Highlights of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

by Lawrence M. Prescott, PhD

Chicago, Illinois, was the venue for the 43rd ICAAC meeting, held from September 14 to 17, 2003. More than 12,000 physicians, infectious-diseases specialists, research scientists, public health workers, and other health care professionals met to hear the latest developments in new drug formulations and in the surveillance, treatment, control, and prevention of infectious diseases.

Some of the novel therapeutic options of particular interest included a once-daily, short-duration therapy for acute exacerbations of chronic bronchitis; an investigational semisynthetic glycopeptide of special value in the treatment of complicated skin and skin structure infections; a new antifungal agent to treat esophageal candidiasis in patients with immunosuppression; a valuable addition to the family of pneumococcal vaccines for persons of all ages; two new nucleoside reverse transcriptase inhibitors (NRTIs); and several unique approaches to improving antiretroviral therapy. Researchers also reported on the effect of increasing the antibiotic dosage on the eradication of Streptococcus pneumoniae in acute otitis media in children.

Short-Duration Fluoroquinolone Therapy for Acute Exacerbations of Chronic Bronchitis

**Speaker:** Robert Wilson, MD, Specialist in Respiratory Medicine, Pneumonology, Royal Brompton Hospital, London, United Kingdom.

Patients with acute exacerbations of chronic bronchitis (AECB) who took a five-day course of once-daily moxifloxacin (Avelox®, Bayer) had a significantly higher cure rate, required fewer follow-up antibiotics to achieve clinical success, and experienced a greater period of time to the next recurrence of AECB than patients receiving a seven-day course of standard antibiotics taken two or three times daily.

Investigators performed prognostic analyses of patient subgroups from a major international clinical trial—Moxifloxacin Compared to Standard Therapy in Acute Infectious Exacerbations of Chronic Bronchitis (MOSAIC). In this multicenter, multinational, randomized, double-blind study, 730 patients with AECB were randomly assigned to receive moxifloxacin 400 mg once daily for five days or a standard treatment regimen consisting of (1) amoxicillin (e.g., Amoxil®, GlaxoSmithKline) 500 mg three times daily for seven days; (2) clarithromycin (Biaxin®, Abbott) 500 mg three times daily for seven days; or (3) cefuroxime axetil (Ceftin®, Lifecycle Ventures) 250 mg twice daily for seven days.

The moxifloxacin group achieved a higher clinical cure rate (70.9% vs. 62.8% for the comparator group) and a higher bacteriological response rate (92% vs. 81%). In addition, fewer of the moxifloxacin patients needed additional antibiotics (31% vs. 40%) or post-therapy systemic antimicrobial agents.

In the subgroup analysis, moxifloxacin demonstrated a higher cure rate in all categories, including (1) among patients with more than four AECB episodes per year (63% vs. 58% in patients receiving the standard antibiotics); (2) in patients with cardiopulmonary disease (62% vs. 42%, respectively); (3) in patients with a forced expiratory volume (FEV,) greater than or equal to 50% (79% vs. 69%, respectively); (4) in patients with an AECB of less than six months since before their enrollment in the randomized study (64% vs. 61%, respectively); and (5) among patients taking steroids concomitantly (67% vs. 62%, respectively).

Nasopharyngeal Eradication of Streptococcus pneumoniae in Acute Otitis Media

**Speaker:** Itzhak Brook, MD, MSc, Professor of Pediatrics and Medicine, Department of Pediatrics, Georgetown University School of Medicine, Washington, DC.

Amoxicillin at a dosage of 90 mg/kg daily was found to be much more effective than 45 mg/kg per day in the eradication of Streptococcus pneumoniae infection in the nasopharyngeal flora of children with acute otitis media after amoxicillin/clavulanate (Augmentin®, GlaxoSmithKline) therapy. Because the growing resistance of S. pneumoniae to penicillin can be overcome by increasing the dose of administered penicillin, it has been recommended that the amoxicillin dose for children with acute otitis media be increased from 45 to 90 mg/kg per day. Investigators conducted a study to assess the value of this recommendation.

Thirty children with acute otitis media who were seen before December 1, 2001, received amoxicillin/clavulanate 45 mg/kg per day in a 7:1 formulation of 400/57 mg per 5-ml suspension. Thirty children with acute otitis media who were seen after December 1, 2001, received amoxicillin/clavulanate 90 mg/kg per day in a 14:1 formulation of 600/42.9 mg per 5-ml suspension. The children’s ages ranged from six months to six years and 10 months, with an average age of two years and seven months.

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Nasopharyngeal specimens were taken for culture before therapy began. On a follow-up visit two to four days after completion of 10 days of antimicrobial therapy, *S. pneumoniae* isolates were screened for susceptibility to penicillin. Sixty-six potential pathogens were isolated, including 26 isolates of *S. pneumoniae*. 19 isolates of *Haemophilus influenzae* non-type B; eight isolates of *Moraxella catarrhalis*, seven isolates of *Streptococcus pyogenes*, and six isolates of *Staphylococcus aureus*. Of 12 *S. pneumoniae* isolates found before therapy in the group receiving 45 mg/kg per day, six isolates were resistant to penicillin; after therapy, the number was reduced from 12 to six. Of the 14 *S. pneumoniae* isolates in the group receiving 90 mg/kg per day before therapy, only one isolate was found after therapy. Both formulations were equally active in eradicating *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, and *S. aureus*.

**Pneumococcal Vaccine for the Prevention of Pneumococcal Disease**

**Speaker:** Cynthia G. Whitney, MD, Medical Epidemiologist, Centers for Disease Control and Prevention, Atlanta, Georgia.

A pneumococcal heptavalent conjugate vaccine (Prevnar®, Wyeth), introduced three years ago, has proved effective in reducing antibiotic-resistant pneumococcal disease in people of all ages, particularly in children younger than two years of age. Laboratory-based data from Active Bacterial Core Surveillance were used to assess changes in antibiotic-nonsusceptible pneumococci from 1998 to 2002. More than 14,000 cases of pneumococcal disease were reviewed from seven sites. These included three counties in Oregon, one in California, seven in Minnesota, 20 in Georgia, six in Maryland, and seven in New York, as well as the entire state of Connecticut. Isolates underwent serotyping and susceptibility testing. The study showed that vaccinating children younger than two years old (the recommended age group) appeared to provide the greatest protection against resistant infections. The rate of disease caused by penicillin-resistant strains of *S. pneumoniae* fell by 88% in children under two years of age and by 71% in children aged two to four years, many of whom had been vaccinated before age two.

The rates of antibiotic-resistant pneumococcal disease fell significantly in older children, adults, and older adults. Because these groups were not targeted for the vaccine, it was thought that the reduction might be attributed to a “herd immunity” effect. In adults aged 65 years and older, a group that is at high risk for pneumococcal disease and infections caused by antibiotic-resistant strains, the rate of penicillin-resistant, invasive pneumococcal disease declined by 41%.

**Semisynthetic Glycopeptide for Complicated Skin and Skin Structure Infections**

**Speaker:** Helen Giamarellou, MD, Infectious-Disease Specialist, Sismanoglion General Hospital, Athens, Greece.

Oritavancin (InterMune, Inc.), an investigational semisynthetic glycopeptide, exhibits activity against all gram-positive pathogens, including methicillin-resistant, linezolid-resistant, and vancomycin-resistant *S. aureus* strains. When administered for three to seven days, it was as effective and much better tolerated than intravenous (IV) vancomycin (Vancocin®, Eli Lilly), followed by oral cephalaxin (Keflex®, Dista), for 10 to 14 days in patients with complicated gram-positive bacterial infections of the skin and its structures.

Investigators conducted a phase III, double-blind, randomized, clinical trial encompassing 1,267 patients from 22 countries. A total of 1,246 patients were randomly assigned, in a 2:1 ratio, to receive IV oritavancin 200 mg once daily for three to seven days, followed by oral placebo or IV vancomycin 15 mg/kg for three to seven days, followed by oral cephalaxin 1,000 mg twice daily, with a total therapy time of 10 to 14 days for the vancomycin/cephalexin combination. The primary endpoint was cure in the clinically evaluable population at first follow-up, at days 21 to 29.

The primary efficacy analysis demonstrated that the clinical cure rate with oritavancin (78.6%) was comparable to that with vancomycin/cephalexin (76.2%). Of the 686 patients in whom the pathogen was isolated bacteriologically, 74.6% of the patients taking oritavancin and 73.3% of those taking vancomycin/cephalexin responded successfully.

It was particularly interesting that when oritavancin was administered for a mean of 5.3 days as active therapy, it was as effective as vancomycin/cephalexin that was administered for a mean of 10.9 days. Furthermore, fewer oritavancin patients (47%) experienced adverse drug events (ADEs) than did the vancomycin/cephalexin patients (58%), fewer of them discontinued therapy because of ADEs (1.8% vs. 4.8%, respectively), and fewer of them experienced study drug–related ADEs (16.1% vs. 23.9%, respectively).

**A Unique Cyclic Lipopeptide Antifungal Agent for Esophageal Candidiasis**

**Speaker:** David S. Krause, MD, Senior Vice President of Clinical Development and Medical Affairs, Vicuron Pharmaceuticals, King of Prussia, Pennsylvania.

Anidulafungin (Vicuron), a broad-spectrum antifungal agent that is highly active *in vitro* against a wide range of *Candida* species, including fluconazole-resistant strains, has been shown to be as effective and as safe as fluconazole (Diflucan®, Pfizer) in the treatment of esophageal candidiasis.

In an effort to assess the safety and efficacy of IV anidulafungin and oral fluconazole, researchers enrolled 601 immunosuppressed patients with endoscopically and microbiologically documented esophageal candidiasis into a large, four-country, randomized, double-blind, double-dummy phase III clinical trial. Patients were randomly assigned to receive a 100-mg IV loading dose of anidulafungin on day one along with an oral placebo, followed by a daily dose of 50 mg of anidulafungin infusions plus oral placebo for 14 to 21 days or oral fluconazole 200 mg on day one, along with an IV placebo, followed by oral fluconazole 100 mg and an IV placebo daily for 14 to 21 days.

Treatment ended when the patient remained symptom-free for seven days, after a maximum of 21 days of therapy. Patients were examined for endoscopic, clinical, and mycological responses at the end of therapy and at two weeks following therapy.
The primary efficacy endpoint was a successful endoscopic result after treatment. At that time, odynophagia, dysphagia, and retrosternal chest pain completely resolved in 504 clinically evaluable patients. Endoscopic success was reported in 242 of 249 patients (97.2%) who had received anidulafungin and in 252 of 255 patients (98.8%) who had received fluconazole, and the statistical requirement for equivalence (“non-inferiority”) was easily met. Anidulafungin was well tolerated, and the ADE and laboratory safety profiles were comparable to those for oral fluconazole.

**New NRTI-Based Regimen for Treatment-Naive, HIV-Positive Patients**

**Speaker:** Edwin DeJesus, MD, Medical Director of IDC Research Initiatives, Infectious Diseases Consultants, Altamonte Springs, Florida.

Over a period of 48 weeks, the combination of abacavir (Ziagen® GlaxoSmithKline), lamivudine (3TC) (Epivir®, GlaxoSmithKline), and efavirenz (Sustiva® DuPont) provided potent and durable responses in HIV-infected adults who were new to antiretroviral therapy. This regimen proved to be equivalent (“non-inferior”) to the commonly administered regimen of zidovudine (Retrovir®, GlaxoSmithKline), 3TC, and efavirenz. The outcome was a significantly better immunological response, thus offering physicians an effective alternative in the armamentarium of antiretroviral agents.

This phase III, multicenter, randomized, double-blind study enrolled 649 patients to compare the virological response of the two combinations of antiretroviral therapy. Patients were randomly assigned to receive abacavir 300 mg twice daily, 3TC 150 mg twice daily, and efavirenz 600 mg once daily or zidovudine 300 mg twice daily, 3TC 150 mg twice daily, and efavirenz 600 mg once daily. Secondary objectives included a comparison of immunological, safety, and tolerability data. At the baseline evaluation, the median plasma HIV-1 RNA level was 4.79/log₁₀ copies/ml, the median CD4+ cell count was 264 cells/mm³, and 39% of the patients had baseline viral loads greater than 100,000 copies/ml.

At 48 weeks’ follow-up, 70% of the patients receiving the abacavir-based regimen and 69% of those receiving the zidovudine-based regimen achieved an undetectable viral load (HIV-1 RNA below 50 copies/ml). Virological failure (the inability to achieve or maintain viral suppression) was infrequent and comparable between the two treatment arms. At 48 weeks, however, the patients taking abacavir showed better immunological responses (an increase of 209 CD4+ cells/mm³) compared with the zidovudine patients (an increase of 155 CD4+ cells/mm³). Overall, the safety profiles were similar after 48 weeks in both treatment arms, and both regimens were well tolerated.

**Antiretroviral-naive, HIV-infected patients were given a novel triple-NRTI regimen that combined emtricitabine (Emtriva™ and Gilead), which is under development and offers potent activity against HBV and HIV; stavudine (d4T) (Zerit®, Bristol-Myers Squibb); and abacavir. These patients achieved and maintained a high level of viral suppression comparable to that seen with the commonly used combination of lamivudine (3TC), zidovudine, and abacavir, given either separately or as one triple-combination tablet (Trizivir®, GlaxoSmithKline).

After performing a retrospective analysis, the researchers at 48 weeks compared the antiretroviral activity of emtricitabine, stavudine (d4T), and abacavir with that of lamivudine (3TC), zidovudine, and abacavir; the latter regimen was given either as separate drugs or as a triple-combination tablet.

Study endpoints included the proportions of patients with (1) viral loads below 400 copies/ml and below 50 copies/ml, (2) a median change in CD4+ cell count from baseline, (3) an incidence of virological failure, and (4) the presence of the M184V/I mutation in HIV reverse transcriptase (HIV RT). The investigators assessed the data for the experimental study group from the 188 patients in the MKC-401 study and data from six clinical trials, encompassing 795 patients and involving 3TC, zidovudine, and abacavir.

At week 48, 63% of patients taking the emtricitabine-based regimen had an HIV-1 RNA level of 400 copies/ml or below; 55% had an HIV-1 RNA level of 50 copies/ml or below. On average, in the six trials of 3TC, zidovudine, and abacavir, 61% of patients had HIV-1 RNA levels of 400 copies/ml or below; 52% had an HIV-1 RNA level of 50 copies/ml or below. The differences between the two treatment arms were not statistically significant.

In contrast, the rate of virological failure was statistically significantly lower for the emtricitabine-based regimen (9%), compared with the 3TC, zidovudine, and abacavir combination (15%). Furthermore, the incidence of the M184V/I mutation was significantly lower in the emtricitabine-based regimen (52%) compared with the 3TC, zidovudine, and abacavir regimen (74%).

**Cost-Effectiveness of an HIV Fusion Inhibitor/ Optimized-Background Antiretroviral Regimen**

**Speaker:** John Hornberger, MD, MS, Clinical Professor of Medicine, Stanford University School of Medicine, Stanford, California.

Enfuvirtide (Fuzeon®, Roche), the first of a novel class of antiretroviral agents known as HIV fusion inhibitors, plus an optimized-background (OB) regimen of antiretroviral agents, has been shown to improve virological response, to increase the time to virological failure, to delay the onset of new AIDS-defining events, and to increase overall survival and quality-adjusted life years (QALY), compared with an OB regimen alone in heavily pretreated HIV-positive individuals. These findings demonstrate a cost-effectiveness comparable to that of existing treatment and prevention strategies for HIV infection.

These conclusions were reached from week 24 efficacy data derived from the pooled analyses of the TORO (T20/Fuzeon vs. Optimized Regimen Only) 1 and 2 trials linked mathematically to published findings of long-term outcome studies and the estimated costs of therapy and health care. The
researchers developed a Markov model to predict time to virological failure, time to a new AIDS-defining event, overall survival, and QALY. The TORO trials enrolled 996 heavily pretreated, HIV-positive patients who were randomly selected, in a 2:1 fashion, to receive subcutaneous enfuvirtide (90 mg twice daily) plus an OB regimen versus an OB regimen alone.

The difference in the HIV-1 RNA and CD4+ cell count between the enfuvirtide + OB regimen and the OB regimen alone at week 24 was \(-0.94\ \text{log}_{10}\) copies/ml and + 44 cells/ml. In the enfuvirtide + OB regimen group, compared with the OB regimen group alone, the mean time to virological failure increased by 0.5 years, the overall life expectancy increased by 1.5 years, and the overall QALY expectancy increased by 1.2 years.

On the basis of published studies, it was estimated that the annual rate of immunological failure would decline from 65% with the OB regimen alone to 27% with the enfuvirtide + OB regimen. The combined effects of an increase in the CD4+ cell count, the delayed time to virological failure, and immunological failure are predicted to increase mean survival by 1.73 years from 4.83 years for the OB regimen alone to 6.56 years for the enfuvirtide + OB regimen.

The cost-effectiveness of the enfuvirtide + OB regimen, relative to the OB regimen alone, is estimated to be $32,795 per year gained and $43,607 per QALY gained. One review of cost-effectiveness analyses has shown that most widely available approved agents have cost-effectiveness values of less than $50,000, but the costs of some treatments exceed this value. Examples include indications for orphan drugs and the availability of few alternative therapies, especially in children.

The cost-effectiveness estimate for enfuvirtide—approximately $40,000—is considered acceptable by current standards, especially for life-threatening conditions such as HIV and AIDS.

**Boosted Protease Inhibitor Salvage Therapy in Pretreated HIV-Positive Patients**

**Speaker:** Vincent Soriano, MD, Section Chief, Department of Infectious Diseases, Instituto de Salud Carlos III, Madrid, Spain.

More than two-thirds of heavily pretreated, HIV-infected patients who received multiple protease inhibitors (PIs) but not saquinavir (Fortovase®, Roche) and who were in current virological failure experienced a significant viral response after completing 48 weeks of treatment with boosted saquinavir/ritonavir–based (Norvir®, Abbott) salvage therapy.

A total of 139 HIV-positive individuals experiencing virological failure after receiving a multiple-PI regimen, but not saquinavir, were enrolled in the Fortovase Genotyping Surveillance Program (the Fortogene Study). The trial was conducted at 20 clinical centers in Spain to evaluate the response to saquinavir/ritonavir–based salvage therapy. The study was also designed to determine the impact of certain baseline variables on patients' responses at different time points, including levels of saquinavir in the blood, genotypic and phenotypic resistance, and the genotypic inhibitory quotient (GIQ), a ratio of the minimum concentration of saquinavir needed to suppress the virus to the number of PI mutations, as measured by genotypic resistance testing.

All patients received saquinavir 1,000 mg twice daily/ritonavir 100 mg twice daily, as boosted saquinavir therapy. Patients were considered to have responded when there was a decline in the viral load of more than 1.0 log_{10} copies/ml or when they achieved undetectable levels of HIV-1 RNA, below 50 copies/ml. The mean plasma HIV-1 RNA level before initiation of saquinavir/ritonavir therapy was 4.3 log_{10} copies/ml, and the mean CD4+ cell count was 350 cells/ml.

At one year, 68.3% of patients receiving boosted saquinavir treatment experienced a reduction in their HIV-1 RNA levels of more than 1.0 log_{10}; in addition, at this point, 60% of patients achieved undetectable levels of HIV-1 RNA, below 50 copies/ml. The median CD4+ cell count gain was +81 cells/ml.

At 12 weeks, the serum saquinavir level was the main predictor of early patient response.

At week 24, the best predictor of intermediate patient response was baseline HIV-1 genotyping, suggesting that viral response in patients taking the drugs depends, in large part, on the presence of mutations that cause resistance.

At week 48, the GIQ was the most accurate predictor of response, suggesting that both saquinavir levels and resistance mutations influence the long-term efficacy of therapy in complementary ways.