

REVIEW ARTICLE

Resistance to Antibiotics: Are We in the Post-Antibiotic Era?

Alfonso J. Alanis

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

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Serious infections caused by bacteria that have become resistant to commonly used antibiotics have become a major global healthcare problem in the 21st century. They not only are more severe and require longer and more complex treatments, but they are also significantly more expensive to diagnose and to treat. Antibiotic resistance, initially a problem of the hospital setting associated with an increased number of hospital-acquired infections usually in critically ill and immunosuppressed patients, has now extended into the community causing severe infections difficult to diagnose and treat. The molecular mechanisms by which bacteria have become resistant to antibiotics are diverse and complex. Bacteria have developed resistance to all different classes of antibiotics discovered to date. The most frequent type of resistance is acquired and transmitted horizontally via the conjugation of a plasmid. In recent times new mechanisms of resistance have resulted in the simultaneous development of resistance to several antibiotic classes creating very dangerous multidrug-resistant (MDR) bacterial strains, some also known as “superbugs”. The indiscriminate and inappropriate use of antibiotics in outpatient clinics, hospitalized patients and in the food industry is the single largest factor leading to antibiotic resistance. In recent years, the number of new antibiotics licensed for human use in different parts of the world has been lower than in the recent past. In addition, there has been less innovation in the field of antimicrobial discovery research and development. The pharmaceutical industry, large academic institutions or the government are not investing the necessary resources to produce the next generation of newer safe and effective antimicrobial drugs. In many cases, large pharmaceutical companies have terminated their anti-infective research programs altogether due to economic reasons. The potential negative consequences of all these events are relevant because they put society at risk for the spread of potentially serious MDR bacterial infections. © 2005 IMSS. Published by Elsevier Inc.

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Introduction

In the last 60 years, major improvements in the early recognition and the treatment of infectious diseases have resulted in an extraordinary reduction in the morbidity and mortality associated with these illnesses. This has been due, in part, to our better understanding of the fine molecular biological mechanisms of these diseases and to our

improved understanding of their pathophysiology and their epidemiology but, most notably, to the rapid development of safe and effective new antimicrobial treatments that have been able to attack the specific agent causing the infection, thus helping the infected host to eliminate the infection being treated.

Seen initially as truly miraculous drugs, access to the first available systemic antibiotics (sulfonamides and penicillin) was not immediately available for the general public. In fact, these drugs were scarce and very expensive and were initially reserved for use by the military during World War II (1).

As more antibiotics were discovered, manufacturing processes were simplified, and newer formulations developed,

Address reprint requests to: Alfonso J. Alanis, M.D., Vice President, Lilly Research Laboratories, Lilly Corporate Center, MC/510/07; Drop Code 6072, Indianapolis, IN 46285; E-mail: aao@lilly.com

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access to antibiotics eased considerably and their use became widespread. Antibiotics had truly become the “panacea” of medicine and were being used to treat even the most common and trivial types of infections, many of these non-bacterial in nature.

Based on the work that he had done in his research laboratory, in an interview with *The New York Times* in 1945, Sir Alexander Fleming warned that the inappropriate use of penicillin could lead to the selection of resistant “mutant forms” of *Staphylococcus aureus* that could cause more serious infections in the host or in other people that the host was in contact with and thus could pass the resistant microbe (2). He was right and within 1 year of the widespread use of this drug a significant number of strains of this bacterium had become resistant to penicillin. Only a few years later over 50% were no longer susceptible to this new drug (2).

Unfortunately, things have not improved in the recent past. In fact, every day more common and uncommon bacteria, previously susceptible to common antimicrobials, are reported to have developed resistance to different antibiotics. Although these bacteria initially caused significant nosocomial infections and were the cause of major morbidity and mortality in hospitalized patients, more recently they have spread to the community, causing severe illnesses in previously healthy and otherwise non-vulnerable patients.

This review tries to provide an overview of the serious problem of antibiotic resistance in the 21st century and to begin to open a new window into the complex challenge of new antibiotic development in the future. For this reason, the scope of the article will focus on the problem of bacterial resistance and will not discuss viral, fungal or parasitic resistance. Excellent reviews related on the development and management of resistance of these other microorganisms can be found elsewhere (3–7).

Antibiotic Resistance: A Long-Term, Serious Problem...Getting Worse

In order to be fit to survive, all living organisms strive to adapt to their environment. Part of this adaptation process includes adjusting to weather conditions, to food, water and in many cases to oxygen availability and also to the presence of potentially dangerous or even lethal external agents. It is no secret that many insects have adapted remarkably well to their environment and so have microorganisms. Thus it should not be surprising to us that bacteria have shown a remarkable ability to endure and adapt to their environment including the development of different mechanisms of resistance to most old and new antimicrobial agents.

The end result of this phenomenon is that many strains of bacteria have become resistant, and in many cases multi-resistant to these therapeutic agents, thus rendering

these drugs ineffective as treatments of choice for severe infections caused by these pathogens.

As stated earlier, the first cases of antimicrobial resistance occurred in the late 1930s and in the 1940s, soon after the introduction of the first antibiotic classes, sulfonamides and penicillin. Common bacteria such as strains of *Staphylococcus aureus* became resistant to these classes of antibiotics at record speed.

For the most part, during the first 25 years after the introduction of the initial antibiotics, resistance was a problem of hospitalized patients. We learned quickly that these bacteria were not only capable of developing resistance to these antibacterial drugs but that they also could remain alive and viable in the hospital environment, thus affecting mostly vulnerable patients (especially critically ill patients in the intensive care unit, those receiving steroids, the immunosuppressed, the debilitated, the chronically ill and the neutropenic) who were at a higher risk and in whom eventually they caused serious nosocomial infections (8–12).

The list of bacteria developing resistance is impressive, from sulfonamide and penicillin-resistant *Staphylococcus aureus* in the 1930s and 1940s (2,13) to penicillin-resistant *Neisseria gonorrhoeae* (PPNG), and β -lactamase-producing *Haemophilus influenzae* in the 1970s, (14–17) methicillin-resistant *Staphylococcus aureus* (MRSA) and the resurgence of multi-drug resistant (MDR) *Mycobacterium tuberculosis* in the late 1970s and 1980s, (18–23) and several resistant strains of common enteric and non-enteric gram-negative bacteria such as *Shigella* sp., *Salmonella* sp., *Vibrio cholerae*, *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, some of these associated with the use of antimicrobials in animals grown for human food consumption in the 1980s and 1990s (24–29).

Recently we have also witnessed the report of very worrisome cases of previously unthinkable resistance as well as the spread of resistant bacteria outside the hospital causing community-acquired infections. Such is the case for strains of Group A *Streptococcus* becoming resistant to macrolide antibiotics (30–33), *Streptococcus pneumoniae* developing resistance to different antibiotic classes, including penicillin, and causing serious infections (34–41) and more virulent strains of MRSA (due to the expression of certain toxins such as the so-called Panton-Valentine leukocidin) spreading to the community (18–21,42–44), as well as *Staphylococcus aureus* and Enterococci becoming resistant to vancomycin (45–50).

Mechanisms of Antibiotic Resistance

At least 17 different classes of antibiotics have been produced to date (Table 1). Unfortunately, for each one of these classes at least one mechanism of resistance (and many times more than one) has developed over the years.

Table 1. Major antibiotic classes by mechanism of action*

Mechanism of action	Antibiotic families
Inhibition of cell wall synthesis	Beta-lactams (penicillins, cephalosporins, carbapenems, monobactams); glycopeptides; cyclic lipopeptides (daptomycin)
Inhibition of protein synthesis	Tetracyclines; aminoglycosides; oxazolidinones (linezolid); streptogramins (quinupristin-dalfopristin); ketolidides; macrolides; lincosamides, Fluoroquinolones
Inhibition of DNA synthesis	
Inhibition of RNA synthesis	Rifampin
Competitive inhibition of folic acid synthesis	Sulfonamides; trimethoprim
Inhibition	
Membrane disorganizing agents	Polymyxins (Polymyxin-B, Colistin)
Other mechanisms	Metronidazole

*Modified from Levy SB and Marshall B (51).

In fact, in some cases these bacteria have been able to develop simultaneous resistance to two or more antibiotic classes, making the treatment of infections caused by these microorganisms extremely difficult, very costly and in many instances associated with high morbidity and mortality (51,52).

Thus it seems that the dream that some clinicians had and the predictions that many others made in the middle of the 20th century about the future eradication of most common infectious diseases from humanity will be unlikely to be achieved. If anything, recent experience with the emergence of totally new infectious diseases (AIDS, SARS, etc.), and the epidemiological trends of antibiotic resistance observed thus far, tend to indicate that we will continue to move in the opposite direction, towards an environment with an ever-growing number of new infectious diseases and of more common bacteria developing antibiotic resistance, more bacteria becoming resistant to several antibiotics at the same time, and some of these bacteria continuing to migrate from the hospital setting to the community. The net result could be even higher morbidity, higher mortality, higher costs, and the potential for the rapid spread of these bacteria and overall a decreasing number of useful antimicrobial agents to combat the infections they cause.

Gaining a good understanding of the molecular basis for the development of resistance is important because it allows us to develop new approaches to manage the infections caused by these bacteria and to create new strategies for the development of new treatments against these bacteria.

In general, it can be said that bacterial resistance has its foundation at the genetic level. This means that in most cases of bacterial resistance, changes in the genetic make-up of the previously susceptible bacteria take place, either

via a mutation or by the introduction of new genetic information. The expression of these genetic changes in the cell result in changes in one or more biological mechanisms of the affected bacteria and ultimately determine the specific type of resistance that the bacteria develops, resulting in a myriad of possible biological forms of resistance (51,52).

Below we will review briefly both the genetic and the biological mechanisms of resistance.

Genetic Mechanisms of Transmission

The development of antibiotic resistance tends to be related to the degree of simplicity of the DNA present in the microorganism becoming resistant and to the ease with which it can acquire DNA from other microorganisms.

For antibiotic resistance to develop, it is necessary that two key elements combine: the presence of an antibiotic capable of inhibiting the majority of bacteria present in a colony and a heterogeneous colony of bacteria where at least one of these bacterium carries the genetic determinant capable of expressing resistance to the antibiotic (51).

Once this happens, susceptible bacteria in the colony will die whereas the resistant strains will survive. These surviving bacteria possess the genetic determinants that codify the type and intensity of resistance to be expressed by the bacterial cell. Selection of these bacteria results in the selection of these genes that can now spread and propagate to other bacteria (51).

Resistance to antibiotics can be natural (intrinsic) or acquired and can be transmitted horizontally or vertically. Whereas the natural form of antibiotic resistance is caused by a spontaneous gene mutation in the lack of selective pressure due to the presence of antibiotics and is far much less common than the acquired one, it can also play a role in the development of resistance.

For the most part, however, the micro-ecological pressure exerted by the presence of an antibiotic is a potent stimulus to elicit a bacterial adaptation response and is the most common cause of bacterial resistance to antibiotics (52). Susceptible bacteria can acquire resistance to antimicrobial agents by either genetic mutation or by accepting antimicrobial resistance genes from other bacteria. The genes that codify this resistance (the “resistant genes”) are normally located in specialized fragments of DNA known as transposons (sections of DNA containing “sticky endings”), which allow the resistance genes to easily move from one plasmid to another (52).

Some transposons may contain a special, more complex DNA fragment called “integron”, a site capable of integrating different antibiotic resistance genes and thus able to confer multiple antibiotic resistance to a bacteria. Integrons have been identified in both gram-negative and gram-positive bacteria, and they seem to confer high-level multiple drug resistance to the bacteria that carry and express them (51).

Once a genetic mutation occurs and causes a change in the bacterial DNA, genetic material can be transferred among bacteria by several means. The most common mechanisms of genetic transfer are conjugation, transformation and transduction.

Conjugation. Conjugation is the most important and the most common mechanism of transmission of resistance in bacteria. This mechanism is normally mediated by plasmids (circular fragments of DNA) that are simpler than chromosomal DNA and can replicate independently of the chromosome. The mechanism of transmission of plasmids among bacteria is via the formation of a “pilus” (a hollow tubular structure) that forms between bacteria when they are next to each other, thus connecting them temporarily and allowing the passage of these DNA fragments.

Transformation. Transformation is another form of transmission of bacterial resistance genes and takes place when there is direct passage of free DNA (also known as “naked DNA”) from one cell to another. The “naked DNA” usually originates from other bacteria that have died and broken apart close to the receiving bacteria. The receiving bacteria then simply introduce the free DNA into their cytoplasm and incorporate it into their own DNA.

Transduction. Transduction is a third mechanism of genetic transfer and occurs via the use of a “vector”, most often viruses capable of infecting bacteria also known as “bacteriophages” (or simply “phages”). The virus containing the bacterial gene that codifies antibiotic resistance (the “resistant DNA”) infects the new bacterial cell and introduces this genetic material into the receiving bacteria. Most times, the infecting bacteriophage also introduces to the receiving bacteria its own viral DNA, which then takes over the bacterial replication system forcing the cell to produce more copies of the infecting virus until the bacterial cell dies and liberates these new bacteriophages, which then go on to infect other cells.

Biological Mechanisms of Resistance

Whichever way a gene is transferred to a bacterium, the development of antibiotic resistance occurs when the gene is able to express itself and produce a tangible biological effect resulting in the loss of activity of the antibiotic. These biological mechanisms are many and varied but they can be summarized as follows.

Antibiotic destruction or antibiotic transformation. This destruction or transformation occurs when the bacteria produces one or more enzymes that chemically degrade or modify the antimicrobial making them inactive against the bacteria. This is a common mechanism of resistance and probably one of the oldest ones affecting several antibiotics

but especially β -lactam antibiotics via the bacterial production of β -lactamases (53).

Antibiotic active efflux. Antibiotic active efflux is relevant for antibiotics that act inside the bacteria and takes place when the microorganism is capable of developing an active transport mechanism that pumps the antibiotic molecules that penetrated into the cell to the outside milieu until it reaches a concentration below that necessary for the antibiotic to have antibacterial activity. This means that the efflux transport mechanism must be stronger than the influx mechanism in order to be effective (54). Efflux was first described for tetracycline and macrolide antibiotics (55,56) but is now common for many other antibiotics such as fluoroquinolones (52,54).

Receptor modification. Receptor modification occurs when the intracellular target or receptor of the antibiotic drug is altered by the bacteria, resulting in the lack of binding and consequently the lack of antibacterial effect. Examples of this mechanism include modifications in the structural conformation of penicillin-binding proteins (PBPs) observed in certain types of penicillin resistance, ribosomal alterations that can render aminoglycosides, macrolides or tetracyclines inactive, and DNA-gyrase modifications resulting in resistance to fluoroquinolones (51,52).

It is likely that more and newer biological mechanisms of resistance will develop in the future. One can only hope that as these appear, we will be able to use these new mechanisms as new targets for the development of newer, effective antibiotics.

What Leads to the Development of Antibiotic Resistance?

Different factors play a role in the development of antibiotic resistance but what exactly determines that some bacteria become resistant to a specific drug and not to others and what is the specific role and the “relative weight” of each one of these factors in this process remains to be defined (Table 2).

Our understanding of how bacteria adapt to their environment and how this process may culminate in the development of resistance against one or more antibiotics is, at best, incomplete. We are only beginning to understand, at the molecular level, what steps take place for this process to occur and need to continue to gain a much better, more detailed understanding of the specific molecular mechanisms that serve as “trigger signals” for this process of adaptation to ultimately occur.

For example, why after more than 60 years Group A β -*Streptococcus* continues to be exquisitely susceptible to penicillin but not always to erythromycin? And why other members of the *Streptococcus* family, such as *Streptococcus pneumoniae*, after many decades of remaining susceptible to penicillin are now capable of presenting high-level

Table 2. Risk factors for the development of antibiotic resistance

Practices associated with the development of antibiotic resistance
Excessive and irrational over-utilization of antibiotics in outpatient practice and in hospitalized patients, either therapeutically or prophylactically
Use of antibiotics in agricultural industry, particularly in the production of food
Longer survival of severely ill patients
Longer life expectancy with increased use of antibiotics in the elderly.
Advances in medical science have resulted in the survival of many patients with severe illness and at risk for infections:
Critically ill patients
Immunosuppression
Congenital diseases (i.e., cystic fibrosis)
Lack of use of proven and effective preventive infection control measures such as hand washing, antibiotic usage restrictions and proper isolation of patients with resistant infections
Increased use of invasive procedures
Increased use of prosthetic devices and foreign bodies amenable to super infection with resistant bacteria

resistance to penicillin? Why after nearly 30 years of exhibiting high degree of susceptibility to vancomycin, *Staphylococcus aureus* developed resistance against this drug? Answering questions like these may help us to not only understand better the fine mechanisms that lead to bacterial resistance but also to develop strategies that result in the better design of new antibiotics that exhibit a long-term degree of activity against bacteria.

In practice, however, some correlations suggest a strong association between specific patterns of antibiotic use, the type and duration of exposure, and the development of resistance.

Abuse in the Use of Antibiotics in Clinical Practice Results in “Selective Pressure”

The use of antibiotics in humans results in “selective pressure” in the host receiving the antibiotic. The broader the spectrum of activity, the higher chances for bacteria to develop resistance (57,58). Third-generation cephalosporins, fluoroquinolones and more recently azithromycin have been linked to these problems (58). The net result is that after the administration of the antibiotic, most susceptible bacteria in the host, the majority of which are part of the normal saprophytic bacteria colonizing that individual, are eliminated thus selecting only those resistant bacteria capable of surviving despite the presence of the antibiotic. The natural consequence of this selection process is that there is excessive growth of one or more resistant strains. In this way, the host becomes a reservoir of resistant bacteria that can cause an infection in this very individual or they can easily spread to other hosts causing serious infections in the most debilitated ones (59–63).

It is for these reasons that antibiotics should be used very cautiously and should be prescribed only to those individuals in whom their use is clearly justified and when

it clearly outweighs the potential risks, including the risk of the development of resistance. Unfortunately, in today’s healthcare system where physicians have only a few minutes to fully evaluate a patient, make a diagnosis and prescribe a treatment, and given the increasingly litigious nature of society, physicians frequently find themselves under tremendous pressure to prescribe an antibiotic even when this may not be appropriate.

In general, it is worth reminding the clinician that it is necessary to be far more selective and, when an antibiotic is prescribed, it should be the one with the narrower spectrum of activity.

Unfortunately, the problem of antibiotic resistance has spread all around the world and in fact it is affecting poor and developing nations much harder than developed countries. This is due to the fact that antibiotics are much easier to obtain without a prescription in many of these countries whereas their access is much more limited in the developed world.

The consequence of this is that poor and very poor countries face yet another challenge of immense proportions. They will have to educate physicians and their populations to be cautious with the use of these drugs and they will have to face the dire economic consequences of facing the problem of antibiotic resistance. This means that a significant number of people will likely die in these poor nations because their health services will not be able to afford the level of sophistication and expenditure that their complex infectious diseases require. It also means that it is quite likely that in these countries the spread of community-acquired infections due to multi-resistant microorganisms will be broad and will likely serve as the reservoir from which these bacteria will migrate to other regions.

Agricultural and Animal Use of Antibiotics

Antibiotics are frequently used in animals as part of the process used to manufacture food, especially meats. This is a non-therapeutic use of very valuable drugs and for this reason they should be preserved for use under very special circumstance only (28,29).

Recent interactions between regulatory authorities and the food-producing industry in the U.S. are resulting in commitments to reduce and eventually eliminate the use of common antibiotics for non-therapeutic use.

Looking at the Future: Is This the Post-Antibiotic Era?

The problem of the explosive growth in the development of antimicrobial resistance in the last two decades has only been made worse by a significant and steady decrease in the number of approvals of new antibacterials in the last 10–15 years (Figure 1) (64).

The different forces contributing to this major paucity in the pace of antibiotic innovation are multiple, very complex and interlinked, and much has been written about these in

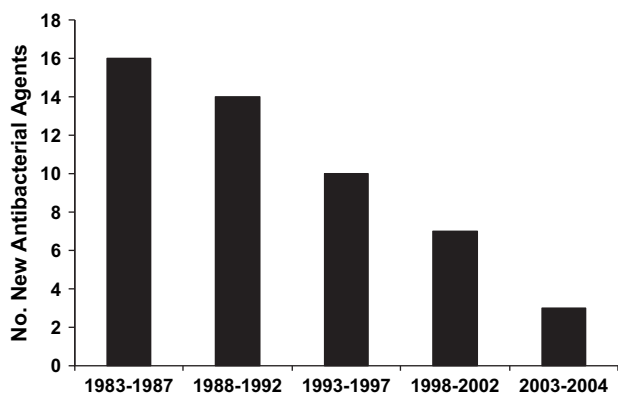


Figure 1. New antibacterial agents approved by the FDA in the U.S from 1983 to 2003. Data from Reference 70.

recent times (64–73). When analyzed individually, these forces seem to have merit on their own weight but they do not appear to be insurmountable. However, when combined, they seem to have had a multiplier effect that has now resulted in the creation of a crisis of major proportions which some predict may have unforeseen and dramatic consequences (65). Some of these key obstacles are explained as follows.

Tradeoffs Have Been Made within Anti-Infectives Therapeutic Class

The emergence of new, life-threatening infectious diseases, especially AIDS, has created significant and unexpected needs for the discovery and development of new safe and effective anti-HIV drugs that are capable of prolonging and improving the life of those infected with the virus and of containing the spread of this global disease. Research in this area has taken place in record time and new targets have been unfolded quite rapidly. The result of this has been the discovery and the development of a significant number of truly life-saving antiretroviral agents that when used in appropriate combinations to treat patients suffering from AIDS are literally able to keep these patients alive for years and to resume as normal a life as possible.

These successes, however, have created significant internal pressure within pharmaceutical companies since these normally develop their R & D budgets by Therapeutic Area. This means that in most companies that have a Division of Infectious Diseases, the budget for anti-infectives is limited (as is the budget for other therapeutic groups), and in recent years a significant amount of the anti-infective investments made in the industry have been directed to new antiretroviral agents at the expense of other antimicrobials, especially antibiotics.

To illustrate this point one only needs to see what has happened in the U.S. in recent years in the field of anti-infectives. From 1998 to 2003 only nine antibacterials were approved in the U.S. by the Food and Drug Administration

(FDA) and of these only two (Daptomycin and Linezolid) had truly novel mechanisms of action. During the same time, nine anti-HIV agents were approved, four of these in 2003 alone. Thus, from 1998 to 2003 the number of antibacterials developed by large pharmaceutical companies and approved in the U.S. by the FDA was the same than the number of new anti-HIV drugs made available to patients with AIDS (64).

Antibacterial research productivity has been lower than expected and there has been higher attrition in the pipeline of new antibiotics. Simply speaking, the new technologies such as genomic research, combinatorial chemistry and throughput screening, once heralded as capable of yielding a large number of novel targets amenable to modulation via their interaction with new drugs, have thus far failed to deliver on their promise in the field of antibacterial discovery and research (65). The consequence of this is that no new antibiotic classes have been discovered through the use of these new techniques and thus we continue to face the same barrier than before, the need for new antibacterial platforms for the delivery of new products (65).

Additionally, my observation is that in the last decade, the pharmaceutical industry has stopped the development of a significant number of new antibacterial molecules at different stages of progress because these did not meet their expectations due to a wide variety of reasons including manufacturing problems, safety concerns, lower efficacy than expected, or simply due to economic considerations. The result is that the development of these drugs was terminated, thus reducing the overall number of molecules in the antibiotic pipeline.

Iterations over “traditional” antibacterial chemical structures have been nearly exhausted. It is extremely unlikely, if not impossible, that incremental change that produces new iterations over these old chemical structures will yield the innovative, safe and effective new antibiotics that society needs. The field of antibacterial research is literally “crying” for transformational change. This means that in order to produce radically different and novel antimicrobials, we need to be capable of approaching the problem with a fresh and different view which results in truly innovative “platforms,” totally unrelated to the old ones. Only experimenting with new targets, new bacterial biological processes and new mechanisms of action we will be able to produce the next new classes of antibiotics, with the desired potency, the right spectrum of activity, the expected therapeutic effect and a clean safety profile, capable of withstand the threat of multi-resistant bacteria.

However, as we have learned from other therapeutic areas such as neurosciences, oncology or cardiovascular diseases in recent years, we need to understand that the creation of these novel platforms will be far more resource intensive, far more expensive and it will take a significantly longer time to be developed than those needed for the

discovery and development of traditional drugs or the “new” iterations of traditional antimicrobial agents.

Because the antibiotic market today is much less attractive to pharmaceutical companies than in the past, in order to generate the necessary resources that need to be invested in this type of effort it will be necessary to establish partnerships among academia, government and the pharmaceutical industry, as well as to offer appropriate incentives that make this investment attractive.

Limitations in the use of new antibiotics further reduces its attractiveness (65–67). Antibiotic resistance has made it essential to institute infection control measures in the hospital and in the community that result in the restriction in the use of antibiotics. Doing this will reduce the development of widespread antibiotic resistance in hospitalized patients and in the community. Unfortunately, these public health and infection control measures to rationalize the use of antibiotics have resulted in a reduction of the market size for these drugs. The consequence is that although these measures make good sense and have proven effective, they have had a net negative effect on the economic incentive to invest in the creation of newer antibiotics, thus making these investments much less attractive.

New Molecular Targets Equal New Drugs

As our knowledge of the pathophysiology and the molecular biology of several diseases has expanded, so has the number of targets amenable to interact with new chemical entities and the business opportunities for the pharmaceutical industry. Thus, in recent years pharmaceutical companies have engaged in the development of new treatments for many common, debilitating, chronic diseases not previously treated (such as osteoporosis) or even for diseases that, while not life-threatening and perceived as affecting more the “lifestyle” of those suffering them (i.e., erectile dysfunction), in fact have a profound negative impact on the quality of life and mental state of these patients. The net result is that due to the higher number of opportunities, pharmaceutical companies need to prioritize these and this has resulted in a loss of interest to invest in new antibiotics.

Economic forces work against the investment to develop new antibacterials (65,69–73). Since their inception in the 1940s, investment in the discovery and especially in the production of new antibiotics, like most other drugs, has been almost exclusively carried out by private pharmaceutical companies in the U.S. In a recent analysis of 284 new drugs (new molecular entities) approved by the U.S. FDA from 1990 to 1999, a total of 93.3% originated from private pharmaceutical companies, whereas only 3.2% came from government and 3.5% from other sources including academic institutions (74).

Because these private companies are publicly owned and their shareholders expect a return on their investment, these

conglomerates look at the development of new antimicrobials not only as a way to deliver on a critical unmet medical need of society but also as a good business opportunity capable of delivering on the economic promise of a return on the investment made.

Pharmaceutical companies today spend large amounts of money in the discovery and the development of new drugs and these expenditures are growing very fast. DiMasi and co-workers (74) at the Center for the Study of Drug Development at Tufts University have estimated the capitalized cost of development of each new drug discovered and developed by the U.S. pharmaceutical industry to be \$802 million (in year 2000 USD) from discovery to pre-approval. This is a very significant increment (nearly 4-fold) when one compares it with the \$231 million (in 1987 USD) cost estimate published by the same authors in 1991 using the same methodology (75), and represents an annual growth of 7.4% above the U.S. inflation during the same period of time.

These growing costs, along with the very long cycle time of 10 to 14 years for the discovery and the development of a new medicine (both at least in part driven by the growing requirements of regulatory agencies to provide much larger data sets on safety and efficacy of these drugs from ever growing clinical trials) (68) and a patent life that lasts 20 years from the date of discovery, in addition to the significant pricing pressures experienced by this industry in recent times, have forced most large pharmaceutical companies to prioritize their research and discovery activities and to reduce the therapeutic areas where they compete, resulting in the loss of several significant anti-infective research and development programs.

The end result is that, as time has progressed, several key factors have converged resulting in an alarming reduction in the development of new safe and effective antibacterial agents for use in patients with serious infections.

The likelihood that this situation will change in the near future is low unless significant incentives are offered to small and large private pharmaceutical companies to start investing in this area.

To this effect, recent efforts by several academic and specialty groups in the U.S. have resulted in specific proposals to government and regulatory authorities that could result in providing significant economic incentives for these companies to invest in anti-infective research (70). However, it is likely that in order to address the problem of antimicrobial resistance, much more public investment in research will be needed resulting in seamless collaborative programs between private companies and academic and research institutions.

Conclusions

In the final analysis, however, the problem of antibiotic resistance will not be solved with the creation of many more,

or stronger, bactericidal antimicrobials. If past history is in any way a good predictor of future history, microorganisms will consistently continue to adapt to their environment by developing resistance to newer antibiotics and serious infections caused by these bacteria will continue to pose a major challenge to the practicing clinician.

It will take a collaborative effort among industry, academia and government for us to strike a “balance” in the war against pathogenic bacteria. An effort which will include the implementation of several strategies simultaneously such as a better and broader use of existing public health and preventive measures to avoid infections in the first place, better infection control practices, better availability of diagnostic tools that allow us to more clearly and rapidly distinguish those patients, especially those in the outpatient community, who truly require an antibiotic prescription. All of this needs to be done at a reasonable cost.

It will also take a far more rational use of antibiotics emphasizing the need to use narrow-spectrum agents while saving the broad-spectrum ones for special circumstances. Finally, it will also take the creation and broader use of vaccines capable of preventing infections with some of these multi-resistant bacteria.

In summary, the post-antibiotic era is far from over. Investment in newer anti-infective platforms is essential and urgent as it is a seamless collaboration among industry, academia and government that results in a revolution in our understanding of bacterial resistance and new approaches to control it. However, the era where acute or chronic bacterial infections used to be treated with “antibiotics-only” appears to have come to an abrupt end.

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