The beginning of the end of the antibiotic era? Part II. Proposed solutions to antibiotic abuse

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The bacteria causing diseases that are now becoming serious public health threats are neither strange nor exotic, but rather shockingly familiar. Tuberculosis, typhoid fever, meningitis, pneumonia, and septicemias are emerging global threats. The infectious agents causing these serious threats are the same bacteria identified many decades ago. The only difference is that these and other microorganisms are no longer killed by the "miracle drugs" that have kept them at bay for the past six decades. Antibiotic resistance has made potential killers out of bacteria that previously posed little threat to mankind. The indiscriminate and reckless use of antibiotics has led to a fast-approaching crisis in which human dominance of the planet is threatened by single, elementary cells of the microbial world. Part I of this article detailed the causes of the crisis. Part II addresses the solutions that are recommended by national and international authorities and organizations. (Quintessence Int 1998;29:223–229)

Key words: antibiotic, antibiotic therapy, bacterial pathogen, bacterial resistance

Clinical relevance

Bacterial antibiotic resistance is a serious worldwide problem that must be attacked on a global scale. The solution must begin with a concerted effort by clinicians to exercise restraint in human therapeutic use of antibiotics.

The problems associated with the abuse and ubiquitous use of antibiotics in human, animal, and plant ecosystems were addressed in part I of this article. It is disturbing to realize that any use of an antibiotic, whether appropriate or not, will do its own share of selecting resistant forms of bacteria. It would be absurd to jump from this fact to a conclusion that antibiotics should not be used. Some degree of resistance is a natural consequence of use, but the increasing level of resistance resulting from six decades of abusive antibiotic use has reached a dangerous level. If this abuse continues, it is entirely possible that we will see the end of the antibiotic era and enter an era when bacteria no longer respond to the "miracle drugs." In effect, we will be reentering the preantibiotic era. Thus, the logical solution is to eliminate antibiotic abuse and to concentrate on appropriate use of these drugs in their most important role, human therapeutics.

Current costs related to treatment of infections with antibiotic-resistant organisms are estimated by the National Centers for Disease Control and Prevention (CDC) to be more than $4 billion annually. As resistance spreads, involving more and more infectious agents, the concern is that infections that cannot be effectively treated with antimicrobial drugs may occur. Also of growing concern is the impact of bacterial resistance on the food production industry and food safety in the United States. Antibiotic resistance is a threat not only to human health from the standpoint of treatment of infectious diseases but also to economic health because of the emerging threat to food production. During the past two decades, US production of poultry, beef, and swine has consolidated under corporate direction, with animals typically concentrated in very large facilities instead of on small-scale family farms. Conditions are such that diseases can spread rapidly through a large number of animals in a herd or flock,

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with dire economic consequences. As is the case for diseases in humans, the number of therapeutic options for treatment of diseases in animals is diminishing rapidly.[1]

Antibiotic-resistant pathogens in animals not only pose a concern with respect to animal health but also pose a growing concern regarding transmission to humans as food-borne pathogens. The role of animals as primary sources of human disease has now been documented.[2,3] Food-borne illness associated with fruits and vegetables is also increasing in this country.[4–6]

Ironically, as the incidence of disease related to antibiotic-resistant bacterial pathogens is increasing, the search for new drugs to combat these pathogens has lost most of its momentum in recent years. The relative utility of available antibiotics is fast eroding, tipping the balance in favor of multidrug-resistant pathogens. These developments amount to an incipient public health emergency, albeit one that is poorly appreciated or recognized. Early successes during the antibiotic era helped to foster widely held beliefs among researchers, the medical, dental, and veterinary communities, and the general population that infectious diseases would soon be conquered and that research and public health attention could safely shift to other problems. Reversing that general perception and overcoming the complacency that has developed around it are not easy undertakings, but must be accomplished.[1]

The first step in finding the solution to any problem is to recognize and acknowledge that the problem exists. Joshua Lederberg, Nobel prize winner (physiology and medicine, 1958), has warned that epidemics such as acquired immunodeficiency syndrome have shocked the world because it still is not understood that microbial epidemics are a natural, almost predictable phenomenon. In a presentation at a conference of Nobel laureates in Paris in 1988, Dr Lederberg stated:

> We will face similar catastrophes again, and will be evermore confounded in dealing with them, if we do not come to grips with the realities of the place of our species in nature. A large measure of humanistic progress is dedicated to the subordination of nature to our ideals of perfectibility and autonomy. Human intelligence, culture, and technology have left all other plant and animal species out of the competition.... We have too many illusions that we can, by writ, govern the remaining vital kingdom, the microbes, that remain our competitors of last resort for dominion of the planet. The bacteria and viruses know nothing of our national sovereignties. In that natural evolutionary competition, there is no guarantee that we will find ourselves the survivor.[7]

Microbes flourished long before humans walked on this earth and have demonstrated their remarkable evolutionary capabilities in adapting to hostile environments, especially those posed by humans, through their amazing genetic plasticity.[8,9] Of the four components of the microbial world, viruses and bacteria are presently the most serious threats to humankind in the developing and developed nations (although fungi and parasites continue to wreak havoc in undeveloped nations). Bacteria present a unique problem because of abuse of the drugs that initially proved so successful against them in human therapeutic use.

The human and animal gastrointestinal tracts are ideal environments for microbial life and events such as genetic transfer because they are densely populated with scores of species of both pathogenic and commensal bacteria. The commensal bacteria help digest food, breaking down fats, sugars, proteins, and unwanted chemicals. In their absence, digestion is a difficult and often painful process. It may help to put things in proper perspective to acknowledge that there are more pathogens and potential pathogens in 1 ft (longitudinal) of human intestine (total length about 25 ft) than there are humans on the entire planet.[10]

Bacterial antibiotic resistance is a worldwide problem that must be attacked on a global scale. This requires international, national, regional, and local (individual health care providers and consumers) comprehension of the problem and concerted efforts to use antibiotics in the most efficacious manner for human therapeutics. This further requires subordination and perhaps elimination of the use of these drugs for animal husbandry (as growth enhancers), agriculture (vegetables, fruits, etc), aquaculture (the commercial fish industry), and other miscellaneous uses that directly influence the resistance gene pool in the human ecosystem.

The following are representative solutions recommended by various international authorities and organizations to combat antibiotic resistance.

Solutions to bacterial resistance

Policy for antibiotic use

A general policy for antibiotic use does not exist and must be developed. Ideally, this would involve national and international agreement, acceptance, and compliance. For human therapeutic use, the policy would require agreement on: *(1)* the indications for antibiotic use, *(2)* the selection of the most appropriate antibiotics for various clinical diseases, and *(3)* the selection of appropriate dosage regimens for each antibiotic for each use. This is complicated by the limited or nonexistent

availability of many antibiotics in many countries,[11] as well as cultural, economic, and political differences.[12]

A key component of any antibiotic use policy is a ban on the use of these drugs as growth enhancers for livestock (such a ban has been in effect in Western Europe for a decade) and for disease prevention in agricultural products.[2,13] The ban would be designed to eliminate (or greatly reduce) the amount of antibiotic residues and resistant bacteria presently found in the human food chain. There is an appropriate use for antibiotics in animal therapeutics to combat bacterial infectious diseases, however.

Selective pressure exerted by widespread antibiotic use is the driving force in the alarming increase in the development of antibiotic resistance. The association between increased rates of antibiotic use and resistance has been documented for nosocomial infections in hospital-based studies,[14,15] and for resistant community-acquired infections in studies associating rates of drug use on a regional or national basis with resistance patterns.[16] Although appropriate use of antibiotics has unquestionable benefits, these agents are commonly used inappropriately by clinicians and the public. According to the American Society for Microbiology (ASM) task force report on antibiotic resistance, inappropriate use results when clinicians provide antimicrobial drugs to treat viral infections, use inadequate criteria for diagnosis of infections, unnecessarily prescribe broad-spectrum antibiotics, and do not follow established recommendations for chemoprophylaxis.[1] Restraint in antibiotic use for human therapeutics is essential for resolving the resistance problem.[17]

Surveillance systems

To control infectious diseases, it is important that nations develop a surveillance system that can detect, monitor, and ensure early investigation and reporting of any emerging infections with the potential for rapid spread.[18,19] An international surveillance system is necessary for control of infectious diseases.[20] The mobility of the world's population has created the potential for the spread of such diseases to any part of the globe within a period of hours or a few days.[21]

It was fortunate that a surveillance system quickly pinpointed the source of the Ebola outbreak and confined the deadly virus to quarantined, isolated villages in Africa, preventing a worldwide epidemic.[22] Although the surveillance system was not national (Zaire has no surveillance system), the quarantine was effective, and the virus killed its victims within 2 weeks. The search continues for the vector (usually a carrier that is not harmed by the microbe), but the rapidity of fatality and the ability to effectively quarantine isolated infected populations was essentially a fortuitous miracle. If the virus had a longer latency period (ie, between infection and death) and had spread to a major population center (where quarantine may be ineffective or impossible), an epidemic of unimagined proportions could be sweeping the globe.

The failure of a national surveillance system is epitomized by the discontinuance of tuberculosis surveillance in the United States in the mid-1980s under the false assumption that the disease had been conquered and no longer presented a threat. By 1993, tuberculosis had become a public health crisis, and the surveillance system was forced to reinstate collection of information on the disease and on antibiotic resistance in *Mycobacterium tuberculosis*.[18,23]

The primary function of government is to protect its citizens. This is usually considered in the context of military and economic issues but also includes the health of the nation's population. It is therefore essential that national surveillance systems be established and become a part of an international network of surveillance systems.[20] This will require investments of millions, and probably billions, of dollars to establish an effective network. Oversight by an international organization such as the World Health Organization (WHO) is necessary to ensure that an adequate infrastructure is established in every nation or, at minimum, in a geographic region of nations. This is a formidable task that will encounter barriers of diverse dimensions by involving, by necessity, national, political, and cultural differences.[12,24] Nations with starving populations will likely have little or no interest in such endeavors, but it is within these undeveloped countries that conditions such as overcrowding, poor sanitation, rudimentary or nonexistent health care, etc, promote the development of infectious diseases.[25]

A 1993 investigation by the CDC discovered that international monitoring was so haphazard as to be nonexistent and cited a long list of serious weaknesses and flaws in its own domestic surveillance system.[10,26] The United States has set a poor example as a developed nation in establishing an effective surveillance system. The various states ultimately decide what is reported to the CDC. Despite CDC guidelines, some states do not report, and have inadequate staffing and laboratories to diagnose, certain infectious diseases. This results in erratic reporting to the degree that two states with the same incidence of a particular disease often report widely variable (or no) data.[18]

In the United States, federal funding should be immediately allocated for the establishment of a national system for the surveillance of antibiotic resis-

tance in animals, humans, and food products. According to the ASM, the lead agency should be the National Center for Infectious Diseases of the CDC. Other agencies, specifically the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH), the US Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration, should be involved in establishing priorities and implementing regulatory policies related to antibiotic resistance. These agencies should receive additional funding, because none has adequate funding to address the magnitude of current problems related to antibiotic resistance.[1,27]

Educational and compliance programs

In combination with any policy on human therapeutic use of antibiotics, strong educational and compliance programs must be established. Educational programs must be designed to ensure that future and present health care providers (and consumers) understand the difference between appropriate and inappropriate use of antibiotics.[28]

Clinicians must comprehend that the continued abuse of antibiotics in human therapeutics will lead to an unacceptable increase in antibiotic resistance.[29] This becomes increasingly important with the curtailment of antibiotic use in animal growth promotion and in agriculture. In theory, such curtailment would eventually leave abuse in human therapeutic use as the primary contributor to the resistance problem. This would place the focus of resolving the problem on the health care provider, who, with appropriate education and comprehension, should welcome the challenge in the interest of benefiting humanity.[17]

As repugnant as it may seem, it is likely that some method of monitoring compliance with accepted antibiotic usage may be necessary. The present system, devoid of any monitoring system, is clearly not working. This is an area that the leadership of the medical, dental, and veterinary professions should address immediately rather than await intervention by federal agencies. There is no doubt that educational and compliance systems will meet strong opposition (as well as total rejection) in certain nations with political and cultural beliefs that do not presently allow the imposition of such measures.[12,30]

The ASM task force on antibiotic resistance concluded that an urgent need exists for more appropriate selection and use of antimicrobial drugs. The task force recommended that the curriculum of health professional (medical, dental, veterinary, and nursing) schools and postgraduate educational programs be strengthened in the areas of sterilization, disinfection, hazards of inappropriate antimicrobial drug use, appropriate diagnosis and treatment of infectious diseases, and antibiotic resistance.[1]

Quality control in pharmaceutical production

In many nations, particularly undeveloped and developing, there is no quality control over the manufacture of antibiotic products.[31–33] Underdosing is a common problem in these countries (eg, a 500-mg dose tablet may contain only 250 mg of the antibiotic).[34] Underdosage is a major factor in the creation of antibiotic resistance.[35] A second and equally important goal of pharmaceutical quality control is to eliminate bacterial deoxyribonucleic acid and ribonucleic acid contaminants from antibiotics.[36] These contaminants carry genetic resistance information that may be directly transferred from the antibiotic to target bacteria causing an infectious disease.[37]

A third goal of pharmaceutical control is to address irrational combinations of antibiotics (as well as vitamins, steroids, and stimulants) in single-dosage packages.[25] Finally, control must be exerted over marketing claims by pharmaceutical companies that greatly mislead clinicians in the therapeutic efficacies of a drug. Evidence strongly suggests that marketing claims by pharmaceutical companies (written) and their representatives (oral) greatly influence the choice of antibiotic selection.[28]

Studies of drug labeling and promotion in Third World countries found that indications are often grossly exaggerated and the hazards are glossed over, minimized, or totally ignored. This is further complicated by the social and cultural attitudes of physicians, medicine dispensers, and consumers who inherently must balance their expectations between Western therapeutics and native drugs. These forces have combined to result in widespread, often irrational, purchases of drugs without prescription, the availability of a confusing array of individual drugs and combinations marketed for inappropriate indications, and disparate and inequitable access to vital drugs and vaccines depending on the ability to pay.[30]

The International Federation of Pharmaceutical Manufacturers Association (IFPMA), based in Geneva, Switzerland, represents 51 member associations of National Pharmaceutical Manufacturers throughout the world. The IFPMA, in collaboration with WHO, has developed a Code of Pharmaceutical Marketing Practices. They are particularly involved with the programs of WHO in helping developing countries improve their control over the quality of the medicines on their markets through the establishment of quality control laboratories.[38]

Research

Research and research funding must be directed toward the discovery and development of new antimicrobial compounds, effective vaccines, and methods to counteract antibiotic resistance.[20] This responsibility will initially fall on developed nations that have the means to conduct both basic and advanced research in microbiology, molecular biology, genetics, and pharmacotherapeutics. Funding will require support from the political arena, a potential problem in any nation, including the United States.[10]

The ASM task force on antibiotic resistance concluded that more basic research is needed to delineate the genetic and metabolic pathways that determine virulence as well as antibiotic susceptibility or resistance in pathogens of human and veterinary importance. More resources should be devoted to the sequencing of the entire genome of microbial pathogens in an attempt to identify common antimicrobial targets. More basic research is also needed to determine the mechanisms of the spread of pathogens and to better understand the genetics of microorganisms and the development of antibiotic resistance. Clinical and epidemiologic research is needed to determine the clinical impact of infection with drug-resistant pathogens and to identify the optimal therapeutic options for treatment of infections with drug-resistant strains.

The laws of evolution dictate that microbes will eventually develop resistance to nearly every antibiotic. Research is thus needed to facilitate development of effective vaccines, the most cost-effective method of infectious disease control and prevention for many diseases.[1]

Discussion

The preceding represents a cursory review of a few of the major solutions recommended by national and international authorities and is certainly not all-inclusive. However, it is apparent that the solutions to antibiotic resistance are fraught with problems and uncertainty. Is it possible to implement some or all of these recommendations on an international basis? Is it possible to implement these recommendations in the United States, in South America, in Asia, in the Middle East? Even if the developed nations could agree to some or all of the recommendations, would this prove effective on a global basis? No matter the level of obstacles that must be overcome, it is incumbent on the scientific and professional communities of the world to support all efforts to combat the antibiotic resistance problem. Such efforts, although limited, have already begun.

The World Health Organization has been active in promoting the rational use of drugs in developing nations and in monitoring the problems associated with the emergence of resistant microorganisms. Working with the United Nations International Children's Emergency Fund, WHO has supported development of national drug policies.[25] Other international organizations addressing the antibiotic-resistance issue include the Alliance for Prudent Use of Antibiotics,[39] the International Network for Rational Use of Drugs,[40] and the International Clinical Epidemiology Network.[30] However, the latter three organizations have a combined annual budget that is less than the amount spent each year in one community-sized hospital in the United States.[25] These international organizations suffer the same problems (lack of interest and funding) in their global efforts faced by national efforts to deal with the problems of antibiotic abuse and resistance.

Antibiotics are unique as pharmacologic agents because they affect not only the patient but also the patient's environment. In the process of killing the targeted pathogen, antibiotics also kill other susceptible strains of bacteria sharing the immediate ecosystem. This creates a potential long-range problem because there is a selection for uncommon (sometimes rare) resistant strains, which survive.[41] These strains multiply in the absence of competitors. With repeated antibiotic doses, environments can become havens for large numbers of resistant bacterial strains. This strong and steady selective force of antibiotics, combined with the intrinsic genetic properties of bacteria, has led to antibiotic-resistant variants of common bacteria, many of which cause severe infections in humans.[42] Although resistance does not directly increase virulence, the chances that an illness will be caused by a resistant strain will increase as the numbers of resistant pathogens and resistant genes increase in the environment.[43,44]

Restraint in antibiotic use, as recommended by the ASM task force report on antibiotic resistance,[1] should be the immediate response by practicing physicians, dentists, and veterinarians. Patients must not dictate the use of antibiotics, and clinicians must avoid the existing philosophy of antibiotics by demand. Broad-spectrum and expanded-spectrum antibiotics should not be prescribed for infections that can be managed by narrow-spectrum antibiotics. Inflammatory responses, viral infections, and minor surgical procedures in medically uncompromised patients should not be considered indications for antibiotic therapy. The time has come to resist the temptation that antibiotics be prescribed "just in case." That luxury and many others have been squandered by the abusive use of antibiotics during the last six decades.[17]

Human immunodeficiency virus is not an aberration; neither is tuberculosis (which now infects one third of

the world's population); they are merely signs of things to come, if changes are not made. Humanity's most ancient enemies are microbes. They have not disappeared as humans advanced to higher and higher levels of intelligence, technology, microbiology, pharmacology, molecular biology, and genetics. They certainly will not become extinct simply because humans choose to ignore their existence.[10]

Physicians, dentists, and veterinarians must acknowledge the problem of antibiotic resistance and accept the responsibility for restraint in antibiotic therapeutic use. The fact that 50% of antibiotic prescriptions are inappropriate or unjustified is a totally unacceptable statistic.[36,45,46] However, these studies relate to the use of antibiotics by physicians. A review of the literature failed to disclose similar studies on the use of antibiotics by dentists or veterinarians. Clinical experience suggests, however, that dentists have a very high rate of inappropriate antibiotic use. This issue will be addressed in a subsequent article.

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Answers to QI 1/98 Questions

1. D	5. D	9. A	13. A
2. A	6. A	10. A	14. B
3. A	7. A	11. A	15. D
4. D	8. B	12. A	16. A