SHEA Position Paper

Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the Prevention of Antimicrobial Resistance in Hospitals

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ABSTRACT

Antimicrobial resistance results in increased morbidity, mortality, and costs of health care. Prevention of the emergence of resistance and the dissemination of resistant microorganisms will reduce these adverse effects and their attendant costs. Appropriate antimicrobial stewardship that includes optimal selection, dose, and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among microorganisms. A comprehensively applied infection control program will interdict the dissemination of resistant strains (*Infect Control Hosp Epidemiol* 1997;18:275-291).

SUMMARY

Antimicrobial resistance results in increased morbidity, mortality, and costs of health care. Prevention of the emergence of resistance and the dissemination of resistant microorganisms will reduce these adverse effects and their attendant costs. Appropriate antimicrobial stewardship that includes optimal selection, dose, and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among microorganisms. A comprehensively applied infection control program will interdict the dissemination of resistant strains. It therefore is recommended that hospitals, large and small, with and without perceived problems of bacterial resistance to antimicrobials, do the following:

- Establish a system for monitoring bacterial resistance and antibiotic usage;
- Establish practice guidelines and other institutional policies to control the use of antibiotics, and respond to data from the monitoring system;
- Adopt the recommendations of the Centers for Disease Control and Prevention's (CDC) "Guidelines for Isolation Precautions in Hospitals," as concerns the isolation of patients colonized or infected with resistant microorganisms;
- Utilize hospital committees to develop local policies and to evaluate and adopt, as appropriate, guidelines from state advisory boards and national

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societies;

- Recognize that the financial well-being of the institution and the health of its patients are at stake and therefore that the hospital administration should be accountable for the implementation and enforcement of policies adopted by hospital committees;
- By measuring outcomes, evaluate the effectiveness of the policies that are put in place.

It is recommended that research to define the mechanism of transfer of bacteria and their resistance determinants among patient populations and to determine methods to prevent emergence and transfer of resistance, including control of antibiotic usage, be supported with increases in targeted research funding.

Antimicrobial resistance is costly in both human and financial terms. Infection with a resistant microorganism increases the cost of health care, length of hospital stay, and mortality compared to infections with organisms susceptible to common, inexpensive antimicrobials.[1,2] The Society for Healthcare Epidemi-ology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have embarked on a joint project to make recommendations regarding the prevention and control of antimicrobial resistance. This task has assumed very broad boundaries and includes the prevention of emergence and control of dissemination of antibiotic-resistant pathogens in hospitals, in other institutions, in outpatient settings, and in both animal and human health.

There is convincing evidence that we share a single ecosystem globally in terms of resistance. The selection of resistance in one organism in one part of the world, even within an animal population, may have long-term, important implications for human health globally. Therefore, management of the problem of antimicrobial resistance within hospitals is a community responsibility, both within and outside of the hospital. The following recommendations are directed toward all hospitals, small to large, with and without currently perceived problems with antibiotic resistance. Good stewardship of antibiotic usage combined with strong infection control will be required. To achieve this, all levels of personnel within the hospital must be involved, from top administration down to individuals performing services and providing patient care. The recommendations promulgated in this set of guidelines reflect this approach.

This report, the first of a series that is emerging from this joint committee on antibiotics, is concerned with two major aspects of antibiotic resistance in hospitals: the selection of antibiotic-resistant organisms and the dissemination of resistance within the hospital setting. The basic genetics of bacterial resistance and the breadth of possibilities available to microorganisms to avoid the toxic effects of antibiotics are reviewed. Various methods of surveillance for resistance in the hospital are considered, and criteria that hospitals might use to identify resistant organisms of epidemiological importance are developed. The critical role of antibiotic use in the hospital in the selection of resistant bacteria is reviewed, and recommendations designed to avoid or retard the selection of resistant bacteria are provided. Specific isolation procedures for patients infected or, in some cases, colonized with resistant organisms that the hospital has chosen to attempt to control also are reviewed.

That infection control committees of hospitals have been struggling with these problems for many years is clear, and many feel frustrated with a real or perceived lack of administrative support. The relation between infection control and the hospital administration regarding these recommendations is examined. It is clear that, without the support of the administration, neither these recommendations nor those of local infection control committees will be of use in the struggle against antibiotic resistance. The guidelines seek to motivate administrators to invest in the infection control effort, given the convincing financial arguments favoring the control of antimicrobial resistance. We also provide an organizational framework for administrators so that they can appreciate their role as part of a team involved in providing the most efficient and highest-quality care for patients in their institutions.

One critical area requiring immediate attention is the existing database from which these and other guidelines are constructed. Clear recommendations have been made regarding further research that might provide the kind of data needed for rational decisions in the management of antimicrobial usage and infection control.

EMERGENCE OF ANTIMICROBIAL RESISTANCE IN HOSPITALS

Genetics of Resistance

Bacteria possess a remarkable number of genetic mechanisms for resistance to antimicrobials. They can undergo chromosomal mutations, express a latent chromosomal resistance gene, or acquire new genetic resistance material through direct exchange of DNA (by conjugation), through a bacteriophage (transduction), through extrachromosomal plasmid DNA (by conjugation), or by acquisition of DNA via transformation. The information encoded in this genetic material enables a bacterium to develop resistance through three major mechanisms: production of an enzyme

TABLE 1
EXAMPLES OF RESISTANCE MECHANISMS AND THEIR GENETIC BASES*

Antibiotic(s)	Mechanisms	Genetic Basis	Example Organisms
β-lactams	Altered penicillin-binding protein targets	Chromosomal	*Staphylococcus aureus*
Penicillins			*Streptococcus pneumoniae*
Cephalosporins			*Staphylococcus epidermidis*
Monobactams			*Haemophilus influenzae*
Carbapenems			*Neisseria gonorrhoeae*
			Neisseria meningitidis
			Escherichia coli
			Pseudomonas aeruginosa
	Reduced permeability	Chromosomal	*P aeruginosa*
			Enterobacter cloacae
			Serratia marcescens
			Klebsiella pneumoniae
			Klebsiella oxytoca
	β-lactamase inactivation	Chromosomal and plasmid	*S aureus*
			S epidermidis
			Enterococci
			P aeruginosa
			Enterobacteriaceae
			N gonorrhoeae
			N meningitidis
Fluoroquinolones	Altered DNA gyrase target	Chromosomal	*S aureus*
Ciprofloxacin			*S epidermidis*
Ofloxacin			*Enterobacteriaceae*
Norfloxacin	Efflux or reduced permeability	Chromosomal	*Enterobacteriaceae*
Lomefloxacin			*P aeruginosa*
Aminoglycosides	Modifying enzyme inactivation	Plasmid	Staphylococci
Amikacin			Enterococci
Gentamicin			Streptococci
Tobramycin			*Enterobacteriaceae*
	Reduced permeability	Chromosomal	*Enterobacteriaceae*
			Pseudomonads
			Bacteroides
	Altered ribosomal target binding	Chromosomal	Streptococci
Macrolides and lincosamides	Methylation of rRNA target	Chromosomal and plasmid	Streptococci
Erythromycin			*S pneumoniae*
Clindamycin			Enterococci
			Staphylococci
	Efflux	Plasmid	Staphylococci, streptococci
Tetracyclines	Efflux	Plasmid	Staphylococci
Tetracycline			Streptococci
Minocycline			Enterococci
Doxycycline			*Enterobacteriaceae*
			Bacteroides
			Haemophilus
	Altered ribosomal target	Plasmid	*N gonorrhoeae*
			Bacteroides
			Listeria
			Mycoplasma
			Ureaplasma

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TABLE 1 *(continued)*
EXAMPLES OF RESISTANCE MECHANISMS AND THEIR GENETIC BASES*

Antibiotic(s)	Mechanisms	Genetic Basis	Example Organisms
Glycopeptides	Altered target	Chromosomal	Enterococci
Vancomycin		and plasmid	Lactobacilli
Teicoplanin			*Staphylococcus hemolyticus*
Folate inhibitors	Altered targets	Chromosomal	Staphylococci
Trimethoprim-sulfamethoxazole		and plasmid	Streptococci
			S pneumoniae
			Enterobacteriaceae
			Neisseria
Rifampin	Altered DNA polymerase target	Chromosomal	Staphylococci
			Streptococci
			Enterococci
			Enterobacteriaceae
			Mycobacterium tuberculosis
			Pseudomonads
Chloramphenicol	Acetyltransferase inactivation	Chromosomal	Staphylococci
		and plasmid	Streptococci
			H influenzae
			S pneumoniae
			Enterobacteriaceae
			Neisseria
	Efflux	Chromosomal	*Enterobacteriaceae*
		and plasmid	Pseudomonads
Mupirocin	Altered target	Plasmid	Staphylococci

* Modified from Neu HC.[3]

that will inactivate or destroy the antibiotic; alteration of the antibiotic target site to evade action of the antibiotic; or prevention of antibiotic access to the target site. Examples of organisms that are known to possess resistance mechanisms of the various types are shown in Table 1, together with the genetic mechanism for the resistance.[3] It is not unusual for a single bacterial strain found in a hospital to possess several of these resistance mechanisms simultaneously.

Some resistance can be acquired by a single genetic mutation that can occur spontaneously, such as the DNA gyrase target alteration that results in fluoroquinolone resistance. Other resistance mechanisms are far more complex and consist of genes that encode production of highly specific enzymes that inactivate several antibiotics (eg, β-lactams or aminoglycosides). There is considerable speculation about the origin of these genes. Some genes can be found naturally occurring in other species of bacteria.[4] It is postulated that there is a substantial pool of antibiotic resistance genes (or related genes) in nature. This gene pool, to be of use to bacteria that are under selective antibiotic pressure, must be accessible, and the bacteria must possess the means to acquire the needed genetic information (gene pickup).

Transposons (so-called jumping genes) and plasmids provide two readily available means for gene transfer. One class of transposons, called integrons, consist of conserved DNA segments that flank a central region into which "cassettes" that encode antibiotic-resistance functions can be inserted. The 5′ conserved segment encodes a site-specific recombinase or integrase, as well as one or more promoters that assure expression of the integrated resistance cassettes. Integron-type transposons provide a model for assembly of multiple antibiotic resistance genes from a variety of sources into R plasmids that have been found to display an ever-increasing array of resistance properties.[4,5]

Transposable elements and plasmids encode not only genetic information for inactivation of antimicrobials, they also may encode genes for the active efflux of antibiotics from the cell, the so-called sump pump mechanism of resistance. Efflux systems may be highly specific for single agents or may involve a variety of classes of antimicrobial agents. Many of the resistances previously thought to be due to permeability barriers subsequently have been found to be

mediated by efflux pumps.[6,7]

Whereas some altered target-site resistance may be due to single mutations, as occur with fluoroquinolones and rifampin, target-site alterations for β-lactam resistance are more complex. Penicillins, cephalosporins, and other β-lactams act by inactivating a number of transpeptidases (or penicillin-binding proteins [PBPs]) essential for the cross-linking reactions of cell-wall synthesis.[8] Because there often are multiple PBP targets, resistance development is slow and often stepwise as each PBP is altered in its affinity for the β-lactam. Development of resistance may occur gradually with the slow accumulation of multiple amino acid substitutions through mutations; however, there also is evidence to support the acquisition of low-affinity PBP genes in *Neisseria gonorrhoeae* and *Neisseria meningitidis* from recombination with commensal *Neisseria* species. In the case of methicillin resistance in *Staphylococcus aureus*, a new PBP 2′ or *mecA* gene, which is part of a transposon, has been acquired by the *Staphylococcus*.

Clearly, bacteria have evolved a wide array of mechanisms to become resistant to antimicrobials and are adept at disseminating the resistance once it has been acquired. Analysis of organisms from the preantibiotic era suggests that evolution of multiresistant R plasmids has occurred over the past 50 years, a period that happens to coincide with the discovery and increasingly widespread use of antimicrobial agents. A causal association between these two temporally related phenomena is quite probable.

Virulence of Resistant Bacteria

Although it often has been stated that antibiotic-resistant bacteria tend to be less virulent than their susceptible parents,[9] this is not necessarily true, and even less virulent bacteria can be dangerous pathogens for some hospitalized patients. For example, bacteria that acquire mutations in genes responsible for vital functions, such as transport of small molecules, can be resistant to some antibiotics, such as aminoglycosides, and tend to be less virulent in animal models of infection.[10] However, some authors argue that such bacteria can be responsible for relapse of infection after treatment, because they are not treated effectively by the antibiotic nor are they cleared effectively by impaired host defenses.[11] Many resistant pathogens appear just as virulent as the susceptible parents in animal models and in patients, as is the case for methicillin-resistant *Staphylococcus aureus* (MRSA), for example.[12] Therefore, antimicrobial resistance per se may not render pathogenic bacteria easier to clear from infected sites. Further, there is evidence that they are transmitted from patient to patient in much the same way as susceptible bacteria, ie, mainly through contact and occasionally through airborne droplets (see below).[13,14]

Surveillance for Resistant Bacterial Pathogens

A major role of the clinical microbiology laboratory is to provide antimicrobial susceptibility testing data on bacterial isolates to guide clinicians in their choice of anti-infective therapy. Susceptibility testing data can serve both as a guide to therapy and, in some instances, as an initial means of strain typing for investigations of potential outbreaks of infection. Other strain typing methods, such as pulsed-field gel electrophoresis, have better discriminatory ability. However, unusual antibiograms, especially multiply resistant patterns, can be helpful early in the course of an investigation for identifying outbreak-related isolates.

Microbiologists can aid in the prudent use of antimicrobial agents in their respective hospitals by testing and reporting drugs using the guidelines developed by the National Committee for Clinical Laboratory Standards (NCCLS; Executive Offices, 940 W Valley Rd, Ste 1400, Wayne, PA 19087) Subcommittee on Antimicrobial Susceptibility Testing in documents M2-A7, M7-A5, M11-A3, and M100-S6. Microbiologists should consult Tables 1 and 1A of NCCLS documents M2-A5 and M7-A3 for recommendations on which drugs to test against various classes of microorganisms. An example of such recommendations is given in Table 2 of this article. Prioritizing of susceptibility reports, in which extended-spectrum drugs such as imipenem are not reported unless resistance to other agents is documented, can contribute to prudent use. Microbiologists should work with infectious disease clinicians, pharmacists, hospital epidemiologists, infection control practitioners, and representatives of clinical departments to choose the drugs that will be tested and reported routinely. Sometimes choices will be limited by the instruments used in the microbiology laboratory for susceptibility testing, and this limitation should be part of discussions concerning the choice of drugs tested.

In conjunction with routine antimicrobial susceptibility testing for guiding antimicrobial chemotherapy, microbiologists also frequently are involved in programs for the surveillance of organisms with novel resistance patterns. There are two components to such surveillance. First, surveillance involves periodic review of minimum inhibitory concentrations (MIC) or zone diameter data for changes in resistance patterns. Changes indicating trends toward increasing resistance may be detected first by noting a decrease in the mean zone diameters around antibiotic disks using the Bauer-Kirby disk-diffusion method or by increases in the MICs of organisms, even though the

TABLE 2
GUIDELINES FOR TESTING BACTERIAL PATHOGENS FOR ANTIMICROBIAL RESISTANCE*

Gram-Positive Organisms	Gram-Negative Organisms
Staphylococci	*Enterobacteriaceae*
Penicillin	Ampicillin
Oxacillin	Cefazolin or cephalothin
Vancomycin	Cefotetan or cefoxitin
Alternate agents as needed, including	Cefotaxime or ceftriaxone
Erythromycin	Gentamicin
Clindamycin	Amikacin
Trimethoprim-sulfamethoxazole	Ciprofloxacin
	Trimethoprim-sulfamethoxazole
	β-lactam–β-lactamase inhibitor combinations
Enterococci	*Pseudomonas* and *Acinetobacter*
Penicillin or ampicillin (β-lactamase test)	Ticarcillin or piperacillin
	Gentamicin
Vancomycin	Ceftazidime
High-level gentamicin and streptomycin (invasive isolates only)	Ampicillin/sulbactam
	Amikacin
	Imipenem
	Ciprofloxacin
	Trimethoprim-sulfamethoxazole
	Cefoperazone or aztreonam
Streptococcus pneumoniae	
Penicillin†	
Cefotaxime or ceftriaxone	
Vancomycin	
Alternate agents as needed, including	
Erythromycin	
Clindamycin	

* This guide is adapted from the National Committee for Clinical Laboratory Standards Document M100-S6 for initial susceptibility testing and reporting of antimicrobial agents for several bacterial pathogen groups. (Not all drugs should be reported routinely.)
† Laboratories may screen for penicillin resistance in pneumococci by using a 1-μg oxacillin disk. Organisms with zone diameters of ≥20 mm are considered susceptible to all β-lactam drugs. Isolates with zone diameters of ≤19 mm should be tested by a minimum inhibitory concentration method against both penicillin and cefotaxime or ceftriaxone, especially if the organism is causing invasive disease.

categorical interpretations of the zone sizes or MIC results still may be within the susceptible range. For example, MICs of ceftazidime for *Klebsiella pneumoniae* may change from 0.1 μg/mL to 8 μg/mL, yet still would be classified as susceptible. Such changes potentially are important, and clinical microbiologists should alert clinicians, particularly infectious disease specialists and hospital epidemiologists, to such trends in their hospitals. Alternate methods of testing to confirm resistance mechanisms (eg, β-lactamase tests for *Haemophilus influenzae* and *N gonorrhoeae* or disk diffusion tests for extended-spectrum β-lactamases) also can be helpful for detecting borderline resistance.

The second component of surveillance is the reporting of novel resistance patterns to local, state, and national public health officials. Unusual resistance patterns, such as vancomycin-resistant *S aureus* or penicillin-resistant *N meningitidis,* would have major public health implications and should be acted on immediately. These should be reported to clinicians and hospital epidemiologists. Such unusual antibiotic-resistance patterns should be confirmed by the laboratory to rule out random laboratory errors. If the resistance profile is confirmed, laboratories should notify the state health department and the CDC. Clinical microbiologists and infectious disease clinicians need to keep abreast of other novel resistance patterns, particularly those that have the potential to spread rapidly.

TABLE 3
MECHANISMS FOR THE APPEARANCE OR SPREAD OF ANTIMICROBIAL RESISTANCE IN HOSPITAL ORGANISMS

Introduction of a resistant organism to a previously susceptible population
Acquisition of resistance by a susceptible strain
Spontaneous mutation
Genetic transfer
Expression of regulated resistance already present in the population
Selection of a resistant subpopulation
Dissemination or spread of resistant organisms

Modified from McGowan JE Jr.[15]

Antimicrobial Use and Resistance

There are multiple mechanisms postulated by which antimicrobial resistance may appear and disseminate within hospital organisms (Table 3).[15] Three of the proposed mechanisms for resistance development are influenced by antimicrobial usage: acquisition of resistance, emergence of dormant resistance, and selection of resistant subpopulations. Often, the introduction of a resistant organism can be documented by contact tracing to an index case that was admitted to the hospital already infected or

colonized with the resistant organism. More frequently, however, the source of resistant organisms remains an enigma. Although the exact magnitude of the problem due to the spread of resistant organisms within the institution is unknown, it is clear that such spread can be minimized by early recognition and effective infection control practices. Regrettably, recognition of cross-infection often is slow, and containment and control measures often are inadequate or ineffective.

Several lines of evidence suggest that there is a causal association between antimicrobial usage in hospitals and antimicrobial resistance.[16] For some pathogens, selection of resistance during treatment or prophylaxis is thought to be a more important factor in the acquisition of infection by a resistant organism than is transmission from patient to patient.[17] Additional compelling observations are as follows:

1. Changes in antimicrobial usage are paralleled by changes in the prevalence of resistance.

2. Antimicrobial resistance is more prevalent in nosocomial bacterial strains than in those from community-acquired infections.

3. During outbreaks of nosocomial infection, patients infected with resistant strains are more likely than control patients to have received prior antimicrobials.

4. Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use.

5. Increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms.[16]

The above observations are derived from review of multiple published reports. However, questions remain unanswered because of the lack of uniformity of definitions of resistance, variation in susceptibility test methodologies, potential study selection biases, and failure to control for confounding variables, especially infection control measures.[18] These and other additional factors that may affect antimicrobial resistance are summarized in Table 4 and typify many of the characteristics of the changing hospital environment.

Recently, Stuart Levy, MD, proposed a provocative hypothesis: the intensity of antibiotic use in a population may be the most important factor in selection of resistance. Moreover, there may be a "threshold" for such selection[19] that may differ for an individual, as compared to a population, and from one population to another. This may explain why, in intensive-care units, where there is usually a small population undergoing intensive antibiotic therapy or prophylaxis, resistance tends to be more common, pathogens are more often multiply resistant, and spread within the population is more likely. The same concept might explain resistance problems in the poultry manufacturing industry and in other settings where antibiotic use is intensive within a small and confined population.

TABLE 4
FACTORS THAT MAY INCREASE ANTIMICROBIAL RESISTANCE IN HOSPITALS

Greater severity of illness of hospitalized patients
More severely immunocompromised patients
Newer devices and procedures in use
Increased introduction of resistant organisms from the community
Ineffective infection control and isolation practices and compliance
Increased use of antimicrobial prophylaxis
Increased empiric polymicrobial antimicrobial therapy
High antimicrobial usage per geographic area per unit time

Modified from McGowan JE Jr.[18]

The growing emphasis on outpatient medical management has increased the severity of illness of those who are admitted to the hospital. Patients with advanced malignancies, organ transplantation, multiorgan failure, or human immunodeficiency virus infection are far more immunocompromised and constitute a larger portion of hospital patients than in the past. These patients often are colonized or infected with unusual opportunistic organisms that are far more resistant to antimicrobials—organisms such as *Pseudomonas, Stenotrophomonas, Acinetobacter, Enterobacter, Serratia,* coagulase-negative staphylococci, enterococci, *Candida,* phycomycetes, and *Aspergillus.*[20] These patients also are more likely to be treated with procedures (such as bone marrow transplantation) and devices (indwelling urinary and intravascular catheters) that increase the risk of infection by specific organisms. Increased treatment of patients in the community can lead to resistance in the community that is introduced to the hospital by patients on admission; methicillin-resistant staphylococci and ampicillin-resistant *Haemophilus* organisms are examples. Infection control and isolation practices vary from hospital to hospital. Their effective use can have considerable influence on reducing the persistence and spread of resistant organisms in the hospital. Changes in antimicrobial usage also may influence resistance. Policies such as systemic and gastrointestinal antimicrobial prophylaxis in intensive-care units[21] and empiric poly-antimicrobial treatment of febrile immunocompromised, as well as immunocompetent patients,[22,23] may add to the risk of antimicrobial resistance in hospital organisms. Taken together, the above factors have led to an increased percentage of hospitalized patients who

TABLE 5
ELEMENTS OF AN OPTIMAL ANTIMICROBIAL CONTROL PROGRAM TO STUDY THE PREVENTION OR REDUCTION OF ANTIMICROBIAL RESISTANCE

Precise definitions of antimicrobial resistance for antimicrobials and organisms
A system for monitoring the frequency of resistance (clinical and environmental)
A determination of which antimicrobial(s) to control
A method to achieve usage control
A determination of who will be responsible for maintaining control
A method to educate and enroll prescribers in the control process
A stable system of hospital infection control
A system to measure use of controlled and uncontrolled antimicrobials
A method to determine antimicrobial use per geographic area per unit time
Ability to distinguish community from nosocomial isolates
Ability to identify isolates by body site and hospital location
A method to assure that clinical care will not be harmed by control measures
Ability to identify known mechanisms of antimicrobial resistance
Ability to type organisms by phenotypic or genetic methods

receive antimicrobials and an increased number of antimicrobials per patient over the past 15 years.[24]

Notwithstanding the complexity of the problem and the need for better data-controlled studies, there nonetheless are sufficient reports of the association of antimicrobial usage in hospitals with emergence of antimicrobial resistance to implicate use as a causal factor in antimicrobial resistance.[15,16,18,20,25-28] Clearly, the degree to which such resistance occurs, and the organisms and drugs affected, is quite variable and not predictable for most drug-organism pairs. This is illustrated by the observation that the rate of ciprofloxacin resistance among MRSA is markedly higher than for methicillin-sensitive *S aureus* or gram-negative organisms.[28] In this case, the ciprofloxacin resistance mechanism has been determined, but it is not clear why these mutational changes apparently are more frequent in MRSA than in other organisms.[29-31] Thus, we need to examine carefully not only the relation of resistance to antimicrobial use for specific organism-drug pairs but also to determine the mechanism of that resistance as an indicator of possible causation.

Prevention of Emergence of Resistance

Prevention of the emergence of antimicrobial resistance and reduction of established resistance are dual goals for which the methods are likely similar if not identical. Preventing the acquisition of resistance is assumed to be the easier task, although data regarding preventive strategies generally are lacking, whereas studies of actions taken once resistance has occurred are plentiful, if not consistent, regarding their efficacy. The elements of a good program for prevention of resistance generally include an active system of surveillance for resistance, an active and effective infection control program to minimize secondary spread of resistance, and an effective program of antimicrobial use stewardship. The latter element, sometimes referred to as "antibiotic control," most often is cited as a means to prevent and control resistance. Appropriate antimicrobial stewardship includes not only the limitation of use of inappropriate agents but also the appropriate selection, dosing, and duration of antimicrobial therapy to achieve optimal efficacy in managing infections.

The effectiveness of antimicrobial control as a means to prevent the emergence of resistance has been reviewed. The results of available studies are suggestive, but not conclusive.[32] However, because resistance among certain species such as enterococci has become so widespread that there are no longer any effective antimicrobial agents, the interest in antimicrobial control as a preventive measure has intensified. Past studies have been criticized for their selection biases, small size, limitation to single institutions, and failure to control for confounding variables.[32] Not only is the effect of antimicrobial control on microbial resistance not known, the most effective methods to achieve antimicrobial control also are not clear. The need for better data from larger and better controlled multicenter studies is apparent. In addition, the relation of antimicrobial resistance to the "defined drug density" (the amount of antimicrobial use per geographic unit per unit time) has been suggested as an evaluation measure that could be useful in relating resistance to use of antimicrobials.[19]

The elements suggested for inclusion in an effective antimicrobial control program to prevent or reduce antimicrobial resistance are shown in Table 5. Because of the complexity of multidrug resistance in many organisms, it can be predicted that not all control measures will succeed. For this reason, it is recommended that monitoring include many of the variables listed in Table 5 (such as mechanism of resistance, molecular typing of organisms, and complete resistance profiles), so that insights can be obtained regarding which control strategies are more likely to succeed than others. For example, multiply antimicrobial-resistant organisms may respond to control of one agent to which

they are resistant, but they may not respond to control of other agents to which they also are resistant.

Initial control efforts are likely to be empiric, simply because the best strategies are not known yet. Uncontrolled resistance no longer can be tolerated. Managed-care networks are likely to demand control of resistance to improve patient-care quality and to reduce costs of healthcare. It is likely, given the trend toward greater outpatient care, that prevention and control of antimicrobial resistance will be as important in the outpatient arena as in the inpatient setting.

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. This is the essence of good antimicrobial use stewardship. Four possible strategies to optimize use are shown in Table 6. The first of these involves the development of guidelines and treatment algorithms, designed to elucidate "pathways" of optimal use. Prescribers are educated to follow them and to seek expert guidance along the way from infectious disease specialists and pharmacists. To date, such programs have not been particularly effective, even with the addition of peer review.[32]

The second method of antimicrobial control, selective removal or control of use of specific agents or classes of agents, has been employed in numerous hospitals. Compliance with the restriction policy easily can be documented from pharmacy prescribing data, and favorable effects on the incidence and prevalence of specific resistant organisms have been documented.[32-40] More studies have been conducted on control of gentamicin resistance (mainly through the restriction of gentamicin and replacement with amikacin) than on any other antimicrobial.[33-38] Most have shown significant reductions in gentamicin resistance during restriction, but return of resistance with resumption of gentamicin use.[34-36] In some instances when this "replacement" strategy was employed, resistance to amikacin developed, and resistance problems became worse[41-43]; however, in most institutions, this did not occur.[33-38,44] Although such studies often were commercially sponsored to promote use of an alternative product, they still provide a model for future efforts to control antimicrobials in that the protocols employed for monitoring resistance and antimicrobial use in each institution were similar. In most instances, the mechanism of resistance to gentamicin was determined (usually plasmid-mediated transferable aminoglycoside inactivating enzymes), and the potential mechanism for amikacin resistance (a different aminoglycoside inactivating enzyme) was monitored.[34-36] Control measures were enforced rigidly and resulted in major usage changes, as had been described by others.[39] Organisms and plasmids were typed using molecular techniques, so that the presence of resistance genes in hospital organisms could be determined during and after antimicrobial changes.[34] Future studies should build on the wide experience of these studies in exploring the effect of control measures on resistance prevention and reduction. The pharmaceutical industry should be encouraged to explore ways in which they can provide support for studies that can lead to preservation of the effectiveness of their drugs in the clinical setting.

TABLE 6
PROPOSED METHODS TO CONTROL ANTIMICROBIAL USE TO PREVENT OR CONTROL ANTIMICROBIAL RESISTANCE

Optimal use of all antimicrobials
Selective removal, control, or restriction of antimicrobial agents or classes
Rotational or cyclic antimicrobial use
Use of combination antimicrobial therapy to prevent the emergence of resistance

The third method suggested in Table 6 is rotational or cyclic antimicrobial use. Few data are available on its impact. The largest experience is reported for changes in aminoglycoside use.[45] Attempts to reintroduce or to cycle gentamicin following use of amikacin resulted in recurrence of gentamicin resistance in three institutions.[34,37,46] Gentamicin use in one of these institutions was reinstituted successfully, subsequently, at a time when the original resistance plasmid no longer was found in hospital organisms.[34] The potential of this strategy as a resistance prevention measure has not been explored adequately, but it is a distinctly testable hypothesis in intensive-care units. In addition to the caveats expressed previously regarding such attempts,[45] it also is important to note that the duration of the cycles and the preferred order in which agents are cycled is unknown. Testing this method will require a multicenter trial, because a large population will be needed to control for several confounding variables.

The last strategy suggested in Table 6, use of combination antimicrobial therapy to reduce emergence of resistance, is theoretically attractive and is the basis for current treatment of tuberculosis with multiple antimicrobials. It has not been adequately tested clinically to determine if overall institutional resistance can be reduced by the use of combination therapy for individual patients.[47] In one study of *Enterobacter,* no benefit in reducing emerging resistance was observed when combined third-generation cephalosporin and aminoglycoside therapy was used.[48] The risks include increased antimicrobial costs and the potential for increasing resistance by raising the number of antimicrobials and antimicrobial

TABLE 7
RECOMMENDATIONS FOR PREVENTION AND REDUCTION OF ANTIMICROBIAL RESISTANCE IN HOSPITALS

Recommendations	Strength of Recommendation*	Quality of Evidence†
It is recommended that hospitals have a system for monitoring antimicrobial resistance of both community and nosocomial isolates (by hospital location and patient site) on a monthly basis or at a frequency appropriate to the volume of isolates.	A	III
Monitoring use of antimicrobials by hospital location or prescribing service is recommended on a monthly basis or at a frequency appropriate to the prescription volume.	A	III
It is recommended that hospitals monitor the relationship between antimicrobial use and resistance, and assign responsibility through practice guidelines or other institutional policies.	A	II
It is recommended that hospitals apply Contact Precautions to specified patients known or suspected to be colonized or infected with epidemiologically important microorganisms that can be transmitted by direct or indirect contact.	A	III

* Categories for strength of recommendation: A, good evidence for support; B, moderate evidence for support; C, poor evidence to support.
† Categories reflecting the quality of evidence on which recommendations are based: I, evidence from at least one properly randomized controlled trial; II, evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees.

courses administered. The use of combination therapy is, however, already widespread for the treatment of seriously ill patients, so controlled trials to determine the effect on resistance prevention are reasonable.

In summary, antimicrobial resistance among some hospital organisms has increased to the point that no antimicrobials are available for treatment. This is a situation that cannot be tolerated. The need for preventive and corrective measures is urgent. There is an almost certain causal association between the use of antimicrobials and resistance to them. Alterations in antimicrobial usage have been shown to affect antimicrobial resistance rates, particularly for the aminoglycosides. Additional large-scale, well-controlled trials of regulation of antimicrobial use employing sophisticated epidemiological methods, molecular typing of organisms, and precise analysis of mechanisms of resistance are required to determine the best methods to prevent and control this emerging problem of antimicrobial resistance and to establish optimal antimicrobial use.

CONTROLLING THE DISSEMINATION OF RESISTANT BACTERIA IN HOSPITALS

The SHEA/IDSA Joint Committee on Antibiotics supports the CDC "Guideline for Isolation Precautions in Hospitals"[13] as it applies to preventing the selection and spread of resistant microorganisms. Our recommendations are summarized in Table 7. Clearly, isolation of individuals infected with organisms for which no effective parenteral therapy remains (80% of vancomycin-resistant enterococci) is recommended universally for all hospitals.[49] Beyond this clear recommendation, hospitals again will have to make choices. Will colonized patients be isolated, for example? In general, it is recommended[13] that hospitals choose which organisms are of special clinical and epidemiological importance to identify patients for isolation. That such policies be adopted and implemented is especially important for hospitals where such resistance is not yet perceived as problematic. How should hospitals carry out surveillance for resistant microorganisms to identify patients requiring isolation? These questions are discussed below.

The Colonized Patient

The recommendations from the CDC[13] are unclear on how to care for patients colonized with resistant organisms. The most conservative approach is to isolate patients colonized with those organisms the hospital has decided to control, because they may be an important reservoir for transmission to, and eventually infection of, other patients or even healthcare workers. On the other hand, colonized patients are difficult to identify, likely to have a smaller burden of organisms than infected patients, and therefore are less likely to be a source of transmission. Isolation, or even cohorting, of every patient colonized with a resistant, epidemiologically important microorganism may not be practical for some hospitals. When possible, patients col-

onized with such an organism, whether they have been recognized through a surveillance effort or by chance, should be handled in the same manner as patients clinically infected with those organisms. Readmission of patients colonized with resistant organisms represents a hidden reservoir that could be monitored and controlled.

Identification of Patients to Be Isolated Because of Colonization or Infection With Resistant Microorganisms

Definition of resistance. According to the CDC,[13] resistant bacteria are those judged by the infection control program, based on current state, regional, or national recommendations, to be of special clinical and epidemiological significance. In its most rigorous form, this should include a quantitative susceptibility testing system that is better able to detect resistance than a simple breakpoint testing system. Under such a system, any epidemiologically important isolate with an unusual and relevant (for the hospital) decrease in susceptibility to one or more antibiotics might prompt institution of isolation precautions for the colonized or infected patient. An example might be *Klebsiella pneumoniae* isolated from the sputum of a patient with pneumonia that has an MIC for cefotaxime or ceftriaxone of 2 μg/mL. Although this ordinarily might be called susceptible by the hospital laboratory and by currently accepted US laboratory guidelines, such as those furnished by the NCCLS, this MIC certainly is unusual for the species. Identifying such an isolate justifiably might call for isolation of the patient, especially because it is unlikely that treatment with cefotaxime or ceftriaxone would be successful.[50] A simple, user-friendly data entry and retrieval system called WHONET has been supported by the World Health Organization for use by hospitals that wish to survey quantitative susceptibility tests (MICs or zone sizes).[51] A recent feature of this system calls attention to unusual drug resistance as the results are being entered.

Hospitals should consider instituting isolation precautions for patients colonized or infected with multiply resistant microorganisms. This seems most important for hospitals where resistance is not yet perceived to be a problem, because it is in such hospitals that the emergence of resistance will have the greatest impact on quality and cost of patient care.[2] An example of this is MRSA (and perhaps even methicillin-resistant *Staphylococcus epidermidis)* currently resistant to all but one effective parenteral antibiotic. Increasingly, data indicate that spread of MRSA in hospitals where such strains are not endemic can be controlled by isolating infected and colonized patients.

CDC Isolation Precautions for Hospitals

All patients are cared for using Standard Precautions. Standard Precautions synthesize the major features of Universal (Blood and Body Fluid) Precautions (designed to reduce the risk of transmission of bloodborne pathogens) and Body Substance Isolation (designed to reduce the risk of transmission of pathogens from moist body substances)[52-54] and apply them to all patients receiving care in hospitals, regardless of their diagnosis or presumed infection or colonization status. Standard Precautions apply to blood,[1] all body fluids, secretions, and excretions, regardless of whether they contain visible blood, nonintact skin, and mucous membranes.[13] Standard Precautions are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in hospitals.

Transmission-Based Precautions. Transmission-Based Precautions are designed for patients documented or suspected to be infected or colonized with highly transmissible or epidemiologically important pathogens for which additional precautions beyond Standard Precautions are needed to interrupt transmission in hospitals. Of the three types of Transmission-Based Precautions discussed in the Hospital Infection Control Practices Advisory Committee (HICPAC) recommendations,[13] only Contact Precautions are thought to be relevant to the transmission of resistant bacteria other than *Mycobacterium tuberculosis.* SHEA supports the HICPAC recommendations for the prevention of transmission of resistant pathogens[13] (Table 7).

Contact Precautions. Contact Precautions are designed to reduce the transmission of epidemiologically important microorganisms by direct or indirect contact. Direct contact transmission involves skin-to-skin contact and physical transfer of microorganisms to a susceptible host from an infected or colonized person, such as occurs when personnel turn a patient, give a patient a bath, or perform other patient-care activities that require physical contact. Direct contact transmission also can occur between two patients (eg, by hand contact), with one serving as the source of infectious microorganisms and the other as the susceptible host. Indirect contact transmission involves contact of a susceptible host with a contaminated intermediate object, usually inanimate, in the patient's environment. *Clearly, the environment can be an important reservoir of resistant microorganisms.* Contact Precautions apply to specified patients known or suspected to be colonized or infected with epidemiologically important microorganisms that can be transmitted by direct or indirect contact.

IMPLEMENTATION OF POLICY TO CONTROL ANTIBIOTIC RESISTANCE

Overview

Despite a strategic vision among hospital epidemiologists and tactical tools within hospitals known to be effective in limiting antimicrobial use, the most difficult aspect of influencing the use of antimicrobial agents has been administrative implementation of guidelines and policies designed to change usage. Implementation, in this context, means the attainment of sustained performance of approved standards of good stewardship. Effective implementation remains a problem, because it is not clear what administrative level of approval and enforcement is needed to ensure sustained positive performance. It is likely that a hierarchy of decision-making groups working together will guarantee implementation of sound antibiotic stewardship guidelines best.[55]

It is important to be aware that control of microbial resistance is not implemented just through control of antimicrobial use, although this may be an essential component. There are very few studies on the relative effectiveness of strategies for implementation of antimicrobial control policies.[55] Most authorities suggest that the pharmacy and therapeutics (P&T) committee should be charged with developing formulary and antimicrobial controls through a variety of mechanisms. Such mechanisms often include approval of orders by the infectious disease service, use of antibiotic order forms, and use of a computerized database to correlate pharmacy and bacteriology results.[56] Ordinarily, the P&T committee submits its policies for executive board review and approval, although this measure is often a rubber stamp of the P&T recommendations. The involvement of hospital administration in this process varies.[57]

Approaches to Implementation

Historically, antibiotic control policies have been used to control costs.[56-58] A side benefit always has been assumed to be reduced selective pressure and thus less antimicrobial resistance. Reduction of antimicrobial resistance using cost-motivated controls has not been documented well.[59,60] Nevertheless, "bottom-up" systems that start with P&T committees within hospitals have been used with variable success in controlling antimicrobial use, as long as the control measures remain in effect or are accepted fully by prescribers.[61] Ultimately, regardless of the mechanisms for control, very few programs have been able to show changes among prescribers that are sustained over a substantial period of time.

Bottom-up approaches have advantages and disadvantages for implementation of changes. Some advantages include the ability to streamline control methods to local resistance problems, the backing of on-site infectious disease practitioners, and a democratic procedure involving clinicians, administrators, and other healthcare workers. Disadvantages include the inability to anticipate national and international resistance trends; the outside pressures brought by physicians, pharmaceutical buying groups, and pharmaceutical representatives; and the lack of consensus among clinicians and administrative personnel regarding the importance of a broad attack on antibiotic resistance and the roles they should play.

Modern electronic communications and computers are revolutionizing hospital practice. In some hospitals, all medication orders must be entered into computer terminals in the hospital or clinics. Such computerized order entry provides the opportunity for real-time physician-pharmacy interactions that otherwise would be impossible with a handwritten order. Although initial reports are encouraging, there is no consensus on the effect of computer-based drug utilization review on reducing antibiotic prescribing practices.[62,63] Regardless of the value of computer-based drug utilization, increasingly sophisticated interactions now possible with computerized ordering will have a profound effect on physician prescribing and education in the future.

Control of antimicrobial resistance requires the implementation of two processes: infection control practices to limit the spread of resistant microorganisms and hospital policies of good antimicrobial use stewardship, which may include antimicrobial usage controls. In outbreak situations, standard infection control measures usually have been shown to reduce the spread of resistant microorganisms.[64] The utility of infection control measures to reduce the *endemic* spread of resistant bacteria is much harder to demonstrate.[65] Nevertheless, all experts urge control measures in such situations.[65,66]

Multiple approaches have been employed to enforce hospital policies to limit or control antibiotic use (see Table 8). The primary motivation for antibiotic control has been to reduce the cost of certain agents[67]; only recently has the need for antibiotic control resulted from an escalation of antimicrobial resistance.[68,69] Previously, cost-benefit analyses could determine which antimicrobial to include or exclude from hospital formulary use. A more difficult determination using risk-benefit analysis—where risk, in part, includes the emergence of antimicrobial resistance—now has become necessary to decide if an agent should be deleted, restricted, or substituted. Proof of the efficacy of these approaches in establishing control of

resistance is lacking. Recommendations for effective implementation of antibiotic control, therefore, remain empirical. Nevertheless, because effective implementation and enforcement of antibiotic control programs are the essential first steps to success, it seems prudent to build first a consensus of various interest groups.[61] Consensus of quality standards for antimicrobial prophylaxis in surgical procedures already has been developed. Implementation of these standards should prove effective in reducing the length of prophylaxis and the total volume of antimicrobial use.[70]

The British approach. The British Society for Antimicrobial Chemotherapy (BSAC) has conducted a large survey to assess national characteristics of control measures in British hospitals. They sampled microbiologists and pharmacists to determine the practice of control measures for their respective hospital[68]; 49% responded. Among respondent hospitals, 86% had a P&T committee, 79% had an antibiotic formulary, 62% had a policy for therapy, and 17% had an antibiotic committee. In 40%, compliance was monitored, and 88% believed their policies for antimicrobial prophylaxis and therapy were beneficial.

Policies included educational campaigns (52%), cost-control programs (50%), regulation of pharmaceutical promotions (48%), therapeutic substitutions (43%), automatic stop orders (26%), antibiotic utilization coordinators (11%), and antibiotic audit (11%). In a country that has had a national health service for years, how would antimicrobial gatekeepers feel about developing national policies for control? Interestingly, very few of the microbiologists (5.6%) and fewer pharmacists (0.7%) advocated a national policy. These attitudes are surprising, because a report with recommendations from the Working Party of the BSAC in 1982 probably resulted in the high prevalence of control measures.[68]

The minimum control measures that the BSAC now recommends are summarized as follows:

1. Updating of antibiotic formulary and policies with appropriate funding for staff and resources.

2. Widespread consultation before inception of antibiotic control programs and constructive feedback thereafter, thus ensuring "continuous consultation."

3. Representative committees to consider introduction of new antibiotics, with the authority to withhold these agents or to make these agents available.

4. Strict restriction of nonformulary agents.

5. Provisions for departments of microbiology (infectious diseases) and pharmacy to have adequate facilities, to ensure the success of educational programs, and to have adequate computer resources.

6. Appropriate personnel to monitor the adherence to policies and formularies.

7. Funded programs to assess and adopt automatic stop orders, antibiotic prescription forms, and use of utilization coordinators.

8. Requirement of permission from administration for pharmaceutical promotions.

9. Susceptibility patterns should be published by microbiology laboratories.

10. Research into novel control measures should be encouraged with provision of adequate facilities, including computerized information systems.

TABLE 8
METHODS TO IMPLEMENT ANTIBIOTIC CONTROL OR RESTRICTION POLICIES

- Written hospital guidelines
  - National[49]
  - Regional (state regulations)
  - Local[68]
- Educational efforts aimed at changing prescribing practices of physicians
  - Face-to-face-presentations[72]
  - Computer interactions[73]
  - Pharmacy "Top 100" expenditures list
- Restriction of hospital formulary through pharmacy and therapeutics committee
  - Cyclic rotation of antimicrobials within a class[34]
  - Antibiotic order forms[74,75]
  - Antibiotic stop orders
    - Therapeutic use
    - Prophylactic use
  - Restriction of use[77]
  - Removal of specific agents[78]
  - Review of medical record by pharmacists[79]
    - Decentralized pharmacies
    - PharmDs to interact with physicians[80]
  - Usage feedback to physician[78]
  - Computerized review
  - Group purchasing practices
  - Generic substitution[81]
- Utilization review with guidelines for rational and appropriate usage
  - Antibiotic utilization subcommittee
    - Multidisciplinary teams[79]
- Requirement of consultation with infectious diseases subspecialists for certain antimicrobial choices
  - By telephone approval[78]
  - By written audit[82,83]
- Antimicrobial susceptibility reporting[84]
- Reduction of pharmaceutical promotion[68]

Consensus-Building to Develop and Implement Antibiotic Control Policies

A new American approach. The British experience may not be applicable to hospitals in other countries. Thus, a recent document representing a

new American approach, "Workshop to Prevent and Control the Emergence and Spread of Antibiotic-Resistant Microorganisms in Hospitals,"[65] has diverged from traditional approaches to implement control programs. In the document, the authors speak of a "striking lack of success in the prevention and control of antibiotic resistance despite career devotion by many health professionals to this objective." To quote further, "Despite guidelines promulgated by the CDC and professional societies, antibiotic-restriction policies, and the entreaties of their colleagues, physicians continue to prescribe antibiotics excessively and inappropriately. . . ." As the authors note, although many American hospitals have a strategic policy for prevention and control of antibiotic resistance, very few hospitals have made antibiotic resistance a strategic priority. Regardless of the reason for inaction by hospitals, we agree with the workshop participants that the time for complacency has long passed.

The workshop advanced two broad focus areas; each area involved strategic goals with steps, process measures, and countermeasures to ensure success. Listed here are those goals that involve implementation of an effective program of good antibiotic stewardship.

The following are strategies to optimize the prophylactic, empiric, and therapeutic use of antibiotics in the hospital, considering their impact on microbial environment, effectiveness, and cost:

Strategic goal 1: Optimize choice and duration of prophylactic antibiotic therapy.

Strategic goal 2: Optimize choice and duration of empiric antibiotic therapy.

Strategic goal 3: Improve antibiotic prescribing practices by educational and administrative means.

Strategic goal 4: Establish a system to monitor and provide feedback on the occurrence and impact of antibiotic resistance.

Strategic goal 5: Define and implement institutional or healthcare delivery-system guidelines for important types of antibiotic use.

The following are strategies for detecting, reporting, and preventing transmission of antibiotic-resistant microorganisms:

Strategic goal 1: Develop a system to recognize trends in antibiotic resistance and to report them promptly to hospital and physician leaders; medical, nursing, infection control, and pharmacy staffs; and others who need to know.

Strategic goal 2: Develop a system for rapid detection of resistant microorganisms in individual patients, with reporting to infection control staff for rapid response by caregivers.

Strategic goal 3: Increase adherence to policies and procedures, especially hand hygiene, barrier precautions, and environmental control measures.

Strategic goal 4: Incorporate detection, prevention, and control of antibiotic resistance into institutional strategic goals, and provide required resources.

Strategic goal 5: Develop a plan for identifying, transferring, discharging, and readmitting patients colonized with specified antimicrobial-resistant microorganisms.

A model using consensus for implementation. The potential for implementing many of the outlined steps, processes, and countermeasures exists at American hospitals. Leadership will be needed. This leadership should come from hospital epidemiologists, microbiologists, pharmacists, physicians, infection control practitioners, and others who participate in the hospital committees providing recommendations. Hospital epidemiologists and others will need to present substantiating information to hospital administration on the morbidity, mortality, expense, and increased length of stay associated with antibiotic resistance. Hospital management will need to become invested in, and accountable for, the control of antibiotic resistance in hospitals, because certain processes and countermeasures are painful and expensive.

With the resistance crisis upon us, incremental change is likely to be ineffective, and a mass mobilization is needed to curb the existing level of resistance. The current system of antibiotic use has resulted in the problem we face. Counteracting forces constantly will come into play, eg, the use of vancomycin for highly penicillin-resistant *Streptococcus pneumoniae* will increase the selective pressure for the emergence of vancomycin-resistant enterococci. The expanding population of neutropenic patients will increase the need for extended-spectrum cephalosporins and thus the likelihood of emergence of extended-spectrum β-lactamases. Companies that develop new antimicrobials for use against resistant organisms may oppose efforts to restrict their use.

Hospitals, led by their committees with the support of hospital management, should develop policies based on their local resistance characteristics, antibiotic usage patterns, input from a state department of health advisory board or other similar body, and input from national organizations (Figure). Hospital-specific formal guidelines then would be delivered from these committees to the hospital administration for implementation. Staff compliance in individual facilities should be compared to quality improvement standards, and these outcomes should be the basis for continuous quality improvement.

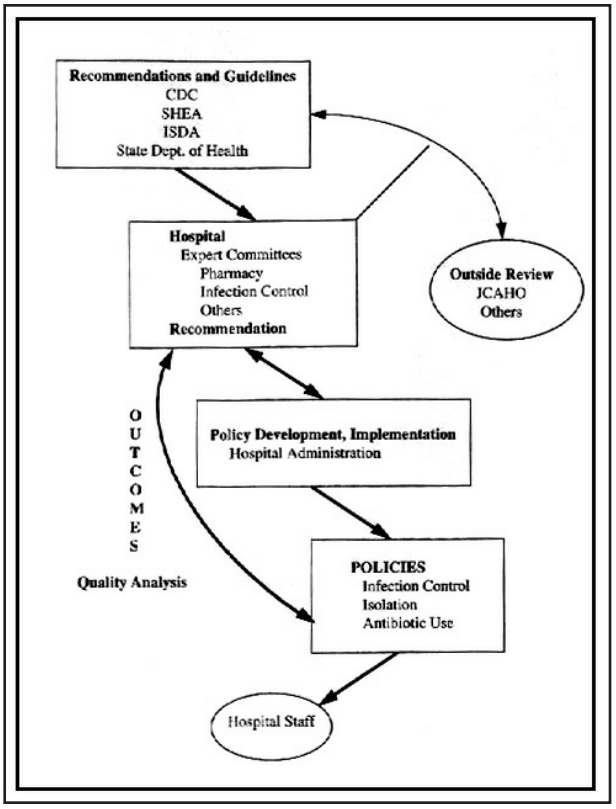

FIGURE. Flow of information, recommendations, and policies for the development of hospital policies to prevent the emergence and dissemination of resistance. Expert committees of the hospital, taking into account the recommendations and guidelines of outside agencies, develop hospital-specific recommendations and guidelines that are forwarded to the hospital administration. The responsibility of the administration is to develop or approve policies and to implement them within the hospital. These then are communicated to the hospital staff. Implementation is monitored by outcomes analysis and quality analysis. These data are analyzed by the expert hospital committees for further action and are communicated to outside agencies such as the Centers for Disease Control and Prevention, the Society for Healthcare Epidemiology of America, and the Infectious Diseases Society of America, as well as to oversight agencies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Outside review by JCAHO and other agencies is aimed specifically at the implementation of recommendations, guidelines, and proposed policies, the primary responsibility of hospital administration.

SHEA proposes that data provided by hospitals be utilized by state and national organizations, such as state health departments, the CDC, SHEA, and IDSA, to feed back information important to the hospital for evaluating its own antimicrobial-resistance policy. A state-supervised system of surveillance, like the one recently described in New Jersey, also would provide trends in emergence and spread of antibiotic-resistant organisms.[71] The Joint Commission on the Accreditation of Healthcare Organizations, or a similar review organization skilled in oversight functions, should take into account the priority hospitals give to antimicrobial resistance; policies, procedures, and measurements hospitals put into place; and evidence of ongoing review of data to judge the effectiveness of the plan.

These recommendations are a beginning of a national program to control antimicrobial resistance in hospitals. Similar standards can be applied to long-term–care facilities, private offices, and ambulatory-care clinics. Methods of implementation that are shown in cooperative studies to be useless in controlling resistance will be rescinded at the state level and abridged in subsequent CDC guidelines. The process thus allows for continuous quality improvement in implementing guidelines and policies to control antimicrobial use and resistance.

TABLE 9
RECOMMENDATIONS FOR FUTURE STUDIES TO EXAMINE MEANS TO PREVENT AND REDUCE THE DEVELOPMENT AND DISSEMINATION OF ANTIMICROBIAL RESISTANCE

The development and testing of protocols for measuring the effect of a variety of antimicrobial usage controls is recommended for use in multiple hospitals to determine the most effective ways to prevent and reduce antimicrobial resistance in specific species to specific antimicrobials.
Pharmaceutical industry and governmental support for such studies is recommended and encouraged.
It is recommended that educational methods, including those that are interactive and computer-based, be developed to improve the appropriateness of antimicrobial prescribing.
It is recommended that protocols to evaluate antimicrobial resistance include the ability to relate resistance rates to the "defined drug density" (the amount of antimicrobial used per geographic area per unit time).
The transfer of resistance determinants in situ in a patient population is very poorly understood. First, the genetics of resistance transfer, the construction of composite transposons, and the actual mechanism of dissemination of these elements in situ, especially intergeneric transfer within the gram-positive bacteria, all should be studied further.
Methods for interdicting transfer of resistance requires further study, especially in the behavioral area. Novel approaches to this area are needed.
The efficacy of various levels of infection control precautions should be documented by controlled trials.
Controlled studies of behavior modification, including novel approaches, to permit the efficient application of recommended guidelines within hospitals are recommended.
The efficacy of quality improvement approaches to control of resistance should be studied.

THE FUTURE

Recognizing that our recommendations frequently are based on inadequate data, we call for

funding for additional studies that will allow us to preserve better our antimicrobial arsenal in the future. Toward this goal, we echo the recommendations of the American Society for Microbiology Task Force on Antimicrobial Resistance. We support, in addition, the recommendations of previous National Institutes of Health workshops regarding new research directions in antimicrobial resistance. Our specific recommendations in this regard are summarized in Table 9.

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