Editorial

Antibiotic-Resistant Bacteria and Healthcare Systems: Four Steps for Effective Response

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That bacteria resistant to multiple antibiotics pose an increasing threat to our health is no longer news. The arrival of this problem now has been addressed extensively by the medical community.[1-3] Moreover, problems associated with multiple-drug-resistant (MDR) bacteria have been detailed for the public in newspapers, newsmagazines, on television, and in other popular media. Books also have been written for the public, informing them of the difficulties that MDR organisms pose and the importance of appropriate antibiotic use.[4]

What should be today's news, then, is the responses that are being made to deal with MDR organisms by the medical community, the public, and the government. Unfortunately, however, these responses have been slow and relatively uncoordinated. While governmental agencies, healthcare organizations, and professional societies try to figure out how best to deal with these new MDR organisms, public and healthcare worker concern grows.

Nowhere is the problem of drug resistance more pertinent than in the acute care hospital. True, the increase in pneumococci with resistance to penicillin has a major impact on the community, and methicillin-resistant ***Staphylococcus*** *aureus* (MRSA) now have become common in extended care facilities and a few communities as well as in hospitals. However, other prominent MDR organisms primarily have been hospital-based to date. Vancomycin-resistant enterococci (VRE) have been reported primarily as nosocomial pathogens, whether in outbreaks or in endemic patterns of occurrence. *Klebsiella pneumoniae, Escherichia coli,* and other Enterobacteriaceae that produce extended-spectrum β -lactamases usually have exploited the hospital setting as well. Formerly rare gram-negative bacilli like ***Acinetobacter*** species have discovered ways to resist all except a few antimicrobials; concurrently they have become the most frequent organism causing infection in intensive care unit patients in many U.S. hospitals.[5] Thus, defining appropriate control measures for MDR organisms is a particular concern for acute care hospitals.

HEALTHCARE SYSTEMS: THE "HOT ZONES" FOR MDR ORGANISMS

At present, MDR organisms primarily present a risk in the acute care hospital. However, this characteristic should change rapidly as integrated healthcare systems finish taking over the medical care system in the United States.[6] Each healthcare system, as it organizes around capitated care, will by its nature increase the contact and interrelation of its group of patients in acute care, extended care, and ambulatory care settings. With this greater rate at which members of a given system rub shoulders in each of these settings, the dilutional effects of the current care system, in which patients progress from the hospital to a variety of extended care or outpatient care units, will be lost. Instead, patients will be funnelled to the stepdown (or stepup) care units within a given healthcare entity. As a result, organisms from the acute care facilities of a system will have more chance to become endemic in the other components as well. Likewise, today home healthcare is

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delivered by a variety of competing providers, while in healthcare systems only employees or affiliates of a given provider will be used to care for the covered patients.

Thus, the close bundling of services within a system will in effect create a superhighway that facilitates exchange of organisms between acute inpatient wards and other settings of care. If the organisms exchanged are MDR ones, then these organisms may become characteristic of a system, almost as a calling card or icon of the system itself. This connection between emerging organizational factors and spread of resistant bacteria is somewhat analogous to the relationship drawn by a recent book between emerging geographic factors and the spread of hemorrhagic fever viruses.[7]

A healthcare system that experiences many MDR organisms, and becomes known for them, will find itself in an uncomfortable competitive position. It seems, then, that dealing with MDR strains will have much greater priority in the healthcare system world of tomorrow. This means that effective responses to MDR organisms will have a higher likelihood of being implemented well. The importance of seeing that the right steps are developed and provided to the forthcoming megahealthcare systems therefore is clear.

Critical pathways and other guidelines for control must be developed for at least three groups: epidemiologists and others attempting prevention, clinicians attempting therapy, and the general public. To do this, the next steps must answer some basic questions pertinent to each.

STEP ONE: GENERATE SYSTEMWIDE EPIDEMIOLOGIC INFORMATION

Critical paths, care plans and practice guidelines to prevent spread of MDR organisms are touted mechanisms for control efforts in the new healthcare system era.[8,9] At present, the best way to generate these procedural documents is not clear because of the lack of reliable information about reservoirs and modes of spread of MDR organisms. Many MDR bacteria are newly important, so their epidemiology often received little attention in the past. What observations have been made may not be valid for these organisms once they acquire new resistance characteristics. In addition, most of the relevant epidemiologic data to date are from single institutions, and the goal for healthcare systems is to provide rules that will be valid in a variety of settings throughout the system. Does a VRE spread in the same fashion as a vancomycin-susceptible strain of the same organism? Is the intensive care unit more important as a reservoir for a *Klebsiella pneumoniae* with an extended-spectrum β-lactamase than for a strain of the same organism that does not possess the enzyme? Is use of newer cephalosporins a risk factor for emergence, persistence, or spread of gram-negative bacilli in smaller acute care hospitals as well as in large ones? Data like these are not known with enough certainty that guidelines for control of MDR strains can be written with confidence.

A logical next step in dealing with MDR strains, then, is to obtain such epidemiologic data for a variety of settings and institutions.[10] The types of studies needed to take this step are typified by the article in this issue by Coronado et al.[11] Using the extensive database of the National Nosocomial Infections Surveillance System (NNIS), these authors have characterized pattern, time course, and risk factors for strains of *S. aureus* and ***Pseudomonas aeruginosa*** resistant to ciprofloxacin. Certain sites of infection were more likely associated with these resistant strains than others. This suggests that factors responsible for emergence are not uniform. It further suggests that when underlying causes for site-specific differences in occurrence are identified, there may be control measures to address them.

Further studies are needed to identify occurrence patterns and risk indicators. Fortunately, a number of investigators in infection control, critical care, microbiology, and pharmacy are making the effort to do this. Examples of these include the NNIS group, which in addition to the current study recently has published an epidemiologic analysis of factors that relate to ceftazidime resistance in nosocomial gram-negative bacilli.[12] In a separate thrust, eight NNIS hospitals are participating in a cooperative project with the Emory School of Public Health to consider antibiotic use, nosocomial infection and microbiologic resistance patterns by hospital area, focusing particularly on the intensive care unit. This effort, called Project ICARE (Intensive Care Antibiotic Resistance Epidemiology) is in a pilot phase. Another effort was announced at the ICAAC conference in October 1994 by a group at the University of Iowa, in association with Lederle Laboratories Inc. Their study is dubbed SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance). This effort will survey nosocomial bacteremia and other issues by extensive testing of organisms collected from microbiology laboratories in a nationwide sample of acute care hospitals. Resistance patterns also are being examined in systematic fashion by an anti-infective surveillance network organized to obtain isolates from microbiology laboratories by MRL Pharmaceutical Services in Franklin, Tennessee.[13] The Society of Critical Care Medicine is conducting a Critical Care Infection Treatment Outcomes Project, which involves a subgroup that is charged with raising awareness and

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developing solutions to the problem of multidrug resistance in the critical care environment. This task force is to work closely with the American Society of Hospital Pharmacists and other pharmacy groups that are attempting to develop data independently on the magnitude and cost of antibiotic use and its impact on resistance.

All of these efforts appear to be aimed at different aspects of the puzzle of antibiotic resistance and antibiotic use.[14] After data for each are collected, collated, and presented, the next step will be to analyze how the data from each fits together to form a coherent base for control recommendations. Who will do this and how it is to be done is not clear at present.

STEP TWO: DEVELOP SOLID EMPIRIC GUIDELINES FOR TREATMENT

The patient's physician needs clear information about how to treat MDR organisms. Empiric drug regimens likely to be effective must be defined, at least in tentative fashion, while better data on therapeutic options is being developed. This step is particularly difficult when the relationship between in vitro testing of MDR organisms and patient response is unclear. For example, when newer cephalosporins like cefotaxime or ceftriaxone are used to treat patients with meningitis due to ***Streptococcus pneumoniae*** isolates with minimum inhibitory concentration of 2 μg/mL to these drugs, the likelihood of cure is variable.[15,16] Issues like this must be clarified by careful clinical studies before suitable alternatives for therapy can be identified.

STEP THREE: DECIDE IF PACKAGE INSERTS SHOULD BE UPDATED

Rational infection therapy must be based in part on the likely spectrum of microbiologic activity of available antimicrobials. Many prescribers, at least in theory, obtain information about the spectrum of a drug's activity from the package insert provided with the drug. These package inserts consist of precise labeling that has been approved by the Food and Drug Administration (FDA) at the time of licensure of the antimicrobial.[17]

For decades, the likely pattern of susceptibility or resistance of given organisms has remained stable for most antibiotics. Thus, there has been little need for follow-up studies to determine whether labeling remains accurate regarding susceptibility. However, the speed and degree to which some MDR organisms have become resistant to newer antimicrobials is impressive. For example, MRSA strains that initially were susceptible to fluoroquinolone antimicrobials demonstrated the ability to become resistant rapidly within institutions.[18] Likewise, the article by Corona do et al documents increasing resistance not only of *S aureus* but also of ***P aeruginosa*** to one of these fluoroquinolones.[11] Yet, labeling of the drugs remains consistent with the situation at the time that these drugs were released. Should one step now in response to MDR organisms be a requirement by the FDA for revalidation of the labeling about microbiologic spectrum of drugs? Proponents of such a step point to the lack of value of labeling that no longer applies. Opponents postulate that most prescribers use drug labeling little, if at all, as a source of information about appropriate prescribing. Clearly, revalidating suscep tibility labeling would be costly, and the emphasis today is on decreasing, rather than increasing, healthcare costs.[19] Yet, surveys continue to show that many physicians receive much of their education about prescribing from manufacturer's representatives.[20] These representatives are bound by FDA guidelines to presenting only information in approved drug labeling.

Thus, deciding how important it is to make sure that current information provided by package labeling and manufacturer's representatives continues accurate is a step of current importance in dealing with MDR organisms.

STEP FOUR: REASSURE THE PUBLIC

Professor G. French, at a recent conference in London on control of resistance, stressed the important step of reassuring the public about the true magnitude today of MDR infections.[21] People and workers for the media like binary characterization—on or off, yes or no, treatable or untreatable. When we have been able to treat virtually all infections for a number of years, it becomes a major issue when at least one organism emerges that is not amenable to therapy. It is reasonable that this change receives attention.

However, natural events often are best considered in quantifiable rather than binary terms, and MDR infection is no exception. The members of every healthcare system must be reassured at this point that the number of organisms that are so resistant as to be untreatable at present is relatively small. They need to hear that most of the infections that they are likely to acquire still can be dealt with efficiently and effectively. In part, fear of MDR organisms has been a byproduct of medical researchers attempting to generate interest in, and funding from, Congress and elsewhere for research on these organisms.[22] These summaries often are based in part on potential spread of organisms and on potential spread of resistance determinants among species and across genera. For the person on the street, however, separating the reality of VRE from the speculative possibility of

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vancomycin-resistant MRSA is difficult. Thus, a reasonable assessment and overview of the relatively low risk that patients face today must be provided, in a calm and objective fashion. This approach will not be welcomed by the tabloids and medical throwaways that depend on sensationalism to sell their product, but it will be infinitely valuable to the public. It also will be valuable to public officials in their attempts to determine the steps needed to deal with the problem and the level of support needed to provide these solutions.

STEPS TO THE FUTURE

Studies like that of Coronado et al[11] enhance our ability to deal with MDR pathogens, especially in the hospital setting. They must be combined with similar progress in completing other steps that are needed to deal with the problem. If this is done, tomorrow's news reports can begin to reflect the phase that the public awaits eagerly-controlling the MDR organisms that bedevil us today as individuals and as members of healthcare systems.

REFERENCES

1. Murray BE. Can antibiotic resistance be controlled? *N Engl J Med* 1994;330:1229-1230.
2. Tomasz A. Multiple-antibiotic-resistant pathogenic bacteria. A report on the Rockefeller University workshop. *N Engl J Med* 1994;330:1247-1251.
3. Kunin CM. Resistance to antimicrobial drugs-a worldwide calamity. *Ann Intern Med* 1993;118:557-561.
4. *SB. The Antibiotic Paradox. How Miracle Drugs Are Destroying the Miracle.* New York, NY: Plenum Press; 1992.
5. Go ES, Urban C, Bums J, et al. Clinical and molecular epidemiol*ogy* of *Acinetobacter* infections sensitive only to polymixin B and sulbactam. *Lancet* 1994;344:1329-1332.
6. Iglehart JK. Health policy report: the struggle between managed care and fee-for-service practice. *N Engl J Med* 1994;331:63-67.
7. Preston R. *The Hot Zone.* New York, NY: Random House; 1994.
8. Woolf SH. Practice guidelines: a new reality in medicine. *Arch Intern Med* 1993;153:2646-2655.
9. Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis* 1994;18:421.
10. Kritchevsky SB, Simmons BP. Toward better antibiotic use in hospitals. *Infect Control Hosp Epidemiol 1994:15:688-690.*
11. Coronado VG, Edwards JR, Culver DH, Gaynes RP, National Nosocomial Infections Surveillance System. Ciprofloxacin resistance among nosocomial *Pseudomonas aeruginosa* and *Staphylococcus aureus* in the United States. *Infect Control Hosp Epidemiol* 1995;16:000-000.
12. Burwen DR, Banejee SN, Gaynes RP, National Nosocomial Infections Surveillance System. Ceftazidime resistance among selected nosocomial gram-negative bacilli in the United States. *J Infect Dis* 1994;170:1622-1625.
13. Thornsberry C. The epidemiology of emerging resistance. Presented at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 4-7, 1994; Orlando, Florida.
14. McGowan JE Jr. Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance? *Infect Control Hosp Epidemiol 1994;15:478-483.*
15. Austrian R. Confronting drug-resistant pneumococci. *Ann Intern Med* 1994;121:807-809.
16. John CC. Treatment failure with use of a third-generation cephalosporin for penicillin-resistant pneumococcal meningitis: case report and review. *Clin Infect Dis* 1994;18:188-193.
17. Billstein SA. How the pharmaceutical industry brings an antibiotic drug to market in the United States. *Antimicrob Agents Chemother* 1994;38:2679-2682.
18. Blumberg HM, Rimland D, Carroll DJ, Terry P, Wachsmuth IK. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus. J Infect Dis* 1991;163:1279-1285.
19. Kissick *WL. Medicine's* Dilemmas-Infinite Needs *Versus Finite Resources.* New Haven, CT: Yale University Press, 1994: 185 pgs.
20. Girard DE. The relationship between physicians in training and pharmaceutical companies. A time for guidelines? *Arch Intern Med* 1992;152:920-921.
21. French G, Percival A. Debate: we are approaching the end of the antibiotic era. Presented at Challenges in Infection Control. November 17-18, 1994; London, England.
22. Culotta E. Funding crunch hobbles antibiotic resistance research. *Science* 1994;264:362-363.