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INSIDE

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Infectious Disease Alert's Physician Editor, Stan Deresinski, MD, FACP, serves on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Pfizer, Bayer, and Wyeth, and does research for Merck.

Antibacterial Prophylaxis for Patients with Cancer: Should We Use It or Not?

ABSTRACTS & COMMENTARY

By J. Peter Donnelly, PhD

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Dr. Donnelly is a consultant for Ortho Biotech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer.

Synopsis: *A large, double-blinded, randomized, placebo-controlled trial done by the Italian GIMEMA group shows that prophylaxis with once daily levofloxacin significantly reduces febrile episodes and infectious complications but not mortality.*

Sources: Bucaneve G, et al. Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia. *N Engl J Med*. 2005;353: 977-987; Cullen M, et al. Antibacterial Prophylaxis After Chemotherapy for Solid Tumors and Lymphomas. *N Engl J Med*. 2005;353:988-998; Baden L R. Prophylactic Antimicrobial Agents and the Importance of Fitness. *N Engl J Med*. 2005;353:1052-1054; Gafter-Gvili A, et al. Meta-Analysis: Antibiotic Prophylaxis Reduces Mortality in Neutropenic Patients. *Ann Intern Med*. 2005;142:979-995.

THE GINEMA STUDY REPORTED BY BUCANEVE AND COLLEAGUES recruited for a formal, double-blind, randomized placebo controlled trial of 500 mg/d levofloxacin among 760 patients who were admitted to the hospital and who were at risk of developing neutropenia resulting from treatment of acute leukemia lymphoma or solid tumors. The primary end point was the development of fever during neutropenia that required empirical therapy. Secondary end points included the sort and number of defined infectious complications, as well as survival. Prophylaxis was started 1-3 days before chemotherapy was initiated, and was continued until the patient was no longer neutropenic. Empirical antibacterial therapy was started to manage fever during neutropenia. Infectious complications were classified as microbiologically defined, clinically defined, or unexplained fever. At the end of treatment, fever had affected 243/375 (85%) of those

VOLUME 25 • NUMBER 2 • NOVEMBER 2005 • PAGES 13-24

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given placebo and 243/375 (65%) of those given levofloxacin, resulting in a relative risk reduction of 24%, an absolute reduction of 20% and, therefore, 5 patients needed to be treated to prevent each episode of fever. This difference was accounted for by the reduction in bacteremia, involving Gram negative and Gram positive bacteria (*see Figure 1*). The rates of clinically defined infection and unexplained fevers were similar for both treatment groups, as were the rates of mortality and tolerability. There were more isolates resistant to levofloxacin in the group given the fluoroquinolone for prophylaxis [41 of 47 (87%), with 10 of the 13 Gram-negative species being resistant than in the placebo group (32/68 (47%), in which only 4 of the 24 isolates were resistant. Bucaneve et al, therefore, concluded that prophylaxis was effective, well tolerated and cost-effective although there was no effect on the risk of death.

The study of Cullen and colleagues differed from that of the GIMEMA group in several important respects. It focused exclusively on patients receiving chemotherapy for lymphoma and solid tumors (*see Table 1*), which led to shorter periods of neutropenia and started a 7-day course of prophylaxis around the time the neutropenia was anticipated. The occurrence of probable infections formed the primary outcome measure (defined as a febrile episode, signs attributed to systemic response to infection, signs of a focus of infection, or the use of antibacterial therapy) and affected 109 (14%) of the 781 given levofloxacin and 152 (19.4%) of the 784 given placebo. Fifty (96.7%) patients given the fluoroquinolone were admitted to hospital because of infection, compared with 81 (10.3) of those given the placebo. At first glance, the relative risk reduction brought about by levofloxacin for the primary outcome measure, bacteremia, and mortality were similar for both studies, the absolute risk reduction and, hence, the numbers needed to treat to achieve this were radically different (*see Table 2*), indicating that prophylaxis would benefit significantly patients admitted to the hospital for treatment of their cancer with intensive chemotherapy, as in the study of GIMEMA group in terms of reducing fever and bacteremia, whereas, it would benefit only a very few of those given less intensive chemotherapy for solid tumors as an outpatient.

In an editorial, Baden acknowledged that these 2 studies provided evidence of the significant benefit of levofloxacin as prophylaxis but questioned whether the costs of prophylaxis in the broadest sense of the word, namely financial, side-effects, emergent resistance among the endogenous bacteria and, theoretically at least, susceptibility to enteric infections would be outweighed by the benefits. In particular, there have been several reports on fluoroquinolone-resistant *Escherichia coli* in centers using these drugs for prophylaxis of their neutropenic patients. In order to achieve the benefits whilst minimizing the risks, Baden suggested restricting prophylaxis to those at highest risk, but then went on to state that this group has yet to be well defined. There is also not enough known about the period of increased risk nor about the likelihood of resistant organism emerging. She concluded that "if prophylactic antimicrobial therapy is to be adopted at a cancer center, it should be accompanied by vigorous infection-control practices and careful monitoring for the emergence of resistant bacteria."

The feeling that we have been here before is confirmed by the meta-analysis of Gafter-Gvilli and colleagues on antibacterial prophylaxis for neutropenic patients. They collected all the trials of prophylaxis reported from 1980 to 2004, and identified 95 that were of sufficient quality to be included in the meta-analysis. Fourteen of these trials involved a fluoroquinolone versus either a placebo or no intervention. The results of the GIMEMA study, but not those of the study of Cullen et al correspond very closely to those reported for the meta-analysis, including the prevention of fever (*see Figure 2*). However, there are some noticeable differences. Whereas the meta-analysis found evidence in favor of fluoroquinolone prophylaxis leading to reduced mortality with a reduction of the risk by 49% from

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

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GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Infectious Disease Alert***, P.O. Box 740059, Atlanta, GA 30374.
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Questions & Comments

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

Table 1

Comparison of Demographic Characteristics

	Cullen, et al.		Bucaneve, et al.	
Number of patients	1565		675	
Male	873	56%	370	55%
Underlying cancer				
Solid tumor	1365	87%	46	7%
Lymphoma	191	12%	212	31%
Hematological malignancy	0	0%	414	61%
Indwelling central venous catheter	129	8%	535	79%
Number with bacteremia	18	1%	177	26%
Number who died	24	2%	28	4%

Table 2

Comparison of Outcome Measures

	Cullen, et al.	Bucaneve, et al.
Primary outcome measure	0.07	0.21
Absolute risk reduction	0.07	0.21
Number needed to treat	14	5
Relative risk reduction	0.18	0.24
Relative risk	0.82	0.76
Bacteremia		
Absolute risk reduction	0.01	0.16
Number needed to treat	131	6
Relative risk reduction	0.5	0.47
Relative risk	0.5	0.53
Mortality		
Absolute risk reduction	0.01	0.02
Number needed to treat	98	44
Relative risk reduction	0.5	0.46
Relative risk	0.5	0.54

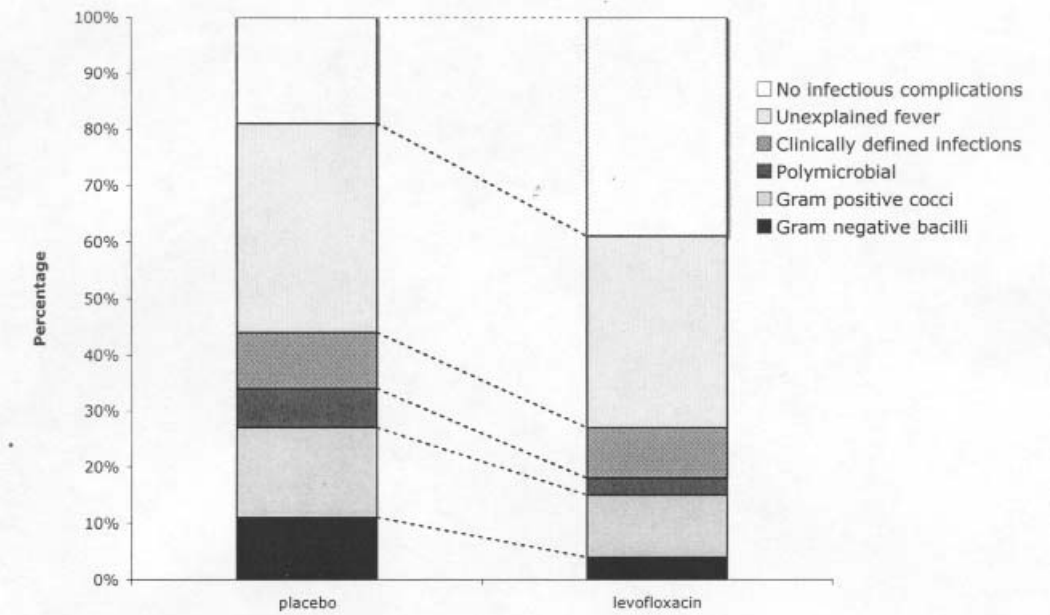
10% to 5%, the GIMEMA study did not, as the mortality rates for prophylaxis and placebo were both 5%. Next, the risk of developing clinically defined infections and adverse events was higher in the GIMEMA study than found in the meta-analysis. Nevertheless, the results of the GIMEMA study fall broadly in line with those of the meta-analysis.

COMMENTARY

There is a distinct feeling of déjà vu concerning this topic, not least because the pros and cons have been rehearsed many times during the last 2 decades, leading the IDSA to conclude that "Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis." (IDSA Guidelines: Hughes WT, et al. 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. *Clin Infect Dis*. 2002;34:730-751. www.journals.uchicago.edu/CID/journal/issues/v34n6/011605/011605.html

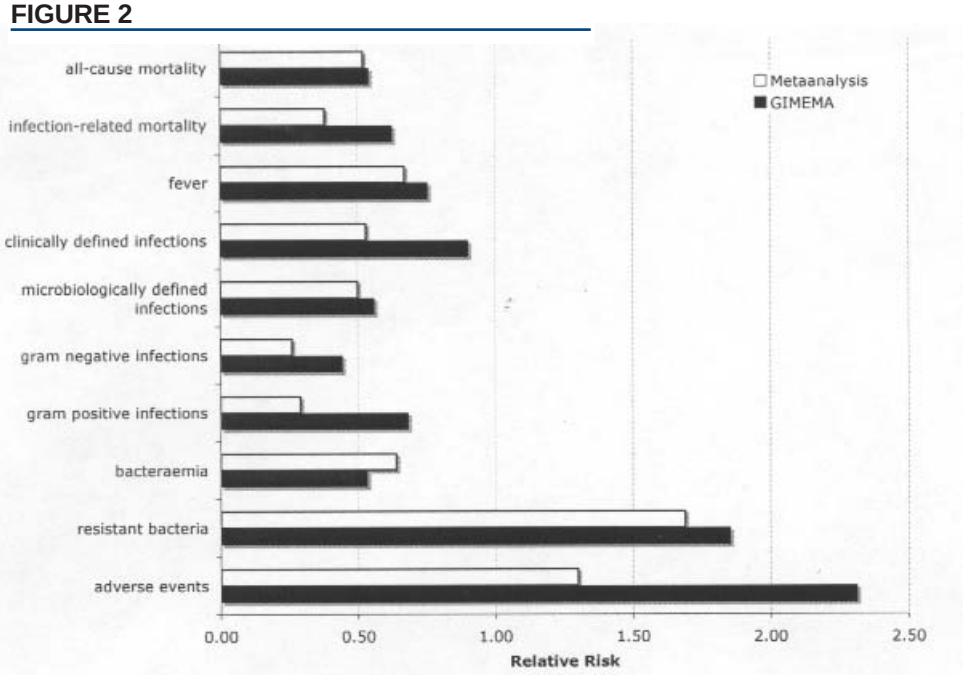
However, never before has there been a study which met all the criteria for a first class clinical trial. Here we are treated to 2 such reports for which the authors deserve our appreciation and editors of the *New England Journal of Medicine* deserve our gratitude for bringing this topic firmly back into the limelight to help us decide the issues once and for all. Indeed, if decisions about prophylaxis are to be based on evidence rather than emotion, the conclusions seem pretty clear. Reserve the practice for

Figure 1 Infectious complications



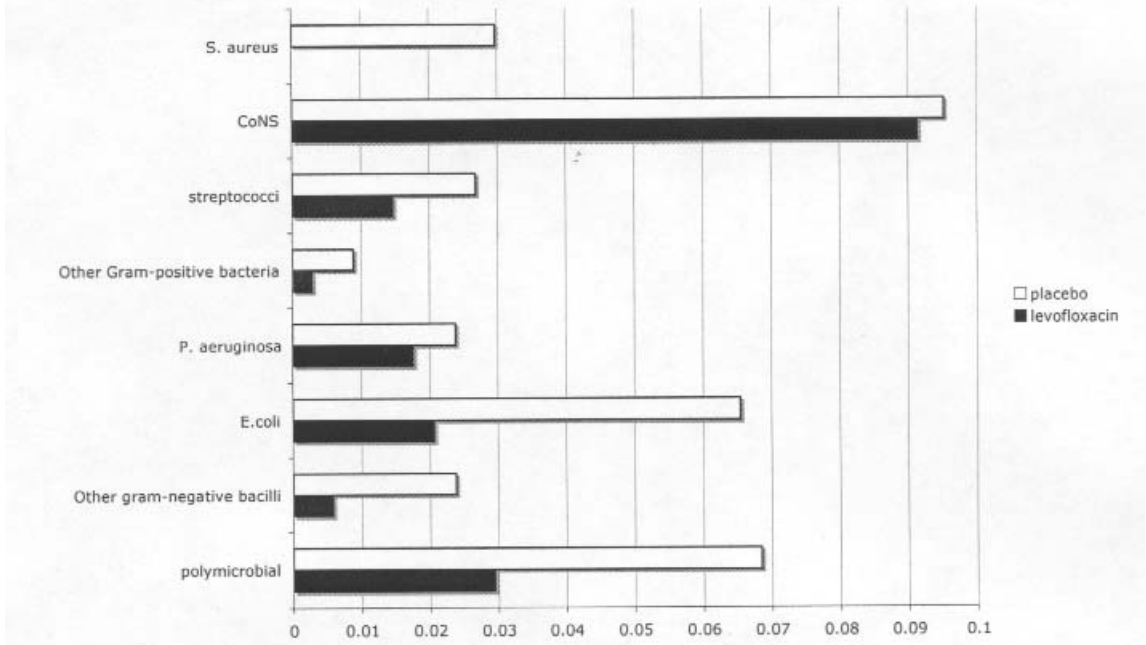
Source: Dr.Donnelly compiled data from article sources and developed figures 1, 2, and 3

FIGURE 2



those who really are at high risk of developing infection during the neutropenia-induced intensive chemotherapy. Certainly the numbers needed to treat to prevent death seem way too high to justify prophylaxis for this purpose, despite the meta-analysis. On the other hand, a relatively small numbers of patients would need to be treated to prevent fever and help stay the hand against giving empirical antibiotics. However, the question remains—what do we want to achieve from prophylaxis. If bacteremia is to be reduced, than only patients neutropenic after intensive chemotherapy would fit the bill of being high-risk. Such patients are characterized by having neutropenia of at least a week's duration and are invariably already in the hospital and are being managed by central venous catheters. Closer inspection of the cause of bacteremia in *Figure 3* shows that the principle benefit is seen by a reduction in *Staphylococcus aureus*, *E. coli*, and polymicrobial bacteremia, and not the rest. Therefore, a further refinement would be

Figure 3 Comparison of causes of bacteraemia.



to restrict prophylaxis to those who harbor *S. aureus* in their nose or *E. coli* in their gut. This could be known on admission by taking a nasal swab for *S. aureus* and a fecal sample for *E. coli*. Although we are getting to the heart of the matter, life is also becoming somewhat complicated, not the least because it would require an active surveillance program which many have long since abandoned for being too costly. The fact remains that prophylaxis with fluoroquinolones had become routine practice in many centers for recipients of hematopoietic stem cell transplants, as evidenced by the Italian participants in the GIMEMA study. Intuitively, it seems better to prevent *E. coli* sepsis than to wait until it happens, as this can lead to an untimely death. These tragedies do still occur despite prompt administration of empiric therapy, as every hematologist can attest and are all the more bitter because they are considered events that can be prevented. I suspect that North America, just as in Europe, lip service is being paid to guidelines that do not recommend the use of fluoroquinolones for prophylaxis, and that patients in and out of hospitals are being given, and will continue to be given, these useful drugs to tilt the odds in favor of a good outcome. Evidence comes in many guises, and though formal, randomized, controlled trials provide the road map for modern medicine, it is experience that forms the compass to guide the physician from the general to the particular. ■

The Effect of Antibiotic Therapy for Intraabdominal Infections on Selection of Antibiotic-Resistant Bowel Flora

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Relative to treatment with either ceftriaxone plus metronidazole or with piperacillin/tazobactam, ertapenem administration is least likely to select for resistant bacterial flora in the gastrointestinal tract.*

Sources: Dinubile MJ, et al. Bowel Colonization with Resistant Gram-Negative Bacilli After Antimicrobial Therapy of Intra-Abdominal Infections: Observations From Two Randomized Comparative Clinical Trials of Ertapenem Therapy. *Eur J Clin Microbiol Infect Dis*. 2005;24:443-449; DiNubile MJ, et al. Acquisition of Resistant Bowel Flora During a Double-Blind Randomized Clinical Trial of Ertapenem Versus Piperacillin-Tazobactam for Intraabdominal Infections. *Antimicrob Agents Chemother*. 2005;49:3217-3221.

SEVERAL RANDOMIZED, COMPARATIVE TRIALS HAVE demonstrated the efficacy of ertapenem in

the treatment of patients with intraabdominal infections. In the course of those trials, each of which demonstrated no significant difference between treatment regimens, fecal samples were collected and DiNubile and colleagues have now examined the effect of the individual treatment regimens on the emergence of antibiotic resistant aerobic Gram negative bacilli.

Two of the trials compared ertapenem to piperacillin/tazobactam (P/T). The proportion of P/T recipients from whom P/T-resistant Enterobacteriaceae was recovered increased from 0.6% at baseline to 12.2% at the end of therapy (EOT). In the second trial examining these same 2 treatment regimens, this proportion increased from 0.8% to 7.8%. Meanwhile, the frequency of recovery of ertapenem-resistant Enterobacteriaceae from ertapenem recipients changed from 0.6% to 0% in OASIS I and from 0.8% to 1.6% in the second trial.

In OASIS II, ertapenem was compared to ceftriaxone plus metronidazole (C/M). Once again, there was no significant recovery of antibiotic-resistant Gram negatives among ertapenem recipients. In contrast, among C/M recipients, the frequency of recovery of ceftriaxone-resistant Enterobacteriaciae increased from 2.6% at baseline to 17.1% at EOT and to 22.4% two weeks later. In addition, ESBL-producing Enterobacteriaceae were recovered from 2.1% of ceftriaxone recipients at baseline, 9.3% at EOT, and 17.2% at 2 weeks post-therapy.

Of particular note is that there was no significant increase in recovery of imipenem-resistant Pseudomonas aeruginosa among ertapenem recipients in any of the 3 trials.

COMMENTARY

The gastrointestinal tract serves as an enormous potential reservoir of resistant bacteria. Whatever the indication, the administration of antimicrobials may have a profound effect on that flora, including the selection of antibiotic resistant bacteria. These organisms may subsequently cause infection in the affected individual, as well as serving as a source for environmental contamination and spread to other patients. As a consequence, one of the important factors that should be taken into account in the selection of antibiotic therapy is its effect on the bacterial ecology of the patient and the environment.

These analyses provide a clear distinction among 3 antibiotic regimens in their likelihood of selection of fecal antibiotic-resistant Enterobacteriaceae. They demonstrate that ertapenem posed no significant risk for the selection of these resistant bacteria, that C/M therapy served as a strong selector of resistance, including ESBL-producing Enterobacteriaceae, and that P/T therapy was intermediate in its effects.

One concern that has been raised regarding the use of ertapenem is that of the potential for selection of resistance to other carbapenems in *Pseudomonas aeruginosa*. However, no significant increase in imipenem-resistant *P. aeruginosa* was identified in any of the trials in patients who were treated with ertapenem. In addition, no significant increase in carbapenem resistance among *P. aeruginosa* or Enterobacteriaceae was identified 19 months after the introduction to the antibiotic formulary at the Ohio State University Medical Center.[1]

Reference

1. Goff DA, Mangino J. Ertapenem Effect on Gram-Negative Pathogens 19 Months After Formulary Addition. 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., December 16-19, 2005, Abstract K-1511.

Valproic Acid for HIV Infection

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD

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Dr. Winslow is a consultant for Bayer Diagnostics and Pfizer/Agouron, and is on the speaker's bureau for Pfizer/Agouron.

Synopsis: *Valproic acid acts as an inhibitor of histone deacetylase 1 (HIDAC1). In a small pilot study valproic acid added to conventional antiretroviral therapy plus enfuvirtide was shown to accelerate clearance of HIV from resting CD4+ T cells in vivo.*

Source: Lehrman G, et al. Depletion of Latent HIV-1 Infection In Vivo: A Proof-of-Concept Study. *Lancet*. 2005;366: 549-555.

THIS PROOF OF CONCEPT CLINICAL TRIAL INTENSIVELY studied 4 patients with HIV infection who had plasma levels of HIV RNA below the lower limit of quantification in a standard viral load assay on standard HAART

therapy. The patients initially had their therapy intensified with enfuvirtide (T-20) for 4-6 weeks to prevent spread of HIV infection, followed by the addition of oral valproic acid 500-750 mg twice daily for 3 months. Patients underwent leukopheresis before and after their valproate treatment course, resting CD4+ lymphocytes were isolated. Both replication competent HIV and total integrated proviral DNA were quantified in these resting T-cells. Expressed as infected units per billion cells (IUBP), the 4 patients were observed to have experienced reductions in frequency of infected resting T-cells of 29% to > 84%.

COMMENTARY

While we can now effectively suppress active replication of HIV in patients by use of HAART therapy, once antiretroviral suppression is removed, levels of plasma virus generally rebound rapidly. This is due to the large reservoir of integrated proviral DNA, which largely resides in resting CD4+ T-cells in lymphatic tissue. The holy grail of potentially curative therapy of retroviral infections is the elimination of HIV from this population of resting cells. A number of approaches have been tried, most notably the activation of T-cells using IL-2 in conjunction with HAART to, in theory, drive the latent virus into active replication where it can be inhibited by antiretroviral therapy with the host cells then presumably being eliminated by apoptosis or some other undefined mechanism. Unfortunately, activation of T-cells does not eradicate HIV since, due to the upregulation of HIV transcription which accompanies T-cell activation and the increased number of susceptible uninfected target cells, the net effect is increased HIV replication beyond the threshold which can be contained by antiretroviral therapy.[1-3]

Histone deacetylation is importnt for quiescence of HIV gene expression in resting CD4+ lymphocytes. Histone deacetylase 1 (HDAC1) mediates chromatin remodeling and represses viral gene expression and virion production.[4] The anticonvulsant valproic acid inhibits HDAC, and has been shown to induce HIV expression ex vivo from resting CD4+ cells from aviremic patients treated with HAART, but does not cause upregulation of cell surface markers of activation nor increase susceptibility of cells to HIV infection de novo.[5] This small pilot study demonstrated that it is possible to reduce the population of HIV-infected resting CD4+ T-cells in vivo from 29%-84%.

While the results of this small pilot study are intriguing and represent first class laboratory science, the clinical application of these data are still quite a long way from being ready for use in the clinic. Some areas which call for additional experimental data include the observation that a substantial decline of integrated proviral DNA was not observed, although as Lehrman and colleagues point out, this may be less significant than the apparent reduction of infected cells containing potentially replication-competent virus. However, such a modest (less than 1 $\log_{10}$) reduction in infected cells may not be significant in a disease process where the total number of infected cells in the body may number in the hundreds of millions. The experimental design of the study does not allow one to separate the effect of enfuvirtide added to HAART vs the effect of valproic acid in reducing the population of infected resting CD4+ lymphocytes. The effect of this treatment on virus-infected cells of monocyte/macrophage origin and of follicular dendritic cells may be minimal (or considerable) since these cells were not studied. The potential toxicities and drug interactions of valproic acid are considerable. In all, however, this is interesting work and is deserving of additional laboratory and clinical studies. ■

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Giardiasis and the Risks of Visiting Grandma

ABSTRACT AND COMMENTARY

By Philip R. Fischer, MD, DTM&H, and Jane R. Rosenman, MD

Dr. Fischer is Professor of Pediatrics, Division of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, and Dr. Rosenman is Instructor, Division of General Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Fischer and Dr. Rosenman report no consultants, stockholders, speaker's bureaus, research, or other financial relationships with companies having ties to this field of study.

Synopsis: *Characteristics of international travel, immigration, and adoption help to shape the epidemiology of giardiasis. The risks to travelers who are visiting friends and relatives in developing countries are significant, and may be decreased with a stronger emphasis on pre-travel counseling.*

Source: Ekdahl K, et al. Imported Giardiasis: Impact of International Travel, Immigration, and Adoption. *Am J Trop Med Hyg*. 2005;72:825-830.

Giardiasis, caused by the waterborne protozoan parasite *Giardia lamblia*, also known as *G. intestinalis*, and *G. duodenalis*, is a common cause of diarrhea worldwide. The highest incidence of disease is seen in developing countries. As overseas travel becomes more accessible, and as international adoption continues to rise, the epidemiology of giardiasis in developed countries is changing.

Ekdahl and colleagues describe the impact of immigration and international travel on the epidemiology of giardiasis in Sweden from 1997 to 2003. In addition, the relative risk estimates of giardiasis are discussed in detail.

Although this study looked at individuals arriving or returning to Sweden between 1997 and 2003, Ekdahl et al assert that the denominator based data from this study can likely be generalized to other Western populations. A total of 11,590 subjects comprised 5 main groups with giardiasis: travel-related (3697; 32%), newly-arrived immigrants (4151; 36%), internationally adopted children (455; 4%), domestic cases (1708; 15%), and a fifth group for which there was not sufficient information to be studied (1441; 13%). The travel-related group included returning travelers having visited friends and relatives (VFRs); these were generally individuals with family roots within the country that was the source of infection.

Risks were evaluated for each of the groups. For returning travelers, the overall risk of having acquired giardiasis was 5.3 per 100,000. The highest unadjusted risks were seen in travelers to the Indian Subcontinent, East Africa, West Africa, South America, and Central America. Twenty-four percent of cases of giardiasis were seen in VFRs. The highest age-related risk of Giardia infection was in young children. There was a 10- to 20-fold higher risk in refugees and other immigrants than in returning travelers (prevalence of 1000 to 2000 per 100,000). Of all internationally adopted children under 10 years of age arriving to Sweden during this period, 8% had giardiasis. Giardia prevalence was 10,000-50,000 per 100,000 children for more than half of the countries from which the children came.

Ekdahl et al acknowledge that some bias may exist in the travel risk calculations. Travelers returning from tropical countries are more likely to seek medical evaluation for gastrointestinal complaints, and medical practitioners are more likely to investigate travelers returning from endemic countries. Due to the sometime insidious nature of giardiasis, it may be difficult to determine the specific onset of infection.

While the risk for giardiasis in immigrants/refugees was much higher than in tourists, there was an even higher risk among internationally adopted children. A contributing factor may be that returning travelers generally are evaluated only if gastrointestinal symptoms are present, whereas most internationally adopted children, symptomatic or not, are routinely screened for giardiasis.

COMMENTARY

Giardia infection can occur by person-to-person contact (via fecal-oral route) but, most commonly, by ingestion of contaminated drinking water, or possibly food. Estimated asymptomatic carriage rates in the United States are 3-20%, depending on the region. In studies of children under 36 months in daycare centers, the prevalence of Giardia cysts was 21-26% in one study.[1] In Santa Clara County, CA, between October 2001 and January 2004, immigrants and refugees presenting to a refugee clinic were screened for parasitic infections. *Giardia lamblia* was the most common protozoan isolated, and was more likely among children than adults.[2]

Asymptomatic carriage, though generally well tolerated, can serve as a reservoir of infection for contacts of returned travelers. Most common clini-

cal manifestations include diarrhea, abdominal cramping, and bloating. A more prolonged, incapacitating disease may occur in those at higher risk, including children, employees in childcare centers, men who have sex with men, travelers to endemic areas, and certain immunodeficient hosts. Failure to thrive and anemia may occur in protracted giardiasis, which may have a lasting impact on the physical and cognitive development of children. In addition to the clinical impact of giardiasis, the financial costs may also be quite significant.[3,4]

During recent decades, a large number of refugees and immigrants have been arriving in Western countries from regions outside the normal tourist routes. Many of these individuals are now returning to visit their countries of origin and taking their families along with them. These travelers visiting friends and relatives, so-called VFRs, are at high risk for travel-related illness, including giardiasis. In the United States, 20% of the population are first-degree immigrants, or their children are. In 2002, 40% of United States international air travelers were VFRs. This group of travelers is less likely to seek pre-travel consultation, more likely to travel to remote areas, and usually stays longer than other tourist travelers. Since children, in general, are at highest risk of acquiring giardiasis. These children, in particular, are at especially high risk and should be monitored closely for gastrointestinal complaints upon returning.[5]

Recommended stool studies for symptomatic individuals are stool enzyme immunoassay (EIA), with 87-100% sensitivity and 100% specificity, or serum immunofluorescence antibody (IFA) determinations, with 100% sensitivity and specificity.[6,7] In addition, stool specimens may be evaluated for ova and parasites by microscopy; one stool sample has a 75-95% sensitivity, and 3 samples collected on different days increase the sensitivity to about 95%. Microscopy in returning travelers is also helpful to identify other concomitant parasitic infections. While asymptomatic carriers do not technically require specific treatment, curative therapy can reduce the risk of transmission. It is, therefore, especially useful for infected children who are contacts of immunocompromised and pregnant individuals.[2,6]

If symptomatic giardiasis does occur, treatment includes rehydration and correction of electrolyte abnormalities. In addition, a 5-7-day course of metronidazole, 250 mg 3 times a day for adults and 15 mg/kg/day divided in 3 daily doses for children, remains the antiparasitic treatment of choice, with cure rates of 80-95%. Furazolidone, 100 mg_5 4 times a day for adults or 6 mg/kg/day divided in 4 daily doses for children, is 70-100% effective when taken for 7-10 days, and is available in a liquid form for children. Due to the risk of mild hemolysis, furazolidone should be avoided in infants under one month old and individuals with known G6PD deficiency. Albendazole is as effective as metronidazole in treating giardiasis and is useful against coexisting helminth infections. Tinidazole has a cure rate of 90-100% when taken as a single dose, but is not currently available in the United States.[6,8,9] Recent evidence suggests that nitazoxanide, a nitrothiazolylsalicylamide derivative, is as effective as metronidazole for giardiasis and may be better tolerated. The recommended dose is 100 mg for children 12-47 months of age, 200 mg for 4-11 year olds, and 500 mg for older children and adults.[10] Related to concerns about teratogenicity of metronidazole during the first trimester, paromomycin may be used in pregnant women, and is 50-70% effective.[6,8]

Traveler's diarrhea is the most common travel-related illness.[5] Giardiasis is a known cause of diarrhea in returned travelers, and it is also seen among internationally adopted children and new immigrants. Former immigrants or refugees returning to their native countries, often with their children to visit friends and relatives, deserve special attention both pre- and post-travel. Children in this group of travelers are at even higher risk for serious consequences, many of which could be avoided with appropriate counseling and the implementation of food and water precautions. ■

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CME Question

5. Which of the following is correct with regard to the relative likelihood of selection of resistant Gram negative fecal flora in patients withe intraabdominal infections being treated with these antibiotics (The first listed would be the most likely to select resistance)?

a. Piperacillin/tazobactam > ertapenem > ceftriaxone/metronidazole
b. Ceftriaxone/metronidazole > piperacillin/tazobactam > ertapenem
c. Ertapenem > piperacillin/tazobactam > ceftriaxone
d. Ertapenem = piperacillin/tazobactam > ceftriaxone

Answer: 5. (b)

CME Objectives

The objective of Infectious Disease Alert are:

-To discuss diagnosis and treatment of infectious diseases;

-To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs.

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

-To present prevalence/surveillance data for various diseases, such as AIDS, tuberculosis, malaria, and pneumonia; and

-To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lea to the development of new therapeutic drugs. ■

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1. Publication Title	2. Publication No.	3. Filing Date
Infectious Disease Alert	0 7 3 9 - 7 3 4 8	10/01/05
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$289.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Robin Salet; Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Lee Landenberger, same as above

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15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1316	1707
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	738	673
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			844	770
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i. Total *(Sum of 15g. and h.*			1316	1707
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			84	53

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2005 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda L. Mooney Publisher — Date: 9/27/05

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In Future Issues:

Blood Cultures—New Recommendations from the American Society for Microbiology

UPDATES

By Carol A. Kemper, MD, FACP

Study Confirms Men Are Dirtier

Lauran Neergaard, *USA Today*, September 21, 2005.

FOLLOWING AN EDUCATIONAL campaign promoting hand washing in public places, and observing 6300 people using public restrooms at various locations across the United States, researchers report slow but steady improvement in rates of hand washing. But men are still not as rigorous as women about their personnel hygiene.

Researchers observed that 92% of women but only 64% of men washed their hands following use of the toilets at Penn Station in New York City. Similar rates of hand washing were observed at Grand Central Station. The worst statistics were observed at a ballgame at the Atlanta stadium, where 84% of women and 63% of men washed their hands. The best figures came from the Ferry Building in San Francisco (where they have the best farmers market on Saturday morning) and Chicago's Shedd Aquarium and Museum of Science, where only 12% forgot to wash up.

These figures are in contrast to a recent Harris telephone poll of 1000 adults, 91% of who claimed they always washed after using a public restroom. Only one-third admitted to washing their hands after coughing or sneezing. Another example of how people over estimate their good behavior. ■

Yaws in the United States?

MMWR 2005;54(37);933-934.

IN OCTOBER 2004, THE CDC received reports of positive syphilis tests in refugee children from Liberia and Somalia. Positive treponemal and non-treponemal tests can not differentiate between the various treponemal diseases, which include *T. pallidum* subsp. pallidum (true venereal syphilis) or one of the endemic non-venereal subspecies, such as *T. pallidum* subsp. pertenue (yaws), *T. pallidum* subsp. endemicum (bejel or endemic syphilis), and *T. carateum* (pinta). All 3 of these latter infections are transmitted by skin contact, are more prevalent in children, and could be endemic in group housing or refugee situations. In contrast, true venereal syphilis is transmitted only sexually or vertically. Thus, a positive test in the mothers of these children, if available for testing, would suggest congenital transmission of *T. pallidum* subsp. pallidum. On the other hand, a negative test in the mother would suggest either consensual or non-consensual sexual transmission - or yaws.

The non-venereal endemic treponemal infections cause progressive skin lesions with severe destructive gummatous changes of skin, ones, and cartilage. Yaws typically starts as a maculopapular rash with regional lymphadenitis, and secondary lesions commonly appear at the mucocutaneous junction ("framboesiform lesions"). Hyperkeratosis of hands and feet, with deep erosions, can occur. The face and the long bones, especially the tibia, are common sites for infection, with periosteal changes and slow bone destruction ("sabre tibia"). In the Middle East, this condition is known as bejel. Following mass eradication campaigns with penicillin in the 1950s, yaws became quite rare in the tropics. Ongoing war and famine in parts of Africa may be contributing to its resurgence. On the other hand, pinta, which is endemic to the New World, and is still occasionally seen in Mexico, Columbia, Ecuador, and Venezuela, causes small papules and slowly expanding plaques, which gradually coalesce and, in the late stages, are often depigmented.

Further information regarding clinical signs or symptoms in the children was not available. The CDC recommends screening of all refugee and immigrant children from areas endemic for non-venereal treponemal infection (including most of Africa, Indonesia, Pakistan, Sri Lanka, Cambodia, India, and the West Pacific Islands). ■

SARS—Just Another 21st Century Plague

"Twenty-first Century Plague: The Story of SARS", by Thomas Abraham (*Johns Hopkins University Press*, 2005); Lau SK, et al, Severe Acute Respiratory Syndrome Coronavirus-Like Virus in Chinese Horseshoe Bats. *Proc Natl Acad Sci USA*. 2005;102:14040-14045; Poon LL, et al. Identification of a Novel Coronavirus in Bats. *J Virol*. 2005;79: 2001-2009.

ABRAHAM'S BOOK IS AN EXCITING must read for anyone in infectious disease, infection control and public health, with good pointers on managing health care crisis. It underscores Truman Capote's contention that "well written non-fiction is more exciting than any fiction." Barely before this book got to press and SARS was declared the plague of the new millennium, avian influenza, swoops down on Europe and Turkey

from the steps of Russia. Meanwhile, we have CCU nurses in revolt at our hospital, refusing to receive influenza vaccine this year, and a floor nurse who is still out on disability from severe airways disease following influenza infection, contracted on the medical wards in April 2005 (she refused vaccination and failed to pick up her gratis prescription of Tamiflu in a timely fashion). Why is the next threat always worse than the present danger?

The origins of SARS are still being investigated, but experts in the field are increasingly skeptical that civets are the reservoir for infection. In surveillance studies of non-caged animals from non-urban areas, researchers at Hong Kong University have identified a SARS--like corona virus from 23 (39%) of 59 anal swabs of wild Chinese horseshoe bats (Rhinolopus sinicus). Sequencing analysis showed that bat-SARS-CoV is closely related to human and civet SARS CoV, and phylogenetic analysis suggest that bat virus forms a distinct cluster within group 2b viruses. The most significant difference between the bat and human corona viruses lay in genes encoding for cellular binding of virus to host cells, leaving open the question of how bat-SARS virus may have jumped species to humans. An insertion sequence found in bat-SARS-CoV, which is not found in humans virus, but was found in civet virus, suggests that the two species may share a common ancestor virus. This may be somewhat belated but happy news to civets—10,000 of which were killed following initial reports fingering them as the suspect reservoir. Neutralizing antibody to human SARS virus was found in some of the horseshoe bats, suggesting that care should be taken when handling these animals.

The group also found a novel group 1 coronavirus isolated from 63% of the fecal samples from 3 different wild bat species from the genus Miniopterus, suggesting that coronaviruses may commonly circulate among bat species in mainland China. ■

Guillain-Barré Syndrome Following Meningococcal Vaccination

FDA and CDC Alerts, Press Release, October 1, 2005; and proMED-mail post dated October 1, October 2, and October 7, 2005. www.promedmail.org.

Five teenagers have developed Guillain-Barré Syndrome (GBS) following administration of Menactra vaccine (meningococcal conjugate vaccine A, C, Y, W135, Sanofi Pasteur). A sixth possible case just reported on October 4th is being investigated. Menactra was licensed by the United States in January 2005 and, in February, the Advisory Council on Immunization Practices (ACIP) recommended the routine use of vaccine for adolescents aged 11-2 years, at entry to high school, and for first year college students living in dormitories or otherwise at high risk. No cases of GBS were reported in pre-licensing clinical trials of about 7000 patients. Thus far, about 2,500,000 dose of vaccine have been used, suggesting a lower than anticipated rate of GBS than that estimated for the general population (annual incidence estimates 0.4 to 4 per 100,000 population). Because additional cases may be underreported, the FDA and CDC are requesting any information about possible cases (www.vaers.hhs.gov or by telephone at 800-822-7967).

All 5 cases occurred in teens aged 17-18 that received vaccine between June 10 and July 25th, and developed symptoms within 14-31 days of vaccination. The 5 patients received vaccine from 4 different lots, and lived in 4 different states on the East Coast. Interestingly, only one of the teens was completely healthy. One of the cases had a history of 2 prior episodes of GBS, following receipt of other vaccines as a child; one had a mother with a history of GBS; and another had sore throat 6 days before the onset of symptoms.

Three different but similarly conjugated vaccines have been used in the United Kingdom (conjugated to either a non-toxic diphtheria toxoid or tetanus toxoid). Following administration of these vaccines, 5 cases of GBS have also been reported in the United Kingdom, which is also a lower than anticipated rate of illness for the general population.

GBS can occur either spontaneously or following any number of viral or bacterial infections, as well as a number of bacterial and viral vaccines. About 20-40% of cases occur following bacterial gastroenteritis from Campylobacter jejuni (an IDA Board question). Dr. Steve Berger from Tel Aviv Medical Center assembled a list of 18 vaccines that have been associated with GBS to date, including DT, DtaP, DTP, HbOC-DTP, HbOC, PRP-D, Hepatitis A, Inactivated Influenza, Japanese encephalitis, MMR, MR, pneumococcal conjugate, oral poliomyelitis, rabies, rubella, rubella-mumps, tetanus toxoid, and varicella vaccines, the most notable of which was the 1976 swine flu influenza vaccine. ■

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.

Roche is Under Pressure Over Its Antiviral Drug Tamiflu

Roche, the manufacturer of oseltamivir (Tamiflu), has found itself struggling to keep up with demand for its antiviral drug in the face of a possible avian flu epidemic. Countries worldwide are stockpiling the drug, which has resulted in hundreds of millions of dollars in sales for the company. But now, Roche is facing pressure from the worldwide community to allow generic production of Tamiflu. Taiwanese officials have indicated that they could begin mass production relatively quickly, and UN Secretary-General Kofi Annan has urged licensing of the drug to generic companies. An Indian drug company has announced that it will begin production of the drug, despite the risk of patent infringement lawsuits. Cipla, based in Bombay, India's third largest drug company, will soon begin production. Meanwhile Roche, which sells Tamiflu for $60 per treatment course, is working to expand production, but has stated that the process is too complex and time-consuming for generic houses to manufacture. Officials from Cipla report that they have reverse engineered the drug and could distribute generic oseltamivir as early as January 2006. They also state that they will sell the drug for "a humanitarian price." Tamiflu is approved for treating both influenza A and B, and for prophylaxis of both viruses. There have been several recent reports that avian influenza A may be showing some resistance to Tamiflu, however, these were based on a single report from Vietnam of a H5N1 virus that was partially resistant to the drug, and not on any evidence of widespread resistance.

ACE Inhibitors or ARBs for Prediabetics?

ACE inhibitors and angiotensin receptor blockers (ARBs) are not only cardio and renal protective for diabetics, the drugs may help prevent the onset of diabetes and those at risk. Researchers from the Mid America Heart Institute conducted a meta-analysis of 12 randomized, controlled clinical trials of ACE inhibitors or ARBs. Over 116,000 patients were entered into the trial, including over 72,000 who did not have diabetes at baseline. ACE inhibitors were associated with a reduction in the incidence of newly diagnosed diabetes of 27%, while ARBs were associated with a 23% reduction. The authors conclude that an ACE inhibitor or ARB should be considered in patients with prediabetic conditions such as metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure, or coronary heart disease (Abuissa H, et al. Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers for Prevention of Type 2 Diabetes A Meta-Analysis of Randomized Clinical Trials. *J Am Coll Cardiol*. 2005;46:821-826).

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) 262-5416. E-mail: leslie.hamlin@thomson.com.

Xigris is Approved for Severe Sepsis

Drotrecogin alfa (DrotAA – trade name Xigris) is approved for the treatment of adults with severe sepsis and a high risk of death. A recent study suggests that the drug is not effective for patients with sepsis and a low risk of death, as determined by an Adult Physiology and Chronic Health Evaluation (APACHE II) score of < 25 or single organ failure. The study enrolled 2640 patients who met criteria of sepsis and the risk of death (1297 in the placebo group and 1316 in the DrotAA group). The study was stopped early because of a low likelihood of making the prospectively defined objective of demonstrating a significant reduction in the 28-day mortality rate with use of the drug. There were no statistically significant differences between placebo and DrotAA in 28-day mortality (17.0% placebo, 18.5% DrotAA; *P* = 0.34;RR 1.08; 95% CI, 0.92-1.28) or in in-hospital mortality (20.5% vs 20.6%; *P* = 0.98; RR, 1.0; 95% CI, 0.86-1.16). The rate of serious bleeding was greater in the DrotAA group than in the placebo group, both during the infusion (2.4% vs 1.2%,*P* = 0.02) and the 28-day study period (3.9% vs 2.2%, *P* = 0 .01). The authors conclude that the lack of benefit coupled with the increase risk of serious bleeding suggest that DrotAA should not be used in patients with severe sepsis who are low risk for death (*N Engl J Med*. 2005;353:1332-1341). An accompanying editorial suggests that DrotAA should still be considered for severe sepsis with an APACHE II score of > 25, but this current study refines the parameters for use in less sick patients (Parrillo JE. Severe Sepsis and Therapy with Activated Protein C. *N Engl J Med*. 2005;353:1398-1400).

ACE Inhibitors Inhibiting Aortic Valve Stenosis?

Conventional wisdom has suggested that ACE inhibitors should be used with caution or not all in patients with aortic valve stenosis. A new study challenges that assumption with the review of 20 patients with an average age of 73, a mean valve area of 0.7 cm^2, and left ventricular ejection fraction of 45%. Patients underwent clinical evaluations, echocardiograms, and exercise echocardiography with and without ACE inhibitor therapy. During therapy, there was no change in patients' subjective functional class. The patients had a lower systolic blood pressure with ACE inhibitors (140 mm Hg vs 159 mm Hg, *P* = 0.02), a higher mean pressure gradient (34 mm Hg vs 28 mm Hg, *P* = 0.037), and a higher left ventricular stroke work loss of apparent 19% vs 14%, *P* = 0 .009). Other baseline functional and hemodynamic parameters were unmodified. The authors conclude that with aortic stenosis, the afterload relief caused by ACE inhibitors is blunted by a parallel increase in the pressure gradient, and that ACE inhibitors favorably affect stress hemodynamic function in most hypertensive patients with aortic stenosis (Jimenez-Candil J, et al. Effects of Angiotensin Converting Enzyme Inhibitors in Hypertensive Patients with Aortic Valve Stenosis: A Drug Withdrawal Study. *Heart*. 2005;91:1311-1318).

FDA Actions

The FDA has approved Schering's estradiol/drospirenone combination for hormone replacement therapy in women with moderate- to-severe menopausal symptoms. The approval has taken several years due to controversy with HRT following the Women's Health Initiative study that was published in 2002. The drug is unique in that it combines estradiol with drospirenone, a spironolactone analogue which serves as a mild diuretic. Because of the antialdosterone effects of the drug and the risk of elevating potassium levels, it should not be used in women with liver, kidney, or adrenal disease. Schering will market estradiol/drospirenone as Angeliq.

The FDA has issued an alert regarding 5 cases of Guillain-Barré Syndrome (GBS) associated with the use of Meningococcal Conjugate Vaccine A, C, Y, and W135 (Menactra, Sanofi Pasteur). The agency is investigating whether the vaccine is implicated in these cases or whether it is coincidence. All 5 cases occurred in 17 or 18 year-old individuals, 2 to 4 weeks after they received the vaccine. They all lived in Ohio, New York, Pennsylvania, or New Jersey. There is a background rate of the GSB, and 5 cases among the 2.5 million patients that have been vaccinated could potentially be by chance. The FDA is making this announcement to seek out other cases that may have gone unreported. All 5 patients are reported to be recovering or to be fully recovered. Menactra is approved for prevention of meningococcal disease in adolescents and adults age 11 to 55 years. It is commonly given to adolescents prior to starting high school or college. ■