Antibiotic resistance

An impending crisis

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ABSTRACT

The global emergence of antimicrobial resistance has become a pre-eminent concern in medicine and public health. Antimicrobial resistance is of particular concern because the problem is widespread, the causative factors are uncontrolled, and national strategies to address the problem are lacking. The persisting burden of infectious diseases makes elimination of antibiotic use unethical, but dramatic overuse and misuse of antimicrobial agents around the world must be reduced to extend the useful lifetimes of these drugs. Population genetic models suggest that resistance emerges rapidly under the selective pressure of antibiotics, but decays slowly once that pressure is removed. Hence, measures to prevent the emergence of resistance must be implemented urgently. A multiplicity of factors drive antibiotic resistance, and solutions require the collaboration of governmental agencies, the pharmaceutical companies, healthcare providers, and consumers. Leadership in the form of a national steering committee on antimicrobial resistance is needed in the Kingdom of Saudi Arabia to guide collective action to control the threat of antibiotic resistance.

Keywords: Antimicrobial, antibiotic, resistance.

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The worldwide emergence of antimicrobial resistance has become a pre-eminent concern in medicine and public health.[1] This phenomenon has raised the specter of untreatable infections and a return to a "post-antimicrobial era". While the molecular basis of antimicrobial resistance is well understood,[2] the prevention and control of resistance continues to challenge the medical community.[3] The emergence of antimicrobial resistance in Saudi Arabia is of particular concern because the problem is widespread, the causative factors are uncontrolled, and national strategies have not been developed to address the problem. The purpose of this review is to enhance awareness of the issue in the hopes that governmental agencies and the medical community will begin to respond to this important threat to human health. The terms antimicrobial and antibiotic will be used interchangeably in this review, and the discussion will focus on bacterial pathogens.

To understand the problem of antimicrobial resistance, 4 concepts must be borne in mind. First, the total elimination of antimicrobial use is impossible because of the persisting burden of infectious diseases worldwide. Second, there is overwhelming evidence that antimicrobial resistance has emerged globally, and in Saudi Arabia. Third, the factors that contribute to the emergence of antimicrobial resistance are understood, and Saudi Arabia possesses an unequal share of these factors due to rapid socioeconomic development. Finally, multidisciplinary solutions are required to address the multifactorial genesis of antimicrobial resistance.

Persisting burden of infectious diseases. Infectious diseases still kill more people in the world than any other category of disease. They cause a third of global deaths, 43% of deaths in developing nations, and 1% of deaths in developed nations.[4] The top 3 infectious-disease killers are acute lower

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respiratory tract infections, tuberculosis, and acute diarrheal diseases. Importantly, antimicrobial therapy plays an important role in the treatment of all these conditions. Ninety-percent of deaths from acute respiratory infections are due to bacterial pneumonias in young children living in developing countries; antibiotics are the mainstay of treatment. One-third of the world's people are infected with *Mycobacterium tuberculosis*, and antimicrobial chemotherapy is the basis for both prevention and treatment of tuberculous disease. Two of the 3 leading causes of diarrheal disease deaths among young children in developing countries are enterotoxigenic *E.coli* and *Shigella species*; antibacterial agents have an occasional role in the former and are always indicated in the latter.[5] Thus, the continuing burden of infectious diseases, many of them still endemic in Saudi Arabia, will ensure an ongoing, legitimate demand for antimicrobial agents. The question that the medical community faces is not whether antibiotic use can be eliminated, but how antibiotics can be used optimally so as to maximize their useful lifetimes.

Emergence of antimicrobial resistance. Unfortunately, the availability of antimicrobial drugs for legitimate uses has also lead to a level of antibiotic overuse and misuse that could be characterized as "antibiotic pollution". Each year, more than 50 million pounds of antibiotics are produced globally.[6] Human beings consume 235 million doses of antibiotics per annum, with 20% to 50% of these doses considered unnecessary.[7] In the United States, 40% of the antibiotics produced are fed to animals, mainly for growth promotion.[6] In Australia, from 1992 to 1996, 582 kg of vancomycin were imported annually for human use, in contrast to the 62,642 kg of avoparcin (a chemically-similar antibiotic conferring cross-resistance) imported for animal use.[8] The widespread overuse and misuse of antibiotics has been associated with the emergence of resistance to these drugs worldwide,[9,10] and Saudi Arabia has also witnessed the emergence of drug resistance among both hospital and community bacterial pathogens.[11-18] As a broad generalization, resistance among aerobic gram-negative bacilli has arisen more quickly than in western medial centers, but resistance among gram-positive cocci has lagged. The increasing prevalence of resistant bacteria will encourage clinicians to use broader-spectrum antibiotics for empirical therapy until organism susceptibilities become available. However, because microbiologic cultures are often not obtained, broad-spectrum agents are used for the entire duration of therapy.

Multifactorial genesis of antimicrobial resistance. The many factors promoting the genesis of antimicrobial resistance can be placed into 3 categories: the stochastic emergence of resistance genes and their dissemination among bacteria, the selection of these resistance genes by antimicrobial agents, and the transmission of antibiotic-resistant bacteria to human beings (Table 1). Resistance genes can occur on chromosomes, transferable loops of deoxyribonucleic acid (DNA) called plasmids, smaller units of DNA called transposons or "jumping genes", and specialized transposons called integrons that can assemble multiple resistance genes into "cassettes".[19] Transmission of these integron cassettes between bacteria is the basis for transferable multiple-drug resistance. Genes encode 3 basic resistance mechanisms in bacteria: production of antibiotic-inactivating enzymes, alteration of the antibiotic target binding site on the bacterial cell, and prevention of antibiotic access to the target site. The occurrence of resistance genes is

Table 1 - Factors responsible for the emergence of antimicrobial resistance.

Emergence and dissemination of resistance genes
Chromosomal mutations
Plasmids
Transposons
Integron cassettes
Selection of resistance genes by antimicrobial pressure
Overuse
Physician beliefs and knowledge Patient expectations Blurring of prescriber/provider distinction
Misuse
Improper dose or duration of antibiotics Failure to modify antibiotics based on susceptibility Inadequate access to microbiologic testing Aggressive marketing of broad-spectrum agents
Over-The-Counter availability and self-prescribing
Transmission of antimicrobial-resistant bacteria
Human travel and migration
Daycare centers
Animal and agricultural use
Healthcare facilities
Hospitals
Nursing homes
Public health factors
Human crowding
Inadequate sanitation
Sexual behaviour

spontaneous and therefore not a preventable aspect of antibiotic resistance, but antibiotic selection pressure and transmission of resistant bacteria can be reduced.

The single most important factor driving the emergence of resistance is the selective pressure of antimicrobial agents. The relationship between antibiotic usage and emergence of resistance is complex and better understood through mathematical modeling methods derived from population genetics. These models show the frequency of antibiotic resistance is affected by the incidence of treatment, the probability of resistance given treatment, the duration of infectiousness of the patient, the degree of reduction in transmission from treatment, and the degree of reduction in competitive fitness of bacteria from treatment.[20] Such models suggest that antibiotic resistance emerges rapidly under antimicrobial selective pressure but decays slowly once this pressure is removed, and that the degree of reduction in resistance is proportional to the degree of reduction in drug consumption.[21] Furthermore, after a period of cessation, reintroduction of an antibiotic will result in rapid resurgence of resistant bacteria on a time scale of days to months.[22] For some diseases such as tuberculosis and gonorrhea, these models suggest that antibiotic cycling policies may speed up the emergence of resistance rather than slow it down.[23] Mathematical models can provide useful insights into the nature of drug resistance, but they are only as good as their underlying assumptions. Better epidemiological studies are required to test the validity of the predictions made by these models, and these predictions should not be used for policy formation until benefits have been demonstrated in controlled trials. Increased antibiotic selection pressure is only the final common pathway for many factors related to the overuse and misuse of antibiotics (Table 1). At the heart of the problem lie the beliefs that doctors and patients have about antibiotics. Kim and Gallis decry the "spiraling empiricism" of antimicrobial prescribing: the tendency of doctors to prescribe antibiotics without obtaining microbiologic cultures; to prescribe antibiotics without a proven treatable infection; and to prescribe the newest, broad-spectrum antibiotics whether or not they are indicated.[24,25] In essence, inappropriate antibiotic-prescribing is used to ameliorate the anxiety and insecurity of the doctor rather than a demonstrated infection in the patient. But patients who expect their doctors to prescribe antibiotics for minor infections or viral infections also share responsibility for the overuse of antibiotics. These expectations result from patient beliefs that there is a pill for every symptom, that antibiotics can cure anything, and that antibiotics are more effective than others kinds of drugs.[26] Antimicrobial resistance is also driven by social, economic, and technological factors that promote the transmission of resistant bacteria[27] (Table 1). These factors are beyond the control of individual persons and require intervention at the societal level. The factors that drive the emergence of antimicrobial resistance generally differ for developed versus developing countries. For example, human crowding and the over-the-counter availability of antibiotics are important in developing countries, whereas nursing homes and animal use of antibiotics are important in developed countries. The Kingdom of Saudi Arabia, a resource-rich, developing nation, has undergone such rapid socioeconomic changes that the characteristics of both developed and developing countries co-exist with respect to generating antibiotic resistance. Any reader of this article will have no difficulty verifying that oral antibiotics can be purchased over-the-counter in the Kingdom's pharmacies without the need for a doctor's prescription. From the educational interactions of the authors of this paper with Saudi physicians-in-training, it is evident that medical schools and residency programs in the Kingdom should devote more time in the curriculum to the principles of infectious disease therapeutics and especially to the issue of antibiotic resistance. Privatization-of-medicine contributes to resistance when physicians have financial incentives to prescribe antibiotics liberally for the common cold, acute bronchitis, and non-dysenteric gastroenteritis conditions that are generally of viral origin or self-limiting.[28] The limited availability of infectious disease specialists, infection control professionals, and clinical pharmacists in the Kingdom's hospitals diminishes our capacity to rationalize and regulate antimicrobial use in these "epicenters" of antimicrobial resistance.[29] Lack of standardized microbiologic susceptibility testing in some healthcare facilities also impedes rational prescribing. Finally, the aggressive promotion of broad-spectrum antimicrobial agents by pharmaceutical companies in the Kingdom, and the absence of more objective sources of drug information, has a negative impact on physician prescribing behavior.

Need for a multidisciplinary response. In discussing responses to the problem of antimicrobial resistance, it should be stated first and foremost that the discovery of new antibiotics and the continuation of the status quo are not the solution. The discovery of a new antibiotic class takes 10 years, and very few new agents are "in the pipeline".[30] Even if new drugs are forthcoming, their usefulness will be inevitably diminished with overuse and misuse as has occurred with every antimicrobial introduced for human use to date. It is crucial to understand that antimicrobial resistance is a societal problem with complex causes, and that solutions will not be simple. What is required is collective action by governments, the pharmaceutical industry, healthcare providers, and consumers to address this problem in a

comprehensive way.[25] An example of a framework for collective action that could be adopted in the Kingdom exists.[31] This action plan calls for the provision of national leadership and policies, the establishment of laboratory capability and surveillance systems to monitor trends in resistance, the identification of local expertise on antibiotic stewardship in healthcare facilities, education of doctors and consumers through the media, and provision of adequate infection control resources in all healthcare facilities. A first step towards such a plan would be the establishment within the Kingdom of a national steering committee of experts on antimicrobial resistance. In fact, the presence of such committees in all Gulf Council for Cooperation countries is highly desirable because antibiotic resistance knows no borders.

In addition to the broad needs outlined in the previous section, the national steering committee should address the following issues. Over-the-counter availability of oral antibiotics should be eliminated; this is primarily an issue of regulatory enforcement since patients in Saudi Arabia already require a prescription to purchase oral antibiotics. Pharmaceutical companies should submit to guidelines for ethical promotion of antibiotics in the Kingdom. Animal and agricultural use of antibiotics, if present in the Kingdom, should be strongly discouraged. Hospitals have tended to respond to the resistance threat with antibiotic restriction policies. These policies, by promoting uniform antimicrobial use, may simply replace resistance to one class of antibiotics with resistance to a different class of antibiotics. Burke calls this unintended result "squeezing the balloon".[32] Ultimately, the best way to contain resistance in hospitals may be the ancient medical principle of tailoring therapy to the individual patient's needs. Such a patient-centered strategy will encourage heterogeneity and individualization of antibiotic prescribing, and avoid the theoretical concerns inherent in policies such as "antibiotic cycling".[23,32] However, such a strategy depends on state-of-the-art, bedside, clinical information systems that most hospitals in the world do not possess.

In a poignant essay, Loefler laments humanity's dismal record of antibiotic stewardship:[33] "We have squandered an immense resource, much of it a true natural resource, by using it frivolously, inappropriately, and ineptly...We wasted resources that, if husbanded, would have helped us to treat infections perhaps for hundreds of years. We squandered because of ignorance, consumerism, mercantilism, cynicism, and carelessness, and also because many of us still think that our own individual patient deserves the 'best', whatever the consequences are for others. The antibiotic age will continue for a few decades. Some specific chemotherapeutic agents will remain in our pharmacopoeia for longer, yet we have been humbled by microbes and insects and worms." Is it too late to conserve the gift of antibiotics for future generations? We believe that an awareness of the threat, the determination to do better, and collaborative effort can still change humanity's antimicrobial destiny, but time is not on our side.

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