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Preface

Antibacterial Agents: Solutions for the Evolving Problems of Resistance

About 10 years ago, multidrug-resistant pathogens were confined largely to the hospital setting. However, in the last decade, the incidence of antimicrobial resistance has increased in both the hospital and community settings. This has resulted in therapeutic failures, the use of increasingly costly and toxic antimicrobials, extended hospital stays, and increased morbidity, mortality, and healthcare costs. Moreover, patents for community-use antimicrobials Augmentin and Cipro have expired and, with the two major macrolides Zithromax and Biaxin expiring in 2005, the lower cost of generic versions will reduce cost pressures and may lead to broader prescribing with a consequential increase in observed resistance.

Community-acquired pneumonia (CAP) infects yearly upwards of four million people in the US, of which 20% require subsequent hospitalization.[1] The most frequently isolated species are *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*. A recent survey by The Respiratory Surveillance Program (RESP; 1999–2000), a group that collects data from 674 office-based practices in nine geographic regions of the US, found that *H. influenzae* is the most frequently-isolated organism from patients with community-acquired pneumonia (38%) and acute exacerbation of chronic bronchitis (35%).[2] *S. pneumoniae* was isolated in 18% of community-acquired pneumonia cases, 13% of acute exacerbation of chronic bronchitis cases, and 11% of sinusitis cases. *M. catarrhalis* was most commonly isolated from the nasopharynx of patients with sinusitis (29%). High-level resistance to penicillin (2 μg/mL or greater; 16% overall) and the macrolides (32–35%) among *S. pneumoniae* varied both with site of infection and with geographic region.[2] The percentage of resistance is influenced by patient age, being significantly higher in children $\leq$18 years of age.[3,4] For example only 48.9% of *S. pneumoniae* strains from North America were susceptible to penicillin in the young age group compared to 62.9–70.6% for other age groups; this same trend was observed with macrolide susceptibility.[3,5]

In the United States, penicillin resistance in pneumococci during 1999–2000 was 34.2%, with 21.5% high-level resistance.[6] β-Lactamase-mediated resistance to ampicillin among *H. influenzae* ranged from 15% in New England to 32% in the East South Central region of the US.[2] In the US[7] and worldwide,[8] clarithromycin-resistant *H. influenzae* were notable in sinusitis (36%) and respiratory tract infections, respectively.[7] In a recent US survey, *M. catarrhalis* was found to have a penicillin resistance rate of 91.5% and an erythromycin resistance rate of 15% in sinusitis isolates.[7]

Resistance is seen also in hospital pneumococcal isolates. In a 1995–1998 study conducted by the CDC,[9] the incidence of resistance increased: penicillin (from 21 to 25%), cefotaxime (from 10 to 15%), meropenem (from 10 to 16%), erythromycin (from 11 to 16%), and trimethoprim-sulfamethoxazole (from 25 to 29%). In a 1999 CDC study, macrolide resistance had further increased to 20.4%.[10] In another CDC surveillance study, multidrug-resistant (MDR) phenotypes increased from 5.9 to 11% when isolates were collected in 1997–1998 or 1998–1999. A more recent surveillance study reported multidrug resistance in 1999–2000 as 22.4%.[6] The most common MDR phenotype for pneumococci was resistance to penicillin, erythromycin, and trimethoprim-sulfamethoxazole.[1,6] Because multidrug resistance is so prevalent, new antimicrobials are needed; some approaches seeking to penetrate the arena of respiratory tract infections are described in this Journal edition.

Fluoroquinolone resistance in the US was seen for the first time in the 1998–1999 pneumococcal isolates.[11] Reports in the US reflect that $<$1% of the *S. pneumoniae* isolates are levofloxacin-resistant.[5] Fortunately, it appears that levofloxacin resistance is not associated with antimicrobial resistance to the nonfluoroquinolone antibiotics.[5] Unlike other antibiotics, fluoroquinolone resistance is found predominantly in the older population ($>$64 years).[5] It will be interesting to see if resistance to this class of antibiotics emerges even faster if they are introduced into pediatric use.

Penicillin resistance is virtually undetectable in Group A streptococci (*Streptococcus pyogenes*), despite many years of clinical use.[12] However, macrolide resistance can vary from relatively low levels in the US (2.6% in isolates collected from 25 states[13] and 5.2% overall in North America[4]) to isolated higher rates of resistance such as those reported from the San Francisco Bay area

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for invasive strains[14] or the clonal outbreak in Pittsburgh in January 2001.[15] Notably, very high frequencies of resistance to macrolides have been reported in Italy (42%) and Finland.[16,17]

Staphylococcus aureus, especially methicillin-resistant *S. aureus* (MRSA) isolates, ranks as the most frequently-isolated pathogen associated with blood stream infections in North America, 1997–2001.[18] Its propensity to establish prolonged carriage among hospitalized patients and increasing resistance to antibiotics makes control difficult for this organism within the hospital setting. In the US, 38.7% of strains were resistant to methicillin.[18] MRSA isolates are generally multidrug-resistant (MDR), with resistances to MLS_B (macrolide-lincosamide-streptogramin B) antibiotics, fluoroquinolones, and other antibiotics like mupirocin. The drug of choice for serious infections caused by MRSA is vancomycin, but emergence of high-level resistance to vancomycin has already appeared twice in the US in 2002.[19,20] Although the emergence of this strain type had been feared for some time, its appearance has also resulted in the concern that vancomycin resistance could become established in a predominant *S. aureus* MDR clone. Papers on oxazolidinone approaches targeting nosocomial Gram-positives appear in this Symposium. One paper on an vancomycin derivative entering Phase II is also included in this issue. Readers are also referred to another paper detailing some interesting structure–activity insights into combating MDR Gram-positive bacteria that was intended for this issue and was accidentally published in *Bioorg. Med. Chem. Lett*. **2000**, *13*, 2933.

Two relatively new drugs that have activity against MDR *S. aureus*, linezolid and quinupristin/dalfopristin (Synercid) have been introduced into hospital use. However, cost, side effects, and reports of emerging resistance to these new agents speak to the need for further new antimicrobials to combat this invasive pathogen.[21,22] A number of the letters in this Symposium issue are devoted to improvements of linezolid either by expanding the spectrum to include Gram-negative respiratory tract pathogens and/or by finding compounds with activity against linezolid-resistant strains.

Enterococcal strains are the fourth most commonly isolated pathogens in blood stream infections in North America.[18] These organisms, part of everyone's natural microflora, were largely not recognized as pathogens until the 1990s. Unfortunately, at last count, 50% of the *Enterococcus faecium* isolates were vancomycin-resistant; moreover, *Enterococcus faecalis* isolates generally have high-level resistance to aminoglycosides and β-lactams. Synercid does not cover *E. faecalis,* and linezolid-resistant strains (although still infrequent) have been identified in both species of enterococci.[23–25] An example that highlights the need for new antibiotics is a linezolid-resistant *E. faecium* isolate that developed in a patient during linezolid treatment; its MDR phenotype included resistance to vancomycin, ampicillin, macrolides, fluoroquinolones, chloramphenicol, rifampin, gentamicin (high-level), nitrofurantoin and trimethoprim/sulfamethoxazole.[26] With the enterococci comes a huge concern for nosocomial spread and inability to clear hospitals of these tenacious pathogens.[27]

Three of the top five pathogens isolated in intensive care units in North America are Gram-negative bacteria, *Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella* spp.[28] Of these important pathogens, *P. aeruginosa* was highly resistant to amoxicillin/clavulanate, ampicillin, ceftriaxone, and was ~25% resistant to several of the new-generation fluoroquinolones. For the other Gram-negative species the incidence of extended-spectrum β-lactamases was >10%, with ~12% fluoroquinolone resistance in *E. coli* and 2.8–5.1% resistance in *Klebsiella*. Further, in bacteremic isolates of *Klebsiella*, only 40.6% and 69% are susceptible to piperacillin/tazobactam and cefepime, respectively.[29] In short, the dream of the fluoroquinolones being the panacea to the antibiotic crisis has not been fulfilled.

Thus, it appears that new antibacterial agents will have to circumvent current and future resistance trends in important pathogens. One way to accomplish this is to discover new agents (which presumably will not be subject to known resistance mechanisms) that target novel, essential enzymes or proteins. Although daptomycin is not a new agent, certainly its mechanism of action is new and two manuscripts describing some structure–activity relationships are included in this Symposium. One paper describes how a structure-based design approach has bolstered activity versus resistant strains. Two papers outline attempts to inhibit intrinsic efflux pumps in Gram-negative bacteria and seek agents that are synergistic with fluoroquinolones.

The worldwide antibacterial market is ~$25 billion dollars. With two-thirds of the prescriptions being written for community-acquired infections where resistance abounds, the introduction of new antibiotics in the community has both financial and medical incentives. Clearly, the time has already come where new agents are needed to overcome multidrug-resistant hospital-acquired pathogens. Popular articles have called attention to the impact that bacterial resistance is having on antimicrobial effectiveness.[30–39] Given the experience of attrition on drug discovery, there is plenty room and need for many more 'shots-on-goal.'

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