A Call to Arms: The Imperative for Antimicrobial Stewardship

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Antimicrobial resistance is a major public health crisis. The prevalence of drug-resistant organisms, such as the emerging NAP1 strain of *Clostridium difficile*, now highly resistant to fluoroquinolones, *Acinetobacter* species, *Klebsiella pneumoniae* carbapenemase-producing organisms, and methicillin-resistant *Staphylococcus aureus*, is increasing nationwide. The sources of antimicrobial resistance are manifold, but there is a well-documented causal relationship between antimicrobial use and misuse and the emergence of antimicrobial-resistant pathogens. As the development of new antimicrobial agents is on the decline, the medical community, across all specialties and in conjunction with public health services, must develop and implement programs and strategies designed to preserve the integrity and effectiveness of the existing antimicrobial armamentarium. Such strategies are collectively known as antimicrobial stewardship programs and have the potential to minimize the emergence of resistant pathogens.

Two of the major health care challenges that face the medical practice are the rapidly evolving problems of *Clostridium difficile* infection (CDI) and the crisis of antimicrobial resistance. These 2 issues are related by the following observations: they are driven by antimicrobial use, and they reflect, to some extent, the abuse of these drugs. Both are epidemics in the US and much of the world, both are focused primarily in hospitals and chronic care facilities with spillage into the community, and—possibly most important for the purposes of this supplement—both are in desperate need for effective programs of antibiotic stewardship.

**CLOSTRIDIUM DIFFICILE INFECTION**

*Clostridium difficile* was identified as the agent of antibiotic-associated colitis in 1978 [1], which was followed by the rapid evolution of information about its epidemiology, clinical features, diagnostic testing with the cytotoxin assay, and treatment with either oral vancomycin or metronidazole. It was known at that time that almost any antibiotic with an antibacterial spectrum of activity could be responsible for this antibiotic-associated colitis, but the major offenders in the first 25 years were clindamycin and broad-spectrum antibiotics. During this period, CDI was regarded as a severe and potentially life-threatening complication of antibiotic use, but management guidelines were well established, and mortality rates were relatively low. In the early 2000s, there was a surge of cases of CDI that was first recognized in Quebec, Canada [2], which was followed by an increase in cases in the United States and much of Europe [3]. There was not only an increase in the number of cases but also a substantial increase in attributable mortality. It now appears that this surge of more disease and more serious disease due to CDI was possibly associated with a new strain identified as the NAP1 strain. The emergence of this organism was thought to be at least partially due to resistance by *C. difficile* to the fluoroquinolones, which was very uncommon in the historic strains, and the widespread use of these drugs was thought to contribute substantially to the surge in incidence of the aforementioned cases [4]. The NAP1 strain was also noted to produce several-fold
more toxin in vitro, which possibly accounted for the increase in severity [5]. Substantial study of the epidemic in Quebec showed a 5- to 10-fold increase in rates of infection and attributable mortality rates of close to 17% [2, 6]. The response in Quebec was aggressive and largely successful because of infection control and antibiotic control.

The 30-year history of CDI has been characterized by important observations that led to the guidelines that are now available from the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) [7], as well as guidelines from Europe [8], which are similar to those from IDSA/SHEA.

CDI is primarily associated with antibiotic use in hospitals and chronic care facilities. This epidemiology reflects the fact that these facilities harbor large populations of elderly patients (who are most vulnerable). Use rates of the antibiotics that induce the disease are high, and the pathogen is widespread in the hospital environment (eg, walls, floors, air, the hands of health care workers) [7, 9]. Hospitals have high rates of colonization with these spore-forming bacteria, which can survive on hard surfaces for years. The role of antibiotic control for prevention includes restraint in unnecessary abuse and, in outbreaks, the sometimes successful intervention of banning use of some agents based on epidemiologic data that define the major offending agent [10].

EMERGING RESISTANCE TO ANTIBIOTICS

Antibiotic resistance is an inevitable consequence of bacterial evolution and would occur even in the absence of antibiotic exposure. Nevertheless, these drugs clearly select for these more resistant bacteria by a simple Darwinian principle. The problem now encountered in the US and in most of the developed world is escalating resistance reflecting the obvious selective pressure of antimicrobial drugs, particularly in the health care environment where antibiotic use is concentrated. However, in contrast to the earlier part of the more than 3 decades of using these drugs, there is a dramatic decrease in the development of new antibiotics to deal with these resistant bacteria. In prior years, there was an evolution of resistant bacteria—primarily within hospitals and chronic care facilities—that was controlled by new drugs from the pharmaceutical industry, which was extremely adept at new drug development. However, that resource is now almost totally closed because of economic realities indicating limited markets and a difficult regulatory environment for antibiotic development compared with alternative health care markets that are far more profitable [11]. It should be noted that the lifetime of an antibiotic is often relatively limited, and antibiotics comprise one of the few segments of the health care market where extensive use of a product leads to a loss of benefit (ie, resistance). The impending crisis of limited new antibiotics was predicted in 2004 with the establishment of IDSA’s Antibiotic Availability Task Force, as well as in the document “Bad Bugs, No Drugs” [12].

The data from that report have been beautifully updated in the technical report “The Bacterial Challenge: Time to React,” issued by the European Centre for Disease Prevention and Control and the European Medicines Agency [13]. This document notes that the last new class of drugs active against Gram-negative bacilli was trimethoprim in the 1970s. More worrisome was their extensive review of the antibiotic pipeline for drugs in phase 2 development or beyond, indicating that there were no new classes of antimicrobials in the foreseeable future. The implication of this observation is that there will be no new drugs that can deal with the multiply resistant Gram-negative bacilli until 2018 at the earliest. This crisis is now so well recognized that the World Health Organization has identified antibiotic resistance as one of the major threats to human health [14].

The specific organisms identified as having evolving problems with resistance are summarized by the acronym ESKAPE (ie, Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) [15]. Five to ten years ago, attention was focused largely on S. aureus, most particularly on the USA300 strain that caused widespread epidemics in diverse settings in the US and similar problems in Europe [16]. More recently, there has been greater attention on the rapid evolution of highly resistant Gram-negative bacilli, accounting for 4 of the ESKAPE organisms, especially extended-spectrum β-lactamase–producing and carbapenemase-producing Enterobacteriaceae [17]. Most recently, we have seen the rapid spread of the New Delhi carbapenemase in ACA Enterobacteriaceae that is now generally resistant to all antibiotics except for tigecycline and colistin [18].

Colistin serves as a reasonable surrogate to use for extremely drug-resistant Gram-negative bacilli because it is generally reserved for cases where alternative antibiotics with activity are not available. It has been extremely difficult to get national sales data for colistin, but use rates at Johns Hopkins Hospital are probably representative of the use trend. There were 96 courses in 68 patients in the calendar year 2009. Based on use during the past 5 years, the projection is for more than 1600 courses by 2014. It should be noted that history has taught us that an average of 8 years is required to bring a drug to market from start to finish, which accounts for the dire predictions of no new antibiotic classes until after 2018. The intent here is to emphasize the need to plan our response in the face of escalating resistance to very limited options and the predictable future problems including colistin in terms of both nephrotoxicity and resistance [19, 20].

STEWARDSHIP

Most important for our discussion is the development of adequate plans for prevention to the extent possible as noted, a medical discipline, and effectiveness based on rates of usage.
Thus, antibiotic stewardship becomes a pivotal issue in our ability to better cope with increasing resistance, which is an inevitable consequence of bacterial evolution but heavily influenced by our use of antibiotics.

ANTIBIOTIC STEWARDSHIP

Antibiotic stewardship is an important component for our challenges in both microbial resistance and CDI. For resistance, the issue is the need to conserve the effectiveness of the currently available antibiotics by limiting their use based on basic and evolving principles; for CDI, the need is development of data to document institutional epidemiologic patterns with both broad and targeted interventions. Guidance in establishing appropriate stewardship programs is available, and effectiveness of these programs is well documented [21]. Specifically, the collected experience documented in this guideline review showed reduction in antibiotic use of 22%–36% and resulted in annual cost savings of $200,000–$900,000. Specifics of these programs will vary by resources, hospital size, and local experiences, but some recent reports with specific opportunities include the following:

- A review of management of infections of skin and soft tissue in hospitalized patients showed extensive over-prescribing of antibiotics that are active against Gram-negative bacteria despite culture data showing Streptococcus or S. aureus in 97% of patients with positive cultures, extensive use of imaging with positive results in only 4%, and excessive duration of antibiotics [22]. The authors specifically called for the need for antibiotic stewardship in managing these infections.
- Microbiology is in a state of transition with the rapid evolution of new tests that require expertise in selection of methods and interpretation of results. An example is the rapid polymerase chain reaction to detect methicillin-resistant S. aureus (MRSA) in blood cultures. Use of this technology at Ohio State University Medical Center showed that antibiotic adjustments were made 1.7 days earlier, the mean length of stay averaged 6.2 days shorter, and mean costs were reduced by $21,387 per patient [23].
- The new guidelines for vancomycin dosing represent a radical change in the use of this antibiotic [24], which represents the most common antibiotic used in US hospitals. Further, these guidelines call for substantial increases in dosing for a drug that now has a tight toxicity:therapeutic ratio and emphasizes the need for alternative agents that target MRSA. Vancomycin issues are further complicated by recent data showing variable in vivo activity based on relative quality of different generic supplies [25].
- Many studies now show that antibiotic conservation can be notably improved by using shorter courses of these drugs than is customary practice in certain diseases. Examples are ventilator-associated pneumonia [26], community-acquired pneumonia [27], and septic arthritis [28].

These examples are a minor component of the total needs of a good antibiotic stewardship program, but they serve to illustrate the magnitude of both the need and the opportunities in this area.

Acknowledgments

Supplement sponsorship. This article was published as part of a supplement entitled “Antimicrobial Stewardship for the Community Hospital: Practical Tools and Techniques for Implementation,” jointly sponsored by the University of Cincinnati and Rockpointe Corporation, ACPE credit provided by Potomac Center for Medical Education, and supported by an educational grant from Ortho-McNeil.

Potential conflict of interest. The author reported no conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

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