Rapid Diagnostics and Appropriate Antibiotic Use

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Most antibiotics are prescribed by physicians lacking postgraduate training in infectious diseases. As such, prescribing physicians have varying levels of interest and sophistication in thinking about how to use molecular and microbiological data to inform therapeutic choices. Strategies designed to modify physician antimicrobial-prescribing practices must therefore choose simplicity over complexity and must acknowledge our fundamental ignorance of many of the specifics of antibiotic-microorganism interactions. They must also acknowledge the critical nature of bacterial illnesses in hospitalized patients and the importance of delivering effective antimicrobial therapy early in the illness. “Back-end” strategies that evaluate therapy at defined intervals will be more readily accepted than strategies limiting physician choices early in the illness. It is therefore critical that we develop rapid and reliable microbiological assays, evidence-based recommendations on appropriate durations of therapy, and accurate surrogate markers of infection resolution.

Antimicrobial resistance is a growing problem that is reaching crisis proportions in many hospitals. Outbreaks of antimicrobial-resistant bacteria are generally attributable to a combination of 2 things: lapses in infection control and the application of selective pressure through exposure to antimicrobial agents. Which factors play the predominant role will depend in part on the nature of the environment and the characteristics of the bacteria. For example, water-rich environments favor the growth and propagation of Acinetobacter baumannii [1]. Infection control lapses may be more important for the spread of methicillin-resistant Staphylococcus aureus (MRSA) because of the rugged nature of this species and its colonization of regions (eg, skin and nares) not reached in significant concentrations by many antimicrobials [2]. Outbreaks of extended-spectrum β-lactamase (ESBL)–producing Klebsiella pneumoniae infection, in contrast, may be more responsive to antimicrobial control interventions, perhaps because of the organism’s colonization of the human gut and the decreased efficiency of ESBLs against penicillins [3]. In practice, interventions in both areas are frequently used to respond to outbreaks of resistant pathogens.

THE PROBLEM OF INCOMPLETE KNOWLEDGE

It is often suggested that one key to reducing unnecessary antimicrobial use is the rapid identification of causative pathogens. Physicians so informed could tailor therapy in ways that minimize the selective pressure favoring emergence and spread of antimicrobial resistance. This rationale makes intuitive sense, but it is based on several questionable assumptions.

The first questionable assumption is that physicians and other antibiotic prescribers (the majority of whom lack fellowship training in infectious diseases) are interested in and moved by laboratory results that inform antibiotic choices. As a way of exploring this assumption, I will recount a personal anecdote that exemplifies some of the chasms that exist between the attitudes of different physicians. A relative of mine was to undergo an orthopedic surgical procedure. I accompanied this relative to the orthopedic surgeon’s office for the pre-procedure visit, where we discussed relevant issues, such as rates of MRSA infection at the institution and practices (such as chlorhexidine baths) to minimize the risk...
of postoperative infection. The surgery was successful, but one of the sutures came loose during the first week after the operation. On return to the office, the surgeon acknowledged that the suture had dislodged, and he expressed some dark material from the wound. He stated that he thought that the material represented an uninfected hematomata, but that he would prefer to prescribe a course of cephalaxin. I agreed that the wound did not appear to be infected but expressed my preference to treat with antibiotics only if signs of infection appeared.

I then asked the surgeon to swab the wound for a culture. He looked uncomfortable and said that culturing uninfected wounds was not the common practice, because it would be difficult to know what to do with a positive culture result. I assured him that I would be happy to take that responsibility, that should the wound begin to look infected I wanted to know what bacteria to treat sooner rather than later. He performed the culture. On day 2, the culture grew \textit{S. aureus}. The wound continued to look uninfected, but I became nervous about the possibility of community-acquired MRSA getting into the joint and asked the physician to prescribe 3 pills of linezolid until susceptibility data for the \textit{S. aureus} strain became available. In the end, the culture grew methicillin-susceptible \textit{S. aureus}, \textit{Streptococcus agalactiae}, and \textit{Moraxella catarrhalis}. Comfortable that the culture did not reflect the reality of the wound, antibiotic therapy was discontinued, and healing proceeded uneventfully.

I relate this anecdote not to suggest that either the surgeon’s or my perspective on testing and antibiotics is necessarily correct. The surgeon’s strategy would have given unnecessary, potentially ineffective (against MRSA) but relatively benign antimicrobial therapy for a noninfected wound. On the other hand, my strategy led to the cost of a culture that provided misleading information that led to unnecessary use of a very expensive antimicrobial agent. In retrospect, the correct strategy would probably have been to withhold antibiotics and refrain from culturing the wound unless it looked infected, but as the circumstances evolved, this ideal course became more difficult to follow. This anecdote exemplifies the large differences in perspective that can exist when 2 well-intentioned, competent physicians consider matters of diagnostic microbiology tests and antimicrobial therapy and demonstrates that the mere availability of a test does not guarantee its use according to defined norms.

The second questionable assumption is that physicians have a common understanding about the relationship between antimicrobial use and resistance. Many physicians seem to think that antimicrobial agents are the answer to the resistance problems. They pursue a “blast ‘em” strategy, in which multiple antibiotics are seen as a means to prevent the emergence of strains resistant to any one of the administered antibiotics. There is a rational historical basis for this strategy found in the early treatment of tuberculosis, for which very early successes with streptomycin therapy were followed by recurrent infections due to streptomycin-resistant \textit{Mycobacterium tuberculosis} strains [4]. Investigators at the time correctly reasoned that mutational resistance arising at a predictable frequency could be suppressed by the addition of a second agent with a different mechanism of action (ie, an agent active against the resistant strains).

Unfortunately, the simple mathematics of tuberculosis resistance do not apply to current nosocomial bacteria that express resistance through a variety of mechanisms, many of which confer resistance to more than one antibiotic. The genome of \textit{Pseudomonas aeruginosa}, for example, may encode as many as 12 Resistance-Nodulation-Cell Division multi-drug efflux pumps [5]. In addition, \textit{P. aeruginosa} is readily able to reduce its complement of outer member proteins (porins) and to increase its expression of a broad-spectrum chromosomal cephalosporinase, with the final effect of creating resistance to a wide variety of antimicrobial agents [6]. Moreover, the exchange of plasmids and transposons (not, as far as we know, a factor in \textit{M. tuberculosis}) in modern nosocomial pathogens makes multidrug resistance the rule rather than the exception in clinical settings. In one particularly telling example, complete genome sequence analysis of susceptible and resistant \textit{A. baumannii} strains revealed the presence of a resistance “island” in which nearly 50 open-reading frames conferring resistance to at least 7 different classes of antibiotics were present [7]. Comparison with the susceptible strain (which in the same genome location had ~20 kb of nonresistance DNA) suggested the real possibility that these genes were acquired from other gram-negative bacilli in a single event. Clearly, more antibiotic exposure is not the answer to resistance in these important nosocomial pathogens.

The opposite perspective on antimicrobial resistance is that antibiotic use is the cause of antimicrobial resistance. This perspective, held by many in the infectious diseases community, has the virtue of being practically true but intellectually tenuous and functionally irrelevant. It is practically true because without the clinical use of antibiotics, resistance would remain unanalyzed and largely unknown to us. It is intellectually tenuous because antibiotics may not be weapons in an age-old struggle between microbes for dominance, but rather small signaling molecules whose purpose is to facilitate interspecies communication when present in much smaller quantities than are used clinically [8]. In this context, some resistance mechanisms may also be part of these communication mechanisms. The perspective is functionally irrelevant, because we cannot live in a world without antibiotics. Much of modern medical technology is predicated on the ability to control and eliminate bacterial and fungal infections that inevitably occur when we treat serious illnesses.

The third questionable assumption is that we have sufficient knowledge of the relationship between use and resistance to be able to adjust regimens in a way that will minimize resistance. The most common catchword for this sort of maneuver is “de-escalation” [9]. A common example of de-escalation is...
a recommendation to switch patients’ regimens from ceftriaxone to ampicillin when ampicillin-susceptible *E. coli* are isolated from the blood of an infected patient. Implicit in this statement is the assumption that the antimicrobial spectrum of ampicillin is “narrower” than that of ceftriaxone, for example. There is no question that ceftriaxone is more active than ampicillin against problematic gram-negative pathogens, such as *Klebsiella pneumoniae* and *Enterobacter* species, as well as against methicillin-susceptible *S. aureus*. However, ampicillin is far more active than ceftriaxone against enterococci and most anaerobes, so which antibiotic is truly more “broad-spectrum”? Do we even know whether broad-spectrum antibiotics promote resistance more than narrow-spectrum ones? Moreover, the designation of “susceptible” or “resistant” is a clinical definition based on likelihood of successful therapy. It does not preclude the possibility that the inactive antibiotic could interact in some manner with the pathogen, perhaps in ways that could promote resistance without our knowledge. Given the woeful state of our knowledge in this regard, the only truly convincing form of de-escalation is discontinuation.

**Can Physicians Be Motivated to Change Their Antibiotic Prescribing Practices?**

Well-organized, coherent programs with clear goals can be successful at reducing antimicrobial prescribing in the community setting. Reduced antimicrobial prescriptions were achieved in response to increases in penicillin resistance in *Streptococcus pneumoniae* in Iceland in the 1990s [10]. The US Centers for Disease Control and Prevention has had a significant impact on pediatric antibiotics prescribing through its “Get Smart” campaign (http://www.cdc.gov/getsmart/). Most recently, antimicrobial consumption in France was reduced by >25% in conjunction with a national program designed to educate prescribers about proper use of antibiotics in the community setting [11]. Time will tell whether resistance in France will be reduced in association with this intervention.

Community interventions are aimed at preventing empirical antimicrobial prescriptions in settings where bacterial infection is unlikely and where the illness in question is rarely, if ever, fatal. It is not clear whether similar strategies can be safely applied to the nosocomial setting. There are now compelling data to suggest that delays in treating serious infections with appropriate antimicrobial agents are associated with worse outcomes [12–16]. Because it is often difficult at the time of admission, or at a time of clinical deterioration, to know whether an illness is a bacterial infection, prudence dictates the empirical treatment of these episodes with antibiotics, often with combinations of antibiotics designed to maximize the chance that at least one of the administered agents will be active against the infecting pathogen(s).

In situations of such uncertainty, programs designed to discourage empirical antimicrobial use are doomed to fail. It could be argued that the viability of “up-front” restriction strategies would be greater if physicians had better information regarding the nature of the patient’s illness—specifically, whether the patient is infected with bacteria and, if so, the identity of the species and its susceptibility profile. Because there are no such rapid tests clinically available at this time, we cannot state with certainty how they would be used. The impact such diagnostic tests will have on clinical practice will, in my view, depend more on the tests’ specificity (whether they can “rule out” specific pathogens) rather than their sensitivity. Physicians are often inclined to treat patients for what “might also be there,” even if a specific pathogen is identified. Unless physicians can be convinced that a negative result means with certainty that the patient does not have the disease, the perceived safety of the antibiotics themselves will be used as justification for continued coverage by many physicians.

**Downstream Is Where the Money Is in Hospitalized Patients**

If it is difficult and potentially unsafe to withhold antimicrobial agents from seriously ill hospitalized patients, but we still want to reduce antimicrobial exposure, then our only alternative is to reduce therapy durations. There are 2 ways to do this. The first is to create a culture in which negative bacteriological test (molecular or traditional) results lead to discontinuation of antimicrobial therapy after 48 h. Such a major culture shift would be greatly aided by the availability of highly reliable rapid diagnostic tools for a variety of infections. The combination of negative test results with clinical stability at 48 h will provide ample data from which stewardship programs can base educational initiatives, especially as physicians become increasingly cognizant of the severity and preventability of *Clostridium difficile* colitis.

The second way of reducing antimicrobial exposure is to reduce the absolute durations of therapy in patients with documented infections. It is very likely that the current recommended durations of therapy, which were never based of comparative experimental data, a far longer than is absolutely necessary [17]. We therefore need to acquire evidence-based data on which to make length of therapy decisions. Recent studies comparing 3 versus 8 days of therapy for community-acquired pneumonia (which were found to be equivalent) [18] and 8 versus 15 days of therapy for ventilator-associated pneumonia (which were found to be equivalent in a large measure) [19] are excellent examples of the kinds of studies that will provide the bases for changing practices. The recent Broad Agency Announcement by National Institutes of Allergy and Infectious Disease (BAA - NIAID - DMID - NIHAI2008025) soliciting studies to look at antibacterial therapy (including therapy lengths) is an excellent start to acquiring more of these data. It is highly unlikely, however, that we will be able to acquire hard data on lengths of therapy for a large number of infections, so physicians must be willing to extrapolate from the available studies to make individual judgments in favor of discontinuation when serious sequelae are unlikely.
It is also unlikely that one size will fit all with regard to duration of therapy, because illnesses vary in severity, patients vary in condition, and bacteria differ in virulence and susceptibility. Such decisions would therefore be greatly aided if we could have an individual measure of a patient’s response to therapy. Procalcitonin, addressed elsewhere in this issue of the journal, may be such a surrogate marker [20, 21].

Changing Practice Will Require Education
As noted above, the mere availability of a test will not change physician practices when it comes to antibiotic prescribing. Educational programs will be required to convince physicians of the reliability of the test and of the potential deleterious consequences (legal and otherwise) of continued antimicrobial therapy when data are available that suggest it is not necessary. As such, research into educational interventions that change physician behavior will be important, so that when the data are available, they can be effectively used to create a safer hospital environment of patients.

It will be important for educational programs to keep the message simple to facilitate acceptance by prescribers. To this end, I would favor emphasis on an on/off approach to antibiotic administration, rather than arcane attempts to distinguish between broad- and narrow-spectrum antimicrobials. As noted above, such distinctions may be useful when considering empirical coverage of an infection, but have no real basis when considering the impact on antimicrobial resistance.

CONCLUSIONS
Although it is often posited that better real-time information is required to improve physician antimicrobial-prescribing practices, physicians often fail to use tests already available or ignore their results. Successful strategies to change physician prescribing behavior will require a better understanding of the dynamics of antibiotic influence on resistance, an appreciation of the importance of broad-spectrum empirical therapy during critical illness, the availability of rapid, reliable tests to exclude specific infections and monitor severity of illness, and a better understanding of the educational techniques that can effectively change physician practices. Our ability to stem the growing problem of multidrug resistance in nosocomial pathogens will depend on our ability to make significant progress in each of these areas.

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