Antibiotic Optimization

Concepts and Strategies In Clinical Practice

edited by
Robert C. Owens, Jr.
Paul G. Ambrose
Charles H. Nightingale

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INFECTIOUS DISEASE AND THERAPY

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Foreword

Among the most critical factors in reducing or reversing the emergence of antimicrobial resistance is the optimization of usage of our highly valuable antimicrobial resources, a concept also known as practicing good antimicrobial stewardship. We squander our antimicrobial resources by using these agents inappropriately for non-bacterial infectious indications, by not dosing them appropriately, and by not using them for the optimal duration to treat infection and avoid unintended consequences of their use. The unintended consequences of antimicrobial use have not been fully appreciated in the past. Certainly immediate adverse events such as rashes and anaphylaxis have long been recognized and have been directly associated with the use of the antibiotic. Other unintended consequences of antimicrobial use are not so readily or immediately recognized. A major unintended consequence of using antimicrobials in hospitals and institutions is *Clostridium difficile* associated disease (CDAD) which most often presents as diarrhea and pseudomembranous colitis. We have long sought to prevent this increasing antibiotic-induced problem by using infection control measures designed to prevent patients from acquiring *C. difficile* spores in the hospital environment. These infection control efforts remain the mainstay of institutional CDAD prevention, but it is now apparent that this problem arises as a direct result of use of specific antimicrobials in the hospital setting, including clindamycin, second and third generation cephalosporins, and newer fluoroquinolone agents. The good news is that controlling or restricting these specific antimicrobials (practicing

better antimicrobial stewardship) has resulted in marked decreases in CDAD rates in these institutions.

An unintended consequence of antimicrobial use that is even more difficult to associate directly with usage is the emergence of antimicrobial resistance, one of the most critical current problems in the treatment of many infectious diseases. Considerable new information has been developed to assist the clinician in the practice of good antimicrobial stewardship. This textbook, prepared under the editorship of Robert Owens, Jr., Paul Ambrose, and Charles Nightingale is a compendium of the best practices developed by experts across the U.S. who have extensive experience in the use of data-driven practices that result in fewer unintended consequences without compromising (and often improving) the treatment of infection in the patient. Considerable sources of information for the practice of good antimicrobial stewardship at both the institutional and individual practitioner level have been developed in the past several years. Both types of information are thoroughly assembled, described, and discussed in this text. Infection control professionals, hospital epidemiologists, pharmacists, infectious disease specialists, and all practitioners who utilize antimicrobials or are tasked with managing the ever increasing problems of the unintended consequences of antimicrobial use will find this text an invaluable asset. The editors and authors are to be congratulated on compiling such a thorough approach to improved antimicrobial practice, an approach that if followed will certainly result in fewer unintended consequences and better antimicrobial stewardship by all antimicrobial users.

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Preface

Institutionally acquired infections impact approximately 2,000,000 people annually in the United States alone. An increasing percentage of these infections are attributed to antimicrobial resistant organisms. Considering that 25 million pounds of antibiotics are produced yearly for human consumption and are administered to 30–50% of hospitalized patients, the utilization of these miracle drugs is of significant health and economic importance. All the while, studies and surveys suggest that as much as 50% of all antimicrobial use is inappropriate. The problem of increasing antimicrobial resistance, due in part to suboptimal antimicrobial use, coupled with the fact that a growing number of pharmaceutical companies have abandoned anti-infective research and development, has resulted in an emerging public health crisis. As hospitals are characterized by high-density antibiotic use, they are target-rich venues for proactive interventions to improve antimicrobial stewardship. "Antimicrobial stewardship," a term coined by Dale Gerding, describes the optimal selection, dose, and duration of an antimicrobial that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient, and minimal impact on subsequent resistance.

Recognizing the importance of drug resistant organisms, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America published recommendations for preventing and reducing antimicrobial resistance in hospitals in 1997. Two years later, the Interagency Task Force on Antimicrobial Resistance, co-chaired by the Centers of Disease Control and Preven-

tion, Food and Drug Administration, and the National Institutes of Health, assembled a more global document addressing the threat of increasing resistance. Both documents stress the importance of improving the use of antimicrobials, or antimicrobial stewardship, at the institutional level in combating antimicrobial resistance.

We have condensed issues stressed by the aforementioned agencies and societies and expanded the content to incorporate emerging data related to the use of antimicrobial agents in the institutional setting. This book is intended to be of relatively broad interest while focusing on contemporary principles essential to optimizing the use of antimicrobial agents. The first section addresses fundamental concepts including the role of the Pharmacy and Therapeutics Committee, antimicrobial resistance, health economics, pharmacodynamics, and benchmarking antimicrobial use, to name a few. The second section reviews practical applications of science, providing examples of programs and strategies designed to foster good antimicrobial stewardship. Issues addressed include antimicrobial stewardship programs, role of computer-assisted decision support, infection control programs, short course therapy, and the institutional use of antifungal agents, among others.

This book is a collaborative effort among recognized authorities in the areas of infectious diseases, hospital epidemiology, medical informatics, clinical pharmacology, and health economics. It is intended to be of interest and value to all clinicians who practice in the institutional setting and prescribe or evaluate antimicrobials. In addition, policy makers and administrators within these institutions will find this book a valuable resource for understanding the crucial interactions of these disciplines, which should help them foster the appropriate development, implementation, and analysis of policies and procedures related to antimicrobial use. While this book is focused on the individual institution, it is hoped that it will encourage the coordination of scientific and practical efforts on regional, national, and global levels that are aimed at the optimal development of current and future antimicrobial strategies.

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Contents

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1

How to Create a Therapeutics Committee That Is Scientifically and Economically Sound

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One of the primary challenges in today's medical environment is to find treatments that provide good clinical outcomes but also satisfy pressures on heath care professionals and hospitals to deliver health care as cost effectively as possible. To

attain this goal, a hospital must have a therapeutics committee that is both scientifically and economically sound. From the combined experience of more than 25 years as both a chairman of a therapeutics committee (R. Quintiliani) and a director of drug informational services (Robert Quercia) at Hartford Hospital, a large tertiary hospital in New England, we discuss ways to accomplish this goal, with particular attention paid to anti-infective agents.

CONFOUNDING PROBLEMS WITH CONTROLLING DRUG COSTS AND BEST DRUG SELECTION OWING TO PHYSICIAN BEHAVIOR

Unfortunately, physicians often view hospital pharmacies as "candy shops" where everything should be available regardless of its cost and without any restriction as to drug availability. Paradoxically, most physicians in their office practice have become compliant with drug limitations mandated by health maintenance organizations (HMOs) but have much greater trouble accepting this approach regarding their hospitalized patients. Often an adversarial relationship develops between physicians and hospitals that interferes with making cost-effective choices, because the physicians lack sympathy or concern for the economic problems of the hospital. Clinicians are beginning to understand that a hospital that constantly loses money will soon be replaced by a more cost-conscious hospital with even harsher restrictions, or be eliminated altogether.

Once a drug goes off patent, small generic companies typically produce the drug at a much lower cost. Traditionally, physicians have a fear of "generic" products, with concerns about the reliability of their bioavailability and quality control issues in general. This is unfortunate because the Food and Drug Administration (FDA) now scrutinizes generic companies as intensely as it does any major pharmaceutical company. Pharmacy departments, without the approval of any committee in the hospital, including the therapeutics committee, should be allowed to make an automatic substitution of a

brand-name drug with a generic equivalent, with the exception of sustained-released medications.

Another disturbing issue is how rapidly clinicians become "obsolete" because they do not keep up with the medical literature and because of infrequent attendance at medical education sessions such as grand rounds and state and national meetings. Because of this obsolescence, clinicians often become easy prey for pharmaceutical representatives, who may provide information that may be overly biased for their product. This problem is now being remedied in many states by requiring physician attendance at a certain number of continuing medical education sessions to maintain medical licensure.

Clinicians are prone to make judgments on anecdotal observations and testimonials rather than from evidence-based medicine. In our therapeutics committee, we try hard to avoid use of any anecdotal or testimonial comments in decision making regarding whether a drug should be added or deleted from the formulary. Once this type of nonquantifiable information is permitted, the entire integrity and effectiveness of the committee is destroyed

Unwillingness to change old prescribing habits has been another dilemma for therapeutics committees. For decades, physicians have adopted the simplistic dosing method often suggested in antibiotic package inserts, i.e., all you have to know is to give a low, moderate, or high dosage of an antibiotic, depending on the severity of the infection. Another mistake is the belief that injectable antibiotics are always more potent than their oral formulations. Dosing in this fashion often results in suboptimal clinical outcomes, increased drug toxicity, and higher costs. The return of dosing beta-lactams by continuous infusion (1), the novel once-daily dosing of aminoglycosides (2), and the growing popularity using oral antibiotics (3) in serious infections are classic examples of using recent pharmacodynamic observations (4, 5) to optimize the best clinical responses and to minimize the emergence of bacterial resistance, toxicity, and increased costs.

To many clinicians, these new dosing methods run such a "collision course" with old dosing methods that they will not accept any changes. To deal with this problem, many hospitals,

including ours, have adopted an automatic conversion policy whereby pharmacists are authorized to change dosing methods if there is adequate scientific information to make these conversions and the policy has been approved by the hospital's therapeutics committee and the medical executive committee of the staff. Educational efforts, such as newsletters distributed to the medical staff, are important and serve a beneficial purpose but by themselves are inadequate. For example, we permit our pharmacists to convert an order for intermittent dosing of gentamicin or tobramycin to once-daily dosing—except for some unusual situations, such as endocarditis—and to switch patients from intravenous to oral therapy for antibiotics with over 90% bioavailability, as long as the patient meets the criteria for transitional therapy, which will be elaborated on later.

CONFOUNDING PROBLEMS CONTROLLING DRUG COSTS AND BEST DRUG SELECTION OWING TO PHARMACEUTICAL COMPANY ACTIVITIES

Influencing physician choices can be accomplished by approaches that are disguised as educational support. Probably one of the most inappropriate ways is for a company to provide a large "educational" grant to a member or a department of the hospital. These grants typically have nothing to do with education or research projects that warrant grant support. These "educational" grants become subtle ways to maintain support for their product by creating a close alliance, typically with members of the staff who are on the therapeutics committee. These uncontrolled grants should really be viewed as bribes and not allowed. These educational grants from drug companies should not be accepted unless the funds are given to a general fund available to anyone in the hospital or are used to defray overall hospital operational expenses.

Use of drug samples is another method to undermine a therapeutic committee's decision and becomes a way to "seed" a drug. Sampling should not be allowed unless the drugs are given for specific indications approved by the therapeutics

committee. Moreover, there is the potential for serious medicolegal problems for the hospital because the pharmacy is required by law to maintain precise records on samples given to patients in case of a major adverse reaction to the drug. Maintaining records and ensuring compliance to the sampling policy creates considerable labor costs for the pharmacy.

Information presented at national and international meetings sponsored by drug companies should be viewed with great skepticism. Only information from these meetings that has been published in peer review journals should be used in comparing and evaluating agents. It should be underscored that of every three abstracts presented at these meetings, only one ever gets published. Unfortunately, pharmaceutical companies often use these types of meetings to popularize a drug for a non-FDA indication, to avoid the major expense of performing a properly scientifically designed study.

Likewise, information presented at drug company–sponsored grand rounds, focus group meetings, continuing education programs at resorts, and dinner meetings should be carefully scrutinized. These presentations can be a valuable source of information as long as the speaker is a highly recognized authority on the subject matter and provides published references for the information given during the presentation.

These unethical approaches to marketing drugs for non-FDA indications have most recently been a primary tactic used by some pharmaceutical companies. It predicted this method of marketing will be deterred by ongoing investigations of these practices by the federal government and new legislation.

Similar to speakers, pharmaceutical representatives may vary tremendously in their knowledge and integrity. It is typical today for representatives from major pharmaceutical companies to attend in-depth training sessions about their products for months. Many are well informed about their products and can provide valuable, accurate information but seldom provide the downside of their products. Moreover, their information about a competitor's product may be meager. To remedy this situation, one should try to integrate the information provided about a product from competing companies, and then match these comments with data obtained from scientifically

designed studies. Unless the therapeutics committee can review so-called data on file from a pharmaceutical company, any information of this type should not be used in determining the merits of a particular drug.

Another important caution of pharmaceutical representatives is their behavior in promoting drugs within the hospital. There needs to be formal policies sanctioned by the therapeutics committee that define promotional practices within the institution. These policies should be designed so that the pharmaceutical representatives' practices are not disruptive to the medical staff or contradictory to the policies and protocols approved by the therapeutics committee. Representatives can promote formulary drugs only according to the protocols or recommendations of the therapeutics committee.

We have a policy that states pharmaceutical representatives are not allowed to meet with physicians, nurses, or pharmacists in patient care areas, and can only meet with them by a prearranged appointment in a non–patient care area. Once business has been completed, the representative must proceed directly to a public hospital area (e.g., main lobby). In addition, in-servicing of nonformulary drugs on the hospital campus is prohibited.

To further control and monitor pharmaceutical representatives' activities, we have created a special committee composed of a hospital pharmacist and pharmaceutical representatives to investigate and punish those representatives who violate the policies mentioned above. In the case of a representative who is judged as having behavior inconsistent with these policies, the punishment usually involves banishment from the hospital facilities for 6 to 12 months. The members from industry on this committee are rotated on an annual basis.

Direct-to-consumer advertising policy by industry has also indirectly become a problem for therapeutics committees. These advertisements often encourage consumers to demand pricey drugs over cheaper ones that work just as well. The clinicians on the hospital staff then often make similar demands to the therapeutics committee to add the more expensive agents to the formulary. The percentage of industry

spending on direct-to-consumer advertising has increased dramatically in the past 10 years. A review of this activity in 2002 by Competitive Media Reporting showed that about 60% of a company's spending on a drug may come from this form of advertising. The major classes of drugs that use this form of advertisement include, in decreasing order, anti-inflammatories, antihistamines, antihyperlipidemics, antiasthmatics, antiulcer drugs, antidepressants, erectile dysfunction drugs, weight loss drugs, oral contraceptives, genital herpes drugs, toenail fungus agents, and hormones. It is interesting that direct-to-consumer advertisement remains relatively low for antimicrobials.

IMPORTANCE OF THE COMPOSITION AND BACKGROUND OF THERAPEUTICS COMMITTEE MEMBERS

The chairperson of the therapeutics committee should be a physician who is economically independent of referrals from other physicians; hence, that person usually is a full-time hospital salaried employee. Unfortunately, chairpersons of many therapeutics committees, especially in small hospitals, often come from private practice, where they earn much, if not their entire income from referrals. This creates a practical dilemma for the chairperson, who is often reluctant to deny a request for a formulary addition, particularly from a colleague who is a major source of referrals.

The membership on the committee should be very broad based and should have representation from all areas of the hospital that have any involvement with drug usage, distribution, or purchase. For instance, at our hospital, we have representation from all medical and surgical departments and their divisions, nursing, nutritional services, pharmacy, research, risk management, emergency department, outpatient department, house staff, administration, drug informational services, clinical pharmacists, and even individuals from outside HMOs. It is unusual to have representatives from HMOs, but we have found that their presence on the committee often in-

fluences their formulary choices, resulting in a greater chance for similar formularies. This similarity usually creates more "seamless" care for the patient leaving the hospital for the community setting.

All members should sign a letter indicating whether they have any conflicts of interest, such as financial involvement with a pharmaceutical company as a paid consultant, major stockholder, recipient of large research grants, or member of speakers' bureaus. If a member has a conflict of interest of this type, that person should not be allowed to vote on the approval or disapproval of any of those companies' products. If a member is commonly absent for the meetings, that person should be replaced.

Except for unusual circumstances, the person requesting the addition of a drug to the formulary should not be present at the therapeutics committee meeting, especially if that person is highly influential. This person's presence may indirectly sway decisions owing to a tendency for members not to anger this person. On rare occasions, having such a person attend makes sense, but no vote should be made in his/her presence.

ESTABLISHMENT OF PRIORITIES BY THE THERAPEUTICS COMMITTEE

A common mistake of therapeutics committees is to spend an inordinate amount of time on drugs that are relatively inexpensive or nontoxic and devote minimal effort in controlling the expensive or toxic agents. Considerable attention should be directed at agents that create a major impact on the pharmacy budget. What is considered "major" will vary with the size of the hospital and the complexity of its services. At our tertiary hospital, any drug that requires more than $100,000 in expenditures is deemed worthy of special attention, to limit its inappropriate use. Special attention usually means the creation of a protocol for its usage along with a drug utilization review, which will be discussed later. Often drugs of this type may be given in an appropriate clinical situation but at the wrong dose, dosing interval, or mode of administration.

At our hospital, where many total knee and hip replacements are performed, about $200,000 was being spent annually on the use of tobramycin powder as a prophylactic agent impregnated in the bone cement. There were two reasons for this large expenditure: one was the large acquisition cost for aminoglycoside powder now that gentamicin powder is no longer available; the other was its use in primary implant procedures in which there were no evidence-based data for its use in this situation. After an extensive review of the literature and discussions with other large academic orthopedic departments, it became apparent that the use of tobramycin powder was inappropriate in primary joint replacements. The only possible acceptable situation for the use of the powder was in secondary or revision procedures. Through meeting with our orthopedic department, we were able to convince them to adhere to these restrictions. Because only 8% of the orthopedic joint replacement at our hospital was for revisions, we immediately recognized $160,000 in savings.

It is important in deciding on the merits of a drug to avoid nonpharmacological issues that do not pertain to the responsibilities of the therapeutics committee. These could include items such as decisions made on the agent from nearby competitive hospitals' therapeutics committees, effects on referral patterns, and nursing time. These are issues that should be addressed by other committees in the hospital. It is crucial that therapeutics committees stay within their "therapeutic box." For instance, if the nursing department is displeased with the addition of a drug to the formulary because it creates more labor time for them, then that issue should be discussed by the nursing department with their administrator and the medical executive committee of the hospital. To maintain an efficient therapeutics committee, issues that cannot be resolved there should not be addressed there.

In highly controversial decisions made by the therapeutics committee, it often makes sense for the chairperson, as well as the director of pharmacy services, to attend the medical executive committee meeting to defend the decision and to respond to any questions or comments.

Because the medical executive committee of the staff must approve all decisions made by the therapeutics committee, this final approval may often be delayed for an excessive time period, resulting in prolonged delays before the actual implementation of an important cost-containing recommendation. To resolve this problem, we have developed a "fast-track" system whereby selective decisions of our therapeutics committee that may translate into major economic savings or the avoidance of serious adverse reactions are given priority at the next meeting of the executive committee.

Another important approach to maintain a well-managed and efficient therapeutics committee is not to review again a drug that was rejected for formulary addition unless acquisition cost has significantly decreased or some very unusual new favorable findings were published pertaining to this agent.

The creation of extremely expensive drugs from new technology has resulted in a huge increase in acquisition costs for pharmacies. Classic examples of this situation are drugs such as drotrecogin alfa (Xigris) and liposomal formulations. For these types of agents, it is crucial to establish a protocol that has to be followed by all physicians and can be monitored with respect to physician compliance to the protocol. Restricting the ordering of these drugs to a selected specialist(s) has been used by many hospitals; however, this policy may not only be ineffective, it also may worsen the economic situation, particularly if the designated specialist(s) uses this power to indirectly increase his/her consultation services. The answer to controlling the expenses of these extremely pricey drugs is to create protocols accompanied by drug utilization evaluations, which will be discussed later.

THE ROLE OF THE DRUG INFORMATION PHARMACISTS IN THE REVIEW OF DRUGS FOR THE HOSPITAL FORMULARY

The primary objective for the drug information pharmacist is to review drugs for formulary addition or deletion based on safety, efficacy, and cost that makes scientific sense. Informa-

tion about an agent for possible addition to or deletion from the formulary should be compared with existing agents in the same drug class. The data for this review should come as much as possible from literature published in peer review journals. Moreover, the data are best when they are quantifiable and subject to statistical analysis. In some instances, further evaluation may require consultation with outside agencies (e.g., FDA) and recognized authorities from other medical institutions pertaining to the agent in question. In drug class reviews, we routinely obtain input and consensus from the appropriate medical or surgical department prior to presentation to the therapeutics committee.

The efficacy data are based almost exclusively on the drug's pharmacokinetic, pharmacodynamic, and safety properties, as well as on clinical outcomes. In comparing two closely similar agents for addition to the formulary, one should avoid making a choice exclusively on acquisition costs, often referred to as a *minimalization analysis*. To do this, both agents should be "mirror images" of each other.

After safety and efficacy are determined, it is important for the pharmacist to provide a comparative financial analysis that is reflective of the institution's cost and reimbursement policies in order to properly integrate cost with the safety and efficacy data in the final evaluation for presentation to the therapeutics committee. Many times, pharmaceutical companies will provide elaborate cost comparative analysis, but in most instances, the data are not reflective of your institution. The drug information pharmacist should seek the assistance of the finance department in analyzing complex reimbursement issues.

Sometimes expensive drugs that have excellent reimbursement by insurance companies or the government may actually create a net profit for the hospital because the reimbursement for the drug may exceed the acquisition cost. This has been a common observation with a number of drugs to treat AIDS and patients on hemodialysis. To determine the economic impact on a hospital's overall budget of bringing a drug onto the formulary, one must always compare revenue versus acquisition cost whenever possible.

It has been our policy that the drug information pharmacist must first evaluate all drugs submitted for formulary addition for a minimum of two weeks before its placement on the agenda of the therapeutics committee. If this review suggests that an agent should not be added to the hospital drug formulary, it has been our practice to have either the drug information pharmacist or the chairman of the therapeutics committee contact the requesting physician before the meeting as to the reasons for the negative review. This approach has been beneficial in our relationship with physicians because it allows them the opportunity to respond before the meeting. The physician is often unaware of the drawbacks to the requested drug and often will withdraw his/her request upon hearing this information. Occasionally the physician will provide us with very important information that we failed to uncover in our review.

After completion of all drug reviews for the agenda, it is very important for the drug information pharmacist to present the results of the reviews to the chairman of the therapeutics committee before the actual meeting so he/she will be prepared to explain the basis for the recommendations from the drug information pharmacist. In brief, the drug information pharmacist behaves as a consultant to the therapeutics committee and especially to its chairperson. As any other good consultant, it is always best to be "on tap," but not "on top."

THE IMPORTANCE OF DRUG USE EVALUATIONS AND PROTOCOLS IN CONTROLLING THE USE OF EXPENSIVE AND/OR POTENTIALLY TOXIC AGENTS

Protocols provide for rational care and result in the best clinical outcomes, lower toxicity, and lower costs. Moreover, they often protect the prescribing physician from malpractice suits because the drug is being used according to acceptable standards. Protocols also create a measurable way to check on physician adherence to the appropriate use of drugs. Because of the importance of the information given in protocols, they

should be developed by persons most knowledgeable with the use of the drug and, if possible, should coincide with recommendations given by nationally recognized academic groups (e.g., Infectious Disease Society, Centers for Disease Control, American Thoracic Society).

Enforcement of protocols is essential. Protocols that are not part of a drug use evaluation (DUE) are more prone to noncompliance, especially when there are staffing deficiencies within the clinical section of the department of pharmacy services. Although a protocol drug should not be dispensed by the pharmacy until all protocol criteria have been met, it is often difficult to enforce when clinical pharmacists are not available and/or not assigned to monitor compliance to the protocol.

The establishment of a DUE protocol is preferable to the establishment of a non-DUE protocol because the criteria in a DUE protocol are usually tracked on a prospective or concurrent basis. At our hospital, noncompliant physicians who arbitrarily and consistently ignore DUE protocol criteria are reported to the therapeutics committee on a monthly basis. The chairperson of the therapeutics committee then sends a formal letter to that physician's department chief requesting him/her to take action on the noncompliance of the prescriber and to report back to the chairperson that appropriate action has been taken. This action is also documented with a letter placed into the physician's file. If the physician continues to be noncompliant, he/she is requested to explain his/her activities to the medical executive committee of the staff and faces potential loss of staff privileges. This quality assurance process for DUEs provides for enhanced compliance to therapeutics committee–approved protocols. In addition, the performing of DUEs meets a requirement of the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO).

In a closely similar fashion, by the use of a "one-time-use" form, we maintain a tightly controlled formulary and do not allow physicians to carelessly use nonformulary drugs when there are appropriate and less expensive alternatives. At our hospital, the physician must complete this one-time-use form describing the reasons for requesting a nonformulary drug. The pharmacists must document that formulary alternatives

were suggested to the physician and make a clinical decision as to whether there is agreement or disagreement with the physician's request. Although we do not hold up medical therapy, if there is disagreement between the physician and the pharmacist, our drug information services and the therapeutics committee, on a monthly basis, review all the one-time-use requests for appropriateness. If the therapeutics committee deems the nonformulary request to be inappropriate, a formal letter is sent from the chairperson of the therapeutics committee to the prescribing physician and copied to his/her department chief indicating the therapeutics committee's reasons for this view and stressing that this practice should not occur again. This practice at our hospital has significantly curtailed the inappropriate use of nonformulary agents.

It must be stressed that protocols are not guidelines. Unfortunately, guidelines, as the word implies, are only suggestions as to how a drug should be used, resulting in too many arbitrary choices by clinicians and the false sense that the hospital is actually controlling drug usage.

THE PHARMACY DEPARTMENT'S ROLE IN THE CREATION OF A THERAPEUTICS COMMITTEE THAT IS SCIENTIFICALLY AND ECONOMICALLY SOUND

Pharmacy services should be integrated in a major way with the activities of the therapeutics committee and the hospital's responsibility to patient care and safety. In addition to the role of the drug information pharmacist discussed above, the following constitutes some of the other major responsibilities of other members of the pharmacy department in ensuring proper drug usage:

- Chair DUE subcommittee of the therapeutics committee and ensure development and implementation of DUE programs.
- Correct improper dosing before the patient actually receives the agent.

- Be allowed to automatically replace intravenous antibiotics with oral agents that have high bioavailability (e.g., greater than 90%) in a clinically stable patient who can ingest and digest a medication. These interchanges are ones that have been approved by the therapeutics committee and the medical executive committee of the staff.
- Alert clinicians to possible adverse reactions and interactions of prescribed drugs.
- Ensure that the physician for nonformulary medications properly completes one-time-use request forms.
- Replace expensive drugs with less expensive, therapeutically equivalent agents that have been established by the therapeutics committee.
- Monitor compliance with protocols for selective drugs and report to the therapeutics committee clinicians who consistently ignore them.
- Make rounds with house staff, particularly in intensive care units, serving as a consultant on drug dosing and interactions.
- Distribute monthly information, usually in the form of a newsletter to all members of the staff, on drugs that have been added or withdrawn from the formulary.

Of all the activities mentioned above, the most effective ones have been those that have involved automatic conversions, particularly the replacement of intravenous with oral agents or so-called transitional or switch therapy (6, 7). Unfortunately, often clinicians feel threatened by empowering pharmacists to change their orders, usually from a concern that the pharmacist is usurping the role of the physician. This is obviously not the case, because it is the clinician who initially establishes the choice of therapy; all the pharmacist is doing is customizing therapy according to appropriate pharmacokinetic and pharmacoeconomic reasons. If transition programs are left entirely up to physicians, they rarely occur at all or occur too late to reap the economic gains (less drug acquisition and supply costs, less nursing and pharmacy labor costs) or

the avoidance of intravenous line sepsis, the leading cause of nosocomial bacteremia or fungemia.

Physicians are often reluctant to change to an oral drug for two major reasons. The first one is that they view "injectables" as more "potent" than oral therapy. It is true that the modest bioavailability, i.e., less than 50%, of some oral antibiotics may be a legitimate reason not to use such agents; however, for drugs with 90% or greater bioavailability, this concern makes little, if any, sense. In fact, we now have a number of antimicrobial agents that meet this criterion, including levofloxacin, gatifloxacin, moxifloxacin, doxycycline, minocycline, trimethoprim/sulfamethoxazole, clindamycin, cephalexin, cefadroxil, cefprozil, ceftibuten, linezolid, rifampin, fluconazole, metronidazole, and voriconazole. It may sound cynical, but we like to remind clinicians that organisms have no idea whether the drug was given intravenously, intramuscularly, or orally, or whether it was given within or outside a hospital!

The second major reason for the poor acceptance of transitional therapy by clinicians relates to the pressures placed on them by some utilization review committees and insurance companies to discharge their patient once the patient has been changed to an oral antibiotic. Pressuring physicians to discharge patients once they are on oral therapy should no longer be done, for often there are many other reasons a particular patient should remain hospitalized. This behavior of utilization review committees and insurance companies has really backfired because the clinicians' response has been merely to leave the intravenous line in place, resulting in a marked increase in the chances for line sepsis, which in turn, causes an appreciable increase in cost, morbidity, and mortality. It is well known that the likelihood of line sepsis increases precipitously in patients in whom the line has stayed in place beyond 4 days. Because of these confounding problems, we have used our pharmacist as a major way to develop a highly effective proactive transitional program, with most conversions to oral therapy occurring within 2 to 3 days.

Successful transitional antibiotic programs require physician acceptance. Indeed, all clinicians within an institution must trust that transition programs will not only be safe and

effective for patients but also provide benefits for the institution. One way to enhance acceptance is to make it clear that even though transitional therapy is appropriate in most cases, it is not expected to be used in all patients. In other words, transition therapy program changes are not intended to supersede clinical judgment.

Some practical steps that we have found to optimize cooperation and support from clinicians include the following:

- Review and present literature demonstrating the benefit of transition therapy.
- Conduct educational sessions to review the goals of the program and practical issues in implementation. Stress that the program addresses not only the financial concerns of the hospital but also the health of the patient, offering the possibility of earlier discharge and a reduced potential for hospitalization-related complications, such as line sepsis.
- Create user-friendly tools to assist in clinical decision making; these may include computer programs for screening and monitoring or simple algorithms with criteria for transition therapy and/or discharge.
- Create an infrastructure for implementing the program with components that include a system for tracking both clinical and economic outcomes.
- Strive to communicate successful results among clinical colleagues and enhance overall confidence in the process through newsletters and in-services.
- Allocate a budget for staffing and support. Consider that the overall savings will be greater than additional costs for support services and staff.
- Empower pharmacy to make automatic conversions based on criteria established by the therapeutics committee and approved by the medical executive committee of the staff.

CONCLUSIONS

Owing to the many confounding problems facing therapeutics committees, it has become extremely difficult to develop a com-

mittee that is both economically and scientifically sound. Most of these confounding problems come from the pressures of nonscientific, immeasurable variables, such as anecdotal observations, testimonials, and unreliable and unpublished data from meetings, abstracts, and non–peer reviewed journals. Quantifiable data are always the best because they are subject to statistical analysis. In fact, many curmudgeons feel if you cannot measure it, it is not worth addressing and until data are published in highly peer-reviewed scientific journals, there are no data! Strong integration of the activities of the therapeutics committee with pharmacy services has become crucial for the creation of a therapeutics committee that is both economically and scientifically sound and is the reason the term *therapeutics committee* is often replaced in hospitals by the name *pharmacy and therapeutics committee.*

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The *Public Health Action Plan to Combat Antimicrobial Resistance* and the Prevention of Antimicrobial Resistance in Health Care Settings

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THE *PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE*

Antimicrobial resistance (AR) will always be with us. The challenge before us is to transform this increasingly urgent threat into a manageable problem. Over the past 10 years, the Institute of Medicine (1,2), the American Society for Microbiology (3), the World Health Organization (4,5), the Congressional

Office of Technology Assessment (6), the General Accounting Office (7,8), and other panels of distinguished experts have provided recommendations and options for government action to address the dangers posed by AR. The experts agree that we need to improve surveillance for emerging AR problems, to prolong the useful life of antimicrobial drugs, to develop new drugs, and to improve vaccine, diagnostic, and infection control measures to prevent and control AR.

Despite the urgency of the problem, the achievement of these goals has not been simple or straightforward, and accomplishments to date have been modest. Monitoring, preventing, and controlling AR requires sustained effort, commitment, and collaboration among many groups in the public and private sectors, and the involvement of the general public. Support and leadership are required from the federal government, combined with a willingness to address complex and sometimes controversial scientific, medical, and economic issues.

To provide a blueprint for federal actions to address the emerging threat of AR, the *Public Health Action Plan to Combat Antimicrobial Resistance* was developed by the Federal Interagency Task Force on AR and released in January 2001 (http://www.cdc.gov/drugresistance/actionplan/index.htm) (9). The task force was formed in 1999 because federal government experts in infectious diseases and AR understood that to adequately address the multifaceted problem of AR, cooperative action by multiple agencies and departments would be required. Co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), the task force also includes the Agency for Healthcare Research and Quality (AHRQ), the Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense (DOD), the Department of Veterans Affairs (VA), the Environmental Protection Agency (EPA), and, since 2001, the U.S. Agency for International Development (USAID). Encouraging the creation of the task force were a forum and a hearing on AR that were held by the U.S. Senate

committees in 1999 and 2000, respectively, chaired by Senators Bill Frist (R-Tenn.) and Edward Kennedy (D-Mass.).

The plan was developed based on input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. The plan has been and will continue to be implemented incrementally, in collaboration with these and other partners, as resources become available. The plan has four focus areas: surveillance, prevention and control, research, and product development. Of eighty-four action items, thirteen are designated top priority (Box 1). Activities have been launched or completed for the thirteen top priority items as well as most of the other action items. The task force continues to meet to monitor implementation of the plan, releases annual progress reports, and seeks comment at public meetings (http://www.cdc.gov/drugresistance/actionplan/2003report/index.htm). This chapter focuses on issues and activities that are relevant to surveillance and prevention and control of AR in the community and health care settings.

Surveillance

In the United States, disease reporting is under state jurisdiction, but most states do not require reporting of drug susceptibility information, and the completeness of reporting varies. In collaboration with state health departments and other partners, CDC monitors resistance for several pathogens of public health importance and collects limited data on antimicrobial drug prescribing. For example, resistance in invasive *Streptococcus pneumoniae* infections is monitored on a population basis in nine states or portions thereof (with two additional states planning similar surveillance) through the Emerging Infections Program (EIP); similarly, health care–associated infections (e.g., *Staphylococcus aureus*, enterococci, gram-negative bacteria) are monitored in approximately 300 hospitals, and food-borne pathogens such as *Salmonella* are monitored in fifty states in a joint project that also involves FDA and USDA. In this project, resistance in food-borne pathogens

Box 1 Top Priority Action Items to Combat Antimicrobial Resistance (All thirteen items have top priority, regardless of their order in the list)

Surveillance

With partners, design and implement a national antimicrobial resistance (AR) surveillance plan that defines national, regional, state, and local surveillance activities and the roles of clinical, reference, public health, and veterinary laboratories. The plan should be consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed. (Action Item #2)

Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, agriculture, veterinary medicine, and consumer products. (Action Item #5)

Prevention and control

Conduct a public health education campaign to promote appropriate antimicrobial use as a national health priority. (Action Item #25)

In collaboration with many partners, develop and facilitate the implementation of educational and behavioral interventions that will assist clinicians in appropriate antimicrobial prescribing. (Action Item #26)

Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for health care and extended care settings and in the community. Promote adherence to practices proven to be effective. (Action Item #39)

In consultation with stakeholders, refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs. (Action Item #58)

Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote appropriate drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied routinely and most cost-effectively on a large scale. (Action Item #63)

Research

Provide the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens. (Action Item #70)

Box 1 *Continued*

Research (*Con't*)
In consultation with academia and the private sector, identify and conduct human clinical studies addressing AR issues of public health significance that are unlikely to be studied in the private sector (e.g., novel therapies, new treatment regimens, and other products and practices). (Action Item #75)
Identify, develop, test, and evaluate new rapid diagnostic methods for human and veterinary uses with partners, including academia and the private sector. Such methods should be accurate, affordable, and easily implemented in routine clinical settings (e.g., tests for resistance genes, point-of-care diagnostics for patients with respiratory infections and syndromes, and diagnostics for drug resistance in microbial pathogens, including in nonculture specimens). (Action Item #76)
Encourage basic and clinical research in support of the development and appropriate use of vaccines in human and veterinary medicine in partnership with academia and the private sector. (Action Item #77)
Product development
Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs in human and animal medicine for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines and other biologics, anti-infective medical devices, and disinfectants). (Action Item #79)
Identify ways (e.g., financial and/or other incentives or investments) to promote the development and/or appropriate use of priority AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate. (Action Item #80)

and commensal organisms is also monitored in animals (and, beginning in 2001, in retail meat products). For the past 10 years, the United States has had a national tuberculosis (TB) surveillance system that includes susceptibility data. The TB surveillance system collects information on drug susceptibility testing (initial and final results), initial drug regimen, and date therapy started and date therapy stopped for culture-positive patients. This information allows monitoring of the epidemiology of drug resistance so that appropriate interventions can be implemented. For example, information on the

initial drug regimen prescribed coupled with information on initial drug susceptibility results allows a judgment about the adequacy of therapy and corrective action on individual cases by public health officials and health care providers if the regimen is judged to be inadequate or suboptimal.

For most other infections in most communities, a similar system that provides patient specific data is not needed to help develop and evaluate national prevention and control strategies. However, awareness of the extent to which resistance is present locally is important to guide treatment decisions and to generate support for local public health interventions such as appropriate drug use and vaccine campaigns. To implement the action plan, CDC seeks to support coordinated national surveillance of drug resistance and use at two levels. One involves surveillance that can be done by most states, communities, and health care systems to meet their local needs; the second consists of more specialized projects to monitor emerging problems and addresses in more detail specific national needs.

At a meeting held at CDC among state health department personnel and other experts in surveillance, there was consensus that statistically sound methods of data collection that capture valid, meaningful, and useful data must also meet the financial restrictions of state budgets (10). Active, population-based surveillance for collecting relevant isolates is considered the gold standard. Unfortunately, this type of surveillance is labor intensive and costly, making it an impractical choice for many states. The challenges of isolate collection, packaging and transport, data collection, and analysis may place an unacceptable workload on laboratory and epidemiology personnel.

Several state health departments have elected to implement enhanced antimicrobial drug-resistance surveillance programs using alternative surveillance methods. Two methods frequently used by states are sentinel (i.e., survey of subset of laboratories) and antibiogram (i.e., cumulative susceptibility data) surveillance. Common difficulties have been identified with implementing sentinel systems. Those difficulties include logistical obstacles with isolate or data processing and communication breakdowns between laboratory, epidemiol-

ogy, and hospital infection control personnel. Care must be taken in selecting the numbers and types of laboratories to participate in a sentinel network. States collecting antibiograms from hospitals and state laboratories may also face challenges, including incompatible formatting of drug-testing panels, the inconsistent inclusion of duplicate or repeat isolates, and inconsistent reporting of denominator data. Solutions to these problems commonly involve improving communication between clinical microbiology laboratories and state health departments, including laboratory input in decision making and providing feedback of data from the system to participants. Guidance for aggregating cumulative susceptibility data (i.e., antibiograms) has been published and may serve as a guide for states and clinical microbiology laboratories in conducting surveillance (11). Another aspect of surveillance focuses on detecting rare events. Such events may include new changes in susceptibility, new mechanisms of resistance, susceptibility of unusual pathogens, and unexpected sources of resistant organisms. Establishing good communication among personnel in health departments and clinical laboratories is important for improving detection and reporting of such events. Allocating resources for improved surveillance is a practical and responsive step for states interested in tracking local resistant trends. Local data are important for raising public awareness, establishing resources and prevention activities, developing and informing treatment guidelines, monitoring trends, and motivating behavior change among clinicians.

At nine CDC EIP sites, surveillance is conducted for invasive bacterial diseases due to pathogens of public health importance through a project called Active Bacterial Core Surveillance (ABCs). For each case of invasive disease in the study population, a case report with basic demographic information is filed and, in most cases, the isolates (which have been cultured from a sample obtained from a normally sterile site such as blood or cerebral spinal fluid) from patients are sent to CDC for laboratory study. For *S. pneumoniae*, objectives are to track AR in pneumococcal isolates, to evaluate the impact of new pneumococcal conjugate vaccines for infants on disease burden, and

to evaluate prevention among the elderly through pneumococcal polysaccharide vaccine use. Other infections under surveillance in this system include group A streptococcus, group B streptococcus, *Haemophilus influenzae*, and *Neisseria meningitidis*. Case finding is active and laboratory based. Because isolation of one of these organisms from a normally sterile site is essential to the case definition, the microbiology laboratories in acute care hospitals and appropriate reference laboratories processing sterile site specimens for residents of the surveillance area are the sources for case identification. Data that are essential for describing the population-based epidemiology of these diseases (e.g., age, residence within the surveillance area, outcome) are not available in many microbiology laboratories. Therefore, the case identification is complemented by additional data collection to complete a standard case report form. ABCs can be utilized to conduct surveillance for emerging infections, as is the case with community-associated methicillin-resistant *S. aureus* (CA-MRSA). Population-based surveillance for MRSA will be conducted in eight ABCs sites starting in 2004. Cases in these areas, with MRSA isolated from a normally sterile site, will be followed up by the health department or its public health partners, to measure the incidence and prevalence of MRSA in the population, characterize risk factors for infection, and describe the molecular epidemiologic patterns and microbiologic characteristics of health care–associated or CA-MRSA. Other population-based data on drug resistance include MRSA carriage in the community through the National Nutrition and Health Examination Survey (NHANES; http://www.cdc.gov/nchs/nhanes.htm) conducted by the National Center for Health Statistics. In NHANES, beginning in 2001, all participants 1 year of age or older were examined for nasal carriage of *S. aureus* and isolates underwent antibiotic susceptibility testing (AST). In addition, demographic and epidemiologic data were collected from participants and a selection of their households.

CDC is developing The National Healthcare Safety Network (NHSN), an Internet-based nationwide network that will monitor trends in adverse events associated with invasive devices, procedures, and medications used in the delivery of

health care. Existing surveillance systems, including the National Nosocomial Infections System, the Dialysis Surveillance Network, and the National Surveillance System for Healthcare Workers will be a part of NHSN. In addition, under the NHSN's medication-associated Adverse Event Module, initial focus will be on use of and resistance to antimicrobial agents and on establishing electronic reporting of antimicrobial use and resistance data to increase efficiency, timeliness, and accuracy of the monitoring effort. When implemented, the NHSN will significantly enhance the ability to monitor and track trends of usage and resistance of microbes to antimicrobial agents in a variety of health care delivery settings. These data can then be used to enhance patient safety by enabling health care workers to develop and deploy strategies to prevent overuse and inappropriate use of these agents, as well as strategies to prevent other pathogens from becoming resistant.

CDC-supported projects monitor drug resistance for several other pathogens or infections, e.g., gonorrhea, influenza, *Helicobacter pylori*, HIV, and malaria.

Reliable surveillance information, as well as patient care and safety, depends on the accurate detection of drug resistance by clinical laboratories. New antimicrobial agents and new resistance patterns pose a challenge to clinical laboratories because testing methods vary with organism/antimicrobial agent combinations. NCCLS standards outline recommended procedures for AST but are difficult for some laboratories to interpret. To improve AST in clinical laboratories, CDC is working with partners such as the Association of Public Health Laboratories and the American Society for Microbiology to develop training and proficiency testing programs. In 2001, the Multilevel Antimicrobial Susceptibility Testing Educational Resource (MASTER) program was introduced on a website that includes discussions of difficult cases in diagnostic microbiology, recommendations and references, and opportunities to question CDC microbiologists (www.phppo.cdc.gov/dls/master/default.asp). In its first year of operation, this site received approximately 33,000 hits from twenty countries. The need for constant updating of clinical laboratory proficiency

offers an opportunity for state public health laboratories to provide important leadership and strengthen their linkages with clinical laboratories. Through the National Laboratory Training Network and other programs, CDC's goal is to work with partners to ensure training and proficiency in drug resistance testing and reporting for clinical laboratories in all states and territories. In 2002, CDC produced a CD-ROM that assists laboratories in applying NCCLS standards, demonstrates the modes of action of each group of antimicrobial agents and the mechanisms organisms develop to resist the agents, describes quality control procedures needed to verify accuracy of testing results, and demonstrates specific procedures laboratories must use to detect resistance in different organisms. The CD may be requested at http://www.aphl.org/ast.cfm. More than 8,000 copies of the CD have been distributed throughout the United States and internationally.

Prevention and Control

Prevention and control of drug resistance primarily involves promoting appropriate use of antimicrobial drugs to extend their useful life and preventing infection transmission (e.g., through appropriate infection control and vaccine use). Appropriate antimicrobial drug use is defined as use that maximizes therapeutic impact while minimizing toxicity and the development of resistance. In practice, this means prescribing antimicrobial therapy when, and only when, beneficial to a patient; targeting therapy to the desired pathogens; and using the appropriate drug, dose, and duration. Prevention and control programs do not obviate the need for a constantly flowing "pipeline" of new drugs, as current drugs will inevitably become less effective with time because of resistance. CDC has been working with a variety of partners to promote appropriate antimicrobial use in the community (outpatient prescribing), in health care settings, and in agriculture (12).

For acute infections in outpatients, a major objective is to reduce antimicrobial drug prescribing for illnesses (e.g., viral respiratory infections) for which these drugs offer no benefit.

In 1995, CDC launched a National Campaign for Appropriate Antibiotic Use that involves partnerships with state and local health departments, health care delivery organizations, health care purchasers and insurers, professional societies, consumer groups, and others. Often working through state-based coalitions, these partners implement coordinated educational and behavioral interventions directed to patients and clinicians, including public education programs, prescribing principles, clinical training materials, and aids (e.g., "viral prescription pads") to help clinicians avoid prescribing an antibiotic when not indicated. Data from controlled trials indicate that these interventions may be effective in reducing inappropriate antibiotic prescribing for respiratory infections in the United States, as has been reported in other countries—although resistance rates of respiratory pathogens, having reached a certain level, may not necessarily decline thereafter (13–16). Encouraging data from the National Ambulatory Medical Care Survey indicate that antibiotic prescribing rates for children seen in physician offices declined in the 1990s, after having increased in the late 1980s (17). Initially focused primarily on pediatrics, the campaign was expanded in 2001 to target prescribing for adults (18) and to develop a model medical curriculum and Health Plan Employer Data and Information Set (HEDIS) Performance Measures (benchmarks for health plans) for appropriate prescribing. In 2003, the campaign was renamed Get Smart: Know When Antibiotics Work, concurrent with the launching of a media campaign targeting parents of young children.

Promoting appropriate antimicrobial drug use in agriculture and veterinary medicine has been complicated by long-standing disagreement between public health and agricultural communities regarding the benefits and risks of these uses, which may have economic implications for major industries. The American Veterinary Medical Association has developed principles for judicious therapeutic use of antimicrobials in veterinary medicine with input from CDC and FDA. CDC has also awarded cooperative agreements to four schools of veterinary medicine to assess the impact of antibiotic use in swine and dairy cattle, develop alternatives to the use of antimicrobi-

als as growth promotants, and evaluate new practices to reduce resistant bacteria in food animals. The FDA issued a guidance document titled *Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* in 2003. This guidance document discusses a recommended approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiologic effects on bacteria of human health concern. The guidance document provides an approach drug sponsors can use before seeking approval to estimate the likelihood of risk to humans if a particular antimicrobial product was used to treat food-producing animals. The estimation is made up of three parts: (i) release assessment—determines the probability that bacteria resistant to an antimicrobial would be present in an animal treated with the antimicrobial; (ii) exposure estimate—estimates the probability that humans would ingest the resistant bacteria; and (iii) consequence assessment—assesses the likelihood that human exposure to the resistant bacteria would result in a human health consequence. A human health consequence is defined as a situation in which a physician would have difficulty treating a person with an antimicrobial drug because the bacteria infecting the human had acquired resistance to the drug and that resistance came from use of the drug in animals (19). The FDA's Center for Veterinary Medicine (CVM) has proposed withdrawing approval for use of the fluoroquinolones in poultry. This action was based on CVM's determinations that the use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a pathogen to humans, in poultry; that fluoroquinolone-resistant *Campylobacter* is transferred to humans and is a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans; and that fluoroquinolone-resistant *Campylobacter* infections are a hazard to human health.

Preventing transmission of infections (e.g., through appropriate use of vaccines, infection control in health care, food safety) reduces disease incidence and drug prescribing (20–22). CDC has supported projects to evaluate the impact

of pneumococcal conjugate vaccine in reducing infections with drug-resistant pneumococci, demonstration programs evaluating comprehensive approaches to infection control in health care settings in Chicago and Pittsburgh, and infection prevention and control research and evaluation programs at seven university-based Centers of Excellence in Healthcare Epidemiology. Regional approaches are important, as illustrated by the early recognition and successful control of the spread of vancomycin-resistant enterococci (VRE) in acute and long-term care facilities in the tristate area surrounding Sioux City, Iowa. With leadership from the Sioux City health department and support from the Iowa, South Dakota, and Nebraska state health departments and CDC, health care institutions rigorously implemented surveillance, prevention and control guidelines, and communicated openly with each other. As a result, they were able to eliminate VRE from hospitals and drastically reduce VRE rates in long-term care facilities, an unprecedented success (23).

CAMPAIGN TO PREVENT ANTIMICROBIAL RESISTANCE IN HEALTH CARE SETTINGS

In health care settings, where infection with multidrug-resistant organisms is a major patient safety issue, promoting appropriate antimicrobial drug prescribing is complicated by the higher stakes involved in treating sicker patients and the need to develop partnerships with a greater number of medical and surgical specialties involved in their care, as well as with other clinical staff and administrators. The CDC's Campaign to Prevent Antimicrobial Resistance in Healthcare Settings aims to prevent AR in health care settings by improving clinician practices. The campaign's programs are created in close partnership with professional societies and key opinion leaders in relevant specialties. The program translates published (i.e., peer-reviewed journals) scientific evidence and guidelines into action steps designed to optimize the care of individual patients in the era of widespread AR. The campaign centers on four main strategies: prevent infection, diagnose and treat in-

fection, use antimicrobials wisely, and prevent transmission. Within the context of these strategies, multiple twelve-step programs are being developed targeting clinicians who treat specialty-specific, high-risk patient populations, including hospitalized adults (Box 2), dialysis patients, surgical patients, hospitalized children, and long-term care patients. Educational tools and materials are being developed for each patient population. The communication strategy includes the goals of informing clinicians, patients, and other stakeholders, raising awareness about the escalating problem of AR in health care settings, and motivating interest in and acceptance of interventional programs to prevent resistance. The campaign targets practicing clinicians, patient care partners, health care organizations, purchasers, patients, and the general public. Educational tools are being developed, including web-based didactic learning modules, pocket cards, and slide presentations. CDC is working with many public, professional, and private sector partners to market the twelve steps for each target group and promote their implementation. Educational tools are available with other supporting material on the Internet at http://www.cdc.gov/drugresistance/healthcare.htm.

Papers have been published discussing the principles of the campaign tailored to dialysis and surgical patients (24,25). For the strategy of "Prevent Infection," recommendations for dialysis patients include use of influenza and pneumococcal vaccines, reducing hemodialysis catheter use, using the lowest risk vascular access (i.e., arteriovenous [AV] fistulae in preference to grafts and minimizing use of hemodialysis catheters), and reducing hemodialysis and peritoneal access–related infections through various means, including consistent use of sterile technique, proper catheter procedures, appropriate dressings, and aseptic techniques, all by trained personnel. Among surgical patients, key principles in the strategy include minimizing the use of invasive devices and vaccinating at-risk surgical patients and staff. Guidelines are provided for prevention of catheter-associated urinary tract infections and prevention of health care–associated pneumonia.

For the strategy of "Diagnose and Treat Infection Effectively," physicians taking care of dialysis patients are in-

Box 2 Twelve Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults

Strategy: Prevent Infection

Step 1. Vaccinate
–Give influenza/pneumococcal vaccine to at-risk patients before discharge.
–Get influenza vaccine annually.

Step 2. Get the catheters out
–Use catheters only when essential.
–Use the correct catheter.
–Use proper insertion and catheter-care protocols.
–Remove catheters when no longer essential.

Strategy: Diagnose and Treat Infection Effectively

Step 3. Target the pathogen
–Culture the patient.
–Target empiric therapy to likely pathogens and local antibiogram.
–Target definitive therapy to known pathogens and antimicrobial susceptibility test results.

Step 4. Access the experts
–Consult infectious disease experts for patients with serious infections.

Strategy: Use Antimicrobials Wisely

Step 5. Practice antimicrobial control
–Engage in local antimicrobial control efforts.

Step 6. Use local data
–Know your antibiogram.
–Know your patient population.

Step 7. Treat infection, not contamination
–Use proper antisepsis for blood and other cultures.
–Culture the blood, not the skin or catheter hub.
–Use proper methods to obtain and process all cultures.

Step 8. Treat infection, not colonization
–Treat pneumonia, not the tracheal aspirate.
–Treat bacteremia, not the catheter tip or hub.
–Treat urinary tract infection, not the indwelling catheter.

Step 9. Know when to say no to vanco
–Treat infection, not contaminants or colonization.
–Fever in a patient with an intravenous catheter is not a routine indication for vancomycin.

Box 2 *Continued*

Strategy: Use Antimicrobials Wisely (*Con't*)

Step 10. Stop antimicrobial treatment
–When infection is cured.
–When cultures are negative and infection is unlikely
–When infection is not diagnosed.

Strategy: Prevent transmission

Step 11. Isolate the pathogen
–Use standard infection control precautions.
–Contain infectious body fluids (use approved airborne/droplet/contact isolation precautions).
–When in doubt, consult infection control experts.

Step 12. Break the chain of contagion
–Stay home when you are sick.
–Keep your hands clean.
–Set an example.

structed in the proper collection and interpretation of blood, peritoneal dialysis exit site, tunnel, and dialysate cultures. Among surgical patients, key principles include targeting likely pathogens, using microbiologic data to tailor antimicrobial therapy, accessing the experts (guidance with difficult issues), and provision of surgical representation on committees that determine hospital formularies, guidelines, and other matters related to health care epidemiology and infection control. Most surgeons cannot remain current on all infectious disease issues; therefore, the identification of a medical or surgical colleague for guidance who is an expert in this area is helpful.

"Use Antimicrobials Wisely" is a strategy among dialysis patients that includes general principles of antimicrobial use defined as "the ideal is to have all patients treated with the most effective, least toxic, and least costly antibiotic for the precise duration of time needed to cure or prevent an infection" (26). Recommendations include proper use of vancomycin and alternatives to vancomycin; reducing use in situations in

which it is inappropriate or for which there are alternatives, such as routine surgical prophylaxis; and continued empiric use when there are negative beta-lactam-resistant organisms. For example, antimicrobial prophylaxis should not routinely include vancomycin for placement of AV grafts or fistulae in the absence of serious beta-lactam allergy. Among patients on dialysis, there are issues of dosing and drug choice that must be considered, including inconvenience and expense of alternatives to vancomycin and lack of supporting pharmacokinetic data for some drugs. Among surgical patients, key principles include practice of thoughtful antimicrobial control, using local data on common pathogens and resistance patterns to guide empiric therapy, limiting treatment of contamination, and treating infection aggressively but not colonization.

Actions that comprise the "Prevent Transmission" strategy among dialysis patients include careful infection control with hand hygiene—the single most important infection-control measure—using soap and water or waterless alcohol-based gels or foams. Additional infection-control precautions should be considered for treatment of patients who might be at increased risk for transmitting pathogenic bacteria. Among surgical patients, hand hygiene is also paramount.

In summary, U.S. federal agencies now have a strategy and an action plan to address AR domestically. Progress to date is encouraging, indicating that additional investments can be expected to pay dividends in converting AR from an urgent to a manageable problem that does not compromise the availability of safe and effective therapy for patients today and in future generations.

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Why Appropriate Antimicrobial Selection Is Important: Focus on Outcomes

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INTRODUCTION

There is a general consensus that antimicrobial resistance in the hospital setting has emerged as an important variable that influences patient outcomes and overall resource utilization (1–3). Hospitals worldwide are faced with increasingly rapid emergence and spread of antibiotic-resistant bacteria. Both antibiotic-resistant gram-negative bacilli and gram-positive bacteria are reported as important causes of hospital-acquired infections (4,5). In many cases, few antimicrobial agents remain

for effective treatment, particularly with methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* (MRSA, VRSA) and gram-negative bacteria producing extended-spectrum beta-lactamases with resistance to many other antibiotics (6–8).

The increasing presence of antibiotic-resistant bacterial infections among hospitalized patients is likely related to numerous pressures promoting resistance as well as the administration of inappropriate antimicrobial therapy. These pressures include the frequent use of broad-spectrum antibiotics; prolonged use of antibiotics; crowding of patients with high levels of disease acuity within relatively small specialized areas of the hospital; reductions in nursing and ancillary support staff due to economic pressures, which increase the likelihood of person-to-person transmission of antibiotic-resistant bacteria; and presence of more chronically and acutely ill patients who require prolonged hospitalizations and often harbor antibiotic-resistant bacteria (9–11). This review focuses on antimicrobial resistance and the importance of administering initial appropriate antimicrobial treatment for serious infections as it applies to hospital-acquired infections, especially hospital-acquired pneumonia (HAP).

IMPORTANCE OF APPROPRIATE INITIAL ANTIMICROBIAL THERAPY

One of the consequences of greater antimicrobial resistance is an increased recognition of inappropriate antimicrobial treatment of infections (12). Inappropriate antimicrobial treatment of serious infections in the hospital setting has been demonstrated to be an important determinant of hospital mortality (Fig. 1) (13–15). Inappropriate antimicrobial treatment represents the use of antibiotics with poor or no *in vitro* activity against the identified microorganisms causing infection at the tissue site of infection. Examples of inappropriate treatment include the absence of antimicrobial agents directed at a specific class of microorganisms (e.g., absence of therapy for fungemia due to *Candida* species) and the administration of

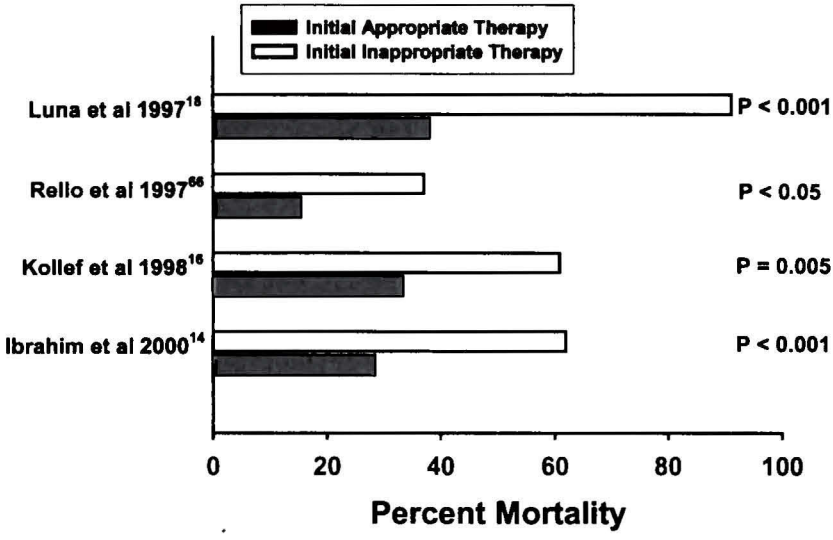

Figure 1 Crude hospital mortality from four clinical studies for patients receiving either appropriate or inappropriate initial antimicrobial therapy for hospital-acquired infections in the intensive care unit setting.

antimicrobial agents to which the microorganism responsible for the infection is resistant (e.g., empiric treatment with nafcillin for pneumonia subsequently attributed to MRSA). Changing antimicrobial therapy based on the subsequent available culture results and antibacterial susceptibilities may not reduce the excess risk of hospital mortality associated with inappropriate initial antibiotic treatment (16,17). Therefore, selection of initial appropriate therapy (i.e., getting antibiotic treatment right the first time) is an important aspect of care for hospitalized patients with serious infections.

Most inappropriate antimicrobial treatment of hospital-acquired infections appears to be the result of bacteria resistant to the prescribed antimicrobial agents (12–18). Although inappropriate antibiotic treatment may explain, in part, the greater mortality rates associated with antibiotic-resistant bacterial infections, other factors may also contribute to this

excess mortality. Antibiotic-resistant gram-positive bacteria such as MRSA express a number of virulence factors potentially contributing to their higher rates of associated mortality (19,20). However, not all investigators have demonstrated greater mortality rates with infections due to MRSA compared with methicillin-susceptible *S. aureus* (21). Similarly, some antibiotic-resistant gram-negative bacteria (e.g., *Pseudomonas aeruginosa*) are associated with increased virulence factors as compared with antibiotic-susceptible pathogens (22,23). This may explain the excess attributable mortality observed with infections due to these pathogens as well.

Hospital-acquired bloodstream infections are among the most serious infections acquired by patients in the intensive care unit (ICU). Antibiotic resistance appears to have contributed to increasing administration of inappropriate antimicrobial therapy for hospital-acquired bloodstream infections that are associated with greater hospital mortality rates (13,14,24,25). The problem of antibiotic-resistant bacteremia also appears to be increasing in the hospital setting as well as in the community (26). Given the current trend of greater severity of illness for critically ill patients, it can be expected that infections due to antibiotic-resistant bacterial strains will be associated with greater morbidity and mortality, particularly when inappropriate empiric antimicrobial therapy is administered (12). Along with greater patient mortality rates, antibiotic-resistant bacterial infections and inappropriate antimicrobial treatment are associated with prolonged hospitalization and increased health care costs relative to antibiotic-sensitive bacterial infections (15,27,28). The overall national costs of antimicrobial resistance have been estimated to be between $100 million and $30 billion annually for the control and treatment of infections caused by antibiotic-resistant bacteria (29).

In addition to selecting the most appropriate antimicrobial agents for the treatment of serious infections, clinicians must insure that antibiotic administration follows certain minimal requirements. These minimal requirements include proper dosing, interval administration, optimal duration of treatment, monitoring of drug levels when appropriate, and

avoidance of unwanted drug interactions (30). Lack of adherence to these minimal requirements may result in unforeseen administration of suboptimal or excessive antibiotic tissue concentrations, which increases the likelihood for antibiotic-resistance, patient toxicity, and lack of effectiveness, despite selecting an appropriate antimicrobial regimen (31).

THE TARGETED APPROACH TO ANTIBIOTIC UTILIZATION

Ideally, clinicians should prescribe antimicrobial therapy with the goals of providing appropriate initial therapy to hospitalized patients with serious infections and minimizing the emergence of bacterial resistance. Various strategies for the prevention of antibiotic resistance have been proposed in terms of improving overall antibiotic utilization (32,33). Table 1 highlights several of these strategies aimed at either limiting the unnecessary use of antibiotics or optimizing their effectiveness when prescribed to hospitalized patients. The targeted approach to empiric antimicrobial therapy is one approach to antibiotic utilization attempting to balance the need to provide appropriate initial treatment while limiting the emergence of antimicrobial resistance (Fig. 2).

An effective approach to targeted antimicrobial therapy necessitates that clinicians be aware of the microorganisms that are most likely to be associated with infection and inappropriate antimicrobial treatment in their practice setting. This requires that hospitals have updated and accurate antibiograms reflecting the bacterial pathogens and their antimicrobial susceptibility encountered at the local level. Variability in the microorganisms associated with hospital-acquired infections among hospitals, as well as within the wards of large hospitals, has been demonstrated to occur (34,35). Additionally, changing temporal patterns of nosocomial pathogens and antimicrobial susceptibility have been described (36). This suggests that hospitals may need to develop systems for updating local antibiograms on a regular basis because of the potential existence of intrahospital and temporal variations. Utiliz-

Table 1 Goals of Targeted Antibiotic Therapy in the Hospital Setting

I. Optimize antimicrobial effectiveness
1. Prescribe initial appropriate empiric treatment based on local pathogen prevalence and antibiotic susceptibility.
2. Use combination antimicrobial treatment to cover the most common bacterial pathogens.
3. Provide education and professional detailing to clinicians on appropriate antibiotic therapy.
4. Use locally developed antibiotic management guidelines.
5. Consult with local infectious disease specialists.
6. Use antibiotic cycling and scheduled antibiotic changes according to changing patterns of pathogens and antimicrobial susceptibility.
7. Consider the use of area-specific empiric antimicrobial regimens in larger hospitals because of area-specific variability in pathogens and their susceptibility patterns.
II. Limit unnecessary antimicrobial utilization
1. De-escalation approach to therapy
a. Use narrow-spectrum or older antibiotics based on patient risk profile and culture results.
b. Use shortest course of antibiotic therapy that is clinically indicated.
2. Avoid prolonged use of prophylactic antibiotics.
3. Apply selective formulary control or restriction of specific "problem" antimicrobial agents or drug classes.
4. Develop/apply local guidelines or protocols detailing optimal indications for and durations of antimicrobial treatment.
5. Use quantitative cultures, when appropriate, to establish diagnostic thresholds for treating specific infections

ing such data can improve the efficacy of antimicrobial therapy by increasing the likelihood that appropriate initial antibiotic treatment will be prescribed to infected patients (36,37).

In order to appropriately target the initial empiric antimicrobial regimen, clinicians must be able to obtain culture specimens prior to starting antimicrobial therapy. However, it is understood that prolonged delays in the administration of appropriate antibiotic treatment should not occur in seriously ill patients while waiting for specific cultures to be obtained (e.g., bronchoalveolar lavage, cerebrospinal fluid). The most com-

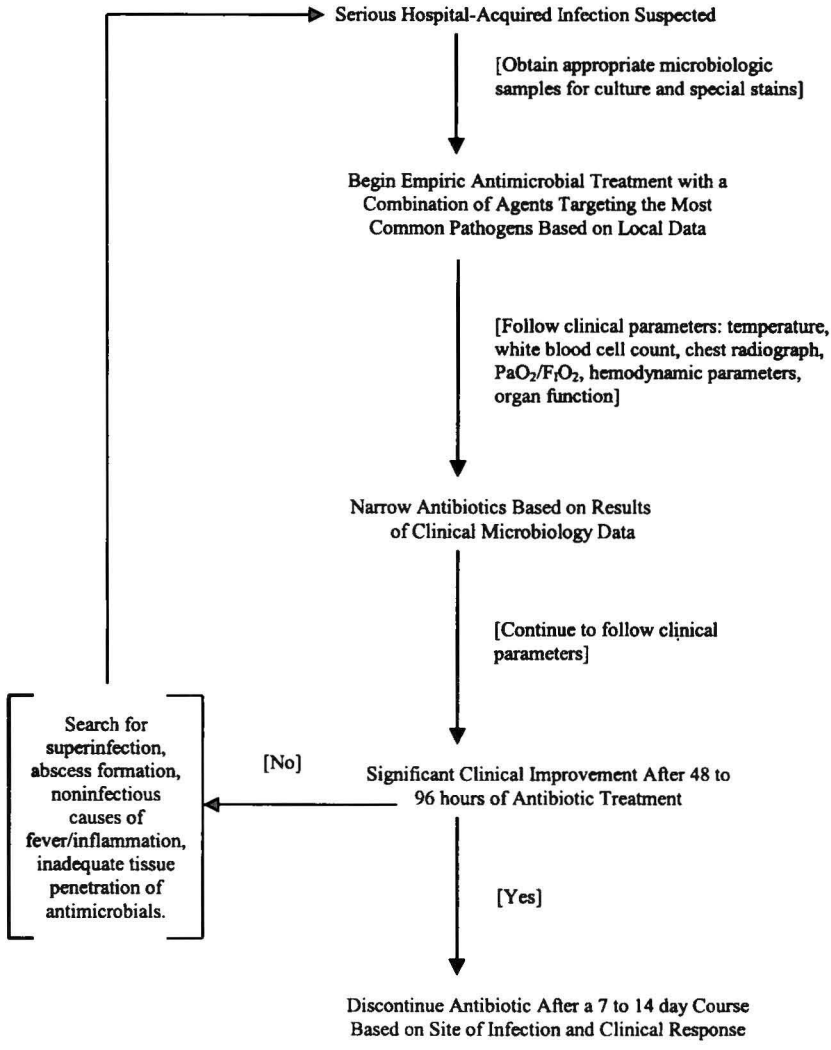

Figure 2 A flow diagram illustrating the targeted approach to antibiotic treatment for hospital-acquired infections.

mon pathogens associated with the administration of inappropriate antimicrobial treatment for hospital–acquired infections include potentially antibiotic-resistant gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, and *Enterobacter* species) and *S. aureus*, especially the strains with methicillin resistance (12–18). Therefore, clinicians should consider initial empiric therapy for these pathogens, especially in patients at high-risk for antibiotic-resistant infections.

Clinicians should also be aware that health care–acquired infections are similar to hospital-acquired infections in terms of the pathogens responsible for infection (38–41). Health care–acquired infections are defined by a positive culture obtained within 48 hours of hospital admission and one of the following criteria: (i) received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; or had self-administered intravenous medical therapy in the 30 days before the infection; (ii) attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days before the infection; (iii) was hospitalized in an acute care hospital for 2 or more days in the 90 days before the infection; (iv) resided in a nursing home or long-term care facility (38). Physicians should be aware of the factors that identify patients as having health care–acquired infections in order to avoid the prescription of inappropriate antibiotic treatment.

EXAMPLES OF THE TARGETED APPROACH TO EMPIRIC ANTIMICROBIAL THERAPY

Trouillet et al. (9) identified risk factors for ventilator-associated pneumonia (VAP) caused by potentially drug-resistant bacteria such as methicillin-resistant *S. aureus*, *P. aeruginosa*, *Acinetobacter baumannii*, and/or *Stenotrophomonas maltophilia* in 135 consecutive episodes of VAP observed in a single ICU over a 25-month period. Seventy-seven (57.0%) episodes of VAP were caused by "potentially resistant" bacteria and fifty-eight (43.0%) episodes were caused by "other" nonresis-

tant organisms. According to logistic regression analysis, three variables were predictors for VAP due to potentially drug-resistant bacteria: duration of mechanical ventilation greater than or equal to 7 days (odds ratio [OR] = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or a carbapenem) (OR = 4.1). Differences in the potential efficacies (ranging from 100% to 11%) against microorganisms for fifteen different antimicrobial regimens were studied to determine their overall level of activity for the pathogens associated with VAP. These investigators observed that the combination of a carbapenem plus amikacin and vancomycin provided the broadest *in vitro* coverage against the spectrum of gram-negative and gram-positive bacteria that were found in their ICU. Although clinical outcomes were not assessed, this study suggests that location-specific empiric antibiotic regimens, tailored to the susceptibility patterns of the local flora, are most likely to be effective. Additionally, this study demonstrates that patients at high-risk for infection with antibiotic-resistant bacteria can be identified based on risk factors that promote colonization with such pathogens (e.g., prior antibiotic therapy, exposure to high-risk environments including hospitals and long-term care facilities).

Ibrahim et al. (37) evaluated fifty consecutive patients in the ICU setting receiving antimicrobial therapy for VAP. They subsequently examined fifty-two consecutive patients with VAP whose antimicrobial treatment was administered according to a unit-specific antimicrobial guideline. The main goal of the guideline was to provide initial administration of appropriate antimicrobial treatment while avoiding the emergence of antimicrobial resistance. This meant providing initial coverage for *P. aeruginosa* and methicillin-resistant *S. aureus*, the two most common pathogens causing VAP in that specific ICU. This was accomplished by providing initial intravenous combination antimicrobial treatment with vancomycin, a carbapenem, and a fluoroquinolone. This combination was selected because it provided *in vitro* coverage for greater than 90% of all the bacterial isolates identified based on a unit-specific antibiogram. The guideline also required that antibiotic treat-

ment be modified after 48 hours based on the available culture results and the clinical course of the patient. In fact, 61.5% of patients had two antibiotics discontinued within 48 hours of beginning therapy, based on special stains and culture data.

The second specified goal of the guideline developed by Ibrahim et al. was to reduce potentially unnecessary antimicrobial administration. This was accomplished by recommending a 7-day course of appropriate antimicrobial treatment for patients with VAP. Continued administration of antimicrobials beyond day 7 was only encouraged for patients with persistent signs and symptoms consistent with active infection (e.g., fever greater than 38.3°C, circulating leukocyte count greater than 10,000 mm^{-3}, lack of improvement on the chest radiograph, continued purulent sputum). Use of the guideline was associated with a statistically significant increase in the administration of appropriate antimicrobial treatment, a decrease in the development of secondary episodes of antibiotic-resistant VAP, and a reduction in the total duration of antimicrobial treatment.

The studies of Trouillet et al. and Ibrahim et al. employed local bacterial susceptibility data in order to develop recommendations for empiric therapy within their respective ICUs. The use of local data should always be taken into consideration when developing empiric regimens for treatment. The American Thoracic Society (ATS) released a consensus statement in 1996 on the diagnosis, assessment, treatment, and prevention of HAP that supported the de-escalation approach to antimicrobial treatment (42). This document identifies those microorganisms commonly implicated in HAP and provides antibiotic recommendations based on the infecting pathogens. According to the consensus statement, the management of HAP should be based on the following factors: severity of illness (i.e., mild to moderate vs. severe as defined in the ATS statement); presence of risk factors suggesting infection with specific microorganisms (to include the use of local data on pathogens and susceptibility patterns); and the time of pneumonia onset (i.e., less than 5 days after hospital admission vs. 5 days or more after admission).