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INSIDE

ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

The following summary of selected abstracts from 3 meetings will be published in multiple parts. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene meets in Philadelphia December 3-7, 2003. — ***Stan Deresinski, MD, FACP***

Antibacterials

Adverse Effects and Pharmacokinetics

Cefepime

Twenty-nine cefepime recipients developed encephalopathy that resolved on discontinuation of the antibiotic. Twenty-five of the 29 had impaired renal function. In a previously published report, the observed neurological abnormality was described as a "prolonged confusional state associated with diffuse rhythmic nonreactive triphasic sharp waves on the EEG," which resolved 24-48 hours after discontinuation of cefepime administration (*Neurophysiol Clin. 2000;30:383; ICAAC A-525*).

Daptomycin

The clinical development of daptomycin was slowed by the occurrence of myopathy associated with > 10-fold CPK elevations in several volunteers. Subsequent studies in dogs found that these problems were significantly reduced by changing from split dosing to once-daily administration of this lipopeptide (*AAC 2003;47:1318*). An analysis of clinical trials data found that 6.4% of recipients of once-daily daptomycin and 5% of recipients of comparator antibiotics developed musculoskeletal complaints. One daptomycin recipient (0.2%) developed elevated CK and muscle symptoms that reoccurred on rechallenge (*ICAAC L-736*).

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Fluoroquinolones

Several prior studies have indicated that fluoroquinolone use is associated with an increased risk of Achilles tendon disorders, including rupture, especially in individuals older than 60 years of age and those receiving adrenal corticosteroid therapy (*Infectious Disease Alert. 2002;22:25-28; BMJ. 2002;324:1306*). In a case-control study involving a managed care population, fluoroquinolone use was again associated with increased risk of Achilles tendon rupture, with the magnitude of risk similar to that observed with oral corticosteroid exposure alone or with diabetes mellitus. The risk seen with fluoroquinolone use was less than that seen with other factors found to be associated with Achilles tendinopathies, including male gender, rheumatoid arthritis, skin or soft-tissue infection, obesity, and injected corticosteroid use. In contrast, however, examination of a large health insurance database found that the risk of Achilles tendon rupture associated with fluoroquinolone use did not significantly differ from the risk associated with the use of antibiotics of other classes. A comparison of 3 different fluoroquinolones—levofloxacin, ofloxacin, and ciprofloxacin—found no difference among them (*ICAAC A-519, IDSA 195*).

Previous studies have suggested that fluoroquinolones may cause tendon disorders as a consequence of chelation of magnesium and the production of local reduced levels of ionized magnesium. Some evidence, however, suggests an alternative or additional explanation. In in vitro studies, 2 fluoroquinolones caused alteration in matrix and signaling proteins, as well as causing tenocyte apoptosis (*ICAAC A-520*).

Fluoroquinolones, like macrolides, have been demonstrated to have a variety of anti-inflammatory effects in vitro. Moxifloxacin exerted anti-inflammatory effects on activated mononuclear and epithelial cells in vitro by inhibition of *NFkB* and ERK activation pathways. On the other hand, moxifloxacin upregulated Toll-like receptor expression on human neutrophils (*ICAAC B-1504, B-1505*).

Some macrolides and fluoroquinolones have been associated with prolongation of ventricular repolarization. Administration of doses of levofloxacin as high as 1500 mg was associated with an increase in heart rate but had no effect on the QTc interval (*IDSA 196*).

Administration of any fluoroquinolone together with magnesium, zinc, or iron is associated with reduced bioavailability of the antibiotic. In addition, levofloxacin Cmax was reduced by approximately 20% when administered with a mineral-fortified breakfast of juice and cereal when compared to administration in the fasting state. Gatifloxacin exposure is also significantly reduced when coadministered with Ensure (*ICAAC A-1626, 1628*).

Ketolides/Macrolides

Coadministration of either telithromycin or clarithromycin was associated with significantly increased exposure to simvastatin. A 12-hour dosing interval between telithromycin and simvastatin reduced the magnitude of this interaction by approximately one-half (*ICAAC A-1623, 1624*).

Linezolid

Linezolid has 100% oral bioavailability, and administration with continuous enteral feedings did not adversely affect the rate or extent of its absorption (*ICAAC A-1614*).

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In a compilation of data from 2 phase-3 trials, the incidence of thrombocytopenia in patients with nosocomial pneumonia given linezolid for > 5 days was not greater than in those given vancomycin. However, linezolid administration beyond 14 days has been associated with an increased risk of the development of thrombocytopenia. Linezolid was administered for a mean of 43 days (range, 1-753 days) to 101 patients who received 119 courses of therapy with the drug. Sixteen percent developed anemia, and 20% developed thrombocytopenia. The subsequent mean time to recovery of a normal platelet count is 15.6 days (*IDSA 198, 199*).

Forty patients with chronic osteomyelitis, 22 of whom had orthopedic device infections, received IV linezolid for 7 days followed by oral administration for a mean duration of 26 weeks (range, 6-36). Therapy was discontinued because of the development of anemia with reticulocytopenia in 14 (35%) at a mean of 8 weeks (range, 4-19) and because of peripheral neuropathy, occurring at a mean of 24 weeks (range, 16-36) in 3. Thrombocytopenia occurred only once but may have been alcohol-related (*IDSA 317*).

Metronidazole

Despite a plasma half-life of approximately 8 hours, metronidazole is inexplicably routinely administered several times daily. Once-daily IV administration of 1500 mg metronidazole and 750 mg levofloxacin to healthy volunteers yielded acceptable pharmacokinetic results, with Cmin of 4.8 + 1.4 mcg/mL and 0.7 + 0.3 mcg/mL, respectively. This once-daily regimen is now being used in a clinical trial in the treatment of intraabdominal infections (*IDSA 193*).

Streptogramins

Approximately one-third of 56 patients given quinupristin/dalfopristin for treatment of VRE infection complained of myalgia and/or arthralgia. These complaints were significantly associated with increased serum alkaline phosphatase. This enzyme elevation was interpreted by the investigators as suggesting that biliary tract dysfunction is associated with musculoskeletal symptoms in recipients of this streptogramin combination (*A-522*).

Tigecycline

The investigational glycylglycine tigecycline appeared safe and effective in phase 2 trials involving hospitalized patients with complicated skin and skin-structure infections and with complicated intraabdominal infections (*ICAAC L-738, 739*). ■

Meeting the Need for Rapid Microbiology

ABSTRACT & COMMENTARY

Synopsis: *Genetically engineered B lymphocytes were used for rapid detection and identification of pathogens, a methodology with potential use in diagnostics, biowarfare defense, and biomonitoring of food and water.*

Source: Rider TH, et al. A B cell-based sensor for rapid identification of pathogens. *Science*. 2003;301:213-215.

THERE IS NO DOUBT THAT BIOTERRORISM HAS SPURRED new science. One of the fields that has been affected acutely is the identification of biowar pathogens. Speed and accuracy of identification are crucial if there are to be effective public notification and specific implementation defense strategies.

Many labs have focused on rapid pathogen identification. In this report published in *Science*, Rider and colleagues at MIT present an ingenious method termed CANARY—cellular analysis and notification of antigen risks and yields.

First the lab produced a way for B cells to respond to specific pathogens. Plasmids were transfected into a B-cell line, M12g3R, and these plasmids encoded constant regions for light and heavy chains and also a variable region specific for the specific pathogen. These cells were able to respond to pathogens like *Yersinia pestis* with speed, sensitivity, and specificity. As few as 50 colony-forming units were detected within 3 minutes. When 200 CFU were used, the probability of detection was 99%. Other pathogens detected included orthopoxviruses and Venezuelan equine virus.

When a pathogen like *E coli* 0157 was spiked onto lettuce, as few as 500 CFU were detected within 5 minutes. Such a reaction would compare favorably with a PCR reaction reported for *E coli*. These detector B cells are quite hardy, with a shelf life of 2 days at room temperature, 2 weeks when refrigerated, and indefinitely when frozen.

■ COMMENT BY JOSEPH F. JOHN, Jr., MD

Leave it to those crafty engineers at MIT to come up with CANARY. Here they take B cells that will glow when the pathogen in question tickles a pathogen's surface protein. Quite tricky indeed!

Technology like this linked to cellular detection will have to compete with DNA chip technology, the latter of which potentially could identify thousands of pathogens on the

same chip. The advantage of the cell-based technology is that it may be less complex than the chips and more specific.

Rider et al have produced B-cell lines whose expressed antibodies are specific at a subspecies and perhaps a strain level. Trials comparing this method with direct PCR methods could be conducted during specific outbreaks; for example, an *E coli* 0157 outbreak in a meat processing plant.

Another advantage to a cell system like the one described here is that direct tissue analysis may be possible. Besides the immediate need for identification of biowar agents (the work was sponsored by the Department of Defense), any surgical sample could theoretically be directly examined for specific pathogens like *Bacteroides* and *Pseudomonas*.

It will be interesting to see if the industry has enough economic incentive to develop this discovery. ■

E-mails to Improve Compliance to a Protocol

ABSTRACT & COMMENTARY

Synopsis: *Compliance with a protocol for managing catheter-related bacteremia was improved from 56% to 75% simply by sending a reminder by e-mail.*

Source: Rijnders BJ, et al. Use of semiautomatic treatment advice to improve compliance with Infectious Diseases Society of America guidelines for treatment of intravascular catheter-related infection: A before-after study. *Clin Infect Dis*. 2003;37:980-983.

DESIGNING PROTOCOLS IS ONE THING; KEEPING TO the recommendations is quite another. This is shown clearly in this study of episodes of catheter-related bacteremia (CRB). The protocol was based on recommendations of the Infectious Diseases Society of America[1] and provided advice on the antibiotic, dosage, and duration for a particular infection (*see Table*). The behavior of physicians familiar with the protocol in question was monitored for 8 months to assess their compliance in managing 52 episodes of CRB. It was not impressive, with noncompliance being recorded at 20%, 40%, and 50% for Candida infections, *Staphylococcus aureus* infections, and coagulase-negative staphylococcal infections, respectively (*see Figure*). A second phase lasting 7 months was then initiated in which the attending physician received standardized advice by e-mail accompanied by a printout that was placed on the physician's desk. Compliance improved dramatically when dealing with CRB due to coagulase-negative staphylococci and moderately when dealing with other infections. Rijnders and associates conclude that their simple intervention was successful in bringing compliance up to 85%.

COMMENT BY J. PETER DONNELLY, PhD

The provision of a simple reminder obviously assisted these particular physicians in managing CRBs, which is encouraging as the system was neither costly nor labor-intensive, consuming less than 10 minutes of laboratory time. Moreover, Rijnders et al estimated that they only needed to send a reminder once a day in their 1700-bed hospital, which is hardly likely to place an intolerable burden on laboratory time. Importantly, their hospital uses an electronic medical record system so the physician encounters the recommendation as part of the routine tasks. The antibiotic formulary is also available online, making access to antibiotic information readily accessible. Interestingly, Rijnders et al did more than just send an e-mail; they also placed the reminder on the physician's desk to ensure he or she got the message. This double security does rather suggest the electronic system is not foolproof. This is not surprising since the physician nominally in charge may not be the one who is caring for the patient on a day-to-day basis. The system will therefore only be as good as the level of communication within and between depart-

Table

Criteria Used to Judge Whether Treatment of CRB was Adequate

Pathogen & Susceptibility	Recommended Antibiotic	Acceptable Dosage	Acceptable Duration
Coagulase-negative staphylococci			
Methicillin susceptible	Flucloxacillin	1-2 g/d	5-10 d
Methicillin resistant	Vancomycin	Serum levels	5-10 d
Staphylococcus aureus			
Methicillin susceptible	Flucloxacillin	1-2 g/d	12-16 d
Methicillin resistant	Vancomycin	Serum levels	12-16d
Candida species	Fluconazole	400 mg/d	14-16 d

ments. This aspect deserves specific study since it is seldom clear why communications break down as they frequently do. The ready availability of PDAs also seems to offer more possibilities for exchanging information between people and systems.

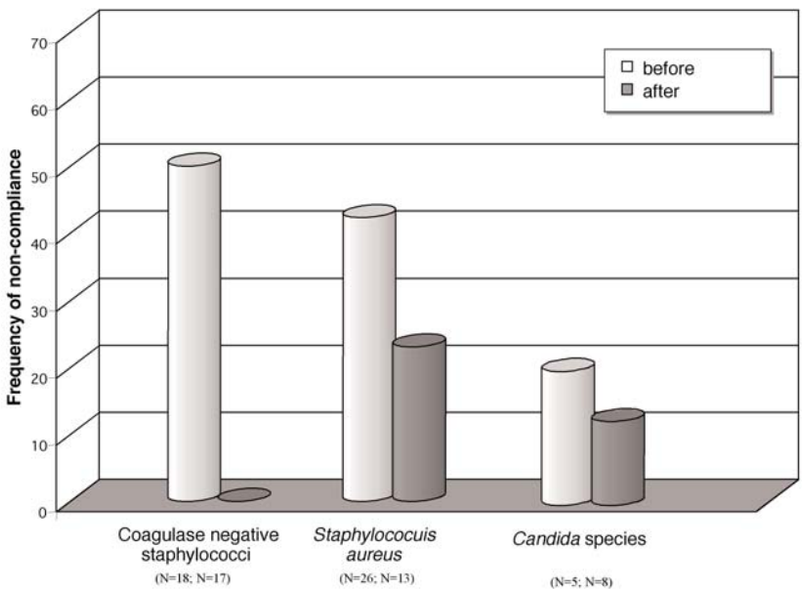
There are grounds for caution with this attractive and simple approach. First, human beings are prone to suffer from information fatigue and overload. This might be avoided by ensuring that the delivery of electronic advice about a specific problem in a specific patient is incorporated into the process of managing the patient. For instance, if the electronic dossier is consulted before doing daily ward rounds, the advice should be available then so that it can be implemented. There is little point in sending the advice out after this time since it might cause confusion if treatment has already been agreed and has to be changed again later on in the day and may even be left until the day after. The approach is also not a substitute for consultation with infectious disease physicians or clinical microbiologists but complementary. However, with this in mind, the study does show a novel way of ensuring compliance to protocols that everyone has agreed to implement. This cannot be a bad thing and might be extended to other settings where protocols form an appropriate part of the care. ■

Reference

1. Mermel LA, et al. *Clin Infect Dis*. 2001;32:1249-1272.

Figure

Compliance Before and After Sending Advice Electronically



'Nailing' Down a *Pseudomonas* Outbreak in Cardiac Surgery

ABSTRACT & COMMENTARY

Synopsis: *An outbreak of* Pseudomonas *surgical-site infections was traced to the infected thumbnail of a cardiac surgeon. The outbreak stopped after the infected nail was removed.*

Source: Mermel LA, et al. *Pseudomonas* surgical-site infections linked to a healthcare worker with onychomycosis. *Infect Control Hosp Epidemiol*. 2003;24:749-752.

During an 8-month period in 2001, 5 surgical-site infections due to *P aeruginosa* occurred in a university hospital. Three were sternotomy infections, and 2 were infections of a saphenous vein harvest site. Infection control records showed that no *P aeruginosa* SSIs had occurred on the cardiac surgery service for the preceding 2 years. Mermel and colleagues identified 5 health care workers (HCWs), including 2 cardiac surgeons, who had been involved in at least 2 of the cases. The one surgeon involved in all 5 infected cases had marked onychomycosis of the thumbnail; none of the other HCWs had infected nails. Culture of the surgeon's nail yielded *P aeruginosa*. Two isolates from sternotomy infections and one from a leg wound infection were available for molecular subtyping. The 2 sternotomy isolates were identical to the surgeon's nail isolate by pulse-field gel electrophoresis; the leg wound isolate was distinct.

Specimens from multiple environmental sites were taken, including intra-operative fluids, povidone iodine solution, instruments, potable water, ice machines, hand lotion, autoclaves, and hemotherm units. None of these cultures yielded *P aeruginosa*.

The surgeon underwent removal of the infected nail; the nailbed culture was also positive for *P aeruginosa*. When the nail

grew back, it was without any sign of onychomycosis, and follow-up culture was negative.

COMMENT BY ROBERT MUDER, MD

Sternal wound infection following cardiac surgery is most commonly due to staphylococci. *Pseudomonas* sternal infections are uncommon, typically causing approximately 1% of such infections. Thus, the occurrence of multiple *Pseudomonas* wound infections on the cardiac surgery service in this hospital was an appropriate stimulus to a detailed investigation.

It is highly likely that the ultimate source of the sternal wound infections in this outbreak was the surgeon's infected thumbnail. This is supported by the observation that he participated in all infected cases and that the *Pseudomonas* isolate from his nail was genetically indistinguishable from the 2 sternal isolates that were tested. The surgeon's link to the leg wound infections is unclear, as the available isolate did not match the nail isolate. It should be noted that *P aeruginosa* is a much more common infecting pathogen of saphenous vein harvest sites than of sternotomy wounds. It's possible that the leg wound infections were independent of the sternal wound infections, particularly since the surgeon in question had limited involvement in vein harvesting procedures.

This report illustrates that the hands of HCWs can serve not only as the means of transmission of infectious agents between patients, but also as the reservoir as well. Contaminated fingernails have been implicated in a number of nosocomial outbreaks; *P aeruginosa* and *Candida* species are the most common organisms implicated.[1-3] Artificial nails are more likely to be the culprits than native nails, as the former are much more likely to be colonized with Gram-negative bacilli and fungi than are the latter.[4] As a consequence, the most recent CDC hand hygiene guidelines appropriately call for restriction of the wearing of artificial nails in patient care settings.[5] It should be noted that the outbreak reported by Mermel et al confirms previous observations that surgical gloves are not adequate to prevent wound contamination in the operative suite when real or artificial nails are heavily colonized with pathogens. ■

References

1. Parry MF, et al. *Candida* osteomyelitis and diskitis after spinal surgery: An outbreak that implicates artificial nail use. *Clin Infect Dis*. 2001;32:352-357.
2. McNeil SA, et al. Outbreak of sternal surgical site infection due to *Pseudomonas aeruginosa* traced to a scrub nurse with onychomycosis. *Clin Infect Dis*. 2001;33:317-323.
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5. Boyce JM, et al. Guidelines for hand hygiene in healthcare settings. *Am J Infect Control*. 2002;30:S1-S46.

Effect of Influenza Vaccination on Otitis Media in Young Children

ABSTRACT & COMMENTARY

Synopsis: *Inactivated trivalent influenza vaccine did not reduce the incidence of acute otitis media among children 6-24 months of age.*

Source: Hoberman A, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children. A randomized controlled trial. *JAMA*. 2003;290:1608-1616.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED trial of inactivated trivalent subvirion influenza vaccine was conducted during 1999-2001 among 786 children aged 6-24 months. Children received 2 doses (0.25 mL each) of vaccine approximately 4 weeks apart. Testing the 66 serum samples collected from children in the vaccine group showed seroconversion rates of 88.6-96.8%, depending on the specific strain. Vaccine efficacy against culture-confirmed influenza was 66% (95% CI, 34%-82%) in 1999-2000, and -7% (95% CI, -247%-67%) in 2000-2001. However, the influenza attack rates were 15.9% and 3.3%, respectively.

The vaccine was well tolerated. Compared to placebo, influenza vaccine did not reduce the proportion of children with at least 1 episode of acute otitis media in the first cohort (1999) during the influenza season (vaccine, 30.5% vs 29.9%), during the respiratory season (vaccine, 49.2% vs placebo, 52.2%; $P = .56$), or during the entire 1-year follow-up period (vaccine, 57.3% vs 61.9%, $P = .35$). Nor did it reduce the proportion in the second cohort (vaccine, 55.8% vs placebo, 48.2%; $P = .17$). There were no differences between vaccine and placebo groups for the monthly rate of acute otitis media, the estimated proportion of time with middle ear effusion, or the use of health care and related resources.

COMMENT BY HAL B. JENSON, MD, FAAP

There have been 4 previous studies, and now a fifth, of the efficacy of influenza vaccine and the possible effect on reduction of acute otitis media in children. Previous studies, some of which have shown a reduction in otitis media after influenza vaccination, have been limited by small sample size, study population selection, nonrandomization, single or incomplete blinding, and lack of standardized criteria for diagnosis. This study showed that the influenza vaccine for 2000-2001 did not have a significant effect on prevention of influenza in this age group; demonstrating this benefit with this number of patients was hampered because the incidence of influenza never reached epidemic proportions in this population during the study years.

There may be age-related factors that account for the different results of this study from previous studies. This study enrolled primarily children 18 months of age and younger (mean age, 14 months) compared to mean age ranges of 20-43 months in 3 of the previous studies. For example, in this study within the subgroup of children 19-24 months of age, the proportions of children who had at least 1 episode of acute otitis media during the influenza and respiratory seasons were suggestively lower in the vaccine group than in the placebo group (19.4% vs 34.3%; $P = .10$; and 36.8% vs 54.3%; $P = .09$, respectively). Age differences could account for some of the differences between studies if the proportion of viral respiratory infections caused by influenza are lower in younger children than in older children, or if the vaccine was less effective in preventing influenza in younger children than in older children. However, this study found seroconversion rates of approximately 90% in both years, with no difference in antibody responses by age group.

In October 2003, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommended that influenza vaccine be provided to all healthy children 6-23 months of age with effective implementation in fall 2004. This recommendation strengthens the previous policy for this age group to a full recommendation. The benefits of the vaccine to reduce the rates of influenza in children and to reduce the burden of influenza in the community justify this new recommendation regardless of the limited effect on acute otitis media. ■

Which Patients with *S aureus* Bacteremia Are at Risk for Serious Disease?

ABSTRACT & COMMENTARY

Synopsis: *By determining whether 4 key risk factors are present, clinicians might be able to identify those patients with* S aureus *bacteremia who are at increased risk of serious, "complicated" infection.*

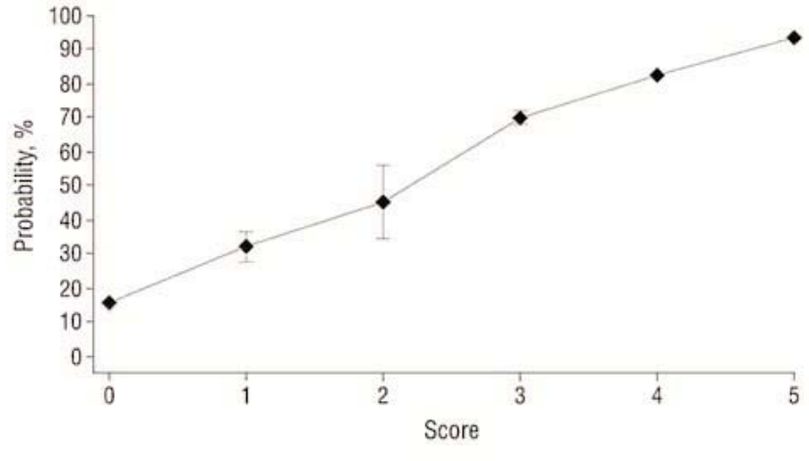
Source: Fowler VG Jr., et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 2003; 163:2066-2072.

THIS STUDY, PERFORMED BY FOWLER AND ASSOCIATES at Duke University Medical Center, attempted to identify whether certain easily discernible demographic, clinical, and laboratory features could predict which patients with *Staphylococcus aureus* bacteremia are at risk of developing some of the most serious complications of the infection. Endocarditis, osteomyelitis and septic arthritis, and visceral or brain abscess are some of the dreaded complications of this infection.

All patients hospitalized with *S aureus* bacteremia over a 5-year period were studied. Excluded were those with polymicrobial bacteremia (blood cultures yielding more than 1 pathogen), patients younger than 18 years of age, and patients with peripheral white blood cell counts <

Figure

Association between *S aureus* Bacteremia Score and Probability of Complicated Infection



1,000/μL. Fowler et al collected data during the patients' hospitalization and for a 12-week follow-up period, specifically noting the presence of "complications": 1) death attributed to staphylococcal infection; 2) hematogenously seeded infection (such as osteomyelitis); 3) local extension of infection beyond the primary focus (such as septic thrombophlebitis or abscess); 4) embolic stroke; and 5) recurrent staphylococcal infection during the follow-up period. Uncomplicated bacteremia was defined by absence of complicated or recurrent infection.

Follow-up blood cultures were drawn 48-96 hours after the initial set of positive blood cultures in most patients (79%, or 571 of the 724 enrolled in the study). Community-acquired bacteremia was present in 17%.

Using a host of such variables as demographic characteristics, clinical findings, and treatment modalities, Fowler et al developed logistic regression models to predict the presence of complicated *S aureus* bacteremia. Of the 40 variables that were examined, positive follow-up blood culture (odds ratio [OR], 4.94), community-acquired bacteremia (OR, 3.08), and fever persisting at least 72 hours after the initial blood culture (OR, 2.00) were the most significant predictors. Cutaneous markers of systemic infection (eg, petechiae, infarcts, and vasculitis), residence on a surgical service, advanced age, presence of a new or diastolic murmur, and the presence of a prosthetic device were also significantly associated with complicated infection but to a lesser degree. Refinement of the statistical model again identified 4 of these factors as the most predictive: positive follow-up blood culture, community-acquired infection, persistent fever, and cutaneous markers suggesting acute systemic infection. Awarding points to each risk factor—2 points for a positive follow-up blood culture and 1 point for each of the others—resulted in a linear relationship showing increasing probability of complicated infection (*see Figure*). Importantly, even in the absence of any of the 4 risk factors, complicated infection was predicted in 16% of the patients.

COMMENT BY JERRY D. SMILACK, MD

Even in the antibiotic era, *S aureus* bacteremia is a serious infection and frequent cause of mortality. The challenge facing clinicians is distinguishing between patients who are at risk of serious morbidity or even death and those who will respond uneventfully to antimicrobial therapy.

Several years ago, associating *S aureus* bacteremia with the presence of a removable focus of infection (eg, an intravascular catheter or drainable cutaneous abscess) was suggested as a basis for short-course antimicrobial therapy since the risk of complications was felt to be low. More recently, use of echocardiography (especially transesophageal echocardiography) has been advocated as a means of identifying those with occult endocarditis.

Fowler et al now offer us another schema for identifying those at high risk, suggesting that patients with none of 4 easily ascertainable risk factors "may be suitable for shorter courses of antibiotic therapy and/or less complex testing," presumably echocardiography. They caution, however, that even in the absence of these risk factors, 1 in 6 patients with *S aureus* bacteremia will have a serious complication from that infection.

Several points of caution must be raised. First, the most important risk factor predictive of complicated infection was a positive follow-up blood culture. However, 21% of the entire patient population in this study failed to have follow-up blood cultures drawn. Was this because the patients responded rapidly to therapy and their treating physicians did not feel that follow-up cultures would be helpful? Could cultures have been obtained with greater frequency in the sicker patients, perhaps those with prolonged fever or other complications? Since Fowler et al did not state what criteria were used to determine when or if follow-up cultures were obtained, it seems possible that bias could have entered into the predictive model. Second, is the ability to predict those at risk going to make a clinical difference? Can physicians treat those with none of the 4 risk factors differently from those with 1 or 2 (or even all 4) risk factors, since even 16% of those free of risk factors could be predicted to have complications?

Nevertheless, this study offers a fresh look into the question of which patients are at increased risk of complications from *S aureus* bacteremia. If similar, more controlled studies confirm its findings, we will have gained a useful tool in confronting a very vexing clinical problem. ■

A Macrolide for *Pseudomonas*? The Wonders of Azithromycin

ABSTRACT & COMMENTARY

Synopsis: *Azithromycin administration to patients with cystic fibrosis and chronic* Pseudomonas aeruginosa *infection was associated with a reduction in number of exacerbations, improvement in airflow, and weight gain.*

Source: Saiman L, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*. *JAMA*. 2003;290:1749-1756.

THE MACROLIDE STUDY GROUP NOTED THE APPARENT beneficial effects of azithromycin in the therapy of

patients with panbronchiolitis, a condition seen mostly in Japan with similarities to cystic fibrosis. Both diseases are thought to have progressive lung damage due, in part, to the release of destructive factors released by neutrophils. Their network of centers in the United States studied 185 cystic fibrosis patients with an average age of about 20 years. Treatment was randomized, double blind, and placebo controlled and consisted of 24 weeks of oral azithromycin given at a dose of 250 or 500 mg 3 times each week for 24 weeks.

They found a clear improvement in the FEV 1 (mean, 0.097-L [SD, 0.26]) in the azithromycin treatment that was statistically significantly better than the placebo group (P = .009). The treatment group also had fewer exacerbations (P = .03) and gained more weight (P = .02) than the placebo group. There were some side effects noted with the azithromycin treatment group, which consisted of nausea (17%), diarrhea (15%), and wheezing (13%). Saiman and colleagues felt the wheezing may well have been a good thing and attributed it to a better ability to clear secretions.

The microbiology of the respiratory tract samples was also studied. The recovery of *Pseudomonas* and its density were not affected. *Staphylococcus aureus* was not eradicated in the repeat samples when it was initially recovered (52%). *Chlamydia* and *Mycoplasma* were not looked for.

Measurement of elastase and IL-8 levels failed to show a difference. A review of the literature for a possible role of known inflammatory mediators failed to reveal any relevant information other than a decline in C-reactive protein levels, which correlate closely with baseline lung function in the groups studied.

COMMENTS BY ALAN D. TICE, MD, FACP

These findings make one wonder about azithromycin and what it actually does aside from what can be demonstrated in the bacteriology lab. It has some activity against staphylococci and a little against *Pseudomonas*, but there was not a clear effect in eliminating the organisms in this study and not even an effect on the amount of *Pseudomonas* recovered. A role for other organisms, such as *Chlamydia* and *Mycoplasma*, could reasonably be postulated but was not studied. Nontuberculous mycobacteria were recovered in 3% of patients and probably played little role.

Inflammatory markers that have been studied with azithromycin provide little insight into how and why azithromycin had such a positive effect in these patients, although excess local neutrophil activity and cytokines are probably at the base of the mechanisms, as they are with alpha-1 antitrypsin deficiency lung disease. Recent studies have indicated macrolides can inhibit GM-CSF production as well as the oxidative burst of phagocytic cells.[1,2]

Looking further into some of the studies about the non-bacterial activities of azithromycin makes one wonder even more about this unusual macrolide. Its clinical activity does not correlate well with serum concentrations, which has been explained by its ability to concentrate in white blood cells, almost in a smart bomb fashion. Its terminal half-life of 30 or more hours also presents a dilemma in dosing. The initial double dose with oral administration made a lot of sense but seems to have been abandoned in the recent marketing of a 3-day 500-mg regimen instead of the 5-day 250-mg one (at a local cash price of $53.75) for respiratory infections.[3] How often it really has to be dosed is also unknown, but it seems best for marketing to leave it at once a day to not go beyond the limits of the imagination of health care providers and payers.

Azithromycin has also been explored for benefits in preventing the progression of coronary artery disease. However, a large recent study could not find a benefit in more than 7000 postinfarction patients after they were given 600 mg per week for 12 weeks, even with a positive serology for *Chlamydia pneumoniae*.[4]

Other clinical studies have found this drug lacking in the treatment of acute bronchitis, even though it is commonly used for that infection.[5] The placebo control of vitamin C appeared to be as effective as azithromycin at Cook County Hospital. While this discrepancy might be explained by the nonbacterial etiology of most cases of acute bronchitis, it makes one wonder. It was also interesting that there were more adverse effects reported with ascorbic acid than with the antimicrobial in that study.

Delving further into PubMed, one can also find other possible benefits of this drug. It is good for trachoma, has been found comparable to levofloxacin for travelers' diarrhea,[6] can inhibit biofilm formation,[7] and even alter the production of Alzheimer's amyloid precursor protein of Alzheimer's disease.[8]

All this information makes me wonder just what to do with this drug. It is clearly beneficial in a number of clinical diseases, although probably overused in common respiratory infections, which are largely viral and/or reactive in etiology. Whether it should be used for long-term administration for chronic inflammatory diseases of the lungs for its anti-inflammatory effects is uncertain, as it will certainly bring antimicrobial resistance to the local pathogens. The potential benefits for a number of diseases that are not of obvious infectious etiology are particularly intriguing. ■

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Special Feature

Atazanavir: Have We Finally Arrived at Once-Daily Dosing for HIV?

By John O'Brien, PharmD, HIV Pharmacy Specialist, Positive PACE Clinic, Santa Clara Valley Medical Center, and Carol A. Kemper, MD, FACP

Introduction

Atazanavir (Reyetaz®), an azapeptide class of protease inhibitors, was approved by the US FDA for use in HIV infection on June 20, 2003. Atazanavir (ATV) has a unique pharmacokinetic profile allowing for once-daily dosing, which is optimized when taken with food.

Clinical Trials Data

Several clinical trials, in both antiretroviral (ARV)-naïve and -experienced patients, comparing combinations of 2 nucleoside reverse transcriptase inhibitors (nRTIs) with either ATV or another protease inhibitor, have been completed, some of which are available for review only in abstract form. In a randomized, dose-blinded clinical trial in which 420 treatment-naïve patients were enrolled, Sanne and colleagues evaluated combinations of d4T, ddI, and various dosages of ATV (either 200, 400, or 500 mg daily) vs nelfinavir (NLF) 750 mg t.i.d.[1] The average CD4 count and viral load for the 4 treatment groups were similar at entry to study (about 350 and 4.7 $\log_{10}$ viral copies/mL, respectively). In the intent-to-treat analysis, 36% of patients receiving ATV 400 mg daily and 39% of those receiving NLF were undetectable (HIV viral load < 50 copies/mL) at 48 weeks of therapy. CD4 count increases were similar for the 2 groups (220 cells/mm^3 and 185 cells/mm^3 for the ATV 400 mg and NLF groups, respectively). Patients receiving ATV had significantly less diarrhea (20%) compared with those receiving NLF (60%) ($P < .0001$). Jaundice occurred in 6% of patients receiving ATV 400 mg daily, compared with none of the patients receiving NLF ($P < .03$). Mean fasting LDL decreased 4% in patients receiving ATV, while LDL increased 30% in patients receiving NLV.

In a second double-blind clinical trial, treatment-naïve patients with CD4 counts > 100 cells/mm^3 were randomly assigned to receive d4T/3TC plus either ATV 400 mg or 600 mg daily, or NLF 1250 mg b.i.d. for 48 weeks.[2] Baseline CD4 and viral loads were similar for both ATV arms and NLF (baseline CD4, ~270 cells/mm^3). In the intent-to-treat analysis following 48 weeks of therapy, 31%, 36%, and 38% of patients receiving ATV 400 mg, ATV 600 mg, or NLF, respectively, had viral loads < 50. Baseline HIV viral loads decreased 2.51, 2.58, and 2.31, respectively ($P < .05$, comparing all 3 groups). Increases in CD4 cell counts were similar.

Haas and colleagues assessed the response of 85 treatment-experienced patients who were randomized to receive 2 nRTIs plus either ATV 400 mg daily or 600 mg once daily, saquinavir (SAQ) 1200 mg once daily, or ritonavir 400 mg/SAQ 400 mg twice daily.[3] At baseline the groups were well matched, with a similar mean CD4 cell count (~330 cells/mm^3), although slightly more than half of the patients receiving ATV 400 mg daily had viral loads > 30,000 copies/mL, compared with 22% of patients receiving RTV/SAQ. Following 48 weeks of therapy, the reduction in HIV viral load was similar for patients receiving either dose of ATV or RTV/SAQ, and CD4 counts increased 109, 55, and 149

cells, respectively (*P* values not reported).

In a fourth study, 358 protease-inhibitor-experienced patients were randomly assigned to receive tenofovir plus one other nRTI plus either ATV 300 mg/RTV 100 mg daily, ATV/SAQ once daily, or lopinavir/ritonavir (LPV/r). The groups were well balanced at entry to study, with an average CD4 count of ~300 cells/mm^3. In the intent-to-treat analysis, 39%, 23%, and 42% of patients receiving either ATV/RTV, ATV/SAQ, or LPV/r, respectively, were undetectable (< 50 particles/mL) at 24 weeks of therapy.

On the other hand, once-daily atazanavir 400 mg/d did not appear to perform as well as LPV/r in another study involving heavily pretreated patients failing their current protease inhibitor. Cohen and colleagues randomly assigned 300 patients failing their current PI, all of whom had baseline CD4 counts > 50 cells/mL, to receive either ATV 400 mg/d (unboosted) or LPV/r.[5] At 24 weeks of therapy, 54% of patients receiving LPV/r vs 38% of those receiving ATV had undetectable viral loads (< 50 particles/mm^3).

Pharmacokinetics

Atazanavir inhibits both cytochrome P450 3A4 (CYP3A4) and uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1). The latter is responsible for bilirubin glucuronidation. Atazanavir, similar to other available protease inhibitors, has the potential to interact with substrates, inhibitors, or inducers of CYP3A4. Important drug interactions can therefore occur with many different drugs, especially those agents with a narrow therapeutic window, such as benzodiazepines (triazolam, alprazolam) and calcium channel blockers. Agents known to induce the CYP3A4 system (eg, nevirapine and efavirenz) markedly lower the blood levels of ATV. To offset this interaction, it is recommended to decrease the ATV to 300 mg and add RTV 100 mg daily, thereby increasing the minimum concentration (C_{min}) and maintaining or decreasing the C_{max} (the latter is believed to be more responsible for potential toxicity).

An interaction between ATV and tenofovir has also emerged. From a pharmacokinetic standpoint, this is difficult to envision: ATV is fully metabolized by the liver, and TDF is eliminated unchanged by the kidneys. Nonetheless, in 34 healthy controls, the C_{min} of ATV was diminished by up to 48% (mean, 40%) in the presence of tenofovir.[6] In patients with HIV infection, an about sevenfold increase in C_{min} of ATV has been found when ATV 300 mg/d is boosted by RTV 100 mg/d. However, when tenofovir was added, the mean C_{min} dropped 26%. Based on these results, ATV 300 mg should always be boosted with RTV 100 mg/d whenever tenofovir is also used in the regimen. The mechanism for this drug interaction is not fully elucidated, but could be some type of pharmacodynamic interaction on the level of P-glycoprotein or some other type of efflux transporter.

Side Effects

In contrast to other protease inhibitors, ATV is associated with fewer GI side effects, although this advantage might be diminished if the drug is boosted with RTV. Atazanavir has been shown to increase the QTc and PR intervals, usually at higher dosages than those used for most HIV regimens. This may have contributed to the death of a patient enrolled in the expanded-access study (which excluded subjects with a baseline QTc interval > 450 msec). This individual was receiving ATV plus delavirdine (a known CYP3A4 inhibitor), as well as verapamil (a substrate for CYP3A4, as well as a potent inhibitor of P-glycoprotein). It is prudent to obtain a baseline EKG in those with known or suspected cardiovascular disease. Furthermore, the clinician should avoid medications that may increase ATV drug levels or that have the potential to alter the QTc interval.

Summary

Adherence to ARV medications is an important consideration when structuring an antiretroviral regimen. Both clinicians and patients have been eagerly awaiting a once-daily regimen with as few pills as possible. Atazanavir is the first FDA-approved once-daily protease inhibitor. Moreover, it appears to be well tolerated, with fewer GI side effects than some of the other PIs, and may be very useful in patients with hyperlipidemia. ■

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CME Questions

13. Once a protocol is implemented, compliance:
a. is assured.
b. needs to be monitored.
c. is likely to be high.
d. is likely to be low.
e. is as good as can be expected.

14. Which of the following organisms has been most commonly involved in an outbreak of surgical wound infections linked to the wearing of artificial nails by a scrub nurse?
a. *Staphylococcus aureus*
b. *Streptococcus pyogenes*
c. *Pseudomonas aeruginosa*
d. *Serratia marcescens*
e. *Stenotrophomonas maltophilia*

15. What are some potential culture-free methods that can be used for rapid identification of biowar agents?
a. Polymerase chain reaction
b. Immunoassays
c. DNA
d. B-cell antibodies
e. All of the above

16. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recently recommended that, effective Fall 2004, influenza vaccine be provided to healthy children of which age group?
a. Children < 12 months of age
b. Children 12-15 months of age
c. Children 6-23 months of age
d. Children 24-36 months of age
e. Children > 5 years of age

17. Which of the following was *not* found to be a helpful predictor of complications resulting from *Staphylococcus aureus* bacteremia?
a. Use of either vancomycin or rifampin as part of the therapy
b. A follow-up blood culture positive for *S aureus*
c. Fever persisting for 72 hours
d. Community acquisition of infection

18. What is the half-life of azithromycin?
a. 2 hours
b. 6 hours
c. 18 hours
d. 30 hours

Answers: 13(b); 14(c); 15(e); 16(c); 17(a); 18(d)

Attention Subscribers

Due to an American Health Consultants error, a mistake has been made with the volume numbering. The October 2003 issue should have started over with Volume 23, Number 1. We regret any confusion this might have caused. ■

SARS Audio Program Updates Guidelines

Leading epidemiologists say a global return of severe acute respiratory syndrome (SARS) is almost inevitable. The current overriding concern is that SARS will resurface as a seasonal illness along with influenza and other respiratory infections. Indeed, it would be a surprising development if the emerging coronavirus did not return, said Julie Gerberding, MD, MPH, director of the Centers for Disease Control and Prevention in Atlanta.

"I think we have to expect that somewhere, some time, this coronavirus is going to rear its ugly head again; and that's the whole purpose of all this preparedness effort," Gerberding said.

What would happen today if a patient with suspect or probable SARS were admitted to your hospital? To help you prepare for the threat, Thomson American Health Consultants offers the upcoming audio conference: The Resurgence of SARS: Why Your Hospital May Not be as Prepared as You Think, on Dec. 9, from 2:30 to 3:30 EST.

Our speakers are Allison McGeer, MD, director of infection control at Mount Sinai and Princess Margaret Hospitals in Toronto. A veteran epidemiologist, McGeer dealt first hand with SARS patients and occupationally infected workers during the prolonged outbreak in Toronto.

If SARS returns, hospital emergency rooms will certainly be on those frontlines. To provide valuable guidance and critical insight in that setting, Susan E. Shapiro, PhD, RN, MSN, CEN, will outline valuable tips and procedures, in addition to addressing and clarifying recently updated CDC recommendations for SARS. Shapiro is a Post Doctoral Fellow in Risk Assessment and Intervention Research with Individuals and Families at Oregon Health & Science University School of Nursing in Portland. Shapiro is also the Emergency Nurses Association's representative to the CDC's SARS task force.

Educate your entire staff for one low fee including 1 hour of CE, CME, or Critical Care credits for all attendees. You may invite as many participants as you wish to listen for the low fee of $249. Information on obtaining audio conference instructions and continuing education forms will be in the confirmation notice, which will be mailed upon receipt of registration. Your fee also includes access to a 48-hour replay following the conference and a CD recording of the program. For information or to register, call customer service at (800) 688-2421 or contact us via e-mail at customerservice@ahcpub.com. When ordering, please refer to effort code 35281. ■

PHARMACOLOGY WATCH

Eplerenone Cleared for CHF Patients with Sustained MI

The FDA has approved Pfizer's eplerenone (Inspra) for the treatment of congestive heart failure (CHF) in patients who have sustained a myocardial infarction. The drug is a selective aldosterone blocker, a new class of drug for the treatment of CHF. It differs from spironolactone in that it selectively blocks the mineralocorticoid receptor, but not the glucocorticoid, progesterone, or androgen receptors. The approval of eplerenone for the treatment of CHF was based primarily on the findings of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which was published in the April 2003 issue of the *New England Journal of Medicine*. In EPHESUS, nearly 7000 patients with acute myocardial infarction and left ventricular dysfunction and heart failure were randomized to eplerenone 25 mg per day titrated up to 50 mg per day or placebo. Both groups also received optimal medical therapy. Following 16 months of follow-up, there was a significant reduction in death rate (RR, 0.85; 95% CI, 0.75-0.96; P = 0.008) in the eplerenone group. The drug also resulted in significant reductions in cardiovascular deaths and sudden cardiac death (*N Engl J Med*. 2003;348:1309-1321). The drug appears to be well tolerated with the primary adverse events being hyperkalemia and increased creatinine levels. Because of the selectivity of the drug for the mineralocorticoid receptor, there is no reported increase in menstrual disorders, gynecomastia, or impotence with eplerenone, adverse reactions that are frequently associated with spironolactone usage. Pfizer will make the drug available through an early access program by December 2003. Eplerenone was previously approved for treatment of hypertension alone or in combination with other antihypertensive agents.

No Adverse Effect with Concomitant Aspirin and ACE Inhibitor Use in CHF Patients

Aspirin does not adversely affect survival in patients with stable CHF who were being treated with an ACE inhibitor, according to a French study published in October. This study contradicts earlier studies, which raised concern about the concomitant use of aspirin and ACE inhibitors in CHF patients. In a retrospective analysis, 755 stable patients with left ventricular systolic dysfunction were followed for nearly 5.5 years. Most patients were on an ACE inhibitor and 317 were on aspirin, the majority on low-dose aspirin (< 200 mg/d). End points included cardiac-related deaths, version transplants, nonurgent transplants, and noncardiac deaths. The analysis revealed no relationship between the use of aspirin and survival among patients taking ACE inhibitors. Brunner-La Rocca and colleagues conclude that aspirin is not harmful for heart failure patients who are taking ACE inhibitors (*Chest*. 2003; 124:1192-1194, editorial 1250-1258).

HIV Treatment Shows High Failure Rate

A once-daily, triple nucleoside reverse transcriptase inhibitor (NRTI) HIV treatment regimen has seen a high number of treatment failures and HIV

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resistance. The rate of virologic failure reached 91% along with a high rate of HIV resistance to NRTIs in treatment-naive patients. Gilead Sciences has taken the step of notifying health-care professionals to discontinue the regimen in a "Dear Doctor" letter. The treatment failures were seen with a regimen containing didanosine enteric-coated beadlets (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead) in HIV-infected treatment-naive patients. Tenovir DF is no longer recommended for use in combination with didanosine and lamivudine in treatment-naive or experienced patients with HIV infections. The FDA is also recommending that patients currently on this regimen should be considered for treatment modification (http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#viread [Accessed Nov. 5, 2003]).

New Psoriasis Treatment Approved

The FDA has approved the second biologic for the treatment of psoriasis. Genentech's efalizumab (Raptiva) was approved for the treatment of moderate-to-severe psoriasis in October. It joins Biogen's alefacept (Amevive), which was approved in January 2003 and will probably soon be joined by Amgen's rheumatoid arthritis drug etanercept (Enbrel), which is also seeking approval for the treatment of psoriasis. Efalizumab is a humanized therapeutic antibody that blocks the activation, reactivation, and trafficking of T-cells that lead to the development of psoriasis symptoms. The drug requires a once-a-week self-injection and will cost $14,000 a year.

THG Controversy Gains Steam

The FDA has issued a warning regarding tetrahydrogestrinone (THG), a synthetic "designer" steroid, which is derived by simple chemical modifications from another anabolic steroid. Little is known about the safety of the drug or its structure, but its relationship to better-known products suggests that it may represent a considerable health risk. THG has been marketed as a dietary supplement; however, the FDA has determined that it is an unapproved drug and as such cannot be legally marketed. Urine assays have recently been developed for THG, and testing of athletes has revealed some disturbing findings. Four US Olympic athletes, as well as Britain's leading sprinter, have tested positive in the initial assay—further tests are to follow. A San Francisco grand jury is looking into a California nutritional supplement manufacturer that may be the source of the drug. The FDA statement is available at www.fda.gov/bbs/topics/NEWS/2003/NEW00967.html (accessed Nov. 5, 2003).

New Study Examines Sulfonamide Nonantibiotics

Is it safe to use a sulfonamide-based nonantibiotic in patients who have an allergy to sulfonamide antibiotics? A large retrospective cohort study from the United Kingdom looked at this issue and suggests that penicillin allergy is as likely or more likely to be associated with nonantibiotic sulfonamide reactions as a history of sulfonamide antibiotics allergy. Nearly 10% of patients with a history of allergy to a sulfonamide antibiotic had an allergic reaction after receiving a sulfonamide nonantibiotic compared to only 1.6% of patients who have no history of allergy to sulfonamide antibiotics. Patients who had a history of hypersensitivity to penicillin were most likely to have an allergic reaction to a sulfonamide nonantibiotic (adjusted odds ratio, 0.6; 95% CI, 0.5-0.8). Strom and associates conclude that there is a relationship between hypersensitivity to sulfonamide antibiotics and subsequent allergic reaction with sulfonamide nonantibiotics such as thiazide diuretics; however, this risk seems to be due to a predisposition to allergic reactions rather than a cross reactivity between sulfonamide-based drugs (*N Engl J Med*. 2003;349:1628-1635).

FDA Actions

Novavax Inc has received FDA approval to market a new topical estrogen therapy for the treatment of hot flashes in menopausal women. The white lotion is an emulsion of estradiol topical that women apply only to their legs, thighs or calves on a daily basis. The topical preparation is absorbed through the skin allowing estradiol to bypass enterohepatic circulation. Estradiol topical emulsion will be marketed under the trade name Estrasorb.

The FDA has issued an approvable letter to Cephalon, Inc. regarding expanded indications for modafinil (Provigil). The drug is currently approved for excessive daytime sleepiness associated with narcolepsy. The letter states that modafinil is approvable for improving wakefulness in patients with excessive sleepiness associated with shiftwork and in patients with obstructive sleep apnea/hypopnea syndrome. Cephalon had also sought approval for other causes of excessive sleepiness including jet lag; however, the FDA panel could not come to agreement on that recommendation. ■