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Antimicrobial Stewardship Programs

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The development of antimicrobial agents represents one of the most significant achievements in medicine during the past century. However, the emergence of antimicrobial resistance combined with the downturn in the development of new antimicrobial agents in the pharmaceutical industry poses unanticipated challenges in the effective management of infection. The issue of how we can most effectively utilize these invaluable resources, antimicrobials, in the face of infections that are ever more difficult to treat arises. This issue serves as the fundamental basis for the concept of antimicrobial stewardship, the topic of this minireview.

With the emergence of antimicrobial resistance, several organizations, including the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the American Society of Health System Pharmacists (ASHP), have identified antimicrobial stewardship as having an important role in today's health care environment (1, 2). What is antimicrobial stewardship? The IDSA broadly defines antimicrobial stewardship as a "rational, systematic approach to the use of antimicrobial agents in order to achieve optimal outcomes" (1). One approach to achieving this is through the development of formal institutional antimicrobial stewardship programs. The intent of this review is to provide some insight into those factors that are important in crafting effective hospital-based antimicrobial stewardship programs.

ANTIMICROBIAL STEWARDSHIP PROGRAM STRUCTURE

The optimum hospital-based antimicrobial stewardship program consists of an oversight group comprised of three individuals: a clinical pharmacologist with a Pharm.D. degree plus 2 years of fellowship training in infectious diseases, preferably obtained in a training program approved by the American College of Clinical Pharmacy; a board-certified infectious disease physician; and a board-certified doctorate-level director of the clinical microbiology laboratory. Preferably, all of these individuals should be full-time employees of the institution in which the stewardship program resides; however, it is understood that in some instances, this may not be possible. It is expected that the clinical pharmacologist will devote all of her or his time to the program. The infectious disease physician and clinical microbiology laboratory director would devote a portion of their effort to the program, with the actual time commitment being dependent on the size, complexity, and scope of the program. Depending on the size of the institution and the nature of the patients cared for in that institution, these staffing requirements may vary.

GENERAL CONSIDERATIONS IN ANTIMICROBIAL STEWARDSHIP

From the perspective of functionality, institutional antimicrobial stewardship programs should be tailored to fit the specific institution or hospital system they are to serve (3). If the primary goal of antimicrobial stewardship is to optimize antimicrobial chemotherapy, an advisable step before formal development of any program is to first attempt to define the most important issues that exist with respect to antimicrobial use in a given institution. Many institutions find that overuse of inappropriate antibiotics is a major problem. Further, multifaceted solutions to usage problems are often required. For example, Hecker et al. performed a retrospective evaluation of antimicrobial use in an inpatient setting in 2001 (4). In a 2-week period, they found 30% (576/1,941) of antimicrobial days of therapy were inappropriate. More specifically, 33.3% (192/576) of inappropriate treatment days were due to therapy which was continued longer than necessary, and 32.5% (187/576) of inappropriate use was for noninfectious or nonbacterial syndromes. Although the two problems result in similar rates of inappropriate use, activities to resolve these issues can be completely different.

Once institution-specific problems have been identified, it is necessary to evaluate potential causes of those problems. An unbiased process evaluation may demonstrate that current practices and policies enable or even encourage health care providers (HCPs) to unwittingly contribute to inappropriate antibiotic use. For example, an institutional process evaluation conducted at the University Medical Center of Southern Nevada found that many antibiotic treatment courses extended well beyond the recommended standard periods of therapy (K. D. Leuthner, unpublished observation). Upon further investigation, it was determined that automatically generated medication renewal forms being provided to the physicians were contributing to the excessive antibiotic usage. The policy in place at the time was to have the pharmacy computer system automatically generate a medication renewal form to be placed in the chart 48 h prior to the expiration of any medication order. As a convenience, the HCP responsible for therapy could choose simply to "renew" or "DC" that medication rather than having to write a complete new order. Unfortunately, when the procedures were audited, it was found in many instances that drugs, including antibiotics, were being renewed regardless of continued need. Once discovered, the policy was modified to exclude antimicrobial agents from these renewals and a process established in which the pharmacy computer system routinely generates a notification for the HCP that their antibiotic is approaching 10 days of therapy and that its administration will

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automatically stop unless a completely new order is written. This simple policy change resulted in a decrease in the average period of antibiotic treatment from between 16 to 20 days to an average of 13.3 days (5).

ANTIMICROBIAL STEWARDSHIP PROGRAM ACTIVITIES

All three primary stewardship program professionals should participate as standing members of whatever entity exists within an institution charged with defining the composition of the antimicrobial formulary. This may be the pharmacy and therapeutics committee or a subcommittee that functions specifically to make antibiotic formulary decisions. An essential part of any effective antimicrobial stewardship program is a formulary structure that discourages the use of ineffective, needlessly expensive, or potentially toxic antimicrobials. Selected agents should be identified which require preauthorization for use. Approval for use of these agents would be the responsibility of the infectious disease physician member of the stewardship program (or his or her designee). Restrictions on antimicrobial use are often viewed negatively by HCPs, especially those HCPs who have grown accustomed to having carte blanche when it comes to prescribing antibiotics. The antimicrobial stewardship program members can play an important role in helping to gain acceptance for a restricted formulary by being available to interface with individuals who lack enthusiasm for such a process.

In addition, all of the stewardship program members should be participants, preferably in a leadership role, in institutional initiatives aimed at developing clinical pathways that are germane to the care of patients known to have or suspected of having infection. Numerous organizations have developed guidelines that are of value in developing care pathways. Implementation and use of care pathways is facilitated by the use of physician computer-based antimicrobial order entry systems. With time and widespread application, care pathways may have the effect of helping to educate HCPs regarding the role of the stewardship team in optimizing antimicrobial usage.

Stewardship program members should be integrally involved in the infection control activities of their institution, including serving as standing members on the institutional infection control committee. Institutional antibiotic use should be monitored and a system for assessing the effectiveness of the stewardship program developed and implemented. Another essential function of stewardship program members is participation in institutional educational activities that emphasize best practice with respect to antimicrobial use. An extension of this is the role of stewardship program members as resources for public outreach endeavors. In addition, a mechanism for communicating the impact of the stewardship program to institutional leadership on a continual basis should be developed.

Most importantly, on a day-to-day basis, whenever possible, the antimicrobial stewardship program should be involved in optimizing the antibiotic management of as many patients with infection as possible in a given care setting. This requires an active process of evaluation and intervention, the ultimate goal of which is to achieve, whenever possible, the most effective management of patients with infection. Simply put, positive patient outcomes remain the primary objective of this process. Other important considerations include the avoidance of unnecessary cost and the use of antimicrobials in a manner that diminishes to the extent possible both drug toxicity and the burden of antimicrobial resistance.

Achieving these objectives requires a process that affords ongoing, real-time assessment of antibiotic prescriptions in patients known to have or suspected of having infection in a given care setting. When resources permit, this assessment would ideally be applied to all antibiotic prescriptions. In resource-limited circumstances, the assessment would be applied to patients of high acuity, to patients in care settings that are generally known to be problematic with respect to antimicrobial resistance (e.g., medical and surgical intensive care units [ICUs], oncology, and transplantation), in specific settings in which antimicrobial use has been shown to be excessive, and, finally, in care settings recognized as experiencing an outbreak of antimicrobial resistance. Preferably, the initial assessment would occur within 24 h following initiation of antimicrobial therapy or within 24 h of admission in cases where admitted patients have been started on antibiotics prior to or at the time of admission. In practice, this work would be conducted by the stewardship clinical pharmacologist.

Patients who have been started on agents in a manner consistent with accepted institutional care pathways would not require review. However, in all circumstances where initial antimicrobial therapy is not consistent with the recommendations of care pathways or in situations where no formal care pathway has been developed, an assessment would be made by the clinical pharmacologist as to the appropriateness of therapy. The clinical pharmacologist would be alerted to circumstances which require assessment in real time, preferably by receiving automatic notifications from the pharmacy information system.

Considerations germane to this assessment include the nature of the infection, both the site of involvement and the known or suspected pathogen(s), patient factors that militate against effective therapy (e.g., age, renal function, comorbidities, history of infection, other concomitant therapies vis-à-vis potential drug-drug interactions), formulary composition, the cost of different agents, institutional antimicrobial resistance profiles, and experience. It is understood that at the time of this initial assessment, the results of cultures and susceptibility studies relevant to the patient being evaluated would probably not yet be available. One exception would be in circumstances where the use of the antibiotic(s) started initially was restricted, that is, was available for use only following authorization, usually in cases of infectious disease. In such cases, secondary assessment of use by members of the stewardship program would be unnecessary.

After consideration of these factors, the clinical pharmacologist would make a formal recommendation regarding therapy; either the therapy the patient had been started on will have been judged acceptable or a recommendation for a change in therapy would be made. In the first case, although not mandatory, this could be noted in the patient's medical record. In the second case, the clinical pharmacologist would directly contact the HCP of record, either by phone or in person, and the recommended alteration in therapy would be communicated. In addition, a notation of the recommendation would be placed in the patient's medical record. In circumstances where there exist medicolegal concerns about having such recommendations permanently placed in patient's medical records, addition of a "sticky note" to the record could suffice. All definitive recommendations for a change of therapy would ultimately be reviewed by the infectious disease physician member of the stewardship team. In instances where recom-

mendations for a change in therapy were ignored, the infectious disease physician member of the stewardship team would intervene. And finally, in instances where questions exist regarding what actually constitutes optimum therapy, the clinical pharmacologist would consult with the infectious disease physician and/or the clinical microbiologist member of the stewardship program prior to making recommendations.

Secondary assessments would occur at the time that the results of direct pathogen detection tests, cultures, and then susceptibility studies become available. Direct detection results are usually forthcoming within 1 to 6 h; culture results are usually available within 18 to 48 h following submission of appropriate specimens to the laboratory, at least with typical bacterial and rapid growing fungal pathogens such as *Candida* spp. Susceptibility test results become available 4 to 24 h following recovery of bacterial pathogens and 24 to 28 h after recovery of fungal pathogens. The objective of this secondary assessment is to optimize therapy with respect to the agent(s) started initially. This includes the possibility of streamlining therapy in patients who have been started on multiple agents initially (i.e., de-escalation), the possible use of less-expensive and/or less-toxic antibiotics, and the potential switch to orally administered agents in patients who were initially receiving parenteral antimicrobials.

A key consideration in this secondary assessment is the timely and effective transfer of test results from the laboratory to the stewardship clinical pharmacologist. This is best accomplished by immediate electronic transfer of laboratory information directly to the stewardship clinical pharmacologist. Currently, at least three commercially available computerized middleware systems exist to accomplish such information transfer: MedMined (CareFusion, San Diego, CA), EPIC (Verona, WI), and TheraDoc Antibiotic Assistance (Hospira, Inc., Lake Forest, IL). Without ongoing secondary assessment performed in a timely manner by the stewardship clinical pharmacologist, rarely in today's clinical practice are therapeutic modifications made at the time culture and susceptibility test results become available (6).

Lastly, a system should be in place for promptly notifying the stewardship program clinical pharmacologist of circumstances where the length of antimicrobial therapy in individual patients exceeds a previously determined standard. This presupposes that there exist institutional guidelines that define optimum periods of therapy. As with the care pathways, the members of the antimicrobial stewardship program should be actively involved in the development of guidelines regarding the optimum length of therapy. Such information is readily maintained in the pharmacy information system, and when patients are identified in whom therapy has progressed beyond the predefined standard, the stewardship clinical pharmacologist should be notified and an appropriate intervention undertaken.

THE ROLE OF THE CLINICAL MICROBIOLOGY LABORATORY IN STEWARDSHIP

The clinical microbiology laboratory plays a central role in antimicrobial stewardship. It is essential for the laboratory to employ processes and methods that ensure the rapid and reliable diagnosis of infection. In addition, the laboratory should utilize antimicrobial susceptibility test (AST) procedures that correctly delineate the activity profile of relevant agents. The selection of a particular AST method should take into account both the accuracy and reproducibility of test results. In the vast majority of instances, a category susceptibility test result (i.e., susceptible, intermediate, or resistant) is sufficient. In circumstances where MICs have been determined based on the results of a quantitative AST method and a determination has been made that reporting of the MIC values is both desirable and justified, a category interpretation should always also be provided. The single most fundamental precept of AST is the restriction of testing to only those organisms that are known or at least thought likely to be of clinical significance. An exception would be circumstances in which testing is being performed for epidemiological purposes. Another important consideration is the prevalence of resistance with given antimicrobial-organism combinations. To wit, when resistance has not yet been recognized with a given antimicrobial-organism combination, it is difficult to justify testing that combination routinely. Susceptibility testing in this setting can yield a result that was known before the test was performed (a poor utilization of laboratory resources), or the laboratory can make a mistake, i.e., can classify the organism as falsely resistant.

The choice of the panel drugs to be tested and reported on isolates recovered from individual patients should be predicated on formulary composition, the specific organism being tested, the prevalence of resistance as noted above, and the site of infection. In some instances, patient factors such as age, renal function, underlying disease(s), and previous antibiotic exposure may also have an impact on which drugs are tested. Guidelines for selection of drugs for testing have been promulgated by several organizations, most notably, the Clinical and Laboratory Standards Institute (CLSI) (7).

Selective or algorithm reporting of AST results is a convenient and cost-effective tool that the laboratory can employ to simplify the process of reporting only relevant results (8). With selective reporting, an individual isolate can be tested against a large number of agents initially, but only the results obtained with desired agents are reported. This approach to AST results reporting can be readily managed by laboratory information systems employing user-defined reporting algorithms. The members of the antimicrobial stewardship committee should be responsible for creating, maintaining, and updating such reporting algorithms.

Having chosen a test method and having decided which agents will be tested and reported, the issue then arises of how best to effectively communicate those results. The results of ASTs should be reported both to HCPs responsible for care decisions and to the antimicrobial stewardship clinical pharmacologist. Computerized result reporting schemes are available for all instrument-based AST systems and for all laboratory information systems. Their use facilitates and expedites the transfer of AST information into the hands of those who can best use it. There is, however, one caveat. Simply generating a computer report that conveys the results of ASTs and launching it into cyberspace does not ensure that anyone will actually see it and then process the information contained in the report. In this regard, although understandably more onerous to accomplish, it is clear that direct communication of AST results to HCPs, especially when accompanied by an explanation of what the results might mean in the care of individual patients, has been shown to have a much more compelling impact on antibiotic usage than passive reports of computerized results (9, 10). This reality provides yet another rationale for active interventions

by a trained clinical pharmacologist as part of a rigorous antimicrobial stewardship program.

As noted above, the length of time to provision of AST results is an important determinant in their clinical value. Two investigations have clearly demonstrated that, in comparison to overnight susceptibility tests, the use of same-day susceptibility tests is associated with significantly greater numbers of positive outcomes in large numbers of patients (11, 12). Same-day susceptibility tests were also associated with significant savings in the overall cost of patient care.

Finally, as mandated by the Joint Committee on Hospital Accreditation, the clinical microbiology laboratory is responsible for generating and distributing cumulative antibiograms (13). Many have pontificated over the issue of whether percent susceptibility or percent resistance results should be reported in cumulative antibiograms. Indeed, it really makes no difference, accepting the fact that if the latter approach is used, the metric should include both resistant and intermediate results, i.e., all nonsusceptible strains. Selection of isolates to be included in antibiograms is also a matter of some debate. The approach advocated by the CLSI includes counting only the first isolate of a particular pathogen recovered from a given patient during each analysis interval (14). This approach would seem to run the risk of failing to capture the more resistant bacteria, the mistake one would least like to make when crafting antibiograms. Further, as demonstrated in an important study by Bantar et al., it is clear that isolates of bacteria recovered from patients with hospital-acquired infections that were selected for inclusion in cumulative antibiograms were often assessed as not of clinical significance when typical laboratory criteria for significance were used (15). When clinician evaluation of patients was used as the basis for defining clinical significance and thus inclusion in the cumulative antibiogram, major differences were observed, with far fewer organisms captured and with a trending toward higher resistant rates. Two other considerations are the matter of generating hospital location-specific antibiograms and the issue of how frequently antibiograms should be updated. With respect to the advisability of generating location-specific antibiograms, this notion clearly has merit; however, it must be understood that at least 30 countable events are required in order to generate a statistically defensible antibiogram value (14). As for the frequency of compiling and publishing antibiograms, once yearly is sufficient.

OUTCOME ASSESSMENT

Surprisingly little published data exist which delineate the value of antimicrobial stewardship programs. It is essential that institutions with active stewardship programs attempt to objectively define the impact of such programs. Essential parameters to track include the frequency with which the therapeutic recommendations of the antimicrobial stewardship team are actually followed and, in cases where therapeutic changes are made, how much time passes after a recommendation is made until the change is actually instituted. Additional factors to be considered, using historical data as a frame of reference, include mortality rates, most especially, mortality attributable to infection, overall length of hospitalization, periods spent in specific care areas such as the medical and surgical ICUs, rates of recurrent infection, the frequency with which specific laboratory studies are performed, antibiotic usage patterns, and institutional antimicrobial resistance patterns. Furthermore, and importantly, cost analyses should be applied whenever possible. Systematic collection and objective analysis of such data can be extremely important in justifying antimicrobial stewardship programs within a given institution and can also serve as the basis for presentations at medical-scientific meetings as well as for publications in peer-reviewed journals. In addition, information of this sort, if packaged appropriately, can have immense public relations value.

SUMMARY

Hospital-based antimicrobial stewardship programs, when structured as described above, can have a major positive impact on optimizing the care of patients with infection. In addition, effective stewardship has the potential for substantial reduction in the costs of health care. The clinical pharmacologist, the infectious disease physician, the clinical microbiologist, and the clinical microbiology laboratory all play important roles in ensuring the success of such programs.

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