



Wildcatters welcome: the need for new antimicrobial agents



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In a 1969 address to the US Congress, the Surgeon General suggested that it was time to close the book on infectious diseases [1]. Twenty years of successes associated with clinical use of penicillin and other antimicrobial agents had buoyed the hopes of clinicians and the public alike. Moreover, the pharmaceutical industry was on the verge of a dramatic expansion in developing new antimicrobial agents that would offer broader coverage, improved safety and more convenient dosing regimens. The success of the smallpox and polio vaccines suggested that major viral illnesses would be controlled and yeasts and molds had not yet become common causes of serious disease.

The Surgeon General may have closed the book that was before him but we have come to realize over the subsequent 4 decades that this book represented merely the first volume in a long-running saga. The introduction of vancomycin, methicillin and the cephalosporins to treat emerging penicillin-resistant staphylococci was rapidly followed by the appearance of resistant Gram-positive species, such as methicillin-resistant staphylococci, vancomycin-resistant enterococci and more recently, vancomycin-resistant *Staphylococcus aureus*. On the Gram-negative side, the use of ampicillin and cephalosporins was followed by the surfacing of resistance in normally susceptible species such as *Escherichia coli* and *Klebsiella pneumoniae*, in addition to the emergence as important pathogens of intrinsically resistance species, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. These and several other pathogens found comfortable homes in the antibiotic rich, immunity poor patients inhabiting the modern hospital, as did many species of yeasts and molds. While it is still quite rare to encounter bacteria resistant to all clinically available antimicrobial

agents, it is not so rare to encounter strains resistant to all but one or two classes. In patients with histories of allergies or other adverse reactions, options may be very limited or nonexistent. The need for new antimicrobial agents, it seems, is quite real.

In contrast to the 1960s, the response of the large pharmaceutical companies to this new challenge has been rather muted. At the 43rd Interscience Conference of Antimicrobial Agents and Chemotherapy (IL, USA) in September 2003, industrial attendance declined. There were 10% fewer presentations of new drug candidates than the previous year [2]. Many large pharmaceutical companies with rich histories of producing anti-infective agents eliminated their antibacterial discovery groups entirely. The reasons for this retreat are primarily economic and include the competitive nature of the industry and its emphasis on blockbuster drugs, the relatively small number of patients infected with bacteria for which no current therapies exist and the difficulty of including patients infected with resistant organisms in clinical development trials. Moreover, antibacterial agents are administered for limited periods of time. Pharmaceutical companies eager to improve their bottom line prefer to target chronic diseases, such as hypertension, diabetes or hypercholesterolemia, since lifelong treatment for these conditions is the rule. Finally, antibacterial agents are probably the only therapeutic agents for which thought leaders argue constantly for less, rather than more use. As a result of these decisions, the development of new and novel antimicrobial agents has been left to relatively small pharmaceutical and biotechnology companies whose sales and profit targets are more in line with those that conventional wisdom states antibacterial agents can offer.

Declining industry interest is also attributable to the difficulty of discovering new antimicrobial agents. The traditional method of isolating natural products from microorganisms themselves was first accidentally employed in 1929 when Alexander Fleming noted inhibition of *S. aureus* on an agar plate that was contaminated by a *Penicillium* mold. Natural

product searches have the virtue of selecting for the desired outcome (death or inhibition of target bacteria) but will predictably identify compounds for which resistance determinants exist. The impressive efficiency with which human pathogens scavenge these determinants for their own use has been remarkable. Modifying existing compounds to expand their spectrum has been a highly effective method of improving antimicrobial activity. However, it is disheartening to realize that in some cases, such as extended-spectrum β -lactamases produced by *K. pneumoniae* and other *Enterobacteriaceae*, a single point mutation can virtually negate a US\$250 million dollar investment in antimicrobial development [3].

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Given the problems inherent in natural product searches and modifications, there was a great sense of optimism associated with the burgeoning availability of entire bacterial genomes. Detailed genomic data offered the promise of new targets, ideally those for which resistance determinants did not already exist. Targets, such as peptide deformylase (PDF), a bacterial metalloenzyme necessary for protein synthesis, have been discovered using this methodology. Compounds that inhibit PDF have been identified and *in vitro* data on their antimicrobial activity published [4] but the clinical utility of these compounds remains speculative. Overall, it is fair to say that the yield of genomic strategies for developing new antimicrobial agents has been disappointing.

Despite these challenges, the current antibiotic pipeline, while somewhat anemic, is not completely barren. Most recently introduced drugs and those in development are notable for their activity against resistant Gram-positive bacteria, although some in development are active against some problematic resistant Gram-negatives as well. Little effort is being directed toward developing drugs with anti-anaerobic activity, since compelling resistance problems are rare in these species.

Antibiotics active against Gram-positive bacteria

The newest licensed antimicrobials on the US market as well as many in the pipeline target serious infections caused by Gram-positive bacteria. The most important impetus for developing these agents in the early 1990s was the emergence and rapid spread of vancomycin-resistant *Enterococcus faecium* (VRE). While the treatment of VRE infections remains an important therapeutic goal, difficulty enrolling evaluable VRE-infected patients in clinical trials and the sharp rise in the importance of methicillin-resistant *S. aureus* (MRSA) in hospitals worldwide has caused some pharmaceutical companies developing new agents to eschew US Food and Drug Administration (FDA) approval for VRE indications in favor of targeting MRSA.

Quinupristin/dalfopristin (Synercid[®], Aventis Pharma) was the first antimicrobial on the US market with clinically important activity against VRE (the vast majority of which are resistant to ampicillin as well as vancomycin). Approved in September 1999, quinupristin/dalfopristin’s anti-enterococcal activity is limited to *E. faecium*, a cause of roughly 30% of enterococcal infections but representing more than 90% of vancomycin-resistant enterococcal isolates [5]. The components of this combination inhibit bacterial protein synthesis by binding to different ribosomal sites, thereby achieving synergy. While its approval was met with enthusiasm, quinupristin, dalfopristin’s clinical utility, has been limited by its intravenous-only formulation and the frequency of side effects including phlebitis, arthralgias and myalgias. Both quinupristin and dalfopristin are derivatives of pristinamycin, an agent widely used in animal feed as a growth promoter. Perhaps as a consequence, resistance to quinupristin/dalfopristin via different mechanisms has been reported in clinical isolates, in some cases before significant clinical use of the agent [6].

In April 2000, linezolid (Zyvox[®], Pharmacia) became the first antimicrobial with a novel mechanism of action to obtain FDA approval in 35 years. The first and only approved oxazolidinone, linezolid inhibits bacterial protein synthesis by interfering with ribosomal initiation of translation [7]. Currently, linezolid is approved for the treatment of infections with VRE including bacteremia, nosocomial pneumonia with *S. aureus* or penicillin-susceptible *S. pneumoniae* and skin and soft tissue infections. Linezolid’s activity is strictly bacteriostatic, therefore

its utility is limited for indications such as enterococcal endocarditis or staphylococcal osteomyelitis. A limitation of long-term linezolid therapy is thrombocytopenia [8]. Although linezolid remains widely active against most Gram-positive bacteria, resistance has been observed in both VRE and MRSA. Single point mutations in the 23S rRNA gene can reduce linezolid binding and the presence of this mutation in two or more of the cellular 23S genes can confer clinically significant levels of resistance [9]. The first point mutation appears to be the important one – after that the bacteria are capable of amplifying the resistance through homologous recombination [10]. Given that an oral as well as intravenous formulation is available, overuse in the community is a concern, as resistance may limit the drug's usefulness.

In September 2003, daptomycin (Cubicin[®], Chiron Corporation) became the first cyclic lipopeptide approved by the US FDA. Derived from the fermentation of *Streptomyces roseosporus*, it has been known as a bactericidal agent for nearly 20 years [11].

Earlier attempts to achieve approval were complicated by myotoxicity and poor clinical efficacy. By increasing the dose (currently approved for use at 4 mg/kg) and administering once per day, toxicity was limited and the concentration-dependent killing activity was improved. Daptomycin's bactericidal activity results from disrupting the cytoplasmic membrane integrity in a reaction that requires sub-physiologic concentrations of calcium and causes depolarization and cell death [12]. Though no mechanism of resistance has yet been identified, rare (<0.2%) resistance was reported by the sponsor (Cubist Pharmaceuticals, MA, USA) during Phase II and III clinical trials. Daptomycin is active exclusively against Gram-positive bacteria as its large size excludes it from the Gram-negative periplasmic space. It is approved for clinical use in serious skin and soft tissue infections. Clinical trials using a higher dose (6 mg/kg) for treatment of staphylococcal bacteremia are ongoing. Daptomycin is not FDA approved for use in the treatment of VRE because large enough clinical trials were not pursued to obtain this approval. Clinical trials indicated that daptomycin was inferior to β -lactam comparator (generally ceftriaxone [Rocephin[®], Hoffmann-La Roche]) in the treatment of community acquired pneumonia, and therefore it should not be used for the treatment of pneumonia.

Semisynthetic glycopeptide derivatives are being developed to treat VRE and provide additional options for MRSA infections. Oritavancin is currently in Phase III clinical trials for skin and soft tissue infections and Phase II for bacteremia. It is bactericidal and has a long half-life. In one Phase III study, when compared with vancomycin, oritavancin was equally efficacious though administered for a shorter duration [13]. Also in clinical trials is dalbavancin, the first antibiotic dosed once weekly. It too is being investigated for the treatment of skin and soft tissue infections as well as bacteremia. Early data suggest efficacy in comparison with standard therapy in skin and soft tissue infections [14].

Ramoplanin is a nonabsorbable glycolipodeseptide which, similar to the glycopeptides, inhibits bacterial cell wall synthesis. It is currently being tested for its ability to eliminate VRE gastrointestinal colonization and thereby reduce infections. One Phase II study showed suppression of colonization in 90% of patients at one week of therapy [15]. A Phase III study of ramoplanin's ability to prevent VRE bloodstream infections in cancer patients is ongoing. *In vitro* data suggest that ramoplanin may also be effective therapy for *Clostridium difficile* colitis [16].

Agents with activity against both Gram-negative & -positive bacteria

Most of the broad-spectrum antimicrobials in development are derivatives of antibiotic classes already in clinical use. Currently in clinical use in Europe and Canada, telithromycin (Ketek[™], Aventis Pharmaceuticals Inc.) is the first ketolide antibiotic. Ketolides are a subclass of macrolides modified to improve ribosomal binding and thereby retain activity against resistant organisms, specifically *S. pneumoniae*. Telithromycin exhibits *in vitro* potency against macrolide-resistant pathogens [17] and Phase III clinical trials have investigated its activity in community acquired pneumonia, acute exacerbations of chronic bronchitis and acute sinusitis with demonstrated high rates of clinical cure [18]. Telithromycin has recently been FDA approved.

Garenoxacin is a novel des-fluoro(6) quinolone designed to have improved activity against resistant respiratory pathogens. Its structural modification is the absence of a fluorine at C-6; however, its mechanism of action is the same as others in its class [19]. Compared with fluoroquinolones already in clinical use, garenoxacin demonstrates enhanced *in vitro* potency against *S. pneumoniae*. This agent has

yet to enter Phase III trials, hence, its clinical efficacy and safety have yet to be determined in larger populations.

Glycylcyclines are a subclass of tetracyclines designed to avoid the problems of resistance faced by the traditional tetracyclines. The prototype is tigecycline, a derivative of minocycline (Arestin[®], OraPharma, Inc.). Currently in Phase II studies for intra-abdominal and complicated skin and soft tissue infections, tigecycline has demonstrated *in vitro* activity and early *in vivo* efficacy against a wide range of pathogens, including MRSA, VRE, lactose-fermenting Gram-negative bacilli and anaerobes [20]. Most of the numerous described tetracycline-resistance mechanisms prevalent in clinical bacteria are inactive against tigecycline. However, RND-type efflux pumps have been shown to contribute to intrinsic resistance in *Proteus mirabilis* and *P. aeruginosa* [21,22]. Tigecycline does demonstrate encouraging activity against *A. baumannii* [23]. Its formulation is intravenous only and its half-life is 36 h, allowing once-daily dosing. More clinical data will be available following Phase III studies.

The present era is clearly a time of transition for Big Pharma and the development of antibiotics. It seems clear that most of the low-hanging fruit has been taken. Given the inexorable progress of resistance, it is also clear that the present antimicrobial classes should be considered nonrenewable resources. Further exploration into new antibiotics will take considerably greater effort and entail a greater risk. The technology (genomics) for creating new antibiotics is available but it appears we really do not know how to best employ this technology at the present time. Consequently, many large pharmaceutical companies, some of whom built their business for years around antimicrobial agents, are deserting this therapeutic area for the presumed safe havens and large profit margins of drugs to treat chronic diseases.

One could argue about the morality of abandoning such an important therapeutic area in which current agents are beginning to show their shelf life. This argument would not be particularly productive. Circumstances, such as these create moral imperatives on more than just the industrial level. On a societal level, they create the imperative to aggressively search for new paradigms for treating infectious diseases, ones that do not rely so heavily on the use of antimicrobial agents. Federally supported research into immunotherapies represents one such response to this

imperative but there is little question that much remains to be explored. On an individual level, there is a clear imperative that we (physicians, patients) use these nonrenewable resources wisely – that we not be profligate in our current use, for that will place unacceptable limits on our descendents. We are beginning to acknowledge the importance of judicious use of antimicrobial agents but there is much room for improvement.

Morality aside, the far more compelling argument is an economic one. Clinical need for anti-infective therapy is likely to grow, rather than decrease, over the next 50 years. Bacteria will continue their adaptation to their environment, ensuring more, not less need for agents proved effective against resistant organisms. Effective antibiotics are critical to the functioning of the entire healthcare system – not just for treatment of infection but for performing surgery, for augmenting our infection control efforts and for keeping patients out of the hospital. There is a huge market out there just waiting to be exploited.

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It is not surprising that many large pharmaceutical companies do not appear to recognize this potential. The frequent consolidations that have occurred over the past decade have created huge conglomerates that are as easy to manipulate as the Titanic. Increasing levels of bureaucracy stifle creative thinking, yielding a risk-adverse environment in which strategies for future development are based on the conditions of today’s market (what is selling the most now?) rather than on intelligent speculation about the markets of the future (what is not selling today but will be essential tomorrow?).

These future markets will be exploited, they always are, primarily by smaller companies, companies willing to take big risks because they have much less to lose. Companies run by eager and creative people who recognize good (and sometimes revolutionary) ideas and the smart people who generate them. These companies will be the pharmaceutical equivalent of the wildcatters of the oil industry, investing time,

money and effort in a high-risk endeavor to find oil in places where the large oil companies do not bother to look. The future role of the Big Pharma companies that have disbanded their discovery efforts will involve either ingesting these smaller companies or offering up distribution and sales forces to move the products created by their more nimble competitors.

Of course, the success of such a scenario will also depend upon a realistic and flexible regulatory environment, one that understands the

difficulty of clinically testing antimicrobial agents and does not set hurdles that are insurmountable. Recognizing the importance of developing new antimicrobial agents, the FDA has shown in recent years that it is willing to recognize these specific difficulties, making allowances that promote drug development while still protecting the consumer. This collaborative spirit will be critical as we move beyond the 'post-antibiotic era' to a new era of therapeutic optimism.

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