

Antimicrobial Stewardship for Inpatient Facilities

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Antibiotic stewardship aims to improve patient care and reduce unwanted consequences of antimicrobial overuse or misuse, including lowered efficacy, emergence of antimicrobial resistance, development of secondary infections, adverse drug reactions, increased length of hospital stay, and additional healthcare costs. Recent guidelines make specific recommendations for the development of institutional programs to enhance antimicrobial stewardship. Optimally, such programs should be comprehensive, multidisciplinary, supported by hospital and medical staff leadership, and should employ evidence-based strategies that best fit local needs and resources. An infectious diseases physician and clinical pharmacist with infectious diseases training are recommended as core members of the multidisciplinary team, although a hospitalist with interest (and perhaps additional training) in antimicrobial therapy may be able to fill the void. Program directors and core members should be compensated for their time. Principal proactive strategies—with evidence supporting their consideration—include prospective audits, with intervention and feedback, formulary restriction, and preauthorization. Other strategies include persistent one-on-one education, guidelines adapted to local needs, and informatics to support clinical decision making. Intervention goals are to prevent unnecessary antimicrobial starts, to streamline or de-escalate therapy early in its course, and to convert from parenteral to oral therapy, optimize dosing, and ensure the appropriate length of therapy. Most community hospitals, if sufficiently resourced, should be able to implement a successful antimicrobial stewardship program. Evidence suggests that good antimicrobial stewardship can lead to less overall and inappropriate antimicrobial use, lower drug-related costs, reductions in *Clostridium difficile*-associated disease, and, in some studies, less emergence of antimicrobial resistance. *Journal of Hospital Medicine* 2011;6:S4–S15 © 2011 Society of Hospital Medicine.

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Nosocomial, or hospital-acquired, infections (HAIs) are a major cause of patient morbidity and mortality in the United States and other countries.^{1–5} In 2002, approximately 1.7 million HAIs occurred in US hospitals and were associated with an estimated 98,987 deaths.¹ Of particular note, increasing percentages of HAIs are now caused by antimicrobial-resistant pathogens, which have been linked with increases in morbidity, mortality, length of hospital stay, and healthcare costs.⁶

The 2004 data summary from the United States National Nosocomial Infections Surveillance (NNIS) System Report highlighted substantial increases for year 2003 versus 1998 through 2002 in vancomycin-resistant enterococci (VRE); methicillin-resistant *Staphylococcus aureus*; *Klebsiella pneumoniae* resistant to third-generation cephalosporins; and *Pseudomonas aeruginosa* resistant to imipenem, quinolones, or third-generation cephalosporins.⁷ Other gram-negative bacteria of concern include *Escherichia coli* and *Acinetobacter baumannii*, as well as *Enterobacter cloacae* and *E. aerogenes*.^{8,9}

The increasing number of multidrug-resistant (MDR) gram-negative bacteria within the healthcare setting is particularly concerning.^{10–13} Too frequently, clinicians in the United States now encounter gram-negative bacteria species that are resistant to many, and occasionally all, currently available antibiotics. For many of these MDR gram-negative pathogens the antimicrobials that potentially remain active (eg, aminoglycosides and polymyxins) are often more toxic and less efficacious for some infections.¹⁴ Particularly problematic is that the pharmaceutical industry's developmental pipeline for new antibiotics, with novel mechanisms of action that might be used against MDR gram-negative pathogens, has virtually come to a standstill.^{15,16} Even if an investigational drug was in phase 2 or 3 trials right now or entered the US Food and Drug Administration (FDA) Fast Track Development Program, it would be at least 10 or 15 years before that drug would be available on the US market.

What this means is that the clinician's current antibiotic armamentarium is all they can expect in the foreseeable future. It also means that special care needs to be taken to

optimally use currently available agents to ensure continued activity against the pathogens encountered in the hospital (and community) setting, now and in the future. Maximizing clinical outcomes, while minimizing the emergence and spread of antimicrobial resistance (and other adverse effects associated with suboptimal antimicrobial drug use), falls under the purview of antimicrobial stewardship, the focus of this paper.

Antimicrobial Stewardship—Why Is It Needed, What Is It, and What Are Its Goals?

Inappropriate Antimicrobial Use

Early in the onset of many infections, the data needed to make a rational, informed decision about specific antibiotic therapy are usually unavailable. For many infections, therapy cannot be delayed waiting for microbiology or other findings, and broad-spectrum empiric therapy is begun on the basis of educated guesses made from the patient's presentation and characteristics, and local or hospital antibiograms. In addition, for many serious infections, delay in antimicrobial therapy will increase patient morbidity and mortality. Generally, what occurs is the decision to treat empirically with one or more broad-spectrum antibiotic agents, which are then continued for the entire course of therapy. Opportunities are often missed to tailor therapy later in the course of infection when microbiologic or other data are available. There is also a tendency for "spiraling empiricism" to occur when a patient is not doing well with initial therapy; additional agents with broad antimicrobial activity, including antifungals and antivirals, are added to the therapeutic regimen, often in a haphazard way.¹⁷

Besides the perceived need to prescribe broad-spectrum and/or multiple antibiotics to cover possible or perceived resistant or uncommon pathogens, a number of other factors contribute to inappropriate antibiotic or antimicrobial use. Many times antimicrobials are initiated when no infection exists, such as for asymptomatic bacteruria, noninfectious pulmonary conditions, or endotracheal tube or Foley catheter colonization. Another example of inappropriate use is treating for longer than needed to eradicate infection. All of these events intensify the exposure of bacteria colonizing or infecting the patient to multiple anti-infective drugs and increase the chances for selection of an MDR pathogen.

Examining antibiotic usage at the hospital level, approximately 60% of adult patients admitted to US hospitals receive at least 1 dose of an antibiotic agent during their stay (range: 44%–74% for individual hospitals).^{18,19} Similarly, at Wake Forest University Baptist Medical Center (WFUBMC), approximately 75% of inpatients receive antimicrobials at some point during their hospitalization (Ohl, unpublished data, 2007). One recent example by Hecker and colleagues conducted in a 650-bed, university-affiliated US hospital reported 30% of the total days of antibiotic therapy received by adult non-ICU inpatients was unnecessary.²⁰ The most common reasons for unnecessary use were

administration for longer than recommended durations, administration for a noninfectious or nonbacterial syndrome, and treatment of colonizing or contaminating microorganisms.

Consequences of antibiotic misuse

Unwanted consequences of antimicrobial therapy include increased morbidity and mortality, adverse drug reactions, increased length of hospital stay and hospitalization costs, predisposition to secondary infections, and emergence and selection of drug-resistant organisms.^{21,22} Selection or induction of antimicrobial resistance and promotion of secondary infection with *Clostridium difficile*—particularly with new, more toxigenic strains²³—are of particular concern in the current hospital environment.²² These untoward consequences can be seen as a calculated risk of antibiotic therapy for any single-treated patient, or as an undesired outcome measure for excessive use at the level of the healthcare institution. For example, a 7-day course of a third-generation cephalosporin in a particular patient increases the risk of subsequent infection from an extended-spectrum beta-lactamase (ESBL)-producing gram-negative rod. For the institution as a whole, excessive use of this antimicrobial will increase the overall prevalence and number of infections due to this troublesome resistance factor.

Definition and Goals of Antimicrobial Stewardship

The above studies show a clear need for improved, more careful and prudent use of antimicrobials, which is key to antimicrobial stewardship. Building on the definition given by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA),²⁴ antimicrobial stewardship is essentially a system of personnel, informatics, data collection, and policy/procedures that promotes the optimal selection, dosing, and duration of therapy for antimicrobial agents throughout the course of their use. An effective antimicrobial stewardship program will limit inappropriate and excessive antimicrobial use, but more importantly improve and optimize therapy for the individual infected patient.

The goals of antimicrobial stewardship are listed in Table 1.^{24,25} It is important to recognize that the primary goals of antimicrobial stewardship are not the reduction of healthcare costs—and certainly not the reduction of drug acquisition or usage costs. As the 2007 IDSA/SHEA guidelines for institutional development of an antimicrobial stewardship program make clear, the primary goal is to focus on patient care; that is, to optimize clinical outcomes, while minimizing unintended consequences of antimicrobial use (emergence of resistance, selection of pathogenic organisms, and adverse drug reactions).²⁴

Reduced healthcare costs without an adverse effect on quality of patient care is, however, a legitimate secondary goal of antimicrobial stewardship, and will result from

TABLE 1. Primary Goals of an Antimicrobial Stewardship Program

Prevent or slow the emergence of antimicrobial resistance
Optimize selection, dose and duration of therapy
Reduce adverse drug events, including secondary infection (eg, <i>C. difficile</i> antibiotic-associated diarrhea)
Reduce morbidity and mortality
Reduce length of stay
Reduce healthcare expenditures

optimized clinical outcomes and decreased potential “collateral damage” associated with pharmacotherapy. Unfortunately, it is much more difficult to measure the impact of an antimicrobial stewardship program on emergence of resistance than on drug acquisition or usage costs. As a consequence, reduction in drug acquisition/usage costs has too often been viewed as the primary (and sometimes only) justification for implementing an antimicrobial stewardship program.²⁶

Finally, the role of effective infection control cannot be overemphasized. Infection control is clearly necessary and often sufficient to reduce HAIs. However, a comprehensive infection control program, combined with an effective antimicrobial stewardship agenda, synergistically limit the emergence and spread of antimicrobial-resistant bacteria, reduce HAIs, control resistance, and improve overall inpatient care.^{24,27} Hence, when instituting an antimicrobial stewardship program, it is essential to ensure the hospital or other healthcare institution already has a robust hospital epidemiology and infection control program in place—or to simultaneously institute one.

Constructing an Antimicrobial Stewardship Program *Infectious Diseases Society of America and Society for Healthcare Epidemiology of America Guidelines*

Whereas the value of antimicrobial stewardship is widely appreciated, actually taking the steps to set up a healthcare facility program can be daunting. The guidelines established by the IDSA/SHEA for developing an institutional program represent a valuable resource and suggest that the best programs are comprehensive—taking into account local antimicrobial use and resistance patterns, as well as available resources.²⁴ The size and nature of the institution can make a big difference in determining what program to set up and what elements it should entail; what works at one institution might not work as well at another. The program components and effectiveness of each will differ for community versus academic medical centers. A comprehensive program includes active monitoring, fostering of appropriate antimicrobial use, and collaboration with an effective infection control program as well as other hospital entities. The role of a multidisciplinary team, with administrative support, is particularly underscored in the guidelines. According to the guidelines, core members of the multidisciplinary team should include an infectious diseases physician and a clinical

pharmacist with infectious diseases training. It should also ideally include a clinical microbiologist, information system specialist, infection control professional, and hospital epidemiologist.²⁴ It is important that all members of the team are passionate about the program, oversee its implementation and daily functions, and have some sense of ownership of it. Compensation for its primary participants is crucial. Compensation not only ensures that adequate time is available for executing the daily activities of the program, but it also helps impart a greater sense of program ownership. Process and outcome measures of the program (discussed below) should be included in the performance evaluations of the compensated key participants.

Although the guidelines indicate that an infectious diseases physician should act as the program leader, this might not always be feasible or necessary. Many of the hospitals most in need of improved antimicrobial stewardship simply do not have an infectious diseases physician available to them. In addition, a lot of community hospitals share their infectious diseases physician on a consultative basis with other medical centers and facilities, and that particular specialist may not have a lot of time to invest in the program. Where having an infectious diseases physician as a core member and leader of the team is beneficial, it is not absolutely necessary. A similar argument can be made concerning the inclusion of a clinical pharmacist with infectious diseases training as a core member. Not all hospitals have or can find a clinical pharmacist with formal infectious diseases training through a didactic pharmacy residency program.

If an infectious diseases physician or clinical pharmacist with formal infectious diseases training is not available at a given institution, the team will need to include others ready to assume a greater leadership role. Although not mentioned in the guidelines, hospital medicine specialists and hospitalists are well-suited to take on this role and can be integral to leadership of the multidisciplinary team. Hospitalists have knowledge of the hospital where they support a wide range of services and, at least in some cases, may have fewer time constraints than a subspecialty. In addition, hospital leadership and administration more often reach out to hospitalists to oversee patient quality care and safety improvement projects, the realm to which antimicrobial stewardship belongs. Regarding clinical pharmacists, an alternative to formal residency training for PharmDs are online certification programs such as MAD-ID (Making a Difference in Infectious Diseases Pharmacotherapy), the Society of Infectious Diseases Pharmacists, or via a limited number of state medical societies.^{28,29} Such certification programs should increase the number of pharmacists and PharmDs with infectious diseases training in the near future.

Antimicrobial stewardship is best considered a medical staff, rather than primary hospital, function. Individuals from the medical staff, and particularly medical staff leadership, are most adept in employing “the 3 Cs” that are

important when constructing, implementing, and operating an institutional antimicrobial stewardship program—conceptualization, communication, and coercion. Conceptualization deals with understanding what needs to be done, why it needs to be done, and how to do it, whereas communication is making sure the providers of antimicrobials receive and understand this information. Coercion might seem like a strong term, but it refers to the pressure exerted by thought leaders and others involved in the process to get things done within the institution, including all units or departments. Although ultimate responsibility for an antimicrobial stewardship program should probably lie with the medical staff, the IDSA/SHEA guidelines correctly indicate that support and collaboration of hospital administration, medical staff leadership, and local providers are essential to the success of any such program.²⁴

A Case Study: the Wake Forest University Baptist Medical Center (WFUBMC) Program

Figure 1A,B provides an overview of the general structure of the antimicrobial stewardship program at WFUBMC implemented in 2000. To establish and provide the information needed for day-to-day operations of a stewardship program at WFUBMC, data are needed on how, where, and by whom antibiotics are used within the institution. In addition, microbiology data, including the frequency and susceptibility of infecting pathogens, are essential. Obtaining these data often requires the help and cooperation of the information technology (IT) staff at the institution. Considerable time and effort may be required at the outset, but once information system programs are established, ongoing data mining is much easier. At the time of program initiation, it was decided to assess antibiotic use or density (amount of drug per inpatient geographic unit) using the defined-daily-dose (DDD) method. This entails assigning a predetermined weight of administered antibiotic as a dose and dividing by a denominator of 1000 patient days. Subsequently, days of therapy per drug has been found to be a more accurate measure of antimicrobial consumption. When developing a program, it is vital to first obtain baseline usage data. Such data should include, if possible, a detailed inventory of usage within different units of the hospital or for particular services, or sometimes even for a particular provider with a history of high antimicrobial usage. Ongoing measurement over time allows the impact of new stewardship interventions and guidelines to be measured, as well as identifying potential new problem areas in usage.

Good microbiology data are also essential to determine problem pathogens at the institution and where they are located. Such data are useful not only to define areas of resistance (potentially warranting changes in antimicrobial policies to alter selection pressures), but also for gathering information necessary for defining local guidelines for antimicrobial use. For example, if the local antibiograms show that a particular pathogen in the hospital ICU has a particu-

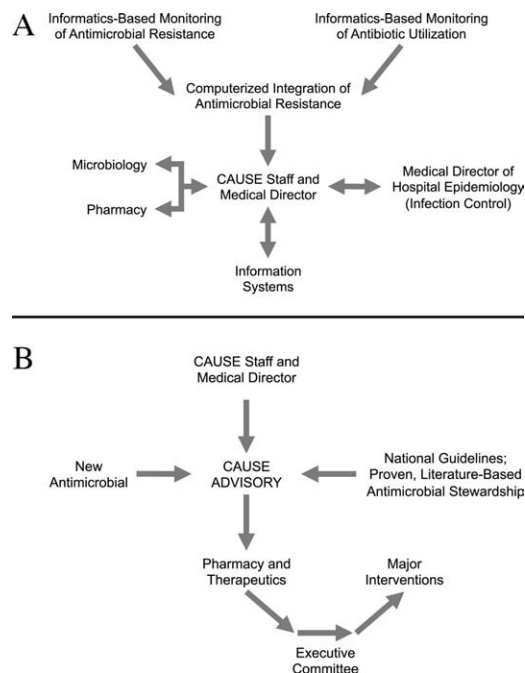


FIGURE 1. Organizational chart of the comprehensive antimicrobial stewardship program at Wake Forest University Baptist Medical Center, illustrating (A) information input and communication between different members of the team; and (B) interactions with the program advisory board and information outflow. CAUSE indicates Center for Antimicrobial Utilization, Stewardship and Epidemiology.

lar resistance pattern, then initial empiric therapy for patients at risk of infection with those organisms should be chosen to cover the problematic resistant pathogen. Once subsequent microbiology data become available, patients not infected with the pathogen can be de-escalated to a more narrow-spectrum antibiotic.

As illustrated in Figure 1A, at WFUBMC, all the collected data are integrated to provide information concerning antibiotic density, usage, and patterns of antimicrobial resistance. This information is received by the staff of the antimicrobial stewardship program, which at WFUBMC is called the Center for Antimicrobial Utilization, Stewardship and Epidemiology (CAUSE). The CAUSE staff works with the day-to-day elements of program administration and operations and includes 2 infectious diseases physicians and 2 infectious disease PharmDs. The CAUSE staff works very closely with the microbiology laboratory, hospital pharmacy, and the medical director of hospital epidemiology and infection control.

The CAUSE program at WFUBMC administratively functions through an advisory board committee that includes thought leaders from different medical specialties and patient units of the hospital—particularly those with high antimicrobial usage, such as hematology/oncology, pulmonary, critical care, and transplantation. The CAUSE staff and advisory board exist to exchange ideas concerning what is

working or not working and where problem areas may be, and to propose possible changes in antimicrobial practices at the institution. In addition, thought leaders on the advisory board also receive and evaluate information from various sources about new antimicrobial agents and national guidelines, and, in turn, help disseminate this information to the hospital personnel who will be involved in program implementation.

At WFUBMC, it is the advisory board committee, working in conjunction with the CAUSE staff/medical director, that presents antimicrobials for formulary consideration to the Pharmacy and Therapeutics (P&T) Committee, in addition to any major interventions CAUSE and its advisory board feel are indicated. The P&T committee then reports to the medical staff executive committee and hospital leadership. As should be evident, the approach to stewardship at WFUBMC is medical staff-driven, rather than a function of administrative constituents.

Finally, no matter how well-organized an antimicrobial stewardship program is, it will not be fully successful if the entire medical staff does not buy into the process and agree with the need for the proposed changes and interventions involving the practice of antimicrobial therapy. It is important to spend some time early in program development to ensure that the need for an antimicrobial stewardship program, the process, and the outcomes (both in terms of patient care and clinical outcomes at the institution) are clearly communicated to the medical staff, and that their full commitment and cooperation are enlisted. In cases where hospital-wide infection or resistance rates are known and antimicrobial utilization data are available, it is important to present such information in an understandable and convincing manner that makes the case for a proposed change or intervention, not only at the hospital level but also at the level of the patient.

Elements of a Successful Program: Basic Strategies

Potential strategies or elements of an antimicrobial stewardship program are listed in Table 2. Two evidence-based fundamental or core strategies have been recommended by the IDSA/SHEA guidelines²⁴ and implemented at numerous institutions with various levels of success. The first is a so-called “back-end” approach to modifying antimicrobial therapy on the basis of prospective audit of antimicrobial use, with intervention and feedback to the provider. The second is a “front-end” approach using formulary restriction and preauthorization requirements for specific antimicrobial agents. Various supplemental strategies, including large group and patient case-based education, guidelines and clinical pathways, antimicrobial order forms, and computerized clinical decision support, are also recommended.

Prospective Audit With Intervention and Feedback

This approach usually involves the use of an antimicrobial support team that reviews initial or ongoing therapy and

then intervenes to provide feedback and suggested modifications to the medical care provider to improve therapy. This can be done by an infectious diseases physician, a clinical pharmacist, or a hospitalist or internist with expertise in antimicrobial therapy. The aim is to provide patient-specific education and/or suggest changes to antimicrobial utilization (when needed) to improve and streamline therapy. Suggested interventions could include discontinuing or changing 1 or more drugs, switching intravenous to oral drug administration, and suggesting a short-course duration of therapy. Occasionally, suggestions are made when appropriate to actually escalate or intensify therapy to increase efficacy. Identification of patients for targeting or focusing prospective audit and feedback efforts typically involves using computer surveillance to single out “problem” antimicrobials or problematic usage, given local resistance patterns or patient characteristics.²⁴ Examples could include a focus on asymptomatic bacteremia, excessive duration of therapy for ventilator-associated pneumonia, or overzealous use of certain classes of antimicrobials. Another potential activity for a prospective audit and feedback team is to review reports of patient-specific blood and sterile body fluid culture results matched to the patient’s current antimicrobial therapy. This allows for daily review of the appropriateness of therapy for potentially serious infections. Some patients seen by the antibiotic support team may be referred for infectious diseases or other expert consultative opinion if their infections or therapy are felt to be too complicated for routine prospective audit and feedback recommendations.

A number of studies have demonstrated that strategies involving prospective audit with intervention and feedback can improve antibiotic stewardship, as measured by reductions in inappropriate antibiotic use,³⁰ reduced antibiotic costs or overall consumption,^{31–35} greater compliance with hospital treatment guidelines or policies^{33,36,37} and, in some cases, reduced number of infections due to *C difficile* infection^{32,37} or resistant pathogens.^{31,32,37} Prospective audit with feedback is probably the best and most effective core strategy for a community hospital program where other interventions are cumbersome or not as well tolerated by the medical staff. One potential disadvantage of the prospective audit with intervention and feedback approach is that medical provider adherence is largely voluntary. The team can make suggestions, but if the provider disagrees or is unobtainable, the suggestion is never implemented. Also, this strategy can also be resource-intensive from a personnel perspective.

Formulary Restriction and Preauthorization

The other major strategy used to achieve antimicrobial stewardship goals involves antimicrobial restriction. This can be accomplished either by not including the particular antimicrobial agent on the hospital formulary or by requiring the medical provider to obtain preauthorization before

TABLE 2. Potential Strategies for an Antimicrobial Stewardship Program

Program Element	Advantages	Disadvantages	Comments
Prospective Audit and Feedback	<ul style="list-style-type: none"> Proven in clinical studies to reduce and modify antimicrobial consumption, improve selected clinical outcomes, and decrease antimicrobial expenditures Provides one-on-one patient-centered education to the clinician Allows optimization of anti-infective pharmacology 	<ul style="list-style-type: none"> Adherence to stewardship interventions by the clinician is voluntary Resource intensive Requires a greater amount of team member training and experience in anti-infective therapy 	<ul style="list-style-type: none"> “Back-end approach” Identify and intervene on patients already started on antimicrobials Interventions include changing, streamlining, de-escalation, pharmacodynamic/dose optimization, IV to PO switch, and limitation of duration of therapy
Restriction or Preauthorization	<ul style="list-style-type: none"> Proven in clinical studies to reduce and modify antimicrobial consumption, improve selected clinical outcomes, and decrease antimicrobial expenditures Together with infection control effective in controlling outbreaks of resistant or secondary pathogens (such as <i>C. diff</i>) 	<ul style="list-style-type: none"> Less appealing to clinicians Loss of prescriber autonomy Potential need for after-hours service Time intensive Potential for delay in antimicrobial administration 	<ul style="list-style-type: none"> “Front-end approach” Formulary restriction or contact a stewardship team member to obtain authorization to prescribe a selected antimicrobial Each intervention is a “mini-consult”
Large Group Education	<ul style="list-style-type: none"> Can reach a large number of prescribers in a short period of time Effective for communicating the need and rationale for subsequent stewardship interventions 	<ul style="list-style-type: none"> Not particularly effective in changing prescribing behavior without other interventions Rapid extinction of gained knowledge 	<ul style="list-style-type: none"> Grand rounds or clinical staff meeting venues Provides information to prescribers and thought leader clinicians on justification for stewardship Feedback antimicrobial susceptibility and use data to clinicians
Guidelines and Pathways	<ul style="list-style-type: none"> Limits variation in therapy of infectious diseases Best evidence-based Assists in adherence with regulatory and third-party payer stipulations 	<ul style="list-style-type: none"> Often not utilized unless combined with other stewardship strategies or elements 	<ul style="list-style-type: none"> Best if local data and conditions are used to adapt guidelines to a specific institution
Computerized Physician Order Entry and Clinical Decision Support	<ul style="list-style-type: none"> Shown in limited clinical studies to reduce and modify antimicrobial consumption, improve selected clinical outcomes, and decrease antimicrobial expenditures Once established can greatly assist with implementation of guidelines and best-evidence therapy. Reduces adverse events related to antimicrobials 	<ul style="list-style-type: none"> Resource intensive during design and implementation Expensive Not readily available 	<ul style="list-style-type: none"> Often entails modification of existing or purchasing of additional informatics
Microbiology Interventions	<ul style="list-style-type: none"> Potential to improve antimicrobial use and anti-infective therapy for the individual patient 	<ul style="list-style-type: none"> Not well studied 	<ul style="list-style-type: none"> Includes cascade reporting to “hide” antimicrobial susceptibilities that might promote suboptimal therapy (eg, fluoroquinolone susceptibility for invasive <i>S. aureus</i>) Assistance with choices of automated susceptibility profile, communication of new or changes in testing protocols Preauthorization of susceptibility testing for unconventional antibiotics
Rapid Diagnostics	<ul style="list-style-type: none"> Provides opportunity for early targeted therapy Assists with de-escalation Shown in very limited studies to decrease antimicrobial consumption and improve clinical outcomes 	<ul style="list-style-type: none"> Not readily available Expensive 	<ul style="list-style-type: none"> Includes PCR and antigen testing of clinical specimens or early culture growth with rapid turnaround of test results
Antimicrobial Cycling	<ul style="list-style-type: none"> Potential to decrease antimicrobial resistance for an institution or geographic unit 	<ul style="list-style-type: none"> Not consistently shown in clinical trials to improve clinical outcomes or decrease resistance Often increases antimicrobial consumption Extremely labor intensive to ensure adherence 	<ul style="list-style-type: none"> Changing antimicrobial protocols periodically in an attempt to reduce selection pressure for resistance

prescribing a restricted drug. A pager system or telephone call is often used for preauthorization, whereby the clinician wishing to prescribe a particular agent calls or pages a member of the stewardship team in order to obtain prescribing permission. When using preauthorization, it is important that the individuals who receive the calls actually see patients and have clinical experience and the respect of the medical staff, as each call may be a “mini-consult.” Oftentimes, the provider or prescriber making the call is asking for suggestions as to what antimicrobial might be used, and not simply to obtain authorization to use a drug that is otherwise restricted. Studies have shown that effective interventions supporting stewardship are better provided by attending infectious diseases staff or clinical pharmacists, rather than persons in training.³⁸

Regarding the identification of antimicrobials for restriction, a program should preferentially choose those drugs that are involved in therapy for complex patients and infections. It is also a reasonable approach for drugs that are, or have the potential to be, overused for certain infections where alternatives exist. For “work-horse” antimicrobials, those drugs overused or misused for several different infectious diseases, prospective audit and feedback is arguably a better strategy to reduce and modulate consumption.

Formulary restriction and preauthorization is clearly effective in modulating antimicrobial use. A large number of studies have demonstrated reductions in antibiotic drug use, and often in cost, after hospital implementation of a formulary restriction or preauthorization approach to antimicrobial stewardship.^{39–47} It has been more difficult to demonstrate other benefits associated with this approach, although there is some support for its aid in controlling nosocomial infection outbreaks. Restriction of clindamycin⁴⁸ (or clindamycin, cefotaxime, and vancomycin²⁷) has been shown to control outbreaks of nosocomial *C difficile*-associated diarrhea and VRE, respectively. More recently, Internet-based antimicrobial restriction programs^{49,50} and a computerized (electronic) approval system⁵¹ have been demonstrated to reduce antibiotic use at tertiary hospitals.

Some studies have reported increased antibiotic drug susceptibilities after implementation of institutional preauthorization policies,^{45,46,51} and at least 1 reported a decreased incidence of ceftazidime-resistant *Klebsiella* species after instituting a preapproval policy for cephalosporins.⁵² However, there is concern that restricting 1 class of antibiotics and replacing it with another will simply replace 1 resistant species with another, the so-called “squeezing the balloon” effect.⁵³ This was observed in the latter study, where a 44% reduction in ceftazidime-resistant *Klebsiella* species at the hospital was accompanied by a 69% increase in incidence of imipenem-resistant *P aeruginosa*.⁵² To assess and enable response to possible “squeezing the balloon” effects, the guidelines recommend monitoring overall trends in antimicrobial use for institutions using preauthorization strategies.

Possible disadvantages of preauthorization and restriction include perceived loss of autonomy for prescribers, the

potential need for all-hours support, inaccurate or misleading information from the prescriber (leading to inappropriate recommendations),²⁴ and significant delay in “stat” antimicrobial administration.⁵⁴ Delay in antimicrobial administration due to the time required to obtain preauthorization and have the approval communicated to the pharmacy was not observed when studied as a process measure at WFUBMC (Ohl, unpublished data, 2008).

A study by Linkin and colleagues showed that 39% of telephone calls for preauthorization of a restricted antimicrobial contained an inaccuracy in at least 1 type of patient data.³⁸ A follow-up by the same group demonstrated that inaccurate communication was significantly associated with inappropriate antimicrobial recommendations (odds ratio [OR] 2.2; $P = .03$); this was particularly the case for inaccuracies in microbiologic data (OR 7.5; $P = .002$).⁵⁵ Also, if all-hours support is not provided, at least 1 study has shown some physicians may engage in “stealth dosing,” that is, avoiding having to obtain preauthorization for restricted antimicrobials by waiting until off-hours to place orders.⁵⁶ The latter can be dealt with by following up on such orders with a prospective audit and feedback component of the program. Preauthorization is usually more difficult to employ and less accepted in non-academic medical centers. Prospective audit and feedback may be more appropriate in such settings.

Supplemental Strategies

A number of additional options are available to supplement the 2 core strategies just described, and are listed in Table 2. Education is generally considered an essential component of any effective antimicrobial stewardship program, but it generally has little lasting impact on providers’ behavior, unless it is incorporated with other active interventions.²⁴ In particular, the large group or Grand Rounds-type education, where someone describes what needs to be done and why, typically does not produce lasting behavioral changes. There might be, and often is, some short-term modification, but long-lasting change at the provider level requires consistent and repeated educational endeavors. Such large group educational venues are more effective and better used as a forum to describe or garner support for an impending stewardship program or intervention, rather than to teach a specific practice.

Using the antimicrobial stewardship program to adapt national guidelines to local antimicrobial use, microbiology, and resistance patterns^{57,58} or using clinical (critical) pathways⁵⁹ has also been shown to improve antimicrobial utilization at hospitals. National guidelines generally enjoy widespread support, but they commonly lack specific information about how to implement recommendations at a given hospital or how to incorporate local data relevant for decision making. A 2006 report by Beardsley and coworkers provides a model from WFUBMC on how local microbiologic data can be used to modify national treatment guidelines to better serve the needs of patients treated at a particular institution.⁶⁰

Using American Thoracic Society (ATS) and IDSA guidelines for the management of hospital-acquired pneumonia (HAP), together with local data on the most common bacterial pathogens and their susceptibility to piperacillin-tazobactam, cefepime, ciprofloxacin, and amikacin (based on length of hospitalization), the WFUBMC CAUSE Advisory Board developed institution-specific HAP guidelines. The new guidelines divided the ATS/IDSA late onset/risk of the MDR pathogens group of patients into 2 subcategories, early-late and late-late pneumonias. Also, unlike the national guidelines, the new guidelines did not recommend ciprofloxacin as empiric therapy, instead recommending amikacin as a component of regimens targeting late-late pneumonias.

Newer (and in some cases not so new) information technologies can be adapted to healthcare delivery and prescriber support to improve antimicrobial stewardship. These include computer decision support⁶¹ and alert systems^{62–65}; computerized physician order entry (CPOE)^{66,67}; electronic medical records²⁴; electronic retrieval of treatment guidelines or clinical texts⁶⁸; and personal digital assistant (PDA) applications providing information on pathogens, diagnosis, medication, and treatment.^{68,69} In addition, computer-based surveillance^{64,70,71} and Web-based systems for antimicrobial approval; automated clinical decision support; and/or enhanced real-time communication between prescribers and other members of the antimicrobial stewardship team show promise for antimicrobial stewardship programs.^{49,50}

Computer-assisted decision support has been shown to improve or reduce antibiotic-susceptibility mismatches (improve selection of effective therapy), overall antibiotic use, excess antimicrobial dosages, excessive-dose days, selection of antimicrobials for which the patient was poorly matched in terms of allergies, and antimicrobial-related adverse events, as well as reduce antimicrobial drug costs, total hospital costs, and length of hospital stay.^{72–77} For their part, CPOE systems have been shown to improve compliance with treatment guidelines, decrease medication and other medical errors, shorten length of hospital stay, and decrease pharmaceutical costs.^{66,67,78} In many cases, CPOE systems can now be modified to include some clinical decision support to improve antimicrobial use.⁷⁸

The IDSA/SHEA guidelines note that antimicrobial decisions can be improved through use of CPOE, clinical decision support, and electronic medical records that enable incorporation of data on patient-specific microbiology cultures and susceptibilities, hepatic and renal function, drug interactions, allergies, and cost. They also point out that computer-based surveillance can facilitate good stewardship by enabling more efficient targeting of antimicrobial interventions, tracking of antimicrobial resistance patterns, and identification of HAIs and adverse drug events.²⁴ Recently, a few proprietary informatics programs that perform such functions for the hospital epidemiologist and antimicrobial steward have become available, including but not limited to TheraDoc (Salt Lake City, UT), SafetySurveillor (Premier, Inc., Charlotte, NC), and BD Protect (BD Diagnostics, Aus-

tin, TX). Perhaps one of the best-known comprehensive hospital information systems that incorporates and integrates several information technologies to improve patient care at the level of the prescriber is the Health Evaluation through Logical Processing (HELP) system at LDS Hospital in Salt Lake City, Utah.^{79–81} Unfortunately, these programs are expensive, need considerable time for installation and validation, and do not always perform the functions needed by the medical center. The medical community has generally been slow to incorporate healthcare information technology to improve antimicrobial use or general medical care, but in the last few years more hospitals are finding their merit.

On the basis of evidence currently available, the 2007 guidelines do not recommend the routine use of antimicrobial cycling or combination therapy to prevent or reduce antimicrobial resistance. Such strategies, where at first glance might intuitively seem to make sense, have not been shown to improve patient care, improve antimicrobial choices, or reduce antimicrobial resistance. In addition, antimicrobial cycling in particular is difficult to implement and labor intensive to oversee.²⁴

One strategy for improving antimicrobial stewardship not mentioned in the 2007 IDSA/SHEA guidelines, but might become increasingly important in the future, is the use of rapid molecular diagnostic testing. Knowing the identity of the causative pathogen sooner or being able to rapidly rule out certain pathogens should enable better decision-making. During the 2009/2010 influenza season with H1N1 influenza, WFUBMC was able to implement rapid viral testing and learned some things that enabled improvement of hospital practices. It was found that approximately 10% to 15% of the pneumonias in immunocompromised patients at the center were not bacterial but viral, the pathogens being respiratory syncytial virus (RSV) or metapneumovirus (Ohl, unpublished data, 2010). Upon finding a viral etiology to a lower respiratory tract infection, rapid de-escalation of antibiotic therapy was possible. If rapid diagnostics are to be performed, it is important that there are systems in place to respond quickly to the findings, so the benefits of having rapid data can be realized.

Evaluating Antimicrobial Stewardship Programs

Two general types of measures are used to evaluate the effectiveness of antimicrobial stewardship: process and outcome. As with most things done in the hospital, process measures are easier. They measure surrogate impacts of a program, accountability, resource use, and cost effectiveness. In essence, process measures evaluate whether the program accomplished what it set out to do in terms of changing certain processes or prescriber behaviors. It is important to measure resource use, as this helps to continue funding and to keep workers involved in the project. Good programs will save money; this can easily be measured, even if it is just as simple as going to the hospital pharmacy and looking at the cost of antimicrobials provided per patient day.

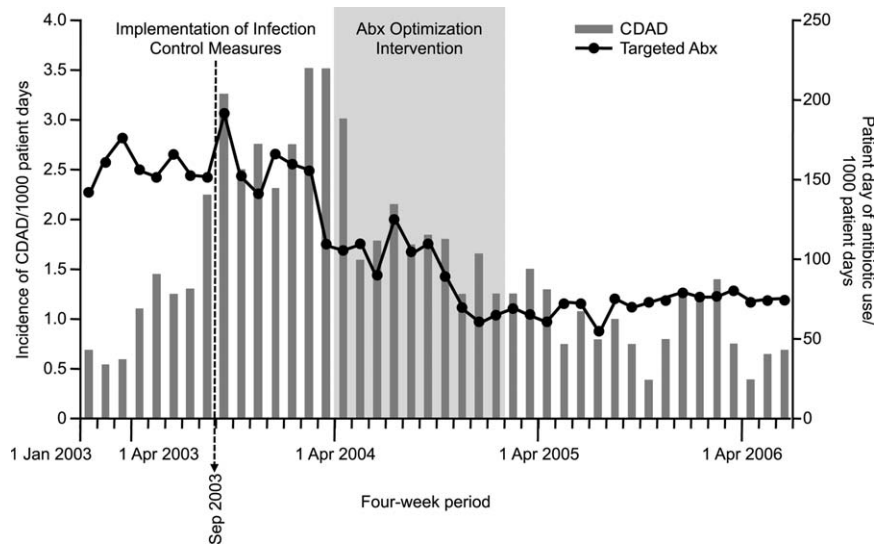


FIGURE 2. Targeted antibiotic (Abx) consumption and nosocomial *Clostridium difficile*-associated disease (CDAD) incidence per 1000 patient-days of hospitalization at a Quebec hospital. (Reproduced with permission from Valiquette et al, 2007.)

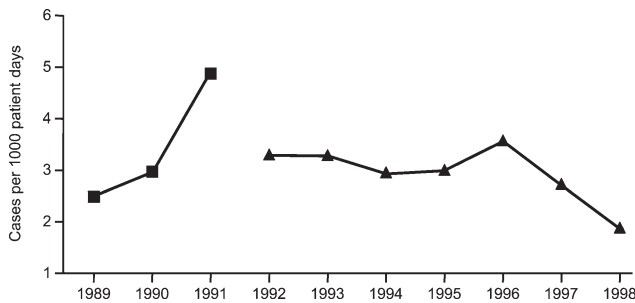


FIGURE 3. Rate of resistant Enterobacteriaceae infections before and after implementation of the antibiotic stewardship program in 1991. (Reproduced with permission from Carling et al, 2003.)

Outcomes like decreases in particular infections, less emergence of antimicrobial resistance, or other patient-specific measures are likely more important in the big picture, but they are also much more difficult to measure. For example, where one would like to measure changes in pathogen resistance after making some changes in antimicrobial stewardship, it often takes years before the benefits of a particular intervention or change materialize in terms of less resistance or reduced emergence of resistance. If that type of change is to be measured, then one needs to be persistent and continue measurements over a long period of time. In addition, given the protracted amount of time before these outcomes may be observed, a number of other changes are likely to happen that coincide with the antimicrobial stewardship interventions and make assessment of causality difficult and biased.

Having said that, a number of studies have demonstrated a relationship between antibiotic restriction^{48,82–85} or other antimicrobial stewardship policies^{32,86} and decreases in nosocomial *C difficile* infections or disease. Figure 2 illustrates the impact of a nonrestrictive antimicrobial steward-

ship program at a secondary/tertiary-care hospital in Quebec, Canada, on an epidemic of *C difficile*-associated disease (CDAD) that occurred at the institution during the latter portion of 2003.⁸⁶ Following program implementation, and the major drop in targeted antibiotic consumption, the incidence of CDAD also significantly decreased. Earlier implementation of infection control measures had no effect on CDAD incidence.

A smaller number of studies have reported decreases in resistant gram-negative bacteria following implementation of antimicrobial stewardship programs. For example, Meyer and colleagues reported a marked reduction in ceftazidime-resistant *K pneumoniae* at a 487-bed general hospital in New York City after implementation of enhanced ceftazidime restriction and barrier precautions following an outbreak of infections caused by the resistant *K pneumoniae*.⁸⁷ Similarly, Carling and coworkers reported a significant decrease in nosocomial infections caused by resistant Enterobacteriaceae following implementation of a multidisciplinary antibiotic stewardship program to minimize inappropriate use of third-generation cephalosporins (Figure 3).³² More recently, a retrospective, longitudinal, multicenter analysis of a consortium of 22 academic health centers in the United States showed that incidence rates of carbapenem-resistant *P aeruginosa* were lower at hospitals that restricted carbapenems than those that did not ($P = .01$).⁸⁸

Evidence suggesting a beneficial impact of antimicrobial stewardship programs on resistance in gram-positive organisms is limited. More specifically, the study by Carling and colleagues reported an apparent decrease in VRE rates following implementation of their program to reduce inappropriate use of third-generation cephalosporins.³² The hospital had VRE rates similar to other NNIS System hospitals prior to beginning the program, but after antibiotic stewardship measures were implemented, the VRE rate began to drop, falling to

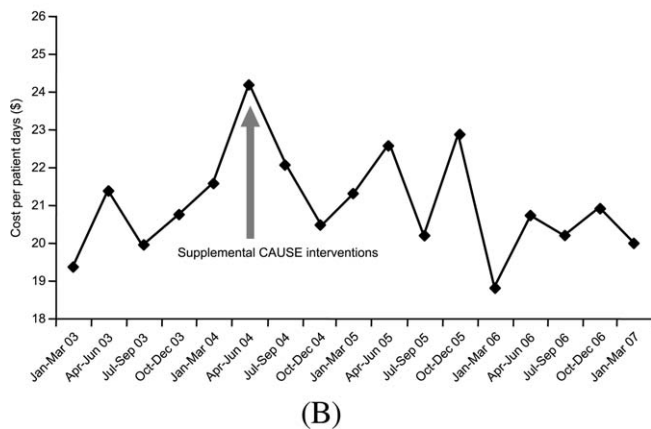
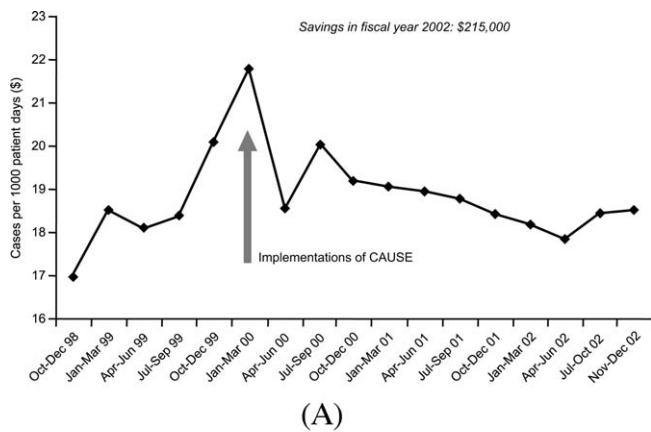


FIGURE 4. Antimicrobial costs at Wake Forest University Baptist Medical Center (A) before and after implementation of the Center for Antimicrobial Utilization, Stewardship and Epidemiology (CAUSE); and (B) after supplemental CAUSE interventions, including enhanced prospective audit and feedback and preauthorization.

6% by 1999. This should be compared with a VRE rate of 24% for similar NNIS System hospitals in 1999.

As far as reducing healthcare costs, Figure 4A illustrates the direct antimicrobial cost savings at WFUBMC after implementation of the CAUSE antimicrobial stewardship program, and Figure 4B after supplemental interventions were implemented. Although decreasing antimicrobial cost is important, one would like to show decreases in overall healthcare costs associated with an antimicrobial stewardship program. Unfortunately, this is often a little more difficult to demonstrate. Extrapolations, however, may be possible. Because antimicrobial resistance, adverse drug effects, and secondary unintended infections such as *C difficile* colitis have been linked with increased patient morbidity and mortality, longer hospital stays, and increased healthcare costs,^{6,89,90} improved antimicrobial stewardship is expected to optimize patient care and lower overall healthcare costs. A study in a large tertiary care academic medical center estimated more than \$4.25 million in total healthcare savings over 1 year with a stewardship program using both preauthorization and, to a lesser extent, prospective audit and

feedback.⁹¹ Despite the fact cost saving should not be a primary goal of an antimicrobial stewardship program, lower antimicrobial costs can help keep a program funded and buttress a proposal for an antimicrobial stewardship program to hospital leadership.

Many hospitals recognize other areas where an antimicrobial stewardship program can demonstrate its value. This includes implementation of a rapid change in drug utilization during antimicrobial supply shortages and assistance with regulatory mandates and surgical infection prophylaxis. Stewardship teams often assist microbiology with protocols for microbiology reporting, antibiograms, planning for susceptibility testing, and communicating changes in microbiology tests or protocols to clinicians.

Conclusions

Overuse or misuse of antibiotics and other antimicrobials for hospital inpatients is relatively common, and can be associated with several unintended negative consequences. Improving medical care necessarily includes better use of antimicrobials to optimize outcomes and preserve the effectiveness of currently available agents. Further, an important additional consequence of effective antimicrobial stewardship and improved patient care is typically a lowering of overall healthcare costs. The recent 2007 IDSA/SHEA guidelines provide recommendations for developing an institutional program to enhance antimicrobial stewardship. However, individual institutions need to look closely at their own systems and patients to develop an antimicrobial stewardship program that best serves the needs of their hospital and the people it serves.

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