Providing Evidence-based Clinical Information for 27 Years

INFECTIOUS DISEASE ALERT®

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosures:

Infectious Disease Alert's Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau for Merck, Pfizer, Wyeth, Ortho-McNeil (J&J), Schering-Plough, and Cubist, does research for the National Institute of Health, and is an advisory board member for Schering-Plough, Ortho-McNeil (J&J), and Cepheid.
Peer reviewer Connie Price, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.
Updates author Carol A. Kemper, MD, FACP, does research for GSK Pharmaceuticals, Abbott Laboratories, and Merck.

Distinguishing Lyme from Septic Arthritis in Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine; Chief Academic Officer, Baystate Medical Center, Springfield, MA

Dr. Jenson is a speaker for Merck.

Synopsis: *A retrospective review of 179 cases of acute monoarticular arthritis in children revealed that the clinical similarities between Lyme arthritis, suppurative arthritis, and other causes of arthritis do not permit reliable discrimination by the clinician using clinical or laboratory criteria.*

Source: Thompson A, et al. Acute pediatric monoarticular arthritis: Distinguishing lyme arthritis from other etiologies. *Pediatrics*. 2009;123:959-965.

A RETROSPECTIVE CROSS-SECTIONAL REVIEW WAS CONDUCTED IN CHILdren £ 18 years of age presenting with acute monoarticular arthritis who underwent arthrocentesis at Boston Children's Hospital emergency department between December 2000 and September 2006. A total of 179 eligible patients were studied, including 46 (26%) with suppurative arthritis, 55 (31%) with lyme arthritis, and 78 (43%) with another etiology. The organisms identified by culture as causing suppurative arthritis included *Staphylococcus aureus* (31), group A Streptococcus (4), *Streptococcus pneumoniae* (2), *Neisseria gonorrhea* (1), *Neisseria meningitidis* (1), Enterococcus (1), Salmonella (1), group B Streptococcus (1), *Haemophilus influenzae* (1), *Haemophilus parainfluenzae* (1), and Actinomyces (1). The majority of patients with lyme disease (84%) did not recall tick exposure.

Patients with lyme arthritis were more likely to have knee involvement ($p < 0.001$), a history of a tick bite ($p = 0.02$), and less likely to have a history of fever ($p < 0.001$) or fever (‡38.0ºC) at presentation ($p < 0.01$). Patients with lyme arthritis also had lower erythrocyte sedimentation levels ($p < 0.01$), C-reactive protein levels ($p < 0.001$), joint

VOLUME 28 • NUMBER 8 • MAY 2009 • PAGES 49-60

NOW AVAILABLE ONLINE
www.ahcmedia.com

white blood cell counts ($p < 0.03$), and joint neutrophil percentages ($p < 0.001$). Multivariate analysis showed that knee involvement was a positive predictor (odds ratio: 12 [95% CI: 2.8-47]) of lyme arthritis and that history of fever (odds ratio: 0.22 [95% CI: 0.051-0.91]) and elevated C-reactive protein level (odds ratio: 0.79 [95% CI: 0.68-0.93]) were negative predictors of lyme arthritis. Amodel with these three factors had a Hosmer-Lemeshow value of 0.78, sensitivity of 88%, and specificity of 82%.

■ COMMENTARY

Distinguishing acute monoarticular suppurative arthritis from lyme disease in endemic areas is a common clinical problem. There are over 60,000 new cases of lyme disease each year, with over 60% of these occurring among children 5-14 years of age. lyme arthritis is a late manifestation of lyme disease. As expected, 51% of cases of lyme arthritis presented outside the tick season of June through October.

Lyme arthritis is characterized by a wide range of laboratory abnormalities, including peripheral white blood cell counts, erythrocyte sedimentation rate levels, C-reactive protein levels, and joint white blood cell counts. The wide range of these values observed with lyme arthritis precludes using these laboratory tests to distinguish lyme arthritis from suppurative and other forms of arthritis.

The clinical differential of suppurative arthritis from lyme arthritis continues to be difficult. The early diagnosis of suppurative arthritis is important to facilitate early drainage and prevent articular damage. The model from these data is not sufficiently powerful to permit use to distinguish lyme arthritis from suppurative arthritis in individual patients; with a sensitivity of 88% and specific of 82%, this model would only acc rately identify 41 of 46 patients with suppurative arthritis. Clinicians in lyme-endemic areas need to consider both lyme disease and suppurative arthritis as potential etiologies in children presenting with acute monoarticular arthritis, regardless of the time of year at presentation. ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Russ Underwood
DIRECTOR of MARKETING : Schandale Kornegay
MANAGING EDITOR: Leslie Hamlin
GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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

Back issues: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@ahcmedia.com
E-Mail Address: jennifer.corbett@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
Add $17.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *36 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the infectious disease specialist. It is in effect for 36 months from the date of the publication.

Questions & Comments

Leslie Hamlin,
Managing Editor, at (404) 262-5416, or
e-mail to leslie.hamlin@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

AHC Media LLC

Beneficial Effects of Protein Synthesis-inhibiting Antibiotics in Bacterial Pneumonia

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University, School of Medicine

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *Mice infected with influenza virus and superinfected with* S. pneumoniae *were treated with ampicillin, clindamycin, or azithromycin. Survival was lowest with ampicillin (56%) and best with either clindamycin alone (82%), ampicillin plus clindamycin (80%), or azithromycin (92%).*

Source: Karlstrom A, et al. Treatment with protein synthesis inhibitors improves outcomes of secondary bacterial pneumonia after influenza. *J Infect Dis*. 2009;199:311-319.

BALB/CJ MICE INFECTED WITH INFLUENZA VIRUS WERE superinfected with an antibiotic-susceptible strain of *S. pneumoniae* and treated intraperitoneally with ampicillin alone, clindamycin alone, ampicillin plus clindamycin, or azithromycin. Survival was assessed, histopathologic examination of the lungs was performed at necropsy, and TNF-alpha levels expressed by macrophages were measured. Improved survival in mice treated with either clindamycin or azithromycin appeared to be mediated by decreased inflammation reflected by lower levels of

inflammatory cells and pro-inflammatory cytokines in the lungs and less severe histopathologic findings.

■ **COMMENTARY:**

While covering the Pediatric ICU on ID consult service recently at our county hospital, the PICU team presented to me the case of a previously healthy 13-year-old girl who developed a severe multilobar pneumonia due to methicillin-resistant *S. aureus* likely following influenza. Fortunately, she survived despite requiring mechanical ventilation with a high-frequency ventilator and the use of vasopressors. Despite the availability of potent antibiotics, pneumonia remains a major cause of death in both the developed and the developing world, and optimum antimicrobial therapy for most patients with bacterial pneumonia remains uncertain. While this paper describes in vivo experimental data, the results are intriguing from a mechanistic standpoint, and dovetail with some preliminary observations that suggest that antibiotics (such as the macrolides, linezolid, clindamycin, the tetracyclines, and rifampin) have potentially beneficial effects independent of their antimicrobial activity.

The possible clinical benefit of adding either clindamycin or linezolid to cell wall-active antibiotics in the treatment of toxic shock syndrome due to either Group A streptococcus or *S. aureus* is widely accepted. This beneficial effect has been attributed to the effects of these antibiotics on inhibiting bacterial toxin production. However, an intriguing paper was recently published which described data from a retrospective study of patients with severe sepsis due to pneumonia. In this study, macrolide use was associated with decreased mortality in these patients despite the fact that the patients were infected with macrolide-resistant pathogens, strongly supporting an anti-inflammatory effect of these agents independent of antimicrobial activity.[1] Another experimental study supporting the direct anti-inflammatory effect of a macrolide antibiotic utilized a rat model of *E. coli* sepsis. Despite having no antimicrobial activity vs. the challenge strain of *E. coli* used, clarithromycin reduced lethality of infection vs. control and reduced plasma levels of endotoxin and TNF-alpha.[2]

While the above data are fascinating and almost certainly have clinical relevance, caution needs to be exercised by clinicians. These bacteriostatic/protein synthesis-inhibiting antimicrobials should be used with discernment. It is important that the hypotheses generated by studies like these be tested in prospective, randomized, controlled trials. One of my "pet peeves" is the widespread addition of rifampin to cell wall-active antibiotics in the treatment of *S. aureus* infections despite lack of well-controlled clinical trial data to support this practice. This has never made sense to me, at least in patients with staphylococcal endocarditis, since rifampin is known to cause in vitro antagonism of the bactericidal activity of cell wall-active agents and we know that bactericidal activity is important for cure of endocarditis due to the relative impermeability to neutrophils of the vegetation's fibrin/platelet matrix. A recent retrospective study closely examined this practice at one institution and found that addition of rifampin resulted in delayed clearance of bacteremia (5.2 vs. 2.1 days), frequent development of rifampin resistance (in 56% of cases), reduced survival (79% vs. 95%), hepatotoxicity, and serious drug-drug interactions.[3] Until better data are available, the use of adjunctive macrolides, linezolid, clindamycin, and rifampin should also be used with caution in patients with known or suspected bacterial meningitis since antagonism could potentially have deleterious consequences due to the impaired opsonization which is present in the cerebrospinal fluid. ■

References:

1. Restrepo MI, et al. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J*. 2009;33:153-159.
2. Cirioni O, et al. Efficacy of the combination of tachyplesin III and clarithromycin in rat models of *Escherichia coli* sepsis. *Antimicrob Agents Chemother*. 2008;52:4351-4355.
3. Riedel DJ, et al. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2008;52:2463-2467.

Lumbar Puncture in HIV-infected Patients with Syphilis

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In this study, 202 patients with HIV infection and syphilis and no neurologic symptoms were studied, and 61 underwent either immediate or delayed lumbar puncture (LP). Using a combination of rapid plasma reagin (RPR) titer ‡32 and CD4+ lymphocyte count £ 350 cells/uL or serologic response to treatment improved the ability to identify asymptomatic neurosyphilis (ANS).*

Source: Ghanem KG, et al. Lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms. *Clin Infect Dis*. 2009;48:816-821.

Eligible subjects in this study included all patients with concurrent HIV infection and syphilis in a prospective cohort who had no neurologic symptoms at time of lumbar puncture. Retrospective stratification was applied as follows: 1) LP in patients with late latent syphilis or syphilis of unknown duration regardless of CD4 count or RPR titer, 2) LP if CD4 £ 350 cells/uL and/or RPR titer ‡1:32 regardless of syphilis stage, and 3) LP in the context of serologic nonresponse to syphilis therapy (lack of ‡ 4-fold decrease in RPR titer ‡ 12 months after receipt of appropriate treatment or ‡4-fold increase in RPR titer ‡30 days after receipt of therapy).

The results showed that 202 patients with syphilis and HIV did not have neurologic symptoms. Immediate LP was performed in 48 patients, and 10 cases (22%) were found to have ANS using standard CSF analysis criteria (any of: WBC > 10/uL, protein > 50 mg/dL, CSF VDRL reactive). With use of criterion 1, two (14%) of 10 cases of ANS would have been missed. With use of criterion 2, no cases of ANS would have been missed but would have required an LP be performed in 88% of all patients. Performance of LP in 13 patients meeting criterion 3 (serologic nonresponse to treatment) yielded four cases (31%) of ANS.

■ COMMENTARY

From an historical perspective, following the advent of the use of penicillin for treatment of syphilis following World War II, the rates of neurologic complications of syphilis declined dramatically and resulted in the abandonment of routine LP for staging of patients with syphilis in the absence of neurologic symptoms. By the 1980s, a number of case reports of neurosyphilis developing in HIV-infected patients, often following treatment with approved antibiotic regimens, including standard doses and schedules of penicillin, prompted the need to revisit the issue of LP for these co-infected patients. Obviously, patients with neurologic symptoms and syphilis need to undergo LP, but controversy exists regarding the need for LP in patients without neurologic symptoms.

While this study has many limitations, including small sample size of patients actually undergoing LP and the retrospective application of stratification criteria, the data are useful. Using the criteria of CD4 £ 350/uL, RPR titer ‡1:32, or serologic nonresponse to treatment results in the need to perform LP in 70%-90% of HIV/syphilis co-infected patients but avoids missing significant numbers of patients with ANS. Unfortunately, no "gold standard" exists for the diagnosis of asymptomatic neurosyphilis. It should be kept in mind that while reactive CSF VDRL is specific for the diagnosis of neurosyphilis, this test lacks sensitivity and has been suggested to be negative in 50% of patients with neurosyphilis. While CSF pleocytosis is sensitive for the diagnosis of neurosyphilis, this lymphocytic pleocytosis lacks specificity since this finding is commonly present in HIV-infected patients without syphilis, particularly in patients not receiving antiretroviral therapy.

We have been following these guidelines in our HIV clinic for several years and perform LPs in our clinic routinely. In individuals found to have evidence of ANS, we generally admit these patients to our hospital and administer 10-14 days of intravenous penicillin G. ■

Antibiotics and Hemolytic Uremic Syndrome

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *Gnotobiotic piglets were challenged orally with a Shiga toxin-producing strain of* E. coli *O157:H7, then on day three left untreated, treated with ciprofloxacin, or treated it with azithromycin. After treatment with ciprofloxacin, infected piglets had diarrhea and severe neurologic symptoms associated with Stx2 and the presence of petechial cerebellar hemorrhage. Azithromycin-treated animals survived and had little or no brain hemorrhage.*

Source: Zhang Q, et al. Gnotobiotic piglet infection model for evaluating the safe use of antibiotics against *Escherichia coli* O157:H7 infection. *J Infect Dis*. 2009;199:486-493.

In vitro treatment of clinical isolates and isogenic strains of *E. coli* O157:H7 with ciprofloxacin increased the production of Stx2 (as measured by ELISA) via phage induction but did not increase the production of Stx1. Azithromycin caused no significant increase in toxin production in vitro. Gnotobiotic piglets were orally challenged with a Stx-producing strain of *E. coli* O157:H7 which had originally been isolated from an outbreak of disease associated with HUS. After treatment with ciprofloxacin, infected piglets had diarrhea and severe fatal neurologic symptoms. At necropsy, characteristic petechial hemorrhages were seen in the cerebellum and were more

severe than that seen in control animals. Azithromycin-treated piglets survived infection and had little or no brain hemorrhage seen.

■ COMMENTARY

Shiga toxin (Stx)-producing *E. coli* (especially O157:H7) causes bloody diarrhea, and some infections are complicated by hemolytic uremic syndrome (HUS). Case-control studies suggest that administration of antimicrobials to patients with Stx-producing strains of *E. coli* is a major risk factor for development of HUS.[1,2] In the commonly referenced CDC study,[1] antimicrobial administration within three days of onset of diarrhea, especially in children < 13 years old, was the strongest risk factor (relative risk 11.5) for development of HUS. In these pediatric patients, 5 of 6 patients who developed HUS who were treated with antimicrobials received trimethoprim/sulfamethoxazole (TMP/SMZ). In the Seattle study,[2] antibiotic administration was associated with a relative risk of 14.3 for development of HUS. The specific relative risk associated with TMP/SMZ was 17.7 and was 13.4 for b-lactam antibiotics. In addition to the case-control data implicating antibiotic administration with the development of HUS, some elegant basic science has been done to explain the mechanism for induction of Shiga toxin production by antibiotics in *E. coli*.[3,4] In Shiga toxin-producing strains, it appears that toxin synthesis is regulated through induction of an integrated bacteriophage, which encodes the toxin gene. Phage production is linked to the bacterial SOS response to DNA damage. SOS-inducing antimicrobials, particularly fluoroquinolones, trimethoprim, and furazolidone were shown to induce toxin gene expression, particularly of Stx2.[4]

These in vitro and in vivo studies nicely explain the observed clinical association of antibiotic administration with induction of HUS. From a practical perspective, it is still probably prudent to withhold antibiotics in patients of all ages who present with the syndrome of afebrile bloody diarrhea (commonly seen with enterocolitis due to Stx-producing *E. coli*); but, realistically, many physicians will still treat such patients with antibiotics. Hopefully, the word will get out that if they decide to use antibiotics in such cases, they should choose a macrolide rather than ciprofloxacin, trimethoprim/sulfamethoxazole, or a b-lactam agent since the former appears much less likely to trigger HUS. Another reason to prefer azithromycin to ciprofloxacin for the empiric treatment of presumed bacterial enterocolitis is that the most common cause of febrile bloody diarrhea, Campylobacter, is now commonly resistant to ciprofloxacin. ■

References

1. Slutsker L, et al. A nationwide case-control study of *Escherichia coli* O157:H7 infection in the United States. *J Infect Dis*. 1998;177:962-966.
2. Wong CS, et al. The risk of hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med*. 2000;342:1930-1936.
3. Kimmitt PT, et al. Induction of type 2 shiga toxin synthesis in *Escherichia coli* O157 by 4-quinolones. *Lancet*. 1999;353:1588-1589.
4. Kimmitt PT, et al. Toxin gene expression by shiga toxin-producing *Escherichia coli*: The role of antibiotics and the bacterial SOS response. *Emerg Infect Dis*. 2000;6:458-465.

Updated Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *The U.S. Department of Health and Human Services (HHS) has updated their guidelines for the prevention and treatment of opportunistic infections (OIs) in HIV-infected adults and adolescents, effective March 24, 2009.*

Source: http://www.cdc.gov/mmwr/pdf/rr/rr58e324.pdf

THESE GUIDELINES WERE LAST UPDATED FOR ADULTS in 2002 and for adolescents in 2004. The document (available in pdf format through the link above) is a 209-page file containing 1,391 references which update current recommendations for the prophylaxis and treatment of HIV-related OIs. As with most guidelines published in recent years by professional societies, a well-qualified expert panel has thoroughly reviewed both new and old data and has developed a relatively comprehensive document which will be of use to physicians who treat complicated HIV patients. An attempt has been made to qualify recommendations with both the strength and quality of evidence supporting each recommendation. Obviously, it is not possible to summarize the entire document, but six major changes from previous

iterations of the OI guidelines stand out in the 24 March 24, 2009 guidelines:

- Emphasis is placed on the importance of antiretrovirals for the prevention and treatment of OIs, especially for those diseases in which specific antimicrobial treatment is minimally effective.[1]
- Guidance on the diagnosis and management of immune reconstitution/inflammatory syndrome (IRIS) complicating specific OIs is given.
- Recommendations on the use of interferon gamma release assays (IGRAs) for the diagnosis of latent tuberculosis infection (LTBI) are made.[2] (At this point IGRAs are considered to be more specific than tuberculin skin testing for the diagnosis of LTBI, especially in HIV patients who may have received BCG or have been exposed to other mycobacteria. However, they are no more sensitive than tuberculin skin testing, especially in HIV patients with more severe immunosuppression.)
- More specific recommendations are made concerning drug/drug interactions, particularly surrounding the use of rifamycins concomitantly with antiretroviral therapy.
- Detailed recommendations are made regarding the treatment of hepatitis B virus/HIV co-infected patients, including the recommendation to avoid HBV antiviral monotherapy with agents such as entecavir due to the risk of selecting M184V HIV reverse transcriptase substitutions.[3]
- A section on the bi-directional effects of malaria and HIV co-infection has been added, which is of great significance in the developing world where both of these infections are endemic.

Lastly, it was interesting to note that these latest guidelines contain a well-reasoned discussion regarding the controversies surrounding routine screening for HPV-related anal intraepithelial neoplasia in men who have sex with men.[4,5]

This latest update to the OI guidelines is an important document which will be of value to all physicians who treat HIV-infected patients. ■

References:

1. Zolopa A, et al. Immediate versus deferred ART in the setting of acute AIDS-related OI: final results of a randomized strategy trial, ACTG A5164. 15th CROI;2008; Boston, MA. Abstract 142.
2. Menzies D, et al. Meta-analysis: New tests for the diagnosis of latent tuberculosis infection: Areas of uncertainty and recommendations for research. *Ann Intern Med*. 2007;146:340-354.
3. Matthews GV, Dore GJ. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *AIDS*. 2007;21:777-778.
4. CDC. Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines. *MMWR*. 2006;55: (No. RR-11).
5. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. *Dermatol Ther*. 2005;18:67-76.

Treatment Options for Community-acquired UTIs Caused by Extended Spectrum b-Lactamase-producing *E. coli*

ABSTRACT & COMMENTARY

By Stefany Bowers, PharmD Candidate, Marisa Chun, PharmD Candidate, and Jessica C. Song, MA, PharmD

Stefany Bowers and Marisa Chun are PharmD Candidates at the University of the Pacific and Jessica Song is PharmD at the University of the Pacific

Stephany Bowers, Marisa Chun, and Jessica C. Song all report no financial relationships relevant to this field of study.

EXTENDED SPECTRUM B-LACTAMASE (ESBL)-PRODUCING *Escherichia coli* has emerged as an increasingly common cause of community-acquired urinary tract infections (UTIs). These isolates are frequently resistant to many standard oral treatments such as trimethoprim-sulfamethoxazole, fluoroquinolones, penicillins, and cephalosporins.[1]

ESBLs can be classified further into specific types of lactamases. Some of the most common examples include CTX-M, SHV, and TEM, CTX-M ESBL-producing isolates such as *E. coli*, have recently become a significant concern for many institutions worldwide. Isolates producing CTX-M ESBLs have been shown to originate from the community setting and are becoming progressively more prevalent globally, as demonstrated by published reports from Europe and Asia. A recent study done at the University of Hong Kong showed that a significant proportion of women in the community had ESBL-producing *E. coli*, mostly due to the

spread of CTX-M 14 b-lactamase. Optimizing the treatment of UTIs caused by ESBL-producing *E. coli* is a pressing concern, because without proper pharmacological therapy, more serious complications such as bacteremia or pyelonephritis may ensue.[2,3,4]

In recent years, the lack of new antibiotics has resulted in the medical community taking a closer look at older antibiotics such as fosfomycin, novel antibiotic combinations such as cefdinir + amoxicillin-clavulanate, and newer carbapenems such as ertapenem for the treatment of resistant isolates such as ESBL-producing *E. coli*. Various studies have indicated that the use of these medications is an effective treatment for UTIs caused by ESBL-producing *E. coli*. This article takes a more in-depth look at the spectrum of activity and pharmacological and pharmacokinetic properties of the previously mentioned drugs and their roles as therapeutic options for patients with community-acquired UTIs.[1,3,5]

Spectrum of Activity and Pharmacological & Pharmacokinteic Properties of Fosfomycin

Fosfomycin, a bactericidal phosphonic acid derivative, is a broad-spectrum antibiotic used to treat both gram-positive and gram-negative bacterial infections. Specifically, it inhibits uridine diphosphate GlcNAc enolpyruvate transferase, thereby inhibiting the first step in the synthesis of peptidoglycan. This action disrupts cell-wall synthesis of bacteria and induces cell death.[2]

Fosfomycin is usually given orally as a soluble salt form known as fosfomycin tromethamine and is available in the United States under the brand name of Monurol. This particular salt formulation of fosfomycin increases the bioavailability of drug in the body. It is approved as safe and effective for adult women as a 3-gram single dose administered orally. Its most common indication is for the treatment of uncomplicated UTIs caused by either *E. coli* or *Enterococcus faecalis*. In recent studies, fosfomycin has been proven to be effective against ESBL-producing *E. coli*.[6]

In a study conducted by Falagas et al, fosfomycin showed impressive antimicrobial activity against gram-positive species such as *Staphylococcus epidermis*, *Streptococcus pneumoniae*, *S. aureus*, and *E. faecalis*. The broad-spectrum activity of fosfomycin also allows it to be effective against gram-negative bacteria such as *E. coli*, *Klebsiella pneumoniae*, Enterobacter species, *Serratia marcescens*, *Salmonella typhi*, and Proteus species.[2]

Fosfomycin tromethamine is administered orally and is rapidly absorbed and converted to the free acid known as fosfomycin. It has a relatively long elimination half-life around 5.7 ± 2.8 hours and a low molecular weight of 138.059. These characteristics give it the ability to easily penetrate various tissues such as the bladder wall, prostate, kidneys, and seminal vesicles, and allows it to cross the placenta. While an individual is fasting, the oral bioavailability is 37%. Under fed conditions, the bioavailability of fosfomycin is reduced to 30%. After administration of a single 3-gram oral dose on an empty stomach, maximum serum concentrations are achieved within two hours. Following administration of the same dose after a high-fat meal, maximum serum concentrations are achieved within four hours. Fosfomycin does not undergo extensive metabolism and is mainly excreted through the urine and feces.[2,6]

Data concerning drug interactions with fosfomycin are limited. Cimetidine, which is a potent cytochrome p450 inhibitor, has no effect on fosfomycin. Metoclopramide can reduce the bioavailability of fosfomycin.[2]

Fosfomycin is associated with a low rate of adverse events. A majority of the adverse events are gastrointestinal (diarrhea, 9%) and dermal in nature and do not usually necessitate discontinuation of treatment. Less common adverse effects include severe nausea, neutropenia, and eosinophil count changes.[2]

Spectrum of Activity and Pharmacological & Pharmacokinetic Properties of Cefdinir + Amoxicillin-Clavulanate

Cefdinir is an oral extended-spectrum, semisynthetic cephalosporin. It is generally classified as a third-generation cephalosporin with activity similar to cefotaxime and cefixime. In a comparison to cefixime, cefpodoxime, cefaclor, and cephalexin in vitro, cefdinir demonstrated superior activity against oxacillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci, *Streptococcus pneumoniae*, *S. pyogenes*, *Escherichia coli*, and *Moraxella catarrhalis*. Cefdinir is approved for treatment of skin infections, a variety of upper respiratory tract infections, and community-acquired pneumonia in both adult and pediatric patients. Formulations include capsules and a strawberry-flavored suspension. Uncomplicated UTIs due to non-ESBL strains treated with cefdinir resulted in a 91.3% clinical cure rate in a study conducted by Prakash et al. Furthermore, this

recent study upheld previous findings that no ESBL-producing *E. coli* isolates showed susceptibility to cefdinir monotherapy.[4,7]

Following oral administration of the capsules or oral suspension, maximal plasma concentrations occur 2-4 hours post dose. The estimated bioavailability of cefdinir capsules is 21% following administration of a 300 mg dose and 16% following administration of a 600 mg dose. Estimated absolute bioavailability of cefdinir oral suspension is 25%. Cefdinir has a half-life of about 1.7 hours, is 60%-70% protein bound, and excretion occurs primarily via renal excretion. Dosage adjustments are recommended in patients with CrCL < 30 mL/min or undergoing hemodialysis.[7]

Clavulanic acid binds to and inhibits b-lactamases, exhibiting weak antimicrobial activity. Clavulanic acid reestablishes amoxicillin's activity against b-lactamase-producing bacteria, making the combination very effective in inhibiting ESBLs in vitro. Amoxicillin-clavulanate is commonly used to treat infections such as acute otitis media, lower respiratory tract infection, sinusitis, skin/skin-structure infections, and UTIs. Although amoxicillin-clavulanate as a monotherapy has shown activity against ESBL-producing *E. coli*, a high degree of resistance to both ESBL-producing and -nonproducing *E. coli* isolates from urine samples have been reported in some areas.[4,8]

Amoxicillin-clavulanate is administered orally as tablets, chewable tablets, extended-release tablets, and oral suspension. Approximately 74%-92% of a dose of amoxicillin is absorbed. Peak serum levels of both amoxicillin and clavulanic acid occur within 1-2.5 hours following an oral dose. It has a half-life of about one hour and displays 25% protein binding. Amoxicillin and its metabolites are excreted into the urine primarily via tubular secretion and glomerular filtration. Both cefdinir and amoxicillin-clavulanate achieve high concentrations in the urine.[8]

Evidence of Cefdinir + Amoxicillin-Clavulanate, Fosfomycin, and Amoxicillin-Clavulanate as Treatment Options for Community-acquired ESBL-producing *E. coli* UTI

A recent case-control study (Spain) assessed different treatment options for cystitis caused by susceptible ESBL-producing *E. coli* isolates. Patients (n = 37) treated with amoxicillin-clavulanate potassium (500 mg/125 mg every 8 hours, for 5-7 days) achieved cure rates of 84%. In this in vitro study, 29% of the isolates showed resistance to amoxicillin-clavulanate, and cure rates dropped below 90% in those with MICs > 8 mcg/mL. In addition, patients (n = 28) treated with fosfomycin (3 g single dose) achieved cure rates of 93%.[1] The estimated costs of generic amoxicillin-clavulanate and fosfomycin are subject to change, depending on vendor sources, but approach $7.35-$10.29 (5-7 day course) and $37, respectively, in San Jose, CA.

A novel combination of antibiotics that appears to be a promising treatment for ESBL-producing *E. coli* UTIs was recently highlighted in an ESBL isolate susceptibility study by Prakash et al. The investigators found that the addition of a fixed concentration of amoxicillin-clavulanate to cefdinir ($9.35-$13.09/course for combination) yielded a susceptibility rate of 89.1%, based upon an MIC < 1 mcg/mL of cefdinir in the presence of the b-lactamase inhibitor combination. The authors reasoned that the clavulanate component of the amoxicillin-clavulanate served to inhibit the ESBL, resulting in effective cefdinir activity against most isolates.[4] This study provides evidence that the co-administration of cefdinir with amoxicillin-clavulanate is not only theoretically promising, but may be a potential treatment for ESBL-producing *E. coli* UTIs due to its high activity and absence of resistance in isolate studies. However, clinical trials will need to be conducted to confirm the clinical utility of this novel antibiotic combination.

Spectrum of Activity and Pharmacological & Pharmacokinetic Properties of Ertapenem

ESBLs cleave the b-lactam ring; carbapenems resist this hydrolysis and, therefore, remain active. Three carbapenems are currently FDA approved for use in the treatment of UTIs: imipenem/cilastatin, doripenem, and ertapenem. Ertapenem, the only carbapenem that can be administered once daily, has a comparable spectrum of activity to the other carbapenems, with activity against gram-positive, gram-negative, and anaerobic organisms. However, unlike the other carbapenems, ertapenem lacks activity against *Pseudomonas aeruginosa* and Acinetobacter spp. Ertapenem exhibits excellent activity against Enterobacteriaceae and, therefore, represents a drug of interest in the treatment of ESBL-producing, gram-negative bacterial infections. Ertapenem is eliminated mainly in urine, where it reaches high concentrations.[9,10,11]

Ertapenem is administered parenterally via intravenous (IV) or intramuscular (IM) routes. Its half-life of about 4.5 hours is prolonged due to extensive

protein binding (95%), allowing for once-daily dosing, while retaining a similar safety profile to other carbapenems. Patients with creatinine clearances below 30 mL/min should receive a 50% lower dose, and this agent should be avoided in patients undergoing peritoneal dialysis.[11]

Evidence of Ertapenem as a Treatment Option for Community-acquired ESBL-producing *E. coli* UTI

Numerous recent studies have been done to test the susceptibility to ertapenem of ESBL-producing Enterobacteriaceae isolated from urine samples in various health care settings. These studies invariably showed that ertapenem provides the highest level of activity against such strains in comparison to various other antibiotics tested. Ertapenem was found to be active against 100% of ESBL-producing *E coli*, including CTX-M, SHV, and TEM isolates.[12,13] Furthermore, ESBL-producing *E. coli* also have shown little to no resistance to ertapenem in several urine isolates during in vitro studies thus far. This provides another desirable advantage over other antibiotic choices, as well as other carbapenems, such as imipenem, which showed a slight level of resistance to ESBL-producing isolates in a study by Taneja et al (8.2%).[12,13,14]

In light of its important antibiotic potency, once-daily dosing, advantageous pricing, safety profile, and lack of resistance shown in vitro, ertapenem may represent a useful therapeutic alternative for UTIs caused by ESBL-producing *E coli*. However, the acquisition cost of this agent (San Jose, CA) approaches $268.85-$376.39 for a five-seven day treatment course.

Conclusion

As community onset CTX-M ESBL-producing *E. coli* UTIs become more prevalent worldwide, more effective therapeutic options are needed. It is important for laboratories to test for ESBL producers from outpatient urine cultures to allow for culture-directed therapy and prevent progression to more serious infections. Several studies of ESBL isolate susceptibility show that fosfomycin, cefdinir + amoxicillin-clavulanate, and ertapenem yield high activity against most isolates. Future investigations should further explore larger patient populations to determine the utility of these treatment options. ■

References

1. Rodriguez-Bano J, et al. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med*. 2008;168:1897-1902.
2. Falagas ME, et al. Fosfomycin: Use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis*. 2008;46:1069-1077.
3. Ho PL, et al. Community emergence of CTX-M type extended-spectrum beta-lactamase among urinary *Escherichia coli* from women. *J Antimicrob Chemother*. 2007;60:140-144.
4. Prakash V, et al. Oral and parenteral therapeutic options for outpatient urinary infections caused by enterobacteriaceae producing CTX-M extended-spectrum beta-lactamases. *Antimicrob Agents Chemother*. 2009;53:1278-1280.
5. Calbo E, et al. Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum beta-lactamases. *J Antimicrob Chemother*. 2006;57:780-783.
6. Fosfomycin tromethamine (Monurol) prescribing information. St. Louis, MO: Forest Pharmaceuticals, Inc.; 1997 December.
7. Cefdinir capsules and powder for oral suspension (Omnicef) prescribing information. North Chicago, IL: Abbott Laboratories; 2007 July.
8. Amoxicillin-Clavulanate (Augmentin) prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2006 December.
9. Berg ML, et al. Efficacy of ertapenem for consolidation therapy of extended-spectrum beta-lactamase-producing gram-negative infections: A case series report. *Ann Pharmacother*. 2008;42:207-212.
10. Lye DC, et al. Ertapenem for treatment of extended-spectrum beta-lactamase-producing and multidrug-resistant gram-negative bacteraemia. *Ann Acad Med Singapore*. 2008;37:831-834.
11. Ertapenem (Invanz) prescribing information. Whitehouse Station, NJ: Merck & Co., Inc.; 2008 February.
12. Alhambra A, et al. In vitro susceptibility of recent antibiotic-resistant urinary pathogens to ertapenem and 12 other antibiotics. *J Antimicrob Chemother*. 2004;53:1090-1094.
13. Tamayo J, et al. Activity of ertapenem and other antimicrobials against ESBL-producing enterobacteria isolated from urine in patients from Madrid. *Rev Esp Quimioter*. 2007;20:334-338.
14. Taneja N, et al. Occurrence of ESBL & Amp-C beta-lactamases and susceptibility to newer antimicrobial agents in complicated UTI. *Indian J Med Res*. 2008; 127:85-88.

CME Questions

22. Which of the following are independent risk factors increasing the likelihood of arthritis being due to lyme disease rather than being septic in children?
a. Knee involvement
b. Higher CRP
c. History of fever
d. Multiple joint involvement

23. Which of the following are the optimal set of criteria for determining which HIV-infected patients with a positive RPR should undergo lumbar puncture?
a. All with late latent syphilis or syphilis of unknown duration regardless of RPR titer or CD4 count.
b. CD4 < 350 and/or RPR > 1:32 regardless of syphilis stage.
c. Inadequate serological response to therapy (< 4-fold decrease in RPR 12 months after therapy) and RPR >1:32.
d. Only in the presence of neurological signs and symptoms.

24. Which of the following is correct?
a. Fosfomycin is a nitrofurantoin derivative active against many ESBL-producing *Escherichia coli*.
b. A component of Augmentin (amoxicillin + clavualanic acid) inhibits extended-spectrum b-lactamase activity.
c. Cefdinir used alone inhibits 100% of ESBL-producing *Escherichia coli*.
d. Ertapenem is rapidly hydrolyzed byextended spectrum beta lactamase from *E. coli*.

Answers: 22. (a); 23. (c); 24. (b)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Acyclovir Shortage

UPDATES

By Carol A. Kemper, MD, FACP

Pathogens and Pet Therapy

Source: Lefebvre SL, Weese JS. Contamination of pet therapy dogs with MRSA and *Clostridium. difficile* (letter). *J Hosp Infect*. 2009 March 28. [Epub ahead of print].

Much is being written about the transmission of MRSA between animals and humans. These investigators explored this problem from another angle, examining colonization of pet therapy dogs with MRSA, VRE, and *C. difficile* during visits to acute and long-term care facilities.

Forepaw and hand samples were obtained from 26 pet-therapy dogs and their handlers before and after each visit. Twelve pairs had visited acute--care facilities and 14 had visited long-term care facilities. One investigator, who cleansed her hands with alcohol before examining each dog, sampled colonization of haircoats by petting each dog from head to tail for one minute after each visit, and then cultured her hands.

None of the pathogens were identified on the paws or hands of the teams before deployment. During visits to the hospital, however, one dog acquired C. difficile on its paws. PCR studies determined this organism was the epidemic strain NAP1/ribotype 027, and carried genes for all three toxins, including binary toxin CDT. This animal had "shook paws" with multiple patients. MRSA was detected on the investigator's hands after petting a pug that had visited a long-term care facility (USA 100). The pug had been placed on the beds of multiple patients and was kissed on the head by two patients. No VRE was identified on any dog or handler.

This small survey demonstrates how readily these organisms can be acquired, even with simple contact with patients' hands, beds, and the floor, and demonstrates the potential for transmission of these organisms between patients and to handlers during pet-therapy visits. The patients these pets visited presumably had unrecognized colonization with these pathogens, as pet-therapy pets are not allowed into contact isolation rooms. This survey also demonstrates how readily visiting family members might acquire these organisms.

Of note, only half the handlers were observed to cleanse their hands between patient rooms. Infection control personnel may wish to consider these data when drafting pet therapy protocols.

Chimps Vulnerable to Human Flu

Source: ProMED-mail post, April 2, 2009; http://www.promedmail.org

Differing strains of influenza are generally species-specific, such as canine influenza causing infection in dogs, although human influenza B has been known to colonize and infect other mammals, such as harbor seals. Chimpanzees and gorillas share much of their DNA in common with humans and, as such, are vulnerable to many human respiratory pathogens, including influenza.

This brief alert describes an outbreak of flu-like illness in a Congolese primate sanctuary just outside of Kinshasa, suspicious for human Influenza. Kinshsasa had just experienced a surge in flu cases in February. At least 10 of 60 Bononos (pygmie chimpanzees) were hard hit with severe respiratory and flu-like symptoms, and four have died. The sanctuary receives 30,000 visitors per year, many of whom are school-aged children. Animal handlers and researchers are now wearing face masks in hopes of limiting spread of this respiratory illness. This brief alert shows how quickly certain human illnesses can threaten vulnerable wildlife.

An Eel on the Loose

Source: Lin CY, et al. Esophageal perforation, mediastinitis, and retropharyngeal abscess after eel intrusion. *Pediatr Infect Dis J*. 2009 March 23. [Epub ahead of print].

Stories seldom get more bizarre that that of Steve Irwin's death from cardiac laceration from a ray tail, but this one does.

A two-year old was standing next to the kitchen table, looking at some eels brought home for dinner, when one of the eels jumped into her mouth and down her esophagus by about 15 cm. The eel was quickly retrieved by her aunt and measured about 47 cm. Although the aunt probably prevented acute respiratory arrest, eels are covered by small teeth and scales, which can lodge in tissues. What kind of bacterial pathogens would you anticipate from this kind of eel attack?

The next day the child was brought to the emergency room with fever and odynophagia, with apparent swelling of the anterior neck. Bulging of the posterior pharyngeal wall was observed on laryngoscopy, and widening of the mediastinum and retropharyngeal abscess was observed on chest CT. Emergent drainage was performed. She subsequently developed empyema, and an esophagram demonstrated a perforation with fistulization. Purulent drainage was observed in the esophagus about 10 cm below the incisors. Following an extensive hospitalization and five surgeries, she was finally discharged to home. Cultures yielded *Pseudomonas aeruginosa*. Various organisms have been described with Moray eel bits and other infections from aquatic animals, including Vibrio, pseudomonas, and aeromonas spp. For this reason, injuries occurring in saltwater should be treated with docycline plus anti-pseudomonal therapy.

Syphilis in Children: A Novel Means of Transmission

Source: Zhou P, et al. Nonvenereal transmission of syphilis in infancy by mouth-to-mouth transfer of pre-chewed food. *Sex Transm Dis*. 2009; 36:216-217.

SYPHILIS IN CHILDREN IN THE PRE-antibiotics era was not uncommon, but has since become so rare that it may readily escape detection. In the Bay Area last year alone, only one case of congenital syphilis infection was reported. Aside from congenital infection, syphilis in children may be acquired through breastfeeding, handling, and oral contact, such as kissing. In the developing world, without access to prepared baby food or food processors, pre-chewing food for infants is commonplace. Pre-chewed food has been associated with transmission of strep infection as well as HIV.

These authors describe two cases of acute, primary syphilis occurring in two infants, ages 10 months and 18 months. Both were accidentally infected by family members recently diagnosed with active syphilis. One infant presented with mucous patches of the tongue, palate, and cheeks, with marked lymphadenopathy. Both grandparents had been recently diagnosed with syphilis, and grandma had signs of secondary syphilis (grandpa admitted to extracurricular activities). The grandmother was in the habit of chewing the baby's food, even when she had oral lesions.

The second infant presented with acute pharyngitis and posterior auricular adenopathy. The mother had been diagnosed two days earlier with secondary syphilis, with oral mucous patches and lingual papules, although she had tested negative for syphilis during her pregnancy (dad also tested positive but wasn't talking). Mom was also in the habit of chewing baby's food.

Acutely, children with syphilis can present with pharyngitis, lymphadenopathy, and headache — pretty common, but not specific, symptoms in children. With the recent re-emergence of syphilis, especially in large urban areas, clinicians should be alert to the presence of children in the home, especially if the parents have oral involvement or secondary syphilis.

Pseudomonas, Sex, and Oozinator Hot Tubs

Source: Dulabon LM, et al. *Pseudomonas aeruginosa* acute prostatitis/urosepsis after sexual relations in a hot-tub. *J Clin Microbiol*. 2009 March 18. [epub ahead of print].

A PREVIOUSLY HEALTHY 38-YEAR-old man hospitalized with fever, dysuria, and suprapubic discomfort was diagnosed with a UTI and pseudomonas bacteremia. Examination demonstrated a boggy, tender prostate. CT confirmed significant soft tissue inflammation surrounding the prostate and seminal vesicles, consistent with acute prostatitis.

How does a healthy man, without a history of instrumentation, acquire pseudomonas prostatitis and bacteremia? He had just purchased an oozinator hut tub one week earlier, and disclosed having had sexual intercourse with his wife in the hot tub three times that week. Although oozinators require less chlorine, and the man stated that he had shock-disinfected the tub per the manufacturer's recommendations, he had filled the tub with water from a stream behind his home. Such systems are designed for potable city or well water, not non-potable water with presumably higher bacterial colony counts (one also wonders how high the phosphate level from fertilizers was). Analysis of the water from the hot tub yielded three morphotypes of pseudomonas, one of which was identical to the blood stream isolate by PFGE.

Pseudomonas has a broad growth temperature range of 4-42° Celcius, and while its growth is inhibited by higher concentrations of chlorine, the organism can flourish (with up to 10^4-10^6 colonies/mL) if chlorine levels fall below 1 ppm. Aeration can actually help dissipate the chlorine, one of the reasons some individuals favor oozinator tubs. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

FDA Warning: Pharmaceuticals in "Natural" Products

In this issue: Aspirin dose and cardioprotection; uncovering modafinil's abuse potential; proton-pump inhibitors and clopidogrel; FDA actions.

Finding pharmaceuticals in natural products

Some natural products are not so "natural" after all. The FDA has warned consumers for several months that a number of weight-loss products contain undeclared pharmaceutical ingredients. The newest products to join the list are Herbal Xenicol which contains cetilistat (a drug similar to orlistat that is not approved in this country), as well as Slimbionic and Xsvelten, both of which contain sibutramine (the prescription medication also known as Meridia®). The FDA's list of over-the-counter weight-loss agents that contain undeclared active pharmaceutical ingredients now includes 72 products. Some of the other undeclared pharmaceutical ingredients found in these products include fenproporex (an amphetamine derivative no longer available in this country), fluoxetine (Prozac®, an SSRI), furosemide (Lasix®, a loop diuretic), and even phenytoin (Dilantin®, an antiseizure medication). The FDA is seeking recalls on many of these products; however, some are available only online and previous recall efforts have proved inadequate.

In a related story, the FDA has announced a voluntary recall of Zencore Plus, the heavily marketed product for "natural male enhancement," which has been found to contain benzamidenafil, a new PDE5 inhibitor not yet available in this country. Benzamidenafil is similar in action to sildenafil (Viagra®) and tadalafil (Cialis®). PDE5 inhibitors are noted to have a drug interaction with nitrates, leading to potential life-threatening risk of sudden and profound drop in blood pressure. Zencore Plus is distributed by Hi-Tech Pharmaceuticals in Norcross, GA, and is widely sold in health food stores, by mail order, and by Internet sales.

Aspirin dose and cardioprotection

What is the best dose of aspirin for patients taking dual therapy with clopidogrel to prevent cardiovascular events? Investigators looked at 15,595 patients with cardiovascular disease or multiple risk factors in an observational analysis from a double-blind, placebo-controlled randomized trial. Patients were randomized to doses of aspirin less than 100 mg (75 mg or 81 mg), 100 mg, or greater than 100 mg (150 mg or 162 mg) with or without clopidogrel. The primary efficacy outcome was the composite of myocardial infarction, stroke, or cardiovascular death and the primary safety endpoint was severe life-threatening bleeding. In patients given aspirin alone, the hazard ratio for the efficacy and safety endpoints were the same regardless of aspirin dose. In patients given aspirin with clopidogrel, there was a statistically nonsignificant associated reduction in efficacy with aspirin doses over 100 mg, and a

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

significantly higher increase in harm (hazard ratio, 1.30 with clopidogrel plus aspirin greater than 100 mg). The authors conclude that daily doses of aspirin greater than 100 mg were not associated with benefit and may be associated with harm in patients also taking clopidogrel. Therefore, daily doses of aspirin 75-81 mg optimize efficacy and safety in patients requiring long-term aspirin therapy, especially in patients receiving dual antiplatelet therapy (*Ann Intern Med* 2009;150:379-386). This is especially important given the recent U.S. Preventive Services Task Force recommendation that encourages men ages 45-79 years to take aspirin preventively when the potential benefit of a reduction of myocardial infarction outweighs the potential harm of an increase in gastrointestinal hemorrhage. Women ages 55-79 years are also encouraged to use aspirin when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of increased gastrointestinal hemorrhage (*Ann Intern Med* 2009;150:396-404).

PPIs and clopidogrel

Increasing evidence suggests that proton pump inhibitors (PPIs) may attenuate the effect of clopidogrel on platelet aggregation. PPIs are often used prophylactically in patients with acute coronary syndrome (ACS), as patients on clopidogrel and aspirin may be at higher risk for GI bleeding. A new study from VA researchers was set up to determine if there are clinical implications from the interaction between PPIs and clopidogrel.

In a retrospective cohort study of 8205 patients with ACS taking clopidogrel, 63.9% were also prescribed a PPI at discharge, during follow-up, or both. Death or rehospitalization for ACS occurred in 20.8% of patients taking clopidogrel without a PPI and 29.8% patients taking clopidogrel with a PPI. Use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without a PPI (adjusted odds ratio, 1.25; 95% confidence interval, 1.11-1.41). Patients taking a combination of the two drugs were at higher risk for hospitalizations for ACS and revascularization procedures, but not for all-cause mortality. Patients taking a PPI without clopidogrel were not at higher risk for rehospitalization. The authors conclude that concomitant use of clopidogrel and a PPI after hospital discharge for ACS is associated with an increase risk of adverse outcomes, suggesting that PPIs may attenuate the benefits of clopidogrel, and that PPIs should only be used with clopidogrel if there is a clear indication, and not for routine prophylaxis (*JAMA* 2009;301:937-944).

Modafinil's abuse potential

Modafinil (Provigil®) is a wake-promoting medication used to treat narcolepsy and other sleep disorders. Recently, the drug has be used off-label to enhance cognition in psychiatric patients and even in healthy patients seeking a memory boost. Modafinil has been touted as having a low abuse potential; however, a new study questions that assumption. Most stimulant medications, such as methylphenidate and amphetamine, increase brain dopamine levels. Modafinil was thought to exert its effect in the brain on pathways other than dopamine, but now there is evidence that dopamine is involved. Researchers from the National Institute on Drug Abuse looked at 10 healthy male volunteers to measure the effects of modafinil at therapeutic dosing of 200 mg and 400 mg given orally. PET scans were used to measure the effect of modafinil on extracellular dopamine and dopamine transporters. Modafinil increased extracellular dopamine and showed evidence of occupancy of dopamine transporters, effects similar to drugs with the potential for abuse. The authors conclude that, considering the increasing use of modafinil, there needs to be heightened awareness for potential abuse of and dependence on modafinil in vulnerable populations (*JAMA* 2009;301:1148-1154).

FDA Actions

The FDA is requiring the manufacturers of metoclopramide (Reglan®) include a boxed warning on their labeling regarding the risk of long-term or high-dose use and tardive dyskinesia. Manufacturers will also be required to implement a risk evaluation and medication strategy (REMS) to ensure patients are provided with a medication guide that discusses the risk. Metoclopramide is approved for the treatment of gastric motility problems associated with GERD, diabetic gastroparesis, and nausea and vomiting.

A new proton pump inhibitor has been approved by the FDA, bringing the number of PPIs on the market to six. Dexlansoprazole is the purified active isomer of lansoprazole (Pepcid®). The drug has a delayed-release formulation designed to provide two separate releases of the medication. It is approved for the treatment of GERD and erosive esophagitis. Takeda Pharmaceuticals will market dexlansoprazole as Kapidex™. ■