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Conference Summaries: ICAAC 2000, IDSA 2000, and ASTMH 2000: Part I

CONFERENCE COVERAGE

Editor's Note: *The following summaries represent a selection of papers dealing with subjects other than HIV infection from those presented at the three meetings listed below. It is important to recognize that many of these summaries are extracted only from the published abstract, and it is possible that some of the material presented at the conference may have differed. The abstracts can be found on-line at the URLs given. The 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Toronto, Canada, Sept. 17-20, 2000; http://www.asmusa.org. The 38th Annual Meeting of the Infectious Diseases Society of America (IDSA), New Orleans, La, Sept. 7-10, 2000; http://www.idsociety.org. The 49th Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH), Houston, Tex, Oct. 29-Nov. 2, 2000; http://www.astmh.org. —Stan Deresinski, MD, FACP*

Bacterial Infections

Enterococcus

Epidemiology. In Europe, gastrointestinal colonization with vancomycin-resistant *Enterococcus* (VRE) is encountered with some frequency among healthy individuals in the community. Epidemiological and molecular evidence has suggested that the source of this colonization is contaminated food, especially poultry that had been fed glycopeptide antibiotics as growth promoters. Another link in the argument has been completed by the demonstration that ingestion of vancomycin-resistant *E. faecium* of chicken origin by six healthy volunteers was followed by gastrointestinal colonization that lasted for at least six days in five patients. (*ICAAC #1962.*)

In the United States, most VRE colonization and infection is hospital acquired and hospital room contamination is an impor-

Volume 20 • Number 4 • November 15, 2000 • Pages 25-32

tant risk factor for acquisition of VRE. A terminal cleaning procedure was more effective in eliminating VRE from the environment than was routine cleaning. Institution of a comprehensive program to improve environmental surface disinfection was associated with reduced VRE prevalence and transmission. (*ICAAC #1960, #1963, and #1965.*)

The results of two studies indicated that the use of cover gowns, as recommended by CDC/HICPAC, appears to decrease nosocomial transmission of VRE. (*IDSA #388, #390.*)

The epidemiology of VRE appears to become intertwined with that of methicillin-resistant *S. aureus* (MRSA)—at one Bronx hospital, MRSA was isolated from 31.1% of 90 patients infected or colonized with VRE. (*ICAAC #725.*)

Antibiotic Susceptibility. Two new antimicrobials with activity against many Gram-positive bacteria resistant to conventional antibiotics, linezolid, and quinupristin/dalfopristin (Q/D), received FDA approval in the United States in 2000.

The SENTRY study of almost 5000 enterococcal isolates obtained in the United States from 1977-1999 found that 17% were vancomycin-resistant and 24% were ampicillin-resistant. Most VRE were *E. faecium*, and 74% had *van* A while 21% were *van* B. A total of 82% of VRE were susceptible to Q/D and 90% to chloramphenicol while all were susceptible to linezolid. All of a group of Canadian VRE isolates were susceptible to nitrofurantoin. (*ICAAC #164, #515.*)

Linezolid was universally active against U.S. isolates of VRE and had an MIC90 of 4.0 mcg/mL against both *E. faecalis* and *E. faecium*. The NCCLS threshold for resistance is 8.0 mcg/mL. (*ICAAC #2299.*) Linezolid was effective, in several open, dose-ranging trials, in the treatment of VRE infections. (*ICAAC #164, #2235, IDSA #62, #63.*)

Virulence. The virulence of VRE has been questioned. A retrospective analysis at one center found that colonization with MRSE or VRE was not associated with increased mortality among orthoptic liver transplant recipients, although it was associated with an increased risk of episodes of infection. (*ICAAC #489.*) However, vancomycin-resistant *E. faecium* (VREF) was isolated from eight solid organ transplant recipients who developed skin and soft tissue infections, including five with necrotizing fasciitis, two with myonecrosis, and one with necrotizing wound infection during one year at one center. The organisms were clonally unrelated. Two had only VREF isolated, while in three others it was isolated together with a "non-virulent organism." Blood cultures grew only VREF from six of the eight patients. (*ICAAC #488.*)

Antibiotic Therapy. Linezolid appeared effective in open trials in the treatment of VRE infections and was well tolerated in these and other clinical trials. It is, however, a weak reversible MAO-inhibitor and may, potentially, cause serotonin syndrome (fever, diaphoresis, restlessness, tremor, myoclonus, confusion, and delirium) when combined with other MAO-inhibitors. In an examination of patients who received a selective serotonin reuptake inhibitor during clinical trials, the incidence of fever and CNS symptoms were low and approximately equal in those receiving linezolid and those receiving comparator agents. (*ICAAC #2235, #2237, IDSA #64.*)

Thrombocytopenia was reported in 2.4% of linezolid recipients in clinical trials compared to 1.5% in those receiving comparators. The degree of thrombocytopenia in a group of seriously ill patients was significantly associated with both linezolid AUC and duration of treatment. (*ICAAC #283.*)

Infectious Disease Alert, ISSN 0739-7348, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Infectious Disease Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $19.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

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Subscription Prices

United States
$279 per year (Student/Resident rate: $110).

Multiple Copies
1-9 additional copies: $206; 10 or more copies: $183.

Canada
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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Deresinski is involved in research with Merck, Sharp & Dohme, Novartis (Systemix), DuPont-Merck, Gilead, Agouron, and Abbott. He also serves as a consultant to Bristol-Myers Squibb, Immunex, and Protein Design Labs and serves on the speaker's bureau of Merck, Sharp & Dohme, Bristol-Myers Squibb, Glaxo Wellcome, Ortho-McNeil, Bayer, and Lederle. Dr. Kemper serves on the speaker's bureau and is involved in research with SmithKline Beecham, DuPont, Merck, Gilead, and Virologics.

Staphylococcus

Epidemiology. In a contribution to our understanding of the epidemiology and transmission of *S. aureus*, it was found that experimental rhinovirus infection of chronic nasal carriers of *S. aureus* was associated with a significant increase in the number of airborne *S. aureus*. (*IDSA #115.*)

The epidemiology of MRSA appears to be evolving with community-acquired MRSA infection rearing its ugly head in some locations. A study of 799 non-hospitalized urban poor in San Francisco found that 22.8% had nasal colonization with *S. aureus* and that 11% of these were MRSA. The prevalence of MRSA colonization was 18.5% in those who had been hospitalized in the previous 12 months and 6% in those without hospitalization in that interval. (*ICAAC #160.*)

The widespread use of certain antibiotics may play a role in the emergence of MRSA in hospitals. Levofloxacin administration was found to be an independent risk factor for the development of nosocomial MRSA infection at one hospital. (*IDSA #163.*) This is a potentially significant problem since the single most commonly prescribed antibiotic in one emergency department (ED) was levofloxacin, having been given in 1999 to 4445 patients, representing 13.2% of all ED patients. The antibiotic was administered intravenously to 68.6%. Levofloxacin use was judged inappropriate in 74.9% of patients: 32% had no evidence of probable bacterial infection, in 12% an alternative antibiotic was preferable, and in 30.8% the IV route was incorrectly used. (*IDSA #23.*)

The optimal means of eliminating MRSA colonization in patients in care facilities remains a matter of discussion. A retrospective review found that a combination of seven days treatment with mupirocin ointment to the nares together with rifampin plus either trimethoprim/sulfamethoxazole or doxycycline was associated with apparent eradication rates at one, three, and six months of, respectively, 97%, 89%, and 100%. However, nasal decolonization with mupirocin prior to liver transplantation and immediately postoperatively was not effective in decreasing the incidence of *S. aureus* infection after transplantation. (*ICAAC #720, #487.*)

Antibiotic Susceptibility. The MIC90 of Q/D, linezolid, and vancomycin against 225 strains of MRSA in Spain were, respectively, 0.5, 1.0, and 1.0 mcg/mL, while the MIC90 of linezolid in The Netherlands and the United States was 4.0 mcg/mL. (*ICAAC #2294, #2296, #2299.*) In addition, the MIC90s of both linezolid and Q/D against hetero-vancomycin-intermediate *S. aureus* were 1.0 mcg/mL for each drug. (*ICAAC #2313.*)

Down-regulation of pbp4 may be required for generation of the GISA phenotype. (*ICAAC #447.*)

Both GAR-936, a novel glycylglycine antibiotic, and minocycline were each more active against adherent (biofilm) *S. epidermidis* than was vancomycin with respective MIC90s of 8, 8, and 32 mcg/mL. (*ICAAC #525.*)

Antibiotic Therapy. In one clinical trial, patients with complicated skin and soft tissue infections (patients with osteomyelitis and with diabetic foot ulcers were excluded) and with prior MRSA colonization were randomized to receive either vancomycin or linezolid. Clinical cure occurred in 54.9% of 51 vancomycin recipients and 63.5% of 52 linezolid recipients ($P = 0.4$), while cure rates among patients with confirmed MRSA infections were, respectively, 73.3% and 79.4% ($P = 0.6$). (*IDSA #60.*)

Streptococcus pneumoniae

The 1999-2000 TRUST study found increasing pneumococcal resistance in the United States to most antibiotics studied, but the level of resistance to both azithromycin and levofloxacin remained stable relative to the previous year. The proportion of *S. pneumoniae* resistant to each antibiotic were: penicillin, 15.2%; amoxicillin/clavulanate, 13.8%; cefuroxime, 26.2%; ceftriaxone, 3.6%; trimethoprim/sulfamethoxazole, 28.5%; azithromycin, 22.1%; and levofloxacin 0.5%. Multidrug resistance was present in 11.3%, most commonly due to resistance to penicillin + azithromycin + trimethoprim/sulfamethoxazole ± ceftriaxone. Multidrug resistance in *S. pneumoniae* is predicted by an amoxicillin MIC of 1 mcg/mL or more. (*ICAAC #1789, #1805.*)

The prevalence of erythromycin resistance in *S. pneumoniae* in Atlanta increased from 16.3% in 1994 to 31.5% in 1999. While the prevalence among all isolates of *ermAM*-mediated resistance remained stable at 6.0%, the prevalence of *mefE*-mediated resistance increased from 8.7% to 26.0%. Such reflux-related resistance is often associated with only modest elevations in MIC. However, the level of resistance associated with *mefE* has increased significantly; by 1999, 93.5% had MIC of 8.0 mcg/mL or greater with 63.0% having MIC of 16 mcg/mL or greater. (*IDSA #4.*)

A number of investigations have suggested that *S. pneumoniae* pays a price for its penicillin resistance. Thus, penicillin resistance in *S. pneumoniae* was associated with reduced virulence in a murine model. In addition, a retrospective review of human infections was consistent with decreased invasiveness of resistant isolates. (*ICAAC #452, #453, #1810.*)

Tolerance to vancomycin, as defined by a significant discrepancy between the inhibitory and bactericidal concentrations of an antibiotic, was recently described in *S. pneumoniae* and attributed to a change in the *VanS* gene, which codes for an element of the two-component external sensing system. Several studies attempted to determine the prevalence of such isolates. Eight (4%) of 215 of nasopharyngeal isolates of *S. pneumoniae* from small healthy children were vancomycin tolerant. Nine (2.2%) clinical isolates of *S. pneumoniae* in Italy were vancomycin tolerant. Finally, 8.7% of 138 CSF isolates of *S. pneumoniae* were moderately or highly tolerant to vancomycin. (*ICAAC #1776-#1778.*)

Newer fluoroquinolones remain active against more than 99% of pneumococci. GyrA is the preferred target in *S. pneumoniae* for both gatifloxacin and moxifloxacin. This targeting pattern may be related to the presence of an 8-methoxy group on each of these antibiotics. Analysis of 33 Canadian isolates of *S. pneumoniae* resistant to ciprofloxacin (MIC ≥ 4 mcg/mL) found that the concentration required to inhibit all 33 was 0.5 mcg/mL for gemifloxacin and 4.0 mcg/mL each for moxifloxacin and gatifloxacin. (*ICAAC #743, #748, #2315.*)

The mutation prevention concentration (MPC), may be defined as the threshold concentration of an antibiotic at which bacterial cells must express two or more resistance mutations for growth in its presence. The MPC_{90} for isolates of *S. pneumoniae* was 16 mcg/mL for levofloxacin, 4.0 mcg/mL for gatifloxacin, and 2.0 mcg/mL for moxifloxacin. This suggests that resistance is least likely to emerge under the selective pressure of moxifloxacin therapy. (*ICAAC #2325.*)

In contrast to the time-dependent killing of *S. pneumoniae* by azithromycin, telithromycin exhibits concentration-dependent killing but with a shorter post-antibiotic effect. Telithromycin is concentrated in respiratory tract mucosa and fluids. (*ICAAC #658, #2143, #2141, #2144.*)

Cefditoren has an MIC90 of 1 mcg/mL against penicillin-resistant pneumococci and appears bactericidal. (*ICAAC #373, #376-378.*)

Faropenem is a new orally available penem with a broad range of activity against oropharyngeal anaerobes, as well as aerobic Gram-negative rods and Gram-positive cocci, including penicillin-resistant pneumococci. (*ICAAC #361-368.*)

Streptococcus pyogenes

S. pyogenes, while increasingly resistant to macrolide antibiotics, appears to be maintaining its susceptibility to penicillin.

Approximately 20% of 2039 *S. pyogenes* isolates in Spain were resistant to macrolide antibiotics; no penicillin resistance was found. In Hong Kong, 56% were macrolide-resistant but penicillin resistance was not detected. Macrolide resistance was found in only 9.6% of isolates in France. (*ICAAC #142-144.*)

The new ketolide antibiotic, telithromycin, remains active against macrolide resistant *S. pyogenes*, regardless of the mechanism of resistance to the latter. (*ICAAC #2145.*)

Analysis of 400 patients with invasive *S. pyogenes* infection found a significant association of risk for necrotizing fasciitis with the presence of the DR5 haplotype, while the DR3 haplotype was protective. Similarly, the DR6 haplotype was associated with increased risk of streptococcal toxic shock syndrome. (*ICAAC #1495.*)

Streptococcus viridans

Ninety percent of bacteremias in recipients of allogeneic hematopoietic stem cell transplantation at the NIH over two years were caused by Gram-positive bacteria and 68% of these were due to viridans streptococci. All *S. viridans* bacteremias except one responded rapidly to treatment with ceftazidime and vancomycin; 89% were susceptible to penicillin and ceftriaxone, while all were susceptible to vancomycin. (*IDSA #31.*)

Gastrointestinal Pathogens

Active surveillance of cases of hemolytic uremic syndrome has been carried out in seven states since 1997 by the FoodNet system. Over two years, 123 cases with a median age of 4 years (range, 0-88 years) were identified; two-thirds were female. The annual incidence among children younger than 16 years of age was 10.6 per million. *E. coli* 0157:H7 was isolated from only one-half the stools cultured. Eleven percent died and, at the time of hospital discharge, 11% required dialysis and 17% had neurological sequelae. (*IDSA #49.*)

Multistate outbreaks of *Salmonella newport*, *S. enteritidis*, and *Shigella sonnei* were described and were associated with consumption of, respectively, mangos, unpasteurized orange juice, and "five-layer party dip." (*IDSA #52, #53, #650.*)

Antibiotic resistance among gastrointestinal (GI) pathogens is an escalating problem. Forty-six (81%) of 56 isolates of *C. jejuni* in Mexico in 1999 were resistant to one or more fluoroquinolones, mostly due to *GyrA* mutations. Among bloodstream isolates in the Western Pacific, 0% of *S. typhi*, 16.7% of *S. paratyphi* A, and 10.8% of nontyphoidal *Salmonella* were resistant to

ciprofloxacin. (*ICAAC #1215, #1217.*)

In 1999, 1% of nontyphoid *Salmonella* isolated from patients in the United States were resistant to ciprofloxacin, while none of the 161 *S. typhi* isolates were resistant to this drug. Fourteen percent of *S. typhi* were, however, multidrug resistant, with resistance to at least ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole. In addition, the first ceftriaxone-resistant *S. typhi* isolate was reported to the CDC. Resistance to ciprofloxacin is likely to be seen in the U.S. cases as well; 4% of *Salmonella* isolates from Spain in 2000 were resistant to ciprofloxacin. (*ICAAC #1216; IDSA #3, ICAAC #1874.*)

Children 6 months to 5 years of age with bloody diarrhea of less than 48 hours duration were randomized, in an international trial, to receive either ciprofloxacin or trimethoprim/sulfamethoxazole. Clinical success, judged at days 3 and 6, was observed in 135 of 142 (95.8%) given ciprofloxacin and in 103 of 131 (78.6%) given trimethoprim/sulfamethoxazole (P = 0.04). In Mexican children, the success rates were, respectively, 81% and 46% (P = 0.0001). Transient joint symptoms were reported in two ciprofloxacin recipients and in one recipient of the comparator product. (*ICAAC #1467.*)

Treatment of children with cholera with a single dose of azithromycin produced significantly faster resolution of symptoms and signs than did a three-day, 12-dose course of erythromycin. Bacteriologic failure occurred in 29% of azithromycin recipients and in 18% of erythromycin recipients. (*ICAAC #1466.*)

Shigella spp. were recovered from the vagina of 59% of prepubertal girls with vaginal bleeding in Argentina. (*ICAAC #1744.*)

The entire story explaining the mechanistic role of antibiotic therapy in the epidemiology of colitis due to *C. difficile* is incomplete. One study contributed to our understanding of this mechanism. A single strain (CD1) of *C. difficile* is associated with approximately 60% of all cases of antibiotic-associated nosocomial *C. difficile* diarrhea in the United Kingdom. CD1, but not a control environmental strain of *C. difficile*, was induced to sporulate in the presence of subinhibitory concentrations of ampicillin. (*ICAAC #950.*)

A prospective study of 2462 inpatients at five Swedish hospitals who received antibiotics found an incidence of antibiotic-associated diarrhea of 4.9% and *C. difficile* was recovered from 55% of these. However, *C. difficile* was also recovered on stool culture of 34% patients without diarrhea receiving antibiotics. Fifty-five percent of *C. difficile* recovered were toxin-producing. (*ICAAC #948.*)

Toxigenic *C. difficile* was isolated from the stool of 36 of 188 (19.1%) hospitalized patients with diarrhea. *B. fragilis* enterotoxin gene was identified by PCR in the stool of 14 of the remaining 152 patients (9.2%), but was also detected in stool of 2.9% controls (P = 0.09). (*ICAAC #952.*)

Improved therapies of *C. difficile* colitis have been slow to develop, but the search continues. COX-2 expression was upregulated in rabbit ileum in response to *C. difficile* toxin A. The COX-2 inhibitor, celecoxib, both blocked inflammation and increased fluid secretion caused by toxin A. (*IDSA #8.*)

Sinusitis, Otitis Media, Acute Exacerbations of Chronic Bronchitis, Pertussis, Bronchiolitis

While effective in eradicating other pathogens, including *S. pneumoniae* unsusceptible to penicillin, high-dose amoxicillin (80 mg/kg t.i.d.) failed to eradicate five of nine (56%) beta-lactamase producing *H. influenzae* from the middle ear of children with acute otitis media. Treatment with "amoxicillin/clavulanate extra strength formulation (A/C14:1)" representing a daily dose of 90/6.4 mg/kg/d was more effective. (*ICAAC #106, #107.*)

A single dose of azithromycin was as clinically effective as 10 days of treatment with amoxicillin/clavulanate in the treatment of acute otitis media in children. (*IDSA #174.*)

Linezolid appeared safe and effective in the treatment of acute otitis media in children in a noncomparative trial. (*ICAAC #65.*)

Bacterial eradication was achieved in 14 of 15 (93%) of patients given moxifloxacin for treatment of acute maxillary sinusitis caused by penicillin-resistant *S. pneumoniae*. These included cures in six of seven treated for seven days and eight of eight treated for 10 days. (*ICAAC #833.*)

Gemifloxacin was demonstrated in randomized trials to appear to be as effective as cefuroxime axetil in the treatment of acute bacterial sinusitis and as clarithromycin in acute exacerbations of chronic bronchitis. In the latter case, gemifloxacin administration was associated with faster eradication of *H. influenzae* and with a reduced frequency of recurrence and of hospitalization in the subsequent 26 weeks. (*ICAAC #812, #814, #815.*)

In randomized trials, cefditoren was similar in safety and efficacy to amoxicillin/clavulanate in treatment of acute maxillary sinusitis, to clarithromycin in acute exacerbations of chronic bronchitis, and to penicillin V in pharyngitis due to *S. pyogenes*. (*ICAAC #3835-3837.*)

In randomized trials, telithromycin appeared as effective as amoxicillin/clavulanate in acute maxillary sinusitis, as both cefuroxime axetil amoxicillin/clavulanate in acute exacerbations of chronic bronchitis, and as both clarithromycin and penicillin V for pharyngitis due to *S. pyogenes*. Five days of treatment with telithromycin was as effective as 10 days in the treatment of acute sinusitis. (*ICAAC #2241, #2242, #2244.*)

The number of deaths due to pertussis in the United States increased from 77 in 1980-1990 to 103 in the subsequent 10 years. The increase was larger due to a greater number of deaths in infants younger than 3 months of age who were too young to be protected by immunization. There were four deaths in the recent decade in individuals older than 20 years of age. (*ICAAC #60.*)

PCR evidence of *Simkania negevensis* was found in nasal washes of 14 of 22 (63.6%) Inuit infants with bronchiolitis. *S. negevensis* is a member of the order *Chlamydiales*, that has previously been found in assocation with bronchiolitis in southern Israel. (*ICAAC #974.*)

Anaerobes

A study of 408 *Bacteroides fragilis* group bloodstream isolates found that 100% were susceptible to both metronidazole and piperacillin/tazobactam. More than 96% were susceptible to the carbapenems, imipenem, meropenem, and MK-826, and more than 95% were susceptible to ampicillin/sulbactam and ticarcillin/clavulanate (although the latter 2 had limited activity against *B. diastonis* and *B. ovatus*). Eighty-six percent of *B. fragilis* group isolates were susceptible to cefoxitin and cetizoxime, while only 63% were susceptible to cefotetan and cefotaxime. Clindamycin susceptibility varied from 49% to 88% among the individual species. (*ICAAC #102.*)

Mycobacteria

Sixty-six patients with *M. marinum* infection were seen over three years; 89% had had exposure to fish, fish tanks, or oysters. A total of 65% had nodular skin lesions and 28% had involvement of bone and/or joints. The MIC90s in mcg/mL were: clarithromycin, 4.0; rifampin, 0.5; minocycline, 4.0; ethambutol, 4.0; doxycycline, 16.0; ofloxacin, 16.0; ciprofloxacin, 8.0; and sparfloxacin, 2.0. A variety of antibiotics were used, most commonly clarithromycin and most commonly in combination and 27 patients had surgery; 86% were cured. (*ICAAC #1586.*)

Susceptibility testing of 25 isolates of *M. szulgai*, most from respiratory sources, revealed that 5% were susceptible to INH, 29% to ethambutol, 33% to rifampin, 38% to streptomycin, and 50% (of 8 tested) to amikacin. (*IDSA #573.*)

The emergence of multidrug-resistant tuberculosis is increasing the importance of older second- and third-line antimycobacterial drugs. Evaluation of the effects of food on absorption found that cycloserine is best given with water on an empty stomach, while PAS can be given with water, an acidic fruit juice, or with a high-fat meal. (*ICAAC #507.*)

Pneumonia

The frequency of colonization with potential respiratory pathogens among healthy individuals was examined. Culture of nasopharyngeal secretions of 99 healthy adults by three different methods using three selective media found evidence of colonization with *S. pneumoniae* in 45%, *H. influenzae* in 30%, and *M. catarrhalis* in 33%; at least one of these pathogens was detected in 73% of volunteers. Culture of nasopharyngeal secretions of 447 adults with symptoms of upper respiratory tract infection for one to three days yielded *S. pneumoniae* in 3.8%, *H. influenzae* in 7.6%, and *M. catarrhalis* in 14.5%, with at least one of these organisms present in 23%. (*IDSA #135, #137.*)

Of 388 patients with a defined etiology of their community-acquired pneumonia, 59% had only typical pathogens, 26% had only atypical pathogens, and 14% had evidence of infection by a combination of typical and atypical pathogens. (*IDSA #140.*) In a prospective study of 468 patients with culture-proven *Legionella pneumoniae*, 83.9% were due to *L. pneumophila* serogroup 1. Thus, the widely used Binax™ urinary antigen test, which is specific to this organism, remains generally useful. (*ICAAC #593.*)

Five hundred seventy-one patients with community-acquired pneumonia were randomized to receive either gemifloxacin or trovafloxacin. The rates of bacteriological eradication were similar in the two treatment groups. The clinical efficacy of gemifloxacin and trovafloxacin were similar in the per-protocol analysis, but gemifloxacin was superior in the intent-to-treat analysis. (*IDSA #167.*)

Linezolid was as effective as cefpodoxime in a randomized trial of patients with community-acquired pneumonia. In individual comparative trials, telithromycin was as effective as either clarithromycin, trovafloxacin, or as high-dose amoxicillin in the treatment of community-acquired pneumonia. (*IDSA #68, ICAAC #2223, #2230.*)

A retrospective multicenter study of 56 non-neutropenic patients with nosocomial pneumonia due to *P. aeruginosa* found a 78% success rate after treatment with cefepime dosed either q12h or q24h. The success rate was 82% for those given the antibiotic every 12 hours and 71% for those given it every 24 hours. This is consistent with pharmacodynamic data indicating that q12h administration of cefepime in those with Ccr of 60 mL/min or more or q24h in those with Ccr less than 60 mL/min (a common occurrence with advanced age) maintains serum concentrations above the MIC of susceptible organisms for 50% or more of the dosing interval. (*ICAAC #742*.)

In a randomized trial in the treatment of nosocomial pneumonia, 3.5% of IV vancomycin recipients, but no linezolid recipients, became colonized with VRE. This result was confounded, however, by a longer length of vancomycin therapy. (*ICAAC #1961*.)

The administration of G-CSF in addition to antibiotic therapy produced no apparent clinical benefit to non-neutropenic patients with nosocomial pneumonia in a randomized, placebo-controlled trial in a total of only 29 patients. (*ICAAC #7399*.)

Controversy exists with regard to the efficacy of selective digestive decontamination (SDD) in the prevention of pneumonia in hospitalized patients at risk. An inverse relationship between methodological study quality and the reported relative risk reduction by SDD was found on systematic review of the literature. (*ICAAC #942*.) ❖

CME Questions

34. Which one of the following is correct with regard to the epidemiology of vancomycin-resistant enterococci (VRE)?

a. Gastrointestinal colonization is virtually never detected in Europe among healthy individuals in the community.
b. Gastrointestinal colonization did not occur in healthy volunteers after ingestion of VRE.
c. Improved elimination of environmental VRE was achieved by terminal cleaning procedures (as opposed to routine cleaning) and by improved surface disinfection.
d. The use of cover gowns for isolation does not reduce nosocomial transmission of VRE.

35. Which one of the following is correct?

a. Penicillin resistance has become widespread among *Streptococcus pyogenes*.
b. Trimethoprim/sulfamethoxazole was superior to ciprofloxacin in an international randomized trial of treatment of bloody diarrhea in children.
c. *Simkania nevegensis* was detected in a group of Antarctic infants with urinary tract infection.
d. A study of 408 *Bacteroides fragilis* bloodstream isolates found that all were susceptible to either metronidazole and to piperacillin/tazobactam and that more than 96% were susceptible to the carbapenems.

36. In the SENTRY study of almost 5000 enterococcal isolates in the United States from 1977-1999, which range did the percentage of isolates resistant to vancomycin fall into?

a. 0-10%
b. 11-20%
c. 21-30%
d. 31-40%

37. Regarding the potential for serious drug interactions in HIV:

a. the dose of rifabutin should be decreased to 150 mg two or three times weekly when used with ritonavir and delavirdine.
b. it's best to maintain a handy flow chart of significant drug interactions if you commonly prescribe HIV medications.
c. the administration of clarithromycin can result in toxic elevations of the statin-lipid lowering agents and rifabutin, as well as other agents metabolized by the hepatic P450 (CYP) system.
d. All of the above

Attention Readers

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 1000 subscribers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Associate Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com.

We look forward to hearing from you. ❖

In Future Issues:

Conference Summaries: Part II

UPDATES

By Carol A. Kemper, MD, FACP

Botox: No Laughing Matter

Source: ProMED-mail post, Nov. 23, 2000; www.promedmail.org.

Officials in brazil warn against the indiscriminant and unpracticed use of Botox (Botulinum A exotoxin), used by dermatologists and plastic surgeons for the treatment of facial wrinkles. The increasing use of Botox in cosmetic salons by non-medical personnel in places like Brazil raises the potential for misuse of the product, and an increased risk of facial paralysis, deformity, and even death.

Direct injections of Botox into facial muscles, such as the orbicularis oculi muscles (for crow's feet) and the mimetic muscles (for laugh lines), is increasingly popular and provides fairly effective, albeit, short-term results. In one study of 18 patients undergoing reconstructive surgery, direct injection of Botox into orbicularis oculi muscles resulted in improvement in crow's feet for nine months in 14 (78%) patients and 10 months in four (22%) (Guerrissi JO. *Plast Reconstr Surg* 2000;105:226-228). Approximately 15-50 IU of toxin were injected directly into each muscle, depending on the size of the muscle and the severity of the wrinkles. Results in a second study were slightly less encouraging, with 39 of 54 patients (72%) achieving a desired effect lasting only six months (Guerrissi J, Sarkissian P. *Ann Plast Surg* 1997;39:447-453). Nonetheless, 39% of subjects demanded a second procedure.

The agent has been used with success in patients with dystonic or spastic muscle groups, especially in the head and neck area. Botox can also be used to block the sympathetic innervation of sweat glands in the axillae, palms, and soles of patients suffering from hyperhidrosis. Experts caution that a precise understanding of anatomy is necessary to achieve optimal results, and that only 2000 IU—a dilution away from dosages used above—can be a lethal dose. ❖

PI Drug Levels in HIV

Source: Durant J, et al. *AIDS* 2000; 14:1333-1339.

Therapeutic drug monitoring of protease inhibitor (PI) levels is arguably the next frontier in attempting to improve the management of antiretroviral therapy in HIV. While a lack of adherence to a regimen is a leading cause of virological failure, other factors, such as drug interaction, poor absorption, and diet can adversely affect concentrations of these critical agents.

Serum concentrations of PIs and HIV RNA levels were serially assessed for 12 months in a subset of 81 patients enrolled in a French study of genotype resistance assays in the management of patients with HIV (VIRADAPT). Optimal concentrations of the drug were found in 67.9% of subjects; 22.1% of subjects had suboptimal concentrations of PIs, as defined by at least two PI concentrations below $2 \times IC_{95}$. Similar results were observed when the IC_{50} was used as the cut-off. There was a significantly greater reduction in HIV RNA levels at 48 weeks in patients with optimal PI concentrations (-1.28 $\log^{10}$ particles/mL) compared with those with suboptimal concentrations (-0.36 $\log^{10}$ particles/mL) ($P < 0.005$).

A significant correlation between higher PI concentration and lower HIV-RNA levels was found for all four PIs. Multivariate analysis showed suboptimal concentrations of PIs to be an independent predictor of virologic failure—not really a surprise. Other studies have shown that higher PI levels can delay the evolution of protease gene mutations. The key question at this juncture is whether real-time feedback about PI blood levels can help the clinician to expeditiously identify those patients at risk for PI failure, in order that appropriate measures may be taken to rectify any potential problems. ❖

More Drug Interactions in HIV

Source: Kuper JJ, D'Aprile M. *Clin Pharmacokinetics* 2000;39:203-214.

It is easy to forget the potential for serious drug interactions between the antimycobacterials and other HIV drugs. Clarithromycin and azithromycin are often used in the treatment of bacterial infections in patients with HIV, in addition to being key components of MAC prophylaxis or treatment regimens. Because of its interaction with the hepatic P450 (CYP) system, the administration of clarithromycin (but not usually azithromycin) can result in toxic elevations of other agents metabolized by this system, including the statin-lipid lowering agents and rifabutin. On the other hand, delavirdine and the protease inhibitors can increase clarithromycin levels, while nevirapine and efavirenz decrease clarithromycin levels.

And, who remembers the initial descriptions of uveitis and leukopenia when rifabutin was first used in patients also receiving fluconazole and/or clarithromycin, both of which were found to raise rifabutin serum concentrations? Similar findings have now been described in patients receiving rifabutin plus ritonavir and/or delavirdine, both of which increase rifabutin levels. As a result, the dose of rifabutin should be decreased to 150 mg two or three times weekly when used with these agents. However, if used with saquinavir soft gel as a single agent, rifabutin does not require modification (Kemper CA. *Infect Dis Alert* 2000;19:104). If you commonly prescribe antiretrovirals and other HIV medications, its best to maintain a handy flow chart of significant drug interactions. Access to an HIV pharmacy specialist is also invaluable. ❖