IDSA LECTURE

The Maxwell Finland Lecture: For the Duration—Rational Antibiotic Administration in an Era of Antimicrobial Resistance and *Clostridium difficile*

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Antimicrobial resistance is frequently associated with clinical use of antibiotics. This close association suggests that efforts to manage our use of these potent agents can have an impact on the prevalence of resistance. Unfortunately, one size does not fit all when considering the response of bacterial pathogens to antimicrobial exposure. Measures that may prevent resistance in some species (such as using multiple antibiotics to treat tuberculosis) may exacerbate the problem of resistance in others (such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*). The simplest approach is to use fewer antibiotics and thereby apply less selective pressure to the prevalent flora. Among available strategies to reduce use, reductions in length of antimicrobial regimens are the safest and are likely to be the most palatable to practicing clinicians. Studies are urgently needed to define minimal lengths of therapy to ensure that efforts at reduced use are safe and effective.

I will talk today about the way we use our antimicrobial agents, the most powerful weapons in our arsenal to treat serious bacterial infections. In particular, I will address the collateral damage associated with our use of antibiotics—primarily, the emergence of resistance and infection with toxigenic strains of *Clostridium difficile*—and ways in which we can minimize this damage.

THE VARIETIES OF ANTIMICROBIAL RESISTANCE

The landscape of resistance is quite varied and complex. As such, rules and strategies that work well for preventing resistance in some bacteria may exacerbate resistance in others. When considering pathogenic bacteria, it is worthwhile to divide antimicrobial resistance into 3 general categories: simple, moderately complex, and highly complex.

Simple resistance is exemplified by *Mycobacterium tuberculosis,* for which resistance can be reduced to a mathematical calculation. In a susceptible population of *M. tuberculosis,* it can be safely predicted that the rate of mutational resistance to isoniazid will be $\sim 1 \times 10^{-6}$ resistant mutants/cfu. The rate of mutational resistance to rifampin in the same population will be roughly 1×10^{-9} resistant mutants/cfu. The rate of spontaneous resistance to both of these agents will therefore be the product of these 2 numbers, or 1×10^{-15}. In grossly infected pulmonary cavities, the number of *M. tuberculosis* colony-forming units will be $\sim 1 \times 10^{12}$, so it can safely be predicted that emergence of resistance to both rifampin and isoniazid in this population will be very rare. Complexities in the treatment of tuberculosis do occur in the setting of multidrug-resistant strains, but the basic mathematics remains the same, because as far as we can determine, resistance in *M. tuberculosis* occurs solely through mutation of chromosomal genes and never through resistance gene transfer [1].

Moderately complex resistance is typified by *Staphylococcus aureus* and enterococci. Resistance in these

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bacteria is, in some respects, simple, in that a susceptible strain at the start of therapy is not likely to emerge resistant during therapy. One exception to this rule is the emergence of vancomycin-intermediate strains of *S. aureus* (VISA) after prolonged exposure to vancomycin [2]. On the other hand, both *S. aureus* and enterococci exhibit complexity in that they both exchange DNA with a variety of other bacterial species [3, 4]. Therefore, it is common to encounter multidrug-resistant strains of either staphylococci or enterococci even in the absence of prior exposure to antimicrobial agents. The emergence of multidrug-resistant *S. aureus* in both the hospital and community and the worldwide spread of a multidrug-resistant clone of *Enterococcus faecium* are examples of this multidrug resistance [5, 6].

Highly complex resistance is exemplified by the nonfermentative gram-negative bacteria *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* These bacteria have a wide array of intrinsic resistance mechanisms that can be expressed in response to antimicrobial exposure (figure 1). It is not unusual for *P. aeruginosa,* in response to antimicrobial exposure, to reduce expression of the outer-membrane proteins (porins) that allow entry into the periplasmic space. In addition, they can activate 1 or more of several multidrug-resistance pumps that efflux a variety of antibiotics. Finally, they can increase production of native enzymes, such as β-lactamases, that further serve to reduce the effectiveness of specific antibiotics [7]. The most troublesome by-products of the porin and pump resistance mechanisms is that they confer resistance to a variety of different antimicrobial classes, leading to the possibility that exposure to one class of antibiotics can result in emergence of resistance to many different classes.

Beyond their ability to emerge resistant during therapy by activating intrinsic mechanisms, both *P. aeruginosa* and *A. baumannii* readily exchange DNA with other species. A dramatic example of this acquisition is the recent report on a comparison of a susceptible and multidrug-resistant *A. baumannii* strain [8]. The resistant strain contained an 86-kb region of the genome that encoded >40 determinants conferring resistance to at least 7 classes of antibacterial agents. The susceptible strain had no resistance genes in this location, suggesting acquisition

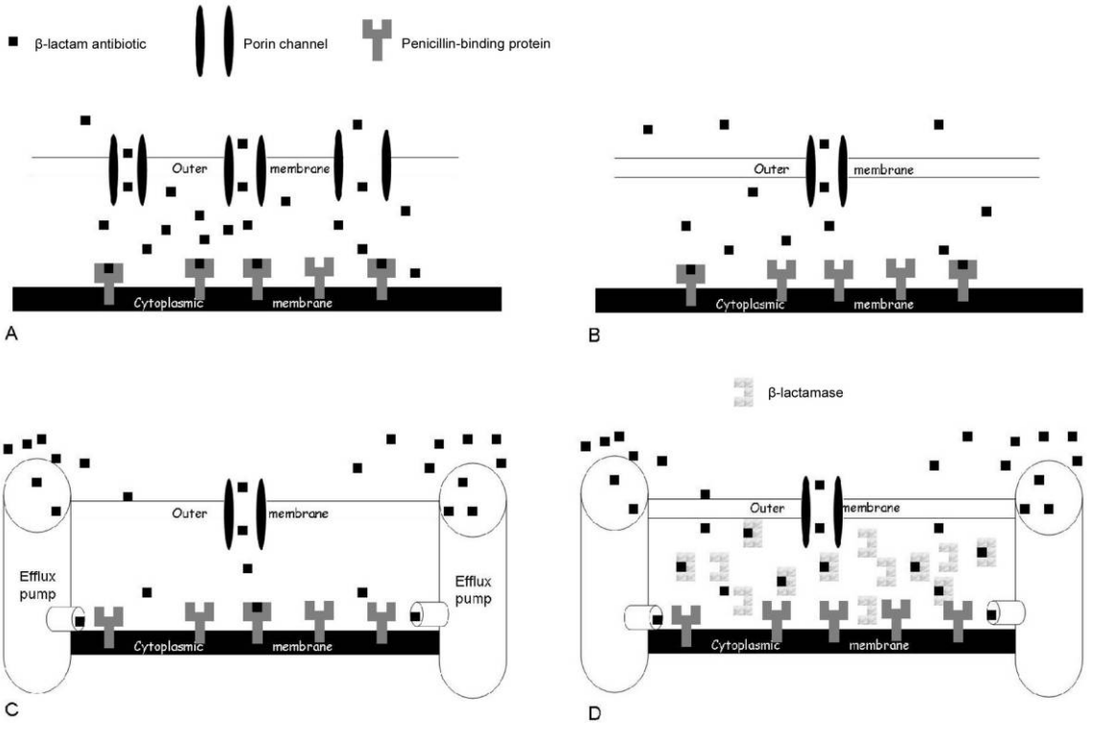

Figure 1. Evolution of intrinsic resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii. A,* The baseline state, in which β-lactam antibiotics can enter the periplasmic space (the space between the outer membrane and the cytoplasmic membrane, where the cell wall exists) and interact with the penicillin-binding proteins, inhibiting cell wall synthesis leading to cell death. *B,* The bacteria can readily reduce their expression of the outer membrane proteins (porins) that allow entry of β-lactams into the periplasmic space. This mechanism by itself does not generally result in clinically significant levels of resistance. *C,* In response to antimicrobial selective pressure, bacteria can increase expression of a variety of multidrug efflux pumps, which number several antimicrobial agents among their substrates. Pump activity generally yields relatively low levels of resistance in the absence of other mechanisms. *D,* Increased expression of β-lactamase, in the setting of porin reductions and efflux pump activations, can result in high levels of resistance to β-lactam antibiotics.

in one or relatively few genetic events. Homology analysis suggested that the genes had been acquired from *P. aeruginosa, Salmonella* species, and *Escherichia coli,* among others.

ANTIMICROBIAL USE STRATEGIES TO REDUCE RESISTANCE

Blast them. The "blast them" strategy is the practice of using >1 antimicrobial agent to prevent the emergence of resistance. This strategy derives from the early observation that multiple antimicrobial agents were effective at preventing the emergence of resistance in *M. tuberculosis.* Application of this strategy to bacteria exhibiting moderately complex or complex resistance is problematic, however, in that the frequency of multidrug resistance in moderately complex bacteria and the emergence of multidrug resistance during therapy in the highly complex bacteria suggest that more antibiotics will likely lead to more resistance. Fluoroquinolone selection for resistance to imipenem in *P. aeruginosa* and cephalosporin selection of resistance to vancomycin in *E. faecium* are 2 examples of coselection [9, 10]. It is therefore not surprising that the use of combinations of antibiotics has never been shown to reduce the emergence of resistance in routine bacteria.

Fool them. A second strategy to prevent resistance emergence has been the "fool them" strategy, best exemplified by antimicrobial cycling or "crop rotation." Under these plans, one class of antibiotics (such as broad-spectrum β-lactam/β-lactamase–inhibitor combinations) is used preferentially for a specified period of time—for example, 3 months. After the 3-month period is over, empirical regimens are switched to feature a different class, such as fluoroquinolones, carbapenems, or cephalosporins. This rotation continues in an effort to intermittently change the selective pressure being applied to the resident bacteria. To date, there are no compelling data to support antimicrobial cycling as an effective technique for preventing or reducing resistance [11].

The failure of cycling in this regard should not be surprising. In practice, firm cycling rotations are difficult to enforce, given varied microbiology, resistance patterns, and patient intolerance of certain antibiotics. More importantly, the theoretical underpinnings of cycling strategies are flawed. The multidrug resistance that is already endemic in many hospitals, combined with the capacity of some antimicrobial classes to select for resistance to other classes, makes designing a regimen to reduce selection virtually impossible. It is a bit like offering an alcoholic the choice to rotate beer, wine, gin, and whiskey as a strategy to prevent liver disease.

Stop irritating them. The most reasonable strategy to minimize resistance is to stop irritating the bacteria—in other words, to reduce our use of antibiotics to the bare minimum necessary to safely treat patients with serious infections, in the hope that this will reduce selective pressure and thereby reduce the prevalence of resistance. There are 3 points at which antimicrobial selective pressure can be reduced: before therapy begins, by treating only those patients who are truly infected; during therapy, by avoiding the use of combination antimicrobial agents when a single agent will suffice; and at the tail end of therapy, by treating only for as long as is required to cure the infection.

Many efforts have been made to reduce physicians' use of antibiotics when they are not necessary. In particular, prescribing antibiotics to treat upper respiratory tract symptoms likely due to allergy or viral illness has been discouraged. Although there have been successes for this strategy, particularly in the treatment of pediatric upper respiratory infections [12], the challenges of implementing it in the nosocomial setting are significant. There are now ample published data indicating that delayed appropriate treatment of patients with a range of serious infections (e.g., bacteremia and pneumonia) will lead to a poorer outcome than early effective therapy [13, 14]. In a setting where failure to adequately treat an infection early could lead to a fatal outcome, physicians are understandably reluctant to withhold therapy if they are unsure about the nature of the patient's illness. Similarly, the imperative to treat with effective therapy encourages—and often mandates—the use of combination therapy, at least until the cause of the infection is identified. Attempts to intervene at the time of acute illness are often poorly received by treating physicians, who may be reluctant to give up control of antimicrobial therapy to physicians who do not know their patients as well as they do.

The most viable strategy for reducing antimicrobial selective pressure is to treat infections only for as long as is necessary. Shortening courses would not only benefit patients appropriately treated with narrow-spectrum antimicrobial agents but would also reduce exposure associated with patients treated inappropriately or patients given more antibiotics than they truly need. Unfortunately, the evidence available for reducing lengths of therapy is similar to evidence supporting our current prolonged dosing regimens: poor. Under these circumstances, physicians will often extend antimicrobial courses even beyond clinical improvement, just "to be sure." Such practices reflect an underlying belief that the administration of antimicrobial agents is, at worst, a neutral therapeutic choice. The emergence and spread of antimicrobial resistance, along with the recent outbreak of severe *C. difficile* infection, are clear indications that such attitudes are ill-advised and potentially dangerous.

THE STATE OF OUR KNOWLEDGE ON LENGTHS OF ANTIBIOTIC COURSES

There are illnesses for which length of therapy has been examined in some detail. There are very reasonable data for administering short (1- or 3-day) courses of therapy to young females with urinary tract infection. Great efforts have been

made to reduce the length of therapy of most sexually transmitted diseases to a single dose, for the obvious reasons of poor compliance on the part of this patient population and the desire to prevent further disease transmission. Endocarditis caused by some bacteria (in particular, viridans streptococci) may be shortened to 2 weeks if penicillin is combined with an aminoglycoside. Treatment of group A streptococcal pharyngitis with penicillin requires 10 days to effectively eliminate colonization. Length of therapy has been studied extensively in tuberculosis in an effort to reduce length of therapy to the shortest possible time without compromising effectiveness. Unfortunately, these infections represent only a small minority of antibiotic prescriptions.

A review of the Infectious Diseases Society of America (IDSA) guidelines for the treatment of specific infections illustrates how limited our knowledge of required lengths of therapy is in most instances. Three days of treatment is recommended for traveler's diarrhea, although the authors acknowledge that 1 day appears to be equally effective [15]. There is no mention of length of therapy for routine cellulitis [16]. A 3–7-day course is recommended for treatment of asymptomatic bacteruria [17]. Meningitis should be treated for 7–21 days, depending on the pathogen ("based more on tradition than evidence-based data") [18, p. 1281], whereas lower-extremity infections in diabetic patients can be treated for 1–2, 2–4, or 4–6 weeks, depending on the severity of the infection [19]. As suggested by the variation even within indications, there is little basis in evidence for most of these recommendations. The recommendations for the treatment of abdominal wound infections are eminently practical and reasonable—"[antimicrobial] therapy for established infections should be continued until resolution of clinical signs of infection occurs, including normalization of temperature and WBC count and return of gastrointestinal function"—but they are based on the results of only a single uncontrolled study [20, p. 1001].

A more detailed look at recommendations for treatment of community-acquired pneumonia (CAP) is instructive. Older versions (1998 and 2000) of the guidelines contained the following comment: "We are not aware of any controlled trials that have specifically addressed the questions of how long pneumonia should be treated." This statement was followed by the statement that patients should be treated for 72 h after they have become afebrile. Revised guidelines in 2007 state, "Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy (level II evidence)" [21, p. 530]. None of these recommendations are supported by well-controlled, prospective clinical trials.

So how long must CAP be treated? It is instructive to review the original literature on the treatment of pneumococcal pneumonia with penicillin. In a 1943 report on treating 500 patients with penicillin, Keefer et al. [22], referring to the subset of patients with pneumococcal pneumonia, stated, "It is plain from the reported cases that…many patients have recovered on less than 100,000 units given over a period of two to three days." Dawson and Hobby [23], in their 1944 report on treating 100 patients with penicillin, stated that "In general, the results were satisfactory with doses of 10,000 units every four hours for one and a half to two days." In another 1944 report, Tillett et al. [24] stated that it may be seen that "most of the patients, 31, were treated for 3 to 4 days. Among this group, when no complicating factors [primarily empyema an underlying chronic obstructive pulmonary disease] existed, the initial improvement persisted as permanent cure."

In 1945, Meads and Finland [25] treated patients with pneumococcal pneumonia "until there was definite clinical improvement and the temperature had remained below 100°F for 12 hours…then given for another two or three days." Forty-four of 54 patients in this study survived. Of the 44 who survived, 2 relapsed. One relapsed with the same pneumococcal serotype after receiving only 24 h of therapy. The other relapsed 10 days after treatment, with an organism of a different serotype. Despite this remarkable success, these relapses weighed heavily on the authors, leading them to suggest, "The need for continuing treatment even after the fever and symptoms subside is suggested by the relapses that have occurred in this series."

In 2006, el Moussaui et al. [26] published a prospective, blinded, randomized trial comparing 3 versus 8 days of amoxicillin therapy for the treatment of community-acquired pneumonia. They concluded that the 3-day regimen was equivalent in efficacy to the 8-day regimen. Although this study is not definitive, it is highly suggestive that the original observations of the early pneumonia investigators were valid. So why did it take us 60 years to get back to this point?

WHAT WENT WRONG?

A variety of factors conspired to cause physicians to "take our eyes off the ball." Antibiotics were a marvelous discovery, and the commercial potential was readily recognized by pharmaceutical companies, leading to massive efforts at antibiotic discovery. These efforts were a huge success, leading to the introduction of increasing numbers of broad-spectrum antimicrobial agents. It is perhaps forgivable that an attitude developed that we had infectious diseases on the run and that soon we would have an antibiotic for every infection. Among the more telling comments of the day was the 1969 statement by William H. Stewart, then Surgeon General, that "[it] is time to close the book on infectious diseases" [27]

It is also a fact that antibiotics are remarkably safe drugs (aside from the collateral damage). This led to their use by a

wide variety of physicians, many of whom developed their own methods of practice with them. Antibiotics are quite different from most commonly prescribed drugs, however, in that they are designed to be dosed for only a limited time. A review of the top 50 prescribed brands from the Humana Web site [28] revealed that only Levaquin (the only antimicrobial agent on the list) is routinely used in a time-limited manner. Physicians felt little obligation to limit therapy with antibiotics, because most did not limit their therapies for anything else.

One can never discount the importance of money in the course of human events. Antibiotics have been huge money-makers for pharmaceutical companies for decades. There is little incentive of the part of pharmaceutical companies to sponsor research into shortening lengths of therapy, and resistance is not a major concern when you plan to release a newer antibiotic with a broader spectrum in the future. Sadly, antibiotics were the center of a large scandal very early in their history, when it became apparent that Henry Welch, the preeminent expert in antibiotics and the Director of the US Food and Drug Administration's Division of Antibiotics, had accepted large sums of money from the pharmaceutical industry while promoting their interests in the journals he edited and the conference he sponsored [29].

Perhaps the most difficult perspective to fathom is that prolonged courses of antibiotics have been considered to be the solution to—rather than the cause of—resistance. One need look no further than the Center for Disease Control's "Get Smart" Web site (http://www.cdc.gov/getsmart), which was designed to inform the general public about the problem of antimicrobial resistance. In a piece clearly designed to talk about factors that will make resistance worse, the site recommends that patients should "[finish] the prescription even if you feel better." This may be excellent advice when one wants to have the patients take an adequate course to treat an infection, but it is poor advice for preventing resistance. That prolonged courses of therapy are associated with increased resistance is documented by 2 recent studies of pneumonia treatment [30, 31]. We need to get our messages straight.

WHERE DO WE GO FROM HERE?

It will be very difficult to alter prescribing practices of physicians to shorten therapeutic courses without a strong basis in evidence supporting the safety and efficacy of such changes. We therefore need well-controlled, randomized studies of routine infectious illnesses to help define the minimum safe courses and the optimal therapeutic regimens. For obvious reasons, it is unlikely that the pharmaceutical industry will be a major supporter of such research, except in the infrequent event that a specific product would be favored by its use in a shorter course. The societal importance of preserving the activity of our antimicrobial agents argues for support of these studies by national agencies. To that end, the IDSA Research on Resistance Working Group has entered into a dialogue with officials at the National Institute for Allergy and Infectious Diseases to promote beginning these investigations. We have initially suggested 3 paradigm studies (a placebo-controlled otitis media trial, a 3-armed CAP trial to examine the value of combination therapy and the length of treatment, and a 3- vs. 7-day trial of simple cellulites). It is hoped that these studies will serve as a nidus for the development of a de facto network of sites that will perform clinical studies to define optimal antimicrobial therapy for a variety of syndromes.

Officials at the National Institutes of Health have been receptive to these suggestions. Given the significance of this work, it will also be important to engage other large funding agencies, including the Department of Veterans Affairs, the Department of Defense, and The Bill and Melinda Gates Foundation, among others.

A TIME OF CHALLENGE AND OPPORTUNITY

Although it may not always seem like it, as infectious diseases physicians, we are living in a time of enormous opportunity resulting from the dynamic nature of health care delivery in the United States. Over the past decade, regulatory agencies and the American public have come to recognize nosocomial infections as a major—and perhaps *the* major—patient safety issue of our time. The relative sluggishness with which physicians and hospital administrators have addressed many issues surrounding nosocomial infections has prompted a strong push from regulatory agencies and the public for institutional changes designed to directly address the problems of hospital-acquired infections in general and antimicrobial resistance in particular. As examples, the Department of Veterans Affairs has recently introduced a wide-ranging effort to control the spread of methicillin-resistant *S. aureus* within its hospital system, investing substantial sums to promote identification and isolation of colonized patients and to promote better infection control practices. At the present time, 24 states have regulations requiring the public or private reporting of infection rates [32], and the Center for Medicare and Medicaid Services has recently announced plans to refuse payment for selected infections deemed to be preventable by employing best practices. Finally, one need not search far on the Internet to find opportunistic personal injury attorneys seeking patients who have fallen victim to nosocomial infections, particularly those caused by resistant bacteria.

The initial implementation of the above plans will be controversial and will certainly result in problems and unanticipated consequences that will need to be addressed. None of the problems are likely to lead to an abandonment of the plans or a reversal of the trend toward holding individuals and institutions responsible for nosocomial infections deemed to be

preventable. Within these challenges lie tremendous opportunities for infectious diseases physicians. For the first time in memory, our knowledge and expertise will be critical to the successful implementation and further development of widespread changes within our health care system. Because money and reputation will be at stake for hospital systems, physicians expert in infectious diseases and infection control will be given a seat at the table like never before. It is critical that we take this seat and use our positions to promote organization and dissemination of presently available knowledge, as well as future studies designed to clarify best practices, including optimization of antimicrobial regimens.

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