causes of the patient's symptoms. In such cases, biomarkers have become an attractive tool, with procalcitonin, a precursor of calcitonin, being the most widely studied candidate. In a meta-analysis including seven clinical trials and 1075 intensive care unit patients with severe sepsis or septic shock, Prkno et al. noted that procalcitonin-guided protocols can be used to safely reduce the duration of antibiotic therapy.[41] In another study, the Procalcitonin to Reduce Antibiotic Treatment Algorithm (PRORATA) trial showed a 23% reduction in antibiotic exposure with 2.7 more antibiotic free days in the procalcitonin algorithm arm.[42] However, mortality was 3.8% higher than the control group.

It should be noted that in the PRORATA trial, protocol compliance was suboptimal, with 53% of patients managed outside of the algorithm. In a prospective, single-blind, randomized, controlled trial conducted in 11 intensive care units in Australia, Shehabi and colleagues investigated whether a procalcitonin-guided algorithm with a low cutoff value of 0.1 ng/mL can reduce antibiotic utilization compared to standard care.[43] In this study, almost 400 patients admitted to the intensive care unit with presumed sepsis were included, with about 200 patients in each of the procalcitonin and standard care arms. Procalcitonin was measured daily, and the proportion of study days where the procalcitonin algorithm was not followed was less than 3%, indicating very high algorithm compliance. The authors found that a strategy based on a procalcitonin algorithm with a cutoff value of 0.1 ng/mL did not significantly reduce antibiotic utilization or time to antibiotic discontinuation when compared to standard care.

Of note, the initial procalcitonin level correlated with higher severity of illness and likelihood of subsequent positive blood culture and a slow decline of procalcitonin level over the first 72 h was associated with hospital and 90-day all-cause mortality. In a Swiss multicenter noninferiority randomized controlled trial involving both academic and nonacademic hospitals, a procalcitonin-guided algorithm was compared with standard care in the treatment of lower respiratory tract infections.[44] This study found that the procalcitonin algorithm was not inferior to treatment based on clinical guidelines in terms of composite overall adverse outcomes occurring within 30 days following presentation to the emergency department, with a statistically significant reduction in antibiotic exposure. This trial included patients with different severities of lower respiratory tract infections, 93% of whom were hospitalized. The community-acquired-pneumonia patients required hospital admission, thereby accounting for the relatively high antibiotic utilization in this group. The procalcitonin algorithm decreased the duration of antibiotics by about 3 days in this group. In acute bronchitis, upper respiratory tract infections, and chronic obstructive pulmonary disease exacerbations, where the indication for antibiotics was less clear cut, the procalcitonin algorithm decreased the initiation of antibiotics up to 75%.

These studies illustrate the many unanswered questions regarding the use of procalcitonin in antibiotic stewardship. Further studies must be undertaken to better delineate the role of this biomarker in antibiotic initiation, deescalation, and duration, in conjunction with sound clinical judgment and a comprehensive ASP.

## PENICILLIN SKIN TESTING

Up to 10% of patients report having a penicillin or other β-lactam allergy, but a vast majority of these reports are inaccurate. In those with a true immunoglobulin E–mediated allergy, hypersensitivity does not persist over time. Only about 10% of patients with reported penicillin allergies have a positive penicillin skin test. Patients with reported penicillin allergies often receive broader-spectrum, suboptimal, or more toxic antibiotics than those without reported penicillin allergies.[45] In a small 1999 study of penicillin skin testing in hospitalized patients, 28 patients were enrolled who had a reported penicillin allergy and the need for antibiotic therapy.[46] Of these patients, 89% tested negative on penicillin skin testing, resulting in a significant reduction in vancomycin, fluoroquinolone, and clindamycin use without a negative impact on patient safety or outcome. In a review article on the use of penicillin skin testing in a variety of health-care settings, Unger and colleagues cited evidence that penicillin skin testing in the wards or the intensive care unit was well tolerated, with 89–95% of patients with a reported history of penicillin allergy testing negative.[47] In those studies that were prospective in nature, antibiotic regimens were switched to β-lactam in the setting of a negative penicillin skin test, resulting in a reduction in the use of alternative antibiotics. As an antimicrobial stewardship strategy, a penicillin skin testing protocol can be implemented to identify those patients with a true β-lactam allergy, thereby reserving the broader-spectrum antibiotics for multidrug-resistant pathogens.

## ANTIBIOTIC CYCLING

The term *antibiotic cycling* refers to the routine scheduled substitution of a specific antibiotic on an institution's formulary in an attempt to preserve the diversity of antibiotic prescriptions and minimize bacterial selection pressure. In a retrospective study of Gram-negative susceptibility in a surgical intensive care unit 6 years into a monthly antibiotic cycling protocol, there was improved susceptibility in *Pseudomonas aeruginosa* and *Escherichia coli* isolates, while there were no significant changes in *Klebsiella pneumoniae* and *Enterobacter cloacae* susceptibility.[48] The susceptibility profiles of Gram-negative organisms in the medical intensive care unit (MICU) where antibiotic cycling was not done did not change significantly during this period. It is unclear how much of the improvement in Gram-negative susceptibility was due to antibiotic cycling alone. Concurrent infection control practices improvements may have contributed to these results. In a prospective before-and-after cohort study of 1172 MICU patients, four classes of antibiotics with Gram-negative activity for empiric use were cycled every 3–4 months over a 2-year period. The frequency of resistant Gram-negative infections seen in this study was about 30%. It was found that routine antibiotic cycling did not significantly change the risk of receiving inappropriate empiric antibiotic therapy for the treatment of intensive care unit infections.[49] At the present time, there is insufficient evidence for the routine use of antimicrobial cycling to reduce resistance over time.

## FACILITATORS AND BARRIERS OF ASPs

Communications is the cornerstone of an effective ASP. In both the preauthorization process and prospective auditing with feedback, a nonconfrontational approach and the development of collegial relationships are important. In a telephone interview of ASP members from 21 large academic medical centers with established ASPs, the face-to-face style of communicating ASP recommendations was preferred.[50] Members also stressed the importance of being collaborators of patient care rather than being seen as the "antibiotics police." As antimicrobial stewardship moves from the cost-cutting arena into the realm of quality and patient safety, this collaboration becomes more important.

Some centers have developed and used antimicrobial stewardship ward rounds to enable face-to-face discussions on the more challenging cases.[45] The treating physicians should be made to feel that the stewardship team is there to help provide patients with optimal care, rather than just trying to cut costs. Inclusion of nonstewardship program clinicians on committees related to the program's activities is an effective way to encourage physician buy-in, while identifying potential barriers. Conflict management is an essential aspect in the successful implementation of stewardship intervention. It is important to garner support for antimicrobial stewardship efforts, especially within clinical specialty areas where antimicrobial use is high, such as critical care, oncology, and transplant services. ASPs often face a lack of resources in the form of personnel and time, since many of the stewardship interventions are time consuming.

## MEASUREMENTS AND BENCHMARKS

The true impact of ASPs on clinical outcome has been difficult to measure.[51] Intuitively, it makes sense that the judicious use of antibiotics would lead to a reduction in antibiotic resistance, *C. difficile* rates, and antibiotic-associated adverse events, hence improving patient outcomes. However, these outcomes are challenging to measure and causal relationship is problematic to substantiate. A study of the impact of a comprehensive ASP in the intensive care unit setting was unable to show statistical relationships with *P. aeruginosa* resistance rates despite changes in antibiotic utilization.[52]

In China, where a national campaign and antimicrobial stewardship policy were enacted to promote judicious antibiotic use, a retrospective study was done over a 6-year period to evaluate its effectiveness in an 1800-bed tertiary care teaching hospital in Shanghai.[53] The hospital developed a computer-assisted program, and antibiotics were divided into three levels of restrictions based on clinical guidelines. During the intervention period, antibiotic utilization of some of the broad-spectrum-restricted antibiotics decreased, but the study was unable to demonstrate any significant improvement in antimicrobial susceptibility among bacteria. Most stewardship studies are single center, making it difficult to detect statistically significant differences in clinical outcomes, such as mortality and length of stay. Changes in bacterial resistance and *C. difficile* incidence occur over time, and other interventions such as infection control practices may also

affect these rates. Antimicrobial utilization and cost are commonly used metrics in ASPs. These data are easy to capture and important to administrators. In a 2011 survey, the IDSA Emerging Infections Network found that 83% of administrators emphasized the importance of cost savings, while 63–72% of physicians cited patient outcomes as the most essential goal for an ASP.[54] Process measures such as acceptance rate of antimicrobial stewardship recommendations and the number of stewardship interventions assess whether an ASP intervention was carried out, but they do not measure whether the intervention affected clinical outcome or antibiotic resistance.

The most commonly accessible measure of an institution's antimicrobial resistance rate is the hospital antibiogram. An antibiogram lists the proportion of organisms that are susceptible to a hospital's formulary antibiotics over a given period of time. Most hospitals update their antibiograms annually, possibly with the help of EHRs or add-on CDSSs. It usually reflects the susceptibility of clinical isolates collected from the entire institution. In the United States, this includes the first isolate per patient per month, as recommended by the Clinical and Laboratory Standards Institute (CLSI). The antibiogram can provide guidance for empiric antibiotic therapy for certain resistant pathogens and help direct formulary decisions. Because antibiograms usually report the percent susceptibility of each antibiotic-pathogen combination, it is unable to monitor multidrug resistance effectively. In a review of eight studies that evaluated antimicrobial stewardship interventions, Schulz et al. found that changes in antibiotic utilization may or may not be reflected in changes in susceptibility as measured by the antibiogram in individual hospitals.[55] Hence, although the antibiogram has its role in antimicrobial stewardship, it does not serve as an effective measure of stewardship interventions.

The core function of an effective ASP is to promote the judicious and appropriate use of antimicrobials. As alluded to earlier in the chapter, a standardized definition of appropriate antibiotic use is lacking, making measurement of such use difficult. In an observational, retrospective, cohort study conducted at four sites in the United States, DePestel and colleagues compared four definitions of appropriateness of select antibiotics in the treatment of suspected or documented infections caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and *P. aeruginosa*.[56] These definitions were (1) study-site specific, (2) supported by in vitro susceptibility data, (3) antimicrobial used for indication with literature support, and (4) reflecting the opinion of the principal investigator. This study found significant inconsistency when these definitions were applied to determine the appropriateness of antibiotic therapy, particularly between principal investigator opinion (clinical judgment) and the other definitions.

Of note, nosocomial pneumonia and urinary tract infection had the highest disparity across the definitions for appropriate use of antibiotics. The CDC recognizes this dilemma and acknowledges the need for standardized assessment of appropriate antibiotic utilization, and has developed worksheets to help physicians assess the appropriateness of antibiotic use for various clinical syndromes, including community-acquired pneumonia and urinary tract infections.[57] It is often difficult to distinguish colonization from infection in these syndromes, leading to overtreatment. Furthermore, quality studies should be undertaken to determine the optimal duration of treatment of various infectious syndromes.

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