

The following abstracts, from medical journals containing literature on antimicrobial use, were selected for their relevance to this Special Report.

### Significant Differences Exist Between Canada and United States in Pathogen Response

*Despite the proximity of Canada and the United States, susceptibility patterns of some respiratory tract pathogens to commonly used antimicrobial agents vary significantly between the 2 countries. Canadian strains are generally more susceptible to currently available antimicrobial agents. Bacterial isolates were collected in 37 sentinel hospitals (8 in Canada, and 29 in the United States) from patients diagnosed with pneumonia. Among the 2757 isolates collected during the study, the 5 most frequently recorded species included Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenzae, Klebsiella spp, and Streptococcus pneumoniae. Researchers found Canadian susceptibility to oxacillin for S aureus to be nearly twice that of the United States—93.8% versus 50.1%. Susceptibility for gentamicin was 97.8% versus 78.7%, and for fluoroquinolones 89.8% to 94.9% versus 49.5% to 53.0%. Amikacin was the most active antimicrobial agent against P aeruginosa (92.8% susceptible), and meropenem was the most potent  $\beta$ -lactam. Most drugs retained a high level of activity against H influenzae. However, only the newer fluoroquinolones—gatifloxacin, levofloxacin, and sparfloxacin—remained highly effective in vitro against pneumonia. Only 2 antimicrobial agents (imipenem and meropenem) were more than 99% active against the Klebsiella spp and Enterobacter spp isolates. Cefepime was significantly more active than*

*other cephalosporins tested. Clonal epidemic outbreaks of multiple-resistant strains were very rare in monitored hospitals.*

Jones RN, Croco MA, Kugler KC, et al. Respiratory tract pathogens isolated from patients hospitalized with suspected pneumonia: Frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997). *Diagn Microbiol Infect Dis* 2000;37:115-125.

### Macrolide Antibiotics Favored for Outpatient Management of Community-Acquired Pneumonia

*Resistance to penicillin and other antimicrobial agents among Streptococcus pneumoniae isolates has been increasing. Resistance has been shown to influence which antimicrobial agents clinicians choose for treatment of pneumococcal pneumonia even more than the status of the patient. Modifying the minimum inhibitory concentration (MIC) break-points so that more pneumococcal pneumonia isolates are reported to be susceptible may improve care and also reduce the use of broad-spectrum antimicrobial therapy. When implicated in cases of pneumonia, S pneumoniae should be considered susceptible if MIC is no greater than 1  $\mu$ g/mL and considered to be of intermediate susceptibility if MIC is 2  $\mu$ g/mL. If MIC is no less than 4  $\mu$ g/mL the infection is considered resistant. For outpatient treatment of community-acquired pneumonia (CAP), suitable empirical oral antimicrobial agents include a macrolide, doxycycline (or tetracycline) for children age 8 years or older, or an oral  $\beta$ -lactam such as cefuroxime axetil, or amoxicillin. Inpatient therapies include intravenous  $\beta$ -lactam. New fluoroquinolones can also be used to treat adults. To avoid fluoroquinolone resistance, use of the new fluoroquinolones should be limit-*

ed to adults who are allergic to other regimens or who have not responded to them, or whose infection is documented as highly drug resistant (eg, penicillin MIC  $\geq 4$   $\mu\text{g/mL}$ ). Vancomycin hydrochloride is not routinely indicated for the treatment of CAP.

Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Macrolide antibiotics favored for outpatient management of community-acquired pneumonia. *Arch Intern Med* 2000; 160:1399-1408.

### Review of the New Fluoroquinolones

This review focuses on the newer fluoroquinolones levofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, gatifloxacin, moxifloxacin, and clinafloxacin. Compared with other antimicrobial agents, including the older quinolones, these newer agents offer several advantages, including increased potency *in vitro*, particularly against resistant organisms, and a broader spectrum of antimicrobial activity. The clinical evidence available at the time of publication suggested their potential enhanced efficacy in the treatment of various community-acquired and nosocomial infections (eg, respiratory, urinary tract and skin infections, and sexually transmitted diseases). More recent clinical data have supported this view. Compared with ciprofloxacin, pharmacokinetic profiles of the new agents demonstrate equivalent or greater bioavailability, higher plasma concentrations, and increased tissue penetration. Although adverse events seen with most quinolones are mild, several of the newer agents appear to offer a better safety profile. Serious adverse effects that may occur include phototoxicity (particularly with sparfloxacin) and prolongation of the  $QT_c$  interval (seen with sparfloxacin and grepafloxacin). Physicians should be aware of the potential drug interactions between multivalent cation-con-

taining compounds and all quinolones and between theophylline and both ciprofloxacin and grepafloxacin. Switch (step-down) therapy, possible with gatifloxacin, levofloxacin, and moxifloxacin, offers a therapeutic and cost-saving advantage. In addition to shortening the hospital stay and reducing the risk of venous complications, switch therapy has been shown to reduce hospital drug costs by 40% and hospitalization costs by 20%.

Blondeau JM. Expanded activity and utility of the new fluoroquinolones: A review. *Clin Ther* 1999;21:3-40.

### Antimicrobial Treatment Guidelines for Rhinosinusitis in Adults

Sinusitis is the fifth most common diagnosis for which antibiotics are prescribed. Acute bacterial rhinosinusitis (ABRS) may be diagnosed in adults or children with symptoms of a viral upper respiratory tract infection that has worsened after 5 to 7 days or has not improved after 10 days. Clinicians should take into consideration the severity of the disease, the rate of progression of the disease, and any recent antibiotic therapies when choosing therapies for ABRS. Lack of response to antibiotic therapy at <72 hours is considered to be a treatment failure. Recommendations for initial therapy for adult patients with mild disease and who have not received antibiotics in the previous 4 to 6 weeks include: amoxicillin/clavulanate, amoxicillin (1.5 to 3.5 g/day), cefpodoxime proxetil, or cefuroxime axetil. Cefprozil has been found to have up to a 25% bacterial failure rate. Bacteriologic failure rates of 20% to 25% are possible with doxycycline, azithromycin, clarithromycin, or erythromycin in patients with  $\beta$ -lactam allergies. Potentially fatal toxic epidermal necrolysis has been associated with the use of trimethoprim/sulfamethoxazole. For adults who have been subjected to antibiotic ther-

apy 4 to 6 weeks prior to the onset of ABRS, recommended therapies include amoxicillin/clavulanate, gatifloxacin, levofloxacin, moxifloxacin, or combination therapy (amoxicillin or clindamycin [gram-positive coverage] plus cefpodoxime proxetil or cefixime [gram-negative coverage]). Switch therapy recommendations for patients who do not improve <72 hours vary, depending on the responsible organism. Patients who continue to be symptomatic following effective antibiotic therapy may need further evaluation.

Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2000;123(1 Pt. 2):5-31.

### Rhinovirus Found to Be a Common Lower Respiratory Tract Pathogen

Rhinoviruses have long been linked to upper respiratory problems such as the common cold. However, recently rhinoviruses have been found to trigger asthma exacerbations, suggesting that infection with these agents may not simply be an uncomfortable but short-lived inconvenience but may result in significant morbidity and even mortality. To support the hypothesis that rhinoviruses can infect and be directly pathogenic to the lower airways, lower respiratory infection was investigated in vitro by exposing primary human bronchial epithelial cells to rhinoviruses and in vivo after experimental upper respiratory infection of human volunteers. The study's objective was to describe replication of rhinoviruses in primary human bronchial epithelial cells and to study proinflammatory responses and cytopathic effect in these cells. Not only was bronchial infection confirmed using both approaches, but results strongly suggest a direct lower respiratory epithelial reaction as the initial event in the induction of rhinovirus-mediated asthma exacerbations. Frequency of infection and observations of inflammatory

response suggest that rhinovirus infections may be one of the most important causes of lower, as well as upper respiratory disease.

Papadopoulos NG, Bates PJ, Bardin PG, et al. Rhinoviruses infect the lower airways. *J Infect Dis* 2000;181:1875-1884.

### Emergence of Antibiotic Resistance in Upper and Lower Respiratory Tract Infections

Increasing antibiotic resistance is of great concern to the medical community. The treatment of respiratory tract infections is significantly impacted by resistance, as 67% of antibiotic use in adults and 87% in children is for the treatment of such infections. The most common pathogens implicated in these infections are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, and isolates of all 3 have developed resistance to some of the antibiotics currently on the market. In 1997, one third of *S pneumoniae* strains were classified as penicillin resistant, up to 50% of *H influenzae* strains produced  $\beta$ -lactamase, and all *M catarrhalis* strains produced  $\beta$ -lactamase. As resistance can vary with geographic region and specific populations, one way to determine the most effective antibiotic for an infection is to ascertain the resistance pattern of these pathogens from local laboratories or national surveillance studies. Breakpoints using pharmacodynamic data based on drug concentration present for at least 40% of the closing interval, or area under the serum concentration curve:minimum inhibitory concentration ratios have been valuable for comparing the activities of oral agents. Of the currently available  $\beta$ -lactams and macrolides, only amoxicillin/clavulanate and daily intramuscular ceftriaxone are active against more than 90% of all 3 respiratory pathogens. Newer quinolones are also active against these pathogens, but overuse is very likely to result in rapid develop-

ment of resistance, and their use should be reserved for patients with treatment failure or significant drug allergies.

Jacobs MR. Emergence of antibiotic resistance in upper and lower respiratory tract infections. *Am J Manag Care* 1999;5(suppl 11):651-661.

### Chronic Obstructive Pulmonary Disease and Bacterial Infections

Antibiotic therapy is frequently used for the treatment of exacerbations of chronic obstructive pulmonary disease (COPD) resulting from bacterial infections, *Haemophilus influenzae* chief among them. The goals of this study were to determine how frequently simultaneous strains of *H influenzae* appeared in sputum. The minimum inhibitory concentrations (MICs) of antibiotics frequently used for the treatment of exacerbations were determined with emphasis on comparison of MICs of strains that are present simultaneously in sputum. In a prospective study, adults with COPD were seen monthly. Sputum cultures were obtained, and individual colonies were subjected to DNA typing and MIC determinations. Researchers found multiple strains of *H influenzae* present simultaneously in the sputum of 26.3% of adults with COPD. They found that 7 of the 31 sputum samples with multiple isolates of *H influenzae* contained isolates that differed in MICs across the breakpoints of susceptible to resistant. These differences were observed for a wide variety of antibiotics. In view of the observations in this study, the common practice in clinical microbiology laboratories of selecting a single colony for determination of species and antimicrobial susceptibility does not adequately guide antimicrobial therapy of lower respiratory tract infections for adults with COPD. This may account for failures of antibiotic therapies in the presence of multiple strains. In that case, clinicians should consider an alteration of antibiotic therapy.

Murphy TF, Klingman KL, Doern GV. Simultaneous respiratory tract colonization

by multiple strains of nontypeable *Haemophilus influenzae* in chronic obstructive pulmonary disease: Implications for antibiotic therapy. *J Infect Dis* 1999;180:404-409.

### Antimicrobial Resistance with *Streptococcus pneumoniae* in the United States

Researchers assessed the prevalence of antimicrobial resistance with *Streptococcus pneumoniae* at 34 US medical centers from 1997 to 1998. Twenty-four of these centers had also participated in an earlier investigation (1994 to 1995) using identical study methods. The overall rate of strains showing resistance to penicillin was 29.5%, with 17.4% having intermediate resistance. Resistance to penicillin as well as at least 2 other non- $\beta$ -lactam classes of antimicrobial drugs were observed in 16.0% of isolates. When patterns of multidrug resistance were analyzed, coresistance to penicillin, the macrolides, tetracycline, trimethoprim/sulfamethoxazole, and chloramphenicol was observed in 5.4% of isolates. Of the 24 medical centers participating in the 1994 to 1995 study, 19 reported penicillin resistance rates increased 2.5% to 39.2%, with similar resistance increases observed with other antimicrobial drugs. Researchers sometimes observed resistance to  $\beta$ -lactam antimicrobial agents and numerous non- $\beta$ -lactam agents in the same organism. One explanation for the increasing prevalence of multidrug- $\beta$  resistant strains is clonal spread of organisms resistant to more than one class of antimicrobial drugs. Under such circumstances, multidrug-resistant organisms may become more prevalent, no matter what drug is used to select for resistance. Clonal spread warrants further study.

Doern GV, Brueggemann AB, Huynh H, et al. Antimicrobial resistance with *Streptococcus pneumoniae* in the United States. *Emerging Infect Dis* 1999;5:757-765.

---

### **Clinical Pharmacokinetics of Clarithromycin**

Researchers report that fewer serious drug interactions occur with clarithromycin compared with older macrolides such as erythromycin and troleandomycin. The chemical structure of clarithromycin differs from that of erythromycin by the methylation of the hydroxyl group at position 6 on the lactone ring. The pharmacokinetic advantages of this drug over erythromycin include increased oral bioavailability (52% to 55%), increased plasma concentrations (mean maximum concentrations ranging from 1.01 to 1.52 mg/L and 2.41 to 2.85 mg/L after multiple 250- and 500-mg doses, respectively), and a longer elimination half-life (3.3 to 4.9 hours), allowing for

twice-daily dosing. Moreover, clarithromycin was found to have extensive diffusion into saliva, sputum, lung tissue, epithelial lining fluid, alveolar macrophages, neutrophils, tonsils, nasal mucosa, and middle ear fluid. Clarithromycin is primarily metabolized by CYP3A isozymes. In vitro and in vivo studies have shown that potent inhibitors of CYP3A alter the metabolism of clarithromycin. Moreover, clarithromycin is involved with drug interactions that are associated with inhibition of CYP3A. These include drugs such as astemizole, cisapride, pimozone, and terfenadine. Concurrent administration of these agents and clarithromycin is contraindicated.

Rodvold KA. Clinical pharmacokinetics of clarithromycin. *Clin Pharmacokinet* 1999;37:385-395.