More than 11,000 physicians, infectious disease specialists, epidemiologists, research scientists, and other health care professionals from around the world gathered (from December 16 to December 19, 2001) to hear the latest developments in the surveillance, control, treatment, and prevention of infectious diseases at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, Illinois. Major areas of interest included improved short-term treatment options for acute exacerbations of chronic bronchitis and acute sinusitis, an effective approach for treating difficult-to-treat nosocomial infections in hospital, a potent antibiotic combination for resistant bacteremias, a novel recombinant human protein for the treatment of severe sepsis, a more effective method to treat genital herpes, and new treatment regimens to improve antiretroviral therapy. Listed below are highlights of some of these presentations.

Short-Duration Antimicrobial Therapy for AECB

Speaker: Marcus J. Zervos, MD, Clinical Professor of Medicine, Wayne State University School of Medicine, Detroit, Michigan, and William Beaumont Hospital, Royal Oak, Michigan.

Five-day therapy with oral telithromycin (Ketek, Aventis), a new ketolide antimicrobial agent, is as effective as standard 10-day treatment with comparators in adult patients with acute exacerbation of chronic bronchitis. When considered along with its convenience of once-daily dosing and tolerability, this new antibiotic becomes a first-line treatment option for patients with AECB.

To reach these conclusions, two multicenter, randomized, double-blind, two-arm, parallel group comparator studies were conducted, comparing the efficacy and safety of telithromycin 800 mg for five days with standard 10-day therapy with comparator antimicrobials (amoxicillin clavulanate 500/125 mg three times daily or cefuroxime axetil 500 mg twice daily). A total of 700 patients with AECB were randomized and 693 individuals were included in the modified intent-to-treat (mITT) population—342 in the telithromycin group and 351 in the comparator group. A total of 509 patients in the mITT population had no major protocol violations and were included in the per protocol (PP) population (telithromycin: 255 patients; comparator: 254 patients).

The pooled clinical cure rate in the telithromycin-treated patients was 86.3% post-therapy (days 17–24) and 78.4% late post-therapy (days 31–45), equivalent to the rate seen in the comparator group (82.7% and 75.6%, respectively), demonstrating that the shorter five-day treatment with telithromycin did not result in a greater number of relapses or reinfections compared with standard 10-day regimens. In addition, telithromycin was equally effective in elderly patients (>65 years) and in patients at increased risk for morbid sequelae.

The majority of adverse events were mild or moderate in severity in both treatment groups. Telithromycin was particularly well-tolerated, with treatment resulting in discontinuations of only 1.9% to 3.3%, compared to 10% of patients treated with amoxicillin/clavulanate and 1.6% of those treated with cefuroxime axetil.

Advanced-Generation Fluoroquinolone for Recurrent/Non-Responsive Acute Otitis Media

Speaker: Ron Dagan, MD, Professor of Pediatrics, Pediatric Infectious Disease Unit, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Preliminary results from an ongoing clinical study designed to demonstrate the effectiveness of fluoroquinolones in treating pediatric ear infections have shown that gatifloxacin (Tequin, Bristol-Myers Squibb) is effective against commonly found respiratory tract pathogens, particularly against resistant Streptococcus pneumoniae (S. pneumoniae). Gatifloxacin is an advanced generation, broad-spectrum fluoroquinolone antibiotic.

In an ongoing study, 70 patients aged six to 48 months (median 11 months, 71% under one year) with recurrent/non-responsive acute otitis media (RNR-AOM) have been enrolled so far and treated with an oral suspension of gatifloxacin 10 mg/kg once daily for 10 days. Middle ear fluid was cultured...
Meeting Highlights: 41st ICAAC

by tympanocentesis pre-treatment (day one) and on days four to six of treatment. Additional cultures were obtained if clinical relapse occurred. Patients were followed for up to 28 days.

A total of 58 of the 70 youngsters completed the course of treatment, with 12 patients discontinuing the study. The mean number of previous acute otitis media (AOM) episodes in this group of patients was 4.5 (range 1–12). Overall, 50 pathogens were identified in 38 (66%) of the patients, with 29 identified as Haemophilus influenzae (H. influenzae), 15 as S. pneumoniae, five as Moraxella catarrhalis (M. catarrhalis), and one identified as S. pyogenes. All 15 S. pneumoniae isolates, 13 of which were resistant to a number of other antibiotics (including penicillin), were susceptible to gatifloxacin, as were all 29 isolates of H. influenzae and five isolates of M. catarrhalis, many of which produced beta-lactamase. Bacteriologic eradication was achieved in 98% (49/50) of the pathogens and clinical improvement/cure at the end of treatment was seen in 97% (56/58) of the gatifloxacin-treated patients. The drug eliminated more than 90% of all pathogens from the middle ear fluid (the site of infection in AOM patients). Clinical relapse was reported in 18 patients before day 28, and a middle ear fluid culture was reported in 16 of these youngsters, with a new pathogen found in 10. True relapse was documented in the other six patients.

Potent Antibiotic Combination for Resistant S. aureus Bacteremias

Speaker: Joseph L. Gugliotta, MD, Infectious Disease Specialist, Hunterdon Medical Center, Flemington, New Jersey.

The combination of quinupristin/dalfopristin (Synercid, Aventis) and vancomycin (Vancocin, Lilly) proved to be highly effective in the treatment of bacteremias caused by oxacillin-resistant Staphylococcus aureus (ORSA) strains, demonstrating enhanced bactericidal activity compared with either antibiotic tested alone.

Two patients with oxacillin-resistant S. aureus bacteremias remained blood culture positive with vancomycin and then with quinupristin/dalfopristin therapy, in both cases alone or with rifampin. Within 48 hours of switching to a combination of quinupristin/dalfopristin and vancomycin, the bacteremias were cleared, with all subsequent blood cultures being negative.

Two ORSA isolates from the two patients with sepsis and S. aureus ATCC 43300 were studied in vitro in a time-kill synergy assay (a>100-fold or 2 \log_{10} decrease in the viable cell count at 24 hours for the combination of quinupristin/dalfopristin and vancomycin compared with the most active agent). The two antibiotics were tested alone and in combination at 0.25, 0.5, and 1 times the minimum inhibitory concentration (MIC) with samples taken at 0, three, six, and 24 hours to determine viable cell counts.

Quinupristin, at 1 times MIC, was more effective than vancomycin in suppressing bacterial regrowth after 24 hours, whereas the combination of quinupristin/dalfopristin plus vancomycin was bactericidal (>99.9% reduction from the initial inoculum) for both isolates and a control isolate (ORSA ATCC 43300) at 1 times MIC after 24 hours. Using this time-kill synergy methodology, the combination of quinupristin/dalfopristin and vancomycin achieved synergy for one clinical isolate and approached synergy for another clinical isolate, demonstrating that quinupristin/dalfopristin used in combination with vancomycin is more effective than either agent alone to treat ORSA infections.

Improved Treatment for Hospitalized Gram-Positive Infections

Speaker: Mark Wilcox, MD, Staff Physician and Lead Investigator, Leeds General Infirmary & University of Leeds Old Medical School, Leeds, United Kingdom.


tedlinezolid particularly valuable economically.

Two ORSA isolates from the two patients with sepsis and S. aureus ATCC 43300 were studied in vitro in a time-kill synergy assay (a>100-fold or 2 \log_{10} decrease in the viable cell count at 24 hours for the combination of quinupristin/dalfopristin and vancomycin compared with the most active agent). The two antibiotics were tested alone and in combination at 0.25, 0.5, and 1 times the minimum inhibitory concentration (MIC) with samples taken at 0, three, six, and 24 hours to determine viable cell counts.

Quinupristin, at 1 times MIC, was more effective than vancomycin in suppressing bacterial regrowth after 24 hours, whereas the combination of quinupristin/dalfopristin plus vancomycin was bactericidal (>99.9% reduction from the initial inoculum) for both isolates and a control isolate (ORSA ATCC 43300) at 1 times MIC after 24 hours. Using this time-kill synergy methodology, the combination of quinupristin/dalfopristin and vancomycin achieved synergy for one clinical isolate and approached synergy for another clinical isolate, demonstrating that quinupristin/dalfopristin used in combination with vancomycin is more effective than either agent alone to treat ORSA infections.

Recombinant Protein for Severe Sepsis

Speaker: Steven P. LaRosa, MD, Associate Staff Physician, Department of Infectious Diseases, Cleveland Clinic Foundation, Cleveland, Ohio.

Drotreogin alfa activated (Xigris, Lilly), a recombinant form of protein C recently approved by the FDA for the treatment of severe sepsis, markedly reduces the risk of all-cause mortality in adult patients, according to findings from the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) clinical trial.
In this prospective, double-blind, placebo-controlled phase III study, a total of 1,690 patients with severe sepsis were randomized to placebo (840 patients) or drotreogin alfa activated 24 mcg/kg of body weight per hour administered intravenously at a constant rate for 96 hours. The primary endpoint of the study was all-cause mortality at 28 days. Patients were also monitored for results of microbiologic cultures, adverse events, changes in vital signs, and laboratory variables. Because the trial results met FDA criteria for efficacy among patients treated with drotreogin alfa (activated), trial enrollment was stopped in the middle of the study.

At 28 days follow-up, administration of drotreogin alfa (activated) to patients with severe sepsis was associated with a statistically significant (19.4%) reduction in the relative risk of death compared to placebo, making this the first study of the treatment of severe sepsis to show such a difference. Further analysis of the data demonstrated that this beneficial treatment effect was independent of the type of bacterial pathogen.

In a comparison of all-cause, 28-day mortality rates by pathogen types (pure gram-positive, pure gram-negative, mixed gram-stain, pure fungal, and mixed bacterial and non-bacterial organisms) in subgroups with at least 150 patients, lower 28-day mortality rates were observed in the drotreogin alfa (activated) treatment group across the four most common pathogen classifications: unknown, pure gram-positive, pure gram-negative, and mixed gram bacterial.

Suppressive versus Episodic Therapy for Recurrent Genital Herpes

*Speaker:* Kenneth H. Fife, MD, PhD, Professor of Medicine, Microbiology & Immunology and Pathology, Division of Infectious Diseases, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana.

New research suggests that managing recurrent genital herpes with 500 mg of oral valacyclovir (Valtrex, GlaxoSmithKline) daily as suppressive therapy—treating daily before symptoms ever appear—is significantly more effective at reducing the number of genital herpes recurrences, the time to first recurrence, and the percentage of patients who are recurrence-free at one year than treating with valacyclovir as episodic therapy (treatment only as outbreaks occur).

Although valacyclovir has been shown to be effective for both acute treatment and chronic suppression of recurrent genital herpes, those treatment approaches have not been assessed to determine whether episodic or suppressive therapy is superior with regard to recurrence. In a randomized, open-label study, 80 otherwise healthy patients with a history of four to nine recurrences annually were randomly assigned to either episodic treatment with self-initiated, oral valacyclovir 500 mg twice daily or suppressive treatment with 500 mg of oral valacyclovir once daily, for one year. Patients maintained daily diaries, were evaluated monthly over the one-year study period, and completed quarterly quality-of-life surveys.

At the one-year follow-up, a total of 66 people (32 episodic and 34 suppressive) completed the study. Suppressive therapy with valacyclovir reduced the number of genital herpes outbreaks over the one-year study period by almost 80%, the average number of weeks to first recurrence being 4.7 days with episodic treatment and 23.27 days with suppressive therapy. Furthermore, 41% of patients receiving suppressive therapy did not experience an outbreak during the study compared to only 3% of those on episodic therapy. In addition, the mean number of days between recurrences of genital herpes was 179.8 days for patients on suppressive therapy, compared with 53 days between recurrences for those on episodic therapy. Overall, patients on suppressive therapy had a mean of 1.6 recurrences of genital herpes outbreaks versus 7.3 recurrences in those on episodic therapy. Finally, according to quality-of-life assessments, treatment with valacyclovir improved quality of life for all patients in the study.

Combination PI-Containing Regimen for HIV-Infected, Treatment-Experienced Patients

*Speaker:* Robert Schooley, MD, Head of Infectious Diseases and Professor of Medicine, University of Colorado, Denver, Colorado.

Based on a preliminary 24-week analysis, amprenavir 600 mg (Agenerase, GlaxoSmithKline)/ritonavir 100 mg (Norvir, Abbott) twice daily might be a better treatment regimen than amprenavir 900 mg/ritonavir 100 mg twice daily because the lower amprenavir dose results in a similar efficacy, a lower incidence of adverse events and patient withdrawals, and a lower pill burden.

To reach these conclusions, a study was designed to provide data on the most efficacious and well-tolerated amprenavir dosage regimen in combination with low-dose ritonavir plus other antiretroviral drugs, to be used as a treatment option for HIV-1-infected adults who are changing from a failing antiretroviral regimen. Two dosages of amprenavir 600 mg twice daily and 900 mg twice daily were chosen to be evaluated in combination with ritonavir 100 mg twice daily. Ritonavir was selected because it enhances the antiviral effect of amprenavir while reducing the pill burden.

A total of 115 treatment-experienced HIV-1 infected adults who had been on failing therapy for more than 12 weeks, whose HIV-1 RNA levels were more than 1,000 copies/ml, whose lymphocyte counts were more than 50 cells/mm², and whose HIV-1 isolates were susceptible to the study drug combination, were enrolled in a 48-week, open-label pilot study. The patients were randomized to the two amprenavir/ritonavir dosage regimens plus either abacavir, another nucleoside reverse transcriptase inhibitor (NRTI) and efavirenz or abacavir, another NRTI, and tenofovir. Data is available for 104 patients, with median duration on the study drugs being 120 days and 113 days for the 600- and 900-mg dosages, respectively, at time of analysis. The primary endpoint used to measure effectiveness is the proportion of patients with plasma HIV-1 RNA levels of less than 200 copies/ml.
copies/ml at week 48. Because the study is still ongoing, the proportion of patients with HIV-1 RNA levels of less than 200 copies/ml at week 24 was presented.

In the primary efficacy analysis, the majority of patients in both amprenavir treatment groups (69% and 73%) achieved plasma HIV-1 RNA levels of less than 200 copies/ml at week 24. For both treatment groups, there was a greater than 2 log_{10} copies/ml reduction in the plasma HIV-1 RNA by week 24. None of the patients in either group experienced progression of HIV disease. Also, changes in the lipid profiles of the patients were minimal. The number of patients who met the definition of virologic failure was low and similar in both the amprenavir 600-mg (3 patients) and 900-mg (2 patients) groups.

**Antiretrovirals Concomitantly with Methadone for Hepatitis C/HIV Co-Infections**

*Speaker:* Lawrence S. Brown, Jr., MD, MPH, Senior Vice President, Addiction Research and Treatment Corporation, Brooklyn, New York, and Clinical Associate Professor of Public Health, Weill Medical College of Cornell University, New York, New York.

Data from a multisite study demonstrate that in opiate-dependent patients with concurrent HIV and hepatitis C, the combination of the protease inhibitor nelfinavir (Viracept, Agouron) as part of the antiretroviral therapy, and methadone (Roxane), as part of the maintenance treatment for opiate dependency, is safe, well-tolerated, effective, and durable.

Drug addiction is a continuing, major risk behavior associated with HIV and hepatitis C. Substance abuse is associated with a higher risk of hepatic toxicity in patients with concurrent HIV and hepatitis C infections. This is especially true because of the potential for hepatotoxicity caused by antiretroviral agents, particularly some protease inhibitors. A retrospective chart review was carried out to identify persons at risk with HIV and hepatitis C co-infection enrolled in a large multiclinical methadone maintenance treatment agency encompassing a total population of 2,800 patients who were being treated for drug addiction. Patients in the study had to be taking nelfinavir as part of their antiretroviral therapy, and must have been on a stable methadone dose for one month prior to initiating nelfinavir.

As of this report, 32 patients have been identified as meeting these criteria, and have data available. Of these patients, 29 had been on a stable dose of methadone for 30 days or longer before starting nelfinavir treatment. Only two of the 29 patients reported nelfinavir-related diarrhea; both were moderate cases. The median length of nelfinavir treatment was 22 months. The prevalence of methadone dose adjustment by patients was only 17%, although 80% of the patients had their methadone adjusted by clinicians. None of these HIV and hepatitis C co-infected patients needed to switch off of their nelfinavir-containing regimens because of virologic failure or drug-related adverse events—which demonstrates the efficacy, safety and durability of this approach. Further studies are needed to corroborate these findings.