

Microbe, An American Society for Microbiology publication – July 2008  
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## **Antimicrobial Resistance and Its Implications for the 21st Century**

**I. W. Fong and Karl Drlica (ed.). Springer Verlag, 2008, 408 p., \$129.**

On 14 March 1942 the first patient was successfully treated for streptococcal septicemia with U.S.-made penicillin. The Golden Age of Antibiotics had begun, and we thought that bacterial diseases would shortly be a thing of the past. How wrong we were.

This book is a compendium of reviews describing and discussing the problem of antimicrobial resistance and the difficulties encountered in its resolution. The loss of susceptibility by organisms to drugs which have been used worldwide for many years emphasizes the need for newer compounds and for the judicious use of available treatment methodologies.

The first chapter considers resistance in gram-positive bacteria with an emphasis on *Streptococcus pneumoniae* and enterococci. The authors note that, in general, “the use of antimicrobials, appropriate or not, encourages the development of resistance in bacterial strains,” and discuss the various resistance mechanisms to penicillin and the cephalosporins. The risk factors for infection by penicillin-resistant *S. pneumoniae* are discussed briefly and include, among other factors, previous  $\beta$ -lactam treatment, nosocomial infection, and previous hospitalization, as well as CAP (community-acquired pneumonia) in the preceding year. The section on the above-mentioned antimicrobials concludes with a discussion of clinical consequences of penicillin resistance in patients with pneumonia and the use of combination therapy.

Resistance mechanisms in streptococci and enterococci and its clinical implications are subsequently discussed for macrolides, tetracycline, quinolones and clindamycin. Multidrug resistance of *S. pneumoniae* is briefly mentioned, noting the increase in such isolates. Issues concerning the use of vancomycin streptogramins, and oxazolidinones are considered. Chapter two discusses an issue which has been in the news of late, namely, the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community.

The study of such characteristics as age, race, ethnicity, and socioeconomic status, as well as sex and urban or rural settings in epidemiology of CA-MRSA show varied results. Colonization is common but varies from persistent to never. Obviously, colonized individuals are more likely to infect susceptible hosts, who may be immunocompromised or have a genetic disposition to infection. The five major factors implicated in CA-MRSA transmission include crowding, skin-to-skin contact, breaks in the skin, shared items and contaminated surfaces (such as soap and whirlpools, and even sports equipment), as well as lack of basic hygiene. The chapter concludes with some suggestions on managing MRSA infections in the community, as well as preventive measures.

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The chapter “Antimicrobial Resistance to Sexually Transmitted Infections” notes that in herpes infections there is relatively low resistance to the cyclovir family, with most isolates coming from immunocompromised patients. No evidence of penicillin resistance by *Treponema pallidum* has been reported. This holds true as well for chlamydia, where a stable, resistant *C. trachomatis* strain has not been isolated from human infection. Not so for gonorrhea, where plasmid or chromosome resistance to a number of anti-microbials has been reported.

The chapter on resistance of gram-negative bacilli to antimicrobials begins with a quote from Jean Carlet, who describes intensive care units (ICUs) as “factories for creating, disseminating, and amplifying resistance to antibiotics.” The authors also comment on the excessive use of antibiotics in long-term care facilities as exacerbating the problem. Mechanisms of resistance are discussed, with an emphasis on  $\alpha$ -lactam antibiotics, quinolones, aminoglycosides, and tetracyclines. The role of biofilms in protecting organisms from antimicrobials is discussed. Efflux-mediated resistance, which decreases intracellular concentration of the desired drug, is common in many gram negatives, including those of nosocomial (and, by definition, ICU) interest, but methods of circumventing this phenomenon have been reported. The importance of handwashing cannot be overstated, and compliance with this procedure has been noted as being less than 50% among hospital personnel. It takes the first 11 pages of the following chapter (“Mycobacterial Antibiotic Resistance”) just to list the countries around the world where drug-resistant tuberculosis is problematic. Mycobacteria, because of their relatively slow generation time, are more apt to develop resistance to antimicrobials, particularly when the patient is treated with a single drug. Since those affected are rarely “in-patients,” poor compliance and supervision may quickly lead to the development of multiple drug resistance. The treatment of multidrug-resistant tuberculosis has been hampered by the lack of new drugs. The biggest single risk for developing tuberculosis is HIV infection. Infection with the virus has also made MAC (*Mycobacterium avium-intracellulare*) the most common of the so-called environmental mycobacteria in HIV-infected individuals in developed countries.

The last of the chapters dealing with bacteria concerns itself with antimicrobial resistance of anaerobes. Several antimicrobial susceptibility tests for anaerobes are subject to discrepancies; others, such as agar dilution (which is considered the reference method), are involved and costly. Though less newsworthy than aerobe resistance, anaerobe resistance, especially among the *Bacillus fragilis* group, has been increasing. This holds true for most commonly used antibiotics.

The following three chapters deal with viral drug resistance, specifically HIV, herpes, and hepatitis viruses. Mutations are a major problem in the development of resistance to anti-HIV drugs, as is crossresistance among similar drugs. Resistance to the cyclovirs in treatment of cytomegalovirus, herpes simplex, and varicellazoster infections is seen mainly in immunocompromised individuals. Alternative compounds are not readily available. Hepatitis B infection is typically chronic, and treatment is aimed towards halting further progression of the disease. In the absence of a cure, resistant variants emerge. Current treatment is mainly with pegylated  $\alpha$ -interferon and inhibitors targeting the reverse transcriptase elucidated by the virus. Add-on therapy is recommended in

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managing resistance. The authors note that, in hepatitis C virus, there are few options for patients not responding to standard pegylated interferon-alpha ribavirin treatment, as this is the only approved therapy.

In discussing antifungal agent resistance, it is noted that there are a goodly number of agents available for treatment. At the same time, there has been an increase in severe fungal infections, due, in large part to patients who are severely immunocompromised, as well as those who are more aggressively treated. Resistance among antifungal agents includes changes in membrane ergosterol (polyenes), decreased uptake of 5-fluorocytosine, and enhanced efflux of azoles, to mention some examples. Resistance seems to be more associated with individual host characteristics than being of a widespread nature. There are several agents under development, both for treatment and for prophylaxis. In the last chapter, the authors begin by considering the difference between microbial populations that acquire resistance and the subsequent dissemination of resistance in patient populations. The emphasis, they note, should be in intervention at the acquisition stage. In proposing an antimutant approach for using antimicrobials, they refer to the mutant selection window hypothesis of Zhao and Drlica, which postulates that resistant mutants are enriched and amplified at certain antimicrobial concentrations. This selection window hypothesis mandates the use of higher drug concentrations, forcing the pathogen to acquire two mutations at the same time and thus decreasing the possibility of mutant multiplication. In general, the spread of resistant pathogens is best countered with proper hygiene and the proper use of antimicrobials. The mutant prevention concentration (MPC) is noted as being that point above which bacterial growth would require two concurrent mutations. The authors refer to the MPC as being the antimicrobial concentration which is the MIC of the least susceptible, single-step mutant. Their results were obtained from work with spontaneously occurring mycobacterial mutants, at varying fluoroquinolone concentrations. These findings were then extended to studies with azoles and *Candida* spp.

The selection window hypothesis suggests that traditional treatment with antimicrobials typically relies on the lowest drug dose for clinical efficacy, and that this can lead to resistance. Unfortunately few laboratories measure MPC, and the values for only a few antimicrobial-pathogen combinations have been studied. In addition, there is often poor correlation between the minimal inhibitory concentration (MIC) and the MPC. Also, the higher concentrations required using the mutant selection window hypothesis may lead to adverse effects in the patients being treated.

In conclusion, there is no easy solution to the problem of antimicrobial resistance. Besides the need for newer and more effective therapies, research, planning and the proper use of the agents available are essential. And Semmelweis' dictum, "Wash your hands," should not be forgotten!

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