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Antibiotic-resistant Infections in the Critically Ill Adult **329**
Fernanda Silveira, Shigeki Fujitani, and David L. Paterson

Intensive care units (ICUs) frequently are the epicenter of nosocomial infections with antibiotic-resistant bacteria. Optimization of antibiotic therapy for seriously ill patients with bacterial infections appears to have a strong influence on outcome. Laboratories can aid in provision of appropriate antibiotic therapy by providing clinicians with "antibiograms" to aid empiric antibiotic choice and by providing minimal inhibitory concentrations of key antibiotics so that antibiotic dosing is optimized to key pharmacodynamic targets. Laboratories also play a crucial role in the prevention of antibiotic resistance in the ICU. Molecular epidemiologic evidence of an oligoclonal outbreak of infections orients prevention measures toward investigation of common environmental sources of infection and prevention of patient-to-patient transmission. In contrast, evidence of polyclonality shifts prevention of antibiotic resistance to antibiotic management strategies.

Antibiotic Resistance in the Institutionalized Elderly **343**
Andrea M. Hujer, Christopher R. Bethel, Kristine M. Hujer, and Robert A. Bonomo

Geriatric patients frequently are cared for in long term care facilities (LTCFs), which are now a major component of our health care delivery system. Nearly half of the 2.2 million people who turned 65 years old in 1990 will enter an LTCF at least once before they die. Infections are one of the principal causes of morbidity and mortality in LTCFs. Because LTCFs are a less costly alternative to hospitalization, clinicians are treating many serious infections in the nursing home. As a result of antibiotic use, LTCFs will increasingly be recognized as sources of organisms resistant to multiple antibiotics. β-Lactams are a valuable class of potent antimicrobials with

broad-spectrum activity against Gram-negative and Gram-positive organisms. The safety and efficacy of this class of antibiotics make them easy choices for empiric treatment of infections in the elderly. Unfortunately, excessive use of these antibiotics has created serious threats to our therapeutic armamentarium: the emergence of methicillin-resistant *Staphylococcus aureus* and of Gram-negative pathogens resistant to third-generation cephalosporins such as cefotaxime, ceftazidime, and ceftriaxone. Of these third-generation cephalosporins, resistance to ceftazidime is most frequently recognized. The major mechanism responsible for ceftazidime resistance in Gram-negative bacteria is the production of β-lactamases. This article summarizes the diversity of β-lactamases, highlights the important enzymes that confer ceftazidime resistance in LTCFs, and details some methods used to identify and characterize these enzymes. A clear challenge is to apply these techniques to epidemiologic and molecular studies conducted in LTCFs.

Antibiotic-resistant Gram-negative Bacteria in Hospitalized Children **363**
Philip Toltzis

Antibiotic-resistant Gram-negative bacilli are a prominent and growing problem among hospitalized children. Epidemics caused by these organisms have been implicated in many outbreaks in children's hospitals, primarily in neonatal intensive care units. These epidemics are characterized by efficient patient-to-patient transmission of the outbreak clone via the hands of caregivers and through exposure of contaminated inanimate sources. The epidemiology of these resistant organisms in pediatric hospitals during endemic periods is more complex. The isolates cultured from hospitalized individuals in the absence of an outbreak usually are unique to each individual and are derived from the patient's endogenous flora or other disparate sources. As in adults, chronic care facilities for children represent significant reservoirs of antibiotic-resistant bacilli that are circulated back into the acute care hospital environment when the child becomes ill.

Vancomycin Resistance in *Staphylococcus aureus* **381**
Peter C. Appelbaum and Bülent Bozdogan

Vancomycin resistance in enterococci, predominantly *Enterococcus faecium,* developed in the latter half of the 1980s, and the long anticipated development of vancomycin resistance in *Staphylococcus aureus* has now occurred. A number of vancomycin-intermediate strains have been described, and these strains have abnormal, thickened cell walls in the presence of vancomycin. Two mechanisms of resistance have been described in the strains: affinity trapping of vancomycin molecules by cell wall monomers and clogging of the outer layers of peptidoglycan by bound vancomycin molecules, and change in the structure or metabolism of teichoic acids. Of more serious concern has been the description in 2002 of two patients with vancomycin-resistant *S aureus* infections. In one instance, the patient had skin lesions coinfected with vancomycin-

resistant, vanA genotype, *E faecalis*, and the vanA resistance genes could have been transferred to the *S aureus* strain. Expression of resistance was high in one *S aureus* strain and low in the other, making detection more challenging in the latter instance. These developments are of great concern, and every effort should be made to prevent further development and spread of vancomycin resistance in staphylococci.

Community-acquired Methicillin-resistant *Staphylococcus aureus* Infections **403**
Elizabeth Palavecino

Staphylococcus aureus causes a variety of minor diseases but also is responsible for staphylococcal pneumonia and sepsis, both of which can be fatal. It is thought to be responsible for many of the pneumonia deaths associated with the influenza pandemics of the 20th century. The introduction of penicillin in the 1940s greatly improved the prognosis for patients with severe staphylococcal infections. However, after a few years of clinical use, most staphylococcal strains were able to hydrolyze penicillin by producing β-lactamases, making penicillin a useless antibiotic to treat staphylococcal infections caused by β-lactamase-producing *S aureus*. Methicillin, a semisynthetic penicillin introduced in 1959, was specifically designed to be resistant to β-lactamase degradation, but resistance developed soon after its introduction into clinical practice. Methicillin-resistant *S aureus* (MRSA) was first reported in the United Kingdom in 1961, followed by reports from other European countries, Japan, and Australia. The first reported case of MRSA in the United States was in 1968. Currently, MRSA is an important pathogen in nosocomial infections and is a problem in hospitals worldwide, and it is increasingly recovered from nursing home residents with established risk factors. More recently, community-acquired MRSA infections have been documented among healthy individuals with no recognizable risk factors, and it seems clear that community-acquired MRSA (CA-MRSA) strains are epidemiologically and clonally unrelated to hospital-acquired strains. This review focuses on the epidemiology, clinical significance, and virulence markers of CA-MRSA infections.

Mechanisms of Resistance Among Respiratory Tract Pathogens **419**
Michael R. Jacobs, Jack Anon, and Peter C. Appelbaum

Antimicrobial resistance among respiratory tract pathogens represents a significant health care threat. Identifying the antimicrobial agents that remain effective in the presence of resistance, and knowing why, requires a thorough understanding of the mechanisms of action of the various agents as well as the mechanisms of resistance demonstrated among respiratory tract pathogens. The primary goal of antimicrobial therapy is to eradicate the pathogen, via killing or inhibiting bacteria, from the site of infection; the defenses of the body are required for killing any remaining bacteria. Targeting a cellular process or function specific to bacteria and not to the host limits the toxicity to patients. Currently, there are four

general cellular targets to which antimicrobials are targeted: cell wall formation and maintenance, protein synthesis, DNA replication, and folic acid metabolism. Resistance mechanisms among respiratory tract pathogens have been demonstrated for all four targets. In general, the mechanisms of resistance used by these pathogens fall into one of three categories: enzymatic inactivation of the antimicrobial, prevention of intracellular accumulation, and modification of the target site to which agents bind to exert an antimicrobial effect. Resistance to some agents can be overcome by modifying the dosage regimens (eg, using high-dose therapy) or inhibiting the resistance mechanism (eg, β-lactamase inhibitors), whereas other mechanisms of resistance can only be overcome by using an agent from a different class. Understanding the mechanisms of action of the various agents and the mechanisms of resistance used by respiratory tract pathogens can help clinicians identify the agents that will increase the likelihood of achieving optimal outcomes.

Macrolide Resistance in Streptococci and *Haemophilus influenzae* **455**
Bülent Bozdogan and Peter C. Appelbaum

Antimicrobial resistance is a growing problem among pathogens from respiratory tract infections. β-Lactam resistance rates are escalating among *Streptococcus pneumoniae* and *Haemophilus influenzae*. Macrolides are increasingly used for the treatment of respiratory tract infections, but their utility is compromised by intrinsic and acquired resistance. This article analyses macrolide-resistance mechanisms and their worldwide distributions in *S pneumoniae, S pyogenes*, and *H influenzae*.

Application of Pharmacokinetics and Pharmacodynamics to Antimicrobial Therapy of Respiratory Tract Infections **477**
David Andes, Jack Anon, Michael R. Jacobs, and William A. Craig

The pharmacologic field that studies antimicrobial pharmacokinetics and pharmacodynamics (PK/PD) has had a major impact on the choice and dosing regimens used for many antibiotics especially those used in the treatment of respiratory tract infections. PK/PD parameters are particularly important in light of increasing antimicrobial resistance. Drug pharmacokinetic features, such as serum concentrations over time and area under the concentration-time curve, when integrated with minimum inhibitory concentration (MIC) values of antibiotics against pathogens, can predict the probability of bacterial eradication and clinical success. These pharmacokinetic and pharmacodynamic relationships also are important in preventing the selection and spread of resistant strains and have led to the description of the mutation prevention concentration, which is the lowest concentration of antimicrobial that prevents selection of resistant bacteria from high bacterial inocula. β-lactams are time-dependent agents without significant post-anti-

biotic effects, resulting in bacterial eradication when unbound serum concentrations exceed MICs of these agents against infecting pathogens for >40% to 50% of the dosing interval. Macrolides, azaolides, and lincosamides are time-dependent agents with prolonged post-antibiotic effects, and fluoroquinolones are concentration-dependent agents, resulting in both cases in bacterial eradication when unbound serum area-under-the-curve to MIC ratios exceed 25 to 30. These observations have led to changes in recommended antimicrobial dosing against respiratory pathogens and are used to assess the role of current agents, develop new formulations, and assess potency of new antimicrobials.

Susceptibility of *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis* to 17 Oral Antimicrobial Agents Based on Pharmacodynamic Parameters: 1998−2001 U.S. Surveillance Study **503**
Michael R. Jacobs, Saralee Bajaksouzian, Anne Windau, Caryn E. Good, Gengrong Lin, Glenn A. Pankuch, and Peter C. Appelbaum

Pharmacokinetic/pharmacodynamic parameters were used to interpret susceptibility data for the oral agents tested in a clinically meaningful way. Among *S pneumoniae* isolates, >99% were susceptible to respiratory fluoroquinolones, 91.6% to amoxicillin, 92.1% to amoxicillin/clavulanic acid (95.2% at the extended-release formulation breakpoint), 90.6% to clindamycin, 80.4% to doxycycline, 71.0% to azithromycin, 72.3% to clarithromycin, 71.8% to cefprozil and cefdinir, 72.6% to cefuroxime axetil, 66.3% to cexime, 63.7% to trimethoprim/sulfamethoxazole, and 19.7% to cefaclor. Among *H influenzae* isolates, 28.6% were β-lactamase positive, but virtually all were susceptible to amoxicillin/clavulanic acid (98.3%, with 99.8% at the extended-release formulation breakpoint), cexime (100%), and uoroquinolones (99.8%), whereas 93.5% were susceptible to cefdinir, 82.8% to cefuroxime axetil, 78.1% to trimethoprim/sulfamethoxazole, 70.2% to amoxicillin, 25.1% to doxycycline, 23.2% to cefprozil, and 5% to cefaclor, azithromycin and clarithromycin. Most isolates of *M catarrhalis* were resistant to amoxicillin, cefaclor, cefprozil, and trimethoprim/sulfamethoxazole. Thus significant β-lactam and macrolide/azalide resistance in *Streptococcus pneumoniae* and β-lactamase production and trimethoprim/sulfamethoxazole resistance in untypeable *Haemophilus influenzae* are still present. The results of this study should therefore be applied to clinical practice based on the clinical presentation of the patient, the probability of the patient's having a bacterial rather than a viral infection, the natural history of the disease, the potential of pathogens to be susceptible to various oral antimicrobial agents, the potential for cross-resistance between agents with *S pneumoniae*, and the potential for pathogens to develop further resistance. Antibiotics should be used judiciously to maintain remaining activity and chosen carefully based on activity determined by pharmacokinetic/pharmacodynamic-based breakpoints to avoid these bacteria developing further resistance, particularly to fluoroquinolones.

Evolution of Amoxicillin/Clavulanate in the Treatment of Adults with Acute Bacterial Rhinosinusitis and Community-acquired Pneumonia in Response to Antimicrobial-resistance Patterns **531**
Thomas M. File Jr, Michael S. Benninger, and Michael R. Jacobs

Current treatment guidelines for community-acquired respiratory tract infections no longer depend solely on the characteristics of the patient and the clinical syndrome, but on those of the offending pathogen, including presence and level of antimicrobial resistance. The most common respiratory tract pathogens known to cause acute bacterial rhinosinusitis (ABRS) and community-acquired pneumonia (CAP) include *Streptococcus pneumoniae* and *Haemophilus influenzae*. The prevalence of antimicrobial resistance, especially β-lactum and macrolide resistance, among *S pneumoniae* and *H influenzae* has increased dramatically during the past 2 decades, diminishing the activity of many older antimicrobials against resistant organisms. A pharmacokinetically enhanced formulation of amoxicillin/clavulanate has been developed to fulfill the need for an oral β-lactam antimicrobial that achieves a greater time that the serum drug concentration exceeds the minimum inhibitory concentration (T > MIC) of antimicrobials against pathogens than conventional formulations to improve activity against *S pneumoniae* with reduced susceptibility to penicillin. The β-lactamase inhibitor clavulanate allows for coverage of β-lactamase-producing pathogens, such as *H influenzae* and *M catarrhalis*. This article reviews the rationale for, and evolution of, oral amoxicillin clavulanate for ABRS and CAP.

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