

Antibiotic use: present and future

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SUMMARY

Antibiotics were initially viewed as “wonder drugs” primarily because they were introduced at a time when only surgical drainage or spontaneous cures were available to treat serious bacterial infections. During the five or six decades since their introduction, several classes of these drugs became available including sulfonamides and trimethoprim, penicillins, cephalosporins, chloramphenicol, tetracyclines, colimycins, macrolides, lincosamides, streptogramins, rifamycins, glycopeptides, aminoglycosides, fluoroquinolones, oxazolidinones, glycyglycines, lipoglycopeptides, and variations on these themes. Unfortunately, through a variety of mechanisms and perhaps as a result of their profigate use, many bacterial groups are exhibiting resistance to these antibiotics. At present, most bacterial infections can still be treated with available antibiotics used alone or in combination, but increasing numbers of clinical failures with the current armamentarium can be expected. Optimizing drug dosing and duration might help minimize the emergence of resistance in some situations. However, the future could look dim, as there are relatively few new agents on the horizon. A bold new look for antibacterial targets is needed. Surely our scientific abilities are up to this challenge. New approaches to antimicrobial chemotherapy are needed if we are to survive the increasing rates of antibiotic resistance predicted for the future.

KEY WORDS: Antibiotics, Resistance, New drugs

INTRODUCTION

When antibiotics were first introduced in the middle of the last century, they were hailed as wonder drugs. Patients and physicians alike were amazed at the almost miraculous effect of these drugs on serious bacterial infections. For the past fifty or sixty years physicians have come to expect that antibiotics would cure almost all of their patient's bacterial infections, and patients expect that the miracle drugs will still work wonders. Prior to 1940 infections were either treated with surgical drainage, antiseptics, silver compounds, arsenicals, or with tincture of time. Bacterial endocarditis was almost uniformly fatal, and a

diagnosis of pneumonia or meningitis was practically a death sentence. The rapid succession of antibiotics over the latter half of the twentieth century was indeed miraculous and provided clinicians with many options to successfully treat a wide range of bacterial infections. Only six decades later we can legitimately ask if the miracle is over. Soon after the first years of penicillin use, staphylococci rapidly became resistant to this wonder drug. In addition, in the early 1960's Kislak and Finland reported a single strain of *Streptococcus pneumoniae* that was resistant to penicillin (Kislak, *et al.* 1965). Since then more and more bacteria have developed resistance to more and more antibiotics. The crisis today is accentuated by a limited pipeline of new antibiotics, mediated in part by disincentives for industrial investment and development as well as the lack of new targets and new compounds. This mini-review will examine the currently available classes of antibiotics (including newly introduced drugs and some in the late stages of investigation), special challenges presented by antibi-

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otic resistant bacteria (especially community associated-methicillin resistant *Staphylococcus aureus*-CA-MRSA), approaches to maintaining or optimizing our therapeutic armamentarium and a look at the future prospects for new therapeutic antibacterial agents.

CURRENT ANTIBIOTIC CLASSES

The available antibiotic classes are well known to clinicians. Sulfonamides are primarily combined with trimethoprim and are indicated in the treatment of some urinary infections, nocardial and community associated MRSA infections. Penicillin remains the drug of choice for the treatment of syphilis and Group A beta-hemolytic streptococcal infections, however rates of penicillin resistance among pneumococci have increased in most countries around the world. Cephalosporins remain useful in some community and nosocomial infections but MRSA and some gram negative bacilli are resistant to many of these drugs. Carbapenems have activity against many Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa* (ertapenem excepted). The aminoglycosides are important bactericidal injectable antibiotics useful in the treatment of Gram-negative bacterial sepsis, and in combination with other agents in the treatment of tuberculosis and enterococcal infections. Macrolides, azalides, streptogramins and ketolides have a niche in the treatment of respiratory tract infections due to susceptible strains of pneumococci, *Haemophilus influenzae*, *Chlamydomphila pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, etc. Clindamycin is primarily used today in the treatment of anaerobic infections or as adjunctive therapy to some streptococcal and staphylococcal toxin mediated infections. The new fluoroquinolones have activity against many gram positive and gram negative organisms but resistance is increasing to many of these compounds. Vancomycin and teicoplanin are familiar glycopeptides active against MRSA, but heteroresistant strains and a very small number of vancomycin-resistant strains have been reported. Daptomycin is a new lipopeptide available for the treatment of MRSA skin and soft tissue infections as well as bacteremia. Tigecycline is a new gly-

cycline antibiotic that is available intravenously with broad spectrum inhibitory activity against MRSA and many Gram-negative bacilli, but not *Pseudomonas* or *Proteus* spp. Linezolid is an oxazolidinone that is active against Gram-positive cocci including MRSA and vancomycin resistant enterococci as well as some "atypical" organisms in the respiratory tract.

INVESTIGATIONAL ANTIBIOTICS

Compared with one or two decades ago there are relatively few antibiotic agents in the development pipeline. There are some new cephalosporins and carbapenems in clinical trials and there are promising glycopeptide derivatives such as the long acting dalbavancin and the lipoglycopeptide telavancin in phase three clinical trials.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Bacteria have amply demonstrated their uncanny ability to rapidly evolve mechanisms to resist the action of most antibiotics (Tenover, 2006). With the consistent exception of penicillin against *Streptococcus pyogenes*, most genera of bacteria have been able to find ways to resist the activities of one or more antibiotics. Bacteria may acquire or develop genes that encode for the production of enzymes that inactivate the antibiotic either within the bacterial cell or in the environmental milieu. A classic example of the former are the beta-lactamase enzymes that cleave the beta-lactam ring of penicillins, cephalosporins, and carbapenems, whereas the aminoglycoside-inactivating enzymes produced by resistant Gram-negative bacteria represent the ability to inactivate or destroy an antibiotic in the extracellular space.

Bacteria can upregulate genes that produce cellular pumps that extrude antibiotics from the cell. As an example, the *mef* gene in *S. pneumoniae* regulates an efflux pump that extrudes macrolides from the bacterial cell and is one of the more common mechanisms of macrolide resistance in pneumococci. Bacteria may acquire genetic material that encodes for metabolic path-

ways that alter the cell wall by modifying or eliminating the binding site for the antibiotic; bacterial genes responsible for the porin channels may be downregulated, limiting access of the drug to its ribosomal or other targets. Mutations can also occur in the bacterial targets themselves as seen in fluoroquinolone resistant bacteria. Bacteria can alter other target proteins such as the penicillin-binding proteins in pneumococci with subsequent expression of penicillin resistance. There are many other examples, of course. Bacteria can develop resistance as a result of spontaneous mutations, or by transposition or transduction of genetic material such as plasmids.

SPECIAL CHALLENGE OF MRSA

The current surge in cases of infections caused by community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) deserves special comment. Although hospital or health-care-associated MRSA (HA-MRSA) are commonplace in many but not all hospitals around the world, CA-MRSA are increasing in frequency as causes of serious skin, soft tissue and lung infections in previously healthy patients with no contact with hospitals or other health care settings (Crum *et al.*, 2006). All MRSA strains contain the *mecA* gene that encodes a low-affinity penicillin binding protein (PBP-2a) that is ultimately responsible for methicillin resistance. The *mecA* gene is carried on a cassette chromosome (SCC*mec*) that is mobile and is an efficient transformer. HA-MRSA are associated with SCC*mec* types I-III, whereas CA-MRSA strains carry the SCC*mec* types IV-V or VI (Ma *et al.*, 2002; Mongkolrattanothai *et al.*, 2003). Many of the clones of SCC*mec* IV-V also carry the *pvl* gene that encodes for the Panton-Valentine leucocidin, a potent toxin that might be responsible for some of the features of CA-MRSA infections. (Holmes *et al.*, 2005; Labandeira-Rey *et al.*, 2007)

In general, HA-MRSA strains are resistant to multiple antibiotics in addition to beta-lactams, but are usually susceptible to vancomycin, daptomycin, linezolid and tigecycline. CA-MRSA strains are susceptible to these four antibiotics but also may be susceptible to trimethoprim-sulfamethoxazole and tetracycline and exhibit

variable susceptibility to fluoroquinolones, clindamycin and macrolides. The incursion of CA-MRSA strains in community skin and soft tissue infections has changed the paradigm for antibiotic therapy of these infections so that cephalosporins are no longer indicated as agents of first choice (Moran *et al.*, 2006).

APPROACHES TO MAINTAIN AND OPTIMIZE THE ANTIBIOTIC ARMAMENTARIUM

Antibiotic stewardship was coined by the Society for Health Care Epidemiology of America and the Infectious Diseases Society of America in their joint guidelines for the prevention of resistance in hospitals (Schlaes *et al.*, 1997). In practice, this concept involves the selection of the most appropriate drug at the correct dosage for the appropriate duration to eradicate the bacteria at the site of infection while minimizing both adverse events for the patient and hopefully the selection of antibiotic resistance. Proper use of antibiotics requires detailed familiarity with the antibiotic spectrum and activity of a given drug, its pharmacokinetics (to be sure it gets to the site of infection) and its pharmacodynamics (to be sure the concentrations will result in the desired antimicrobial effect e.g. bacterial killing or inhibition). Obviously, clinical considerations such as drug allergy, drug interactions, formulary issues etc., will influence the correct choice of antibiotic for a given patient.

As recently reviewed (Fishman, 2006), antibiotic stewardship subsumes physician education, practice guidelines and computer-assisted decision support programs (Pestonik *et al.*, 1996), formulary restriction (decisions on which should include infectious disease physicians), antibiotic streamlining (modifying initial antibiotic choices based on microbiological results and clinical course), and approval for release of specified antibiotics. Antibiotic cycling also is included in some institutions. This process requires the scheduled rotation of two or more antibiotic classes with similar antibacterial activity spectra over a defined time period with a rotation schedule that ultimately includes a return to the original regimen.

While there is some evidence that some or all of

these methods improve antibiotic use and appropriate initial therapy, control expenditures for antibiotics, reduce adverse effects of antibiotics (particularly CDAD) (Khan *et al.*, 2003), the overall impact of these procedures alone or together on the emergence of antibiotic resistance has been difficult to assess.

Maximizing antimicrobial activity and minimizing resistance with the consideration of pharmacodynamic principles. Recently there has been considerable attention devoted to the potential for optimizing the antibacterial effect of available antibiotics as well as minimizing the emergence of resistance. There have been relatively few studies that directly link pharmacodynamic activity with clinical results, but the few examples in the literature support the concept of maximal antimicrobial effect with optimized pharmacodynamics. A landmark study a few years ago established a relationship between a levofloxacin C_{\max}/MIC greater than 12.2 and clinical success (Preston *et al.*, 1998).

There have been few if any clear cut clinical demonstrations that antibiotic resistance can be prevented with the application of pharmacodynamic principles, but recent work using *in vitro* dynamic models is very encouraging. In three to five-day studies in an *in vitro* model in collaboration with Professor Alexander Firsov, our laboratory has demonstrated that fluoroquinolone concentrations that exceed the "mutant prevention concentration" (Zhao and Drlica, 2001) over most of the dosing interval were less likely to select resistant mutants of both *Staphylococcus aureus* and *Streptococcus pneumoniae* (Firsov *et al.*, 2003; Zinner *et al.*, 2003). Similar conclusions were suggested by another recent study with *Pseudomonas aeruginosa* (Tam *et al.*, 2005). More clinical studies are needed to test these hypotheses in patients.

FUTURE PROSPECTS FOR ANTIBIOTIC THERAPY

As resistance to available antibiotics continues to increase, it will become necessary to develop new agents with novel targets or mechanisms of action. Combination of currently available antibiotics might remain useful in the treatment

of resistant pathogens, but it is possible that physicians will run out of options at some time in the future. Several experimental molecules are in the literature and are under consideration for clinical development. For example, bacteriocins such as two-peptide lantibiotics and other molecules are being studied for potential antibacterial chemotherapy (Cotter *et al.*, 2005) as are molecules that block receptors on the bacterial surface that mediate cell adhesion (the initial phase of infection). Other approaches include hybridization and other modifications of existing antibiotics; bacteriophages are also under investigation to possibly revive interest in them as antibacterial agents.

There is no doubt that as antibiotic resistance increases worldwide, enormous challenges will be placed on physicians and industry alike to find new products to continue the antibiotic miracle long into the future. Every attempt should be made today to preserve and optimize the agents in our therapeutic armamentarium.

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