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.

MRSA Central-Line Bacteremias Decline in U.S. ICUs

ABSTRACT & COMMENTARY

By Robert Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia

Synopsis: *Surveillance data from the CDC show that central-line associated bloodstream infections due to methicillin-resistant* Staphylococcus aureus *in U.S. intensive care units showed an overall decrease of 50% during 1997-2007. There was a concomitant decline in infections due to methicillin-susceptible* S. aureus *total central-line-associated BSIs during that period as well. The reason for this favorable change in infection rates is not ascertainable from the surveillance data.*

Source: Burton DC et al. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997-2007. *JAMA*. 2009;301:727-736.

DATA COLLECTED FROM THE CDC'S TWO SURVEILLANCE SYSTEMS[1] for hospital-acquired infections tracked the rate of central-line-associated blood stream infections (CLA-BSIs) from 1997-2007. Data were not collected in 2005 during the transition between the two systems. A total of 1,684 ICUs reported CLA-BSI data to the CDC. The reporting facilities changed during the period, as facilities entered or left the program. Prior to 2007, the median number of facilities participating was 244; in 2007 the number increased to 518. The rate of MRSA CLA-BSI increased significantly from 1997 to 2001, from 0.3 to 0.4 cases per 1,000 central line days, then fell significantly from 2001 to 2007, reaching 0.2 cases per 1,000 central line days. The overall decline during the entire reporting period was 49.7%. During the entire 11-year reporting period, the rate of CLA-BSI due to methicillin-susceptible *S. aureus* declined steadily from 0.3 to 0.09 cases per 1,000 patient days, a 70% reduction. During the same period, there was a continuous and significant decrease in the rate of CLA-BSIs due to all pathogens; this decrease was consistent across ICU types.

VOLUME 28 • NUMBER 7 • APRIL 2009 • PAGES 37-48

NOW AVAILABLE ONLINE
www.ahcmedia.com

■ **COMMENTARY**

To begin with, I have a quibble with the title. It would be more accurate to bill this as "central-line-associated bloodstream infections declined substantially. . .but the decline in MRSA infections took a bit longer." MRSA accounted for less than 10% of CLA-BSIs in the units studied, and the change in the rate of MRSA infection is a very small contributor to the overall change in the rate of CLA-BSIs.

Having said that, this report shows that CLA-BSIs are clearly decreasing in ICUs — at least among those reporting through NNIS and, later, NHSN. There are some weaknesses in the way that the data were collected. Facilities entered and left the system during the reporting period, and the number of facilities participating was substantially higher in the final year of the system than in the earlier years. This could introduce reporting bias, as facilities volunteering to participate, or to continue to participate for prolonged periods of time, may be significantly different than other facilities. They may, for example, be more invested in active infection prevention. However, Burton et al examined the trends in CLA-BSIs among facilities participating during the entire reporting period and noted a decline in infection rates due to all pathogens similar to that observed in the larger group, providing reasonable assurance that there wasn't systematic bias based on the population of reporting facilities. The overall rate of catheter usage in ICUs remained stable over that period. Further, the rate changes were consistent across medical, surgical, and combined medical-surgical units.

This is certainly good news for patient safety. However, the impressive numbers leave a very large unanswered question: What was the reason for this decline in CLA-BSIs? New CDC guidelines on prevention of CLA-BSIs were published in 2002,[2] but this is unlikely to have had a dramatic effect for several reasons. First, the rates of infection due to methicillin-susceptible *S. aureus* and to all pathogens declined continuously starting in 1997. Although the reversal in the rise of the rate of MRSA CLA-BSIs was temporally associated with the guidelines, a cause-and-effect relationship is unlikely since the guidelines target infections generally, not one antibiotic resistant organism.

During the same period of the study, healthcare- and device-associated infections due to MRSA increased in the United States,[3] suggesting that the declines in overall CLA-BSIs and MRSA CLA-BSIs were independent of any MRSA control efforts.

The NNIS and NHSN data collection methodology isn't designed to answer the question. It would have been quite useful to have been able to identify any changes in practice that were associated with the decrease in infection rates. Changes in insertion techniques, catheter care, or catheter composition (i.e., antimicrobial coatings) are all potential contributors to improvements in the rates of CLA-BSIs. Unfortunately, surveillance data alone cannot provide us with any insight in that regard. Even though the data are very encouraging, it's frustrating to know the "what" without understanding the "why." ■

References

1. National Noscomial Infecions Surveillance (NNIS), 1997-2004; National Healthcare Safety Network (NHSN), 2006-2007.
2. Centers for Disease Control and Prevention. Guidelines for prevention of intravascular catheter-related infections. *MMWR*. 2002;51:1-26.
3. Klein E et al. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999-2005. *EID*. 2007;13:1840-1846

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.

AHC Media LLC

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.

In Vitro Activity of Tigecycline Against Rapidly Growing Mycobacteria

ABSTRACT AND 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: *The in vitro activities of tigecycline and 10 other antimicrobials were examined against 165 clinical isolates of rapidly growing mycobacteria. Tigecycline was the most active agent studied and inhibited all strains at ≤ 1 ug/mL.*

Source: Fernandez-Roblas R, et al. In vitro activities of tigecycline and 10 other antimicrobials against non-pigmented rapidly growing mycobacteria. *Antimicrob Agents Chemother*. 2008;52:4184-4186.

In this study, 165 clinical isolates of rapidly growing mycobacteria (including *M. abscessus*, *M. chelonae*, *M. peregrinum*, *M. fortuitum*, *M. mucogenicum*, *M. mageritense*, *M. alvei*, *M. smegmatis*, *M. porcinum*, *M. septicum*, and *M. wolinskyi*) were tested for in vitro susceptibility to tigecycline and 10 other antibiotics (erythromycin, clarithromycin, azithromycin, ciprofloxacin, levofloxacin, amikacin, tobramycin, cefoxitin, doxycycline, and trimethoprim-sulfamethoxazole) using a broth microdilution method. All isolates were inhibited in vitro by ≤ 1 ug/mL of tigecycline. Against some of the more common rapidly growing mycobacterial species, impressively low MICs were seen (*M. abscessus* MIC_{50} 0.06 ug/mL, *M. chelonae* MIC_{50} 0.12 ug/mL, *M. fortuitum* MIC_{50} ≤ 0.03 ug/mL).

■ COMMENTARY

Rapidly growing mycobacteria are not uncommonly encountered as significant pathogens by infectious disease clinicians. Over my own 30-year career, I have been involved in the management of numerous serious infections due to rapidly growing mycobacteria. In addition to the commonly encountered skin and soft-tissue infections due to local inoculation of tissue with these organisms, more complicated infections included patients who had developed sternotomy infections possibly related to contaminated bone wax, a handful of progressive pulmonary infections, orthopedic device-related infections, and even infections of indwelling venous lines. The last case I saw just a couple of months ago was a child with acute lymphoblastic leukemia who developed bacteremia due to *M. chelonae* from an infected tunneled central-venous catheter.

Obviously, removal of infected devices is of paramount importance, but antimicrobial therapy is often critically important as well. While there are no data from prospective, controlled trials to support the use of any given antimicrobial agent in the treatment of rapidly growing mycobacterial infections, most clinicians who have treated these infections believe that in vitro susceptibility testing is useful in guiding the selection of appropriate antimicrobials. The newer macrolide antibiotics (clarithromycin and azithromycin) have become mainstays of treatment of rapidly growing mycobacterial infections, but these agents are not uniformly active. In fact, some isolates of *M. fortuitum* in the present study had MIC_{90} values of > 64 ug/mL with azithromycin and 16 ug/mL with clarithromycin, levels unlikely to be achieved with normal dosing. Tigecycline is a drug with which I honestly have little personal clinical experience. However, it is definitely an agent that we will use with increasing frequency in the future, particularly as we encounter multi-drug resistant pathogens such as *Acinetobacter baumannii*. Tigecycline's dramatic activity in vitro against rapidly growing mycobacteria should be kept in mind, and this agent should be considered as part of our arsenal to treat infections caused by these organisms. ■

A Nutty Idea for Controlling the Spread of Malaria

ABSTRACT & COMMENTARY

Ellen Jo Baron, PhD, D(ABMM)

Professor of Pathology and Medicine, Stanford University; Medical School Director, Clinical Microbiology Laboratory, Stanford University Medical Center

Dr. Baron reports no financial relationships relevant to this field of study.

Malaria ranks among the world's most important infectious diseases. The last year for which good statistics have been amassed, 2006, saw 250 million cases and at least one million deaths.[1] The number of new malaria cases in the world each year dwarfs the

same statistic for other well-known scourges.[2] AIDS newly infected 2.7 million people and killed approximately 2 million in 2006.[2] Tuberculosis also killed more people than did malaria (~ 2 million), but new infections were in the range of 4-5 million.[2] Progression in malaria reduction can be attributed to several factors. The expanding use of insecticide-treated bed-nets has greatly reduced transmissions, particularly in sub-Saharan Africa.[3] In the past five years, use of such insecticide-treated bed-nets has increased more than five times. Prevention of malaria reduces the need for antimicrobial treatment and, thus, conserves limited healthcare dollars. Widespread treatment of malaria with combination therapy, particularly utilizing the Chinese herbal medicine artemisinin, also has reduced both morbidity and mortality more than 50% over the last five years.[4,5] Although the parasite has developed resistance to many Western antimicrobials in response to the widespread use, these drugs seem to regain efficacy when combined with artemisinin, a compound derived from a plant known as Sweet Wormwood (*Artemisia annua*).[3,6] Used in ancient times by Chinese herbalists to treat fevers, the herb had fallen out of favor until a Chinese herbal pharmacopeia originally written in 340 A.D. was rediscovered in 1970.[6]

One important point often overlooked when malaria statistics are quoted is epitomized by the results of a study conducted several years ago in Ghana.[7] Most diagnoses (from which prevalence statistics are derived) are clinical only. In carefully conducted trials using highly trained laboratory scientists, at best only 15% of cases diagnosed as malaria by physicians (and treated as such) were substantiated by laboratory test results.[7] Other infections, such as bacterial meningitis and sepsis, were the primary true causes of the patients' symptoms. So although it is possible that malaria is not so prevalent as has been thought, it still affects an immense proportion of the populations in tropical countries of both hemispheres.[1,2]

Rapid diagnostic tests are being suggested for resource-poor areas to aid physicians' diagnoses. Unfortunately, a new study from Mali evaluating the efficacy of one rapid test (Paracheck-Pf) compared with laboratory microscopy for *Plasmodium falciparum* diagnosis found that although the test was 83% sensitive and 79% specific, the "treat all" strategy was more cost-effective than the "test and treat" strategy.[8] This is one of several sandwich immunoassays used throughout the world. Recently a similar test was FDA-cleared for use in the United States. The Binax (Binax, Inc., Portland, Maine) is an immunochromatographic test in the same format as the Binax tests for respiratory syncytial virus and *Streptococcus pneumoniae* antigen in urine. A comparison of the malaria test to microscopy and the gold standard polymerase chain reaction showed the Binax to be 94% sensitive for the detection of *P. falciparum* malaria but only 84% for non-*P. falciparum* infections.[9] Another evaluation of the Binax performed at the patient's bedside revealed a slightly less desirable 88% sensitivity for *P. falciparum* diagnosis.[10] US laboratories are advised to use the rapid test as an adjunct to current tests and not as a replacement. Better diagnostic tests are needed along with better prevention strategies. One creative approach to prevention deserves better publicity.

Malaria is spread by the bite of the female Anopheles mosquito. Mosquito abatement has been the basis of preventive efforts throughout much of the world.[11] Removing standing water and treating ponds and other sites of larvae development with insecticides has been successful, but mosquitoes seem to develop resistance to the insecticides quickly.[12] Global climate change also seems to have extended the range of Anopheles and other mosquitoes.[13,14] A simple community-based but more sustainable mosquito larvae-killing method is needed. Recently, I worked side-by-side for a week in Mozambique with a Peruvian scientist who clearly was thinking outside of the box. Her story was so extraordinary that I wanted to write about it for this newsletter.

Dr. Palmira Ventosilla had a stroke of genius back in the mid-1990s. She was working with a strain of *Bacillus thuringiensis* (subspecies israelii), the very effective insect-larvae-destroying bacterium. Strains of this same species are used to kill pests throughout the American agricultural industry because of their virtual lack of toxicity to humans or any other organism and their single-minded attack on the larvae of insect pests. The bacterium is voracious in its destruction of mosquito larvae, but how could one provide sufficient cultures of BT1 to rural, economically-challenged communities in the malaria-prone parts of the developing world? The organism itself is expensive when purchased directly from microbial suppliers. Microbiological skills, even incubators, were non-existent. The villagers had coconuts, though, so Dr. Ventosilla created a mini-incubator in a coconut! The method is deceptively simple. You provide swabs laced with the organism's spores to the villagers, and you teach the locals (mainly schoolchildren) to recognize mosquito larvae in water. One drills a hole in the top of a coconut, swishes the swab in the coconut milk, and seals the hole with candle wax. The coconuts are allowed to sit out in the sun for several days, while the organisms multiply logarithmically in the warm coconut milk. The wax seal is then popped open and

the Bacillus-laden coconut liquid is poured onto the offending water source. The bacteria remain active for at least 45 days. Nearly complete mosquito abatement ensued, and follow-up studies in a demonstration project in a Peruvian village have shown not only major reduction in malaria, but in dengue as well.[12,15]

■ **COMMENTARY**

Using low-tech methods to deliver high-tech solutions to global problems will be the path to the future we hope to realize. Understanding the local culture and working with it, rather than above it or against it, is reaping rewards in places from Peru to India. Dr. Palmira Ventosilla is showing us the way. ■

References

1. World Health Organization. World Malaria Report 2008. WHO Press, 1211 Geneva 27, Switzerland.
2. World Health Organization Global Burden of Disease. Online publication at: http://www.who.int/healthinfo/global_burden_disease/en/
3. World Health Organization. Impact of long-lasting insecticidal-treated nets (LLINs) and artemisinin-based combination therapies (ACTs) measured during surveillance data, in four African countries: Preliminary report based on four country visits. Geneva, World Health Organization, 2007.
4. Bhattarai A et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Medicine*. 2007;4:1784-1790.
5. Wiese L, et al. Bedside diagnosis of imported malaria using the Binax Now malaria antigen detection test. *Scand J Infect Dis*. 2006;38:1063-1068.
6. Willcox ML, et al. Rapid diagnostic tests for the home-based management of malaria, in a high-transmission area. *Ann Trop Med Parasitol*. 2009;103:3-16.
7. World Health Organization. World Malaria Report 2008. WHO Press, 1211 Geneva 27, Switzerland
8. Willcox M, et al. Rapid diagnostic tests for the home-based management of malaria, in a high-transmission area. *Ann Trop Med Parasitol*. 2009;103:3-16.
9. Koram KA, et al. Comparative efficacy of antimalarial drugs including ACTs in the treatment of uncomplicated malaria among children under 5 years in Ghana. *Acta Trop*. 2005;95:194-203.
10. Zighelboim A. Malaria control in a nutshell: Palmira Ventosilla. *International Development Research Centre Reports*. 1995;22:21.
11. World Health Organization. Impact of long-lasting insecticidal-treated nets (LLINs) and artemisinin-based combination therapies (ACTs) measured using surveillance data, in four African countries: Preliminary report based on four country visits. Geneva, World Health Organization, 2007.
12. Graves P et al. Effectiveness of malaria control during changing climate conditions in Eritrea, 1998-2003. *Trop Med Int Health*. 2008,13:218-228.
13. Polage CR, et al. Laboratory use in Ghana: physician perception and practice. *Am J Trop Med Hyg*. 2006;75:526-531.
14. Reyes E. Participación communitaria en el control de la malaria. La experiencia de Salitral (Sullana, Piura). *Páginas, Centro de Estudios y Publicaciones (CEP)*. 1996;21:61-67.
15. Zighelboim A. Malaria control in a nutshell: Palmira Ventosilla. International Development Research Centre Reports. 1995;22:21.

That Troublesome Enterococcus

ABSTRACT & COMMENTARY

By John F. Joseph, MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston

Dr. John is a consultant for Cubist, Genzyme, and bioMerieux, and is on the speaker's bureau for Cubist, GSK, Merck, Bayer, and Wyeth.

Sources: Grupper M, et al. Enterococcal-associated lower respiratory tract infections: a case report and literature review. *Infection*. 200937:60-64; Bergman R, et al. Pleural *Enterococcus faecalis* empyema: an unusual case. *Infection*. 200937:56-59.

ENTEROCOCCUS USED TO BE CONSIDERED THE CABOOSE of pathogens; maybe it mattered, but it still was at the far rear. Times have changed, and the enterococcus has taken more prominence as a pathogen, particularly in nosocomial infection. Yet, in regard to pneumonia and pleural disease, it ranks far at the bottom still. In fact, some would regard its causation in pneumonia as rare.

Grupper et al from Haifa, Israel, report a case of enterococcal bacteremia apparently caused by a lower respiratory tract infection in an 81-year-old man. The patient had undergone multiple urologic procedures and resided in a nursing home. He had a ureteral stent and needed a percutaneous nephrostomy. Many antibiotic courses preceded the current admission for pneumonia. His blood culture grew *E. faecalis* susceptible to penicillin and vancomycin but highly resistant to gentamicin. The sputum

also grew *E. faecalis* with the same antibiogram. He was treated with intravenous ampicillin and did well.

Because of the rarity of the microbiologic findings in this case, Grupper et al reviewed the literature on the topic of enterococcal pneumonia. They found nine cases, with three caused by *E. faecium*. Two of the patients died; only three cases were nosocomial. Complications included lung abscess in two and septic shock in two. Penicillin resistance was common. Three of the patients had no underlying disease.

Grupper et al agree that the condition is rarely described, but they do not succumb to the idea that the rare reporting of enterococcal pneumonia accurately describes the epidemiology. They argue that the findings in their patients are very similar to pneumonia caused by more common respiratory pathogens. They also note that the enterococcus colonizes the upper airway as frequently as its bacterial counterparts. Finally, the tedium in identifying all those bacteria that seem to be normal flora surely underestimates how frequently enterococci may be in pathologic sputum.

In another unusual enterococcal case, *E. faecalis* was proven as a cause of empyema in a 63-year-old lady admitted with stroke and septic shock to a Dutch hospital in Ede, The Netherlands. The pleural fluid had only 291 cells but had a protein of 22.5 g/L. A chest tube was needed to drain the pus. Two other loculated areas developed during therapy, found during the initial chest tube drainage. Treatment with amoxicillin and clavulanic acid eventually, over five weeks of therapy, allowed resolution of the empyema and reversal of the septic shock.

■ COMMENTARY

These cases and reviews raise the specter of an ever-evolving spectrum of disease due to enterococcus. This genus is certainly no longer an innocent bystander, though these cases highlight that in some organ systems, like the lung, their pathogenicity is not well recognized. I like to think of enterococcus as a weakened hemolytic streptococcus. In fact, we once referred to the group by their Lancefield designation as a Group D streptococcus. But we have come a long way since the early classification by Rebecca Lancefield: Enterococcus now holds a premier seat as the maestro of antibiotic resistance, both inherent and acquired, and newer studies are recognizing more virulence mechanisms, some of which have an association with its antibiotic resistance (*Clin Microbiol Rev*. 2000:13:513-522).

These current reports also highlight the need to be vigilant about isolating enterococcus from otherwise sterile fluid, or when seeing enterococcal bacteremia without a common focus like the endocardium or the urinary tract. The key is to regard isolation of an enterococcus, particularly the species *E. faecalis*, as a pathogen until shown clinically that it is not. Having made that admission, the clinician's job is far from over, since the problem of eradicating the organism may not be simple and the use of synergistically bactericidal combinations may be necessary for cure.

Clearly, in this 200th year since Darwin's birth, indeed an age of recognizing evolution, particularly in bacteria as a driving force in medicine, we can look to the lowly enterococcus as the great demonstrator of the impact of antibiotic exposure in the selection of the fittest. ■

Mannose-binding Lectin Concentrations and Susceptibility to Respiratory Infections

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP

Synopsis: *Serum mannose-binding lectin (MBL) concentrations and MBL2 gene polymorphisms were examined in 473 Finnish military recruits. An MBL serum level below the median was a risk factor for respiratory infections. Of the six single-nucleotide polymorphisms (SNPs) examined in the MBL2 gene, a promoter Y/Y genotype was associated with infections.*

Source: Rantala A, et al. Mannose-binding lectin concentrations, MBL2 polymorphisms, and susceptibility to respiratory tract infections in young men. *J Infect Dis*. 2008;198: 1247-1253.

THIS EXPLORATORY STUDY INVESTIGATED THE RELATIONSHIP between respiratory infections and MBL serum concentrations and the presence of six SNPs in the MBL2 gene promoter region (alleles H/L, X/Y, and P/Q) and exon 1 (wild type allele A and variant alleles B, C, and D) using real-time PCR. In this study, 111 Finnish military recruits with asthma and 362 recruits without asthma were studied. Paired serum samples were obtained at the beginning and end of service (which was generally between six and 12 months duration), as well as paired samples for each infectious episode. No promoter region or exon 1 genotypes were associated with asthma. However,

there was a significant association between the frequency of respiratory tract infections in subjects with MBL levels above and below the mean concentration of 1087.5 ng/mL. Thirty percent of subjects under the mean vs. 16% of subjects above the mean MBL concentration had ≥ 2 infectious episodes during their term of service, and were associated with an odds ratio (OR) of 2.5 adjusted for asthma status. Similarly, a Y/Y MBL2 promoter genotype variant was associated with an OR of 2.3 for infection. A trend toward association between exon 1 alleles associated with low levels of MBL was seen but did not reach statistical significance.

■ **COMMENTARY**

Over the last 20 years, understanding of the importance of various components of the innate immune system has grown. MBL is an important serum protein that selectively recognizes the carbohydrate patterns of micro-organisms, or infected cells, then promotes opsonization directly, as well as by activation of the alternate complement pathway through the lectin system. While this study is small, the associations between MBL levels, MBL2 promoter region polymorphisms, and respiratory infections observed in this relatively homogenous population of young Finnish men are intriguing. While clearly many factors play a role in individual host susceptibility to respiratory infections (and likely vary in relative importance with different pathogens), this study sheds light on the importance of MBL in defense against common respiratory pathogens in a population of healthy individuals. Clearly, this is a fruitful area for research, and data from larger studies are eagerly awaited. ■

Management of War Wounds in Iraq

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *Sixty-eight patients whose war wounds were treated by the Plastic Surgery Department at Naval Medical Center San Diego between April 2003 and December 2005 were reviewed. Extremities were the site of injury in 91.2% of patients. Limb salvage rate was 93.6%, and was attributed to aggressive surgical management, use of wound vacuum-assisted closure, and appropriate antibiotic use.*

Source: Geiger S, et al. War wounds: lessons learned from Operation Iraqi Freedom. *Plastic and Reconstructive Surgery*. 2008; 122:146-153.

A RETROSPECTIVE REVIEW OF ONE MAJOR CONTINental United States (CONUS) tertiary care medical center's plastic surgery department's experience in the management of combat wounds was performed and included all cases seen between April 2003 and December 2005. Of the 68 patients treated, 16.2% sustained injuries to the head/face/neck, 61.8% had lower extremity injuries, 29.4% had upper extremity injuries, 15.6% had both upper and lower extremity injuries, and 35.9% had multiple sites of injuries. All patients underwent debridement within 24 hours of arrival. Almost all had wound vacuum-assisted closure dressings as part of this initial procedure. The average number of surgical procedures (mainly repeated aggressive wound debridement) was five prior to definitive closure, which was generally accomplished with a flap procedure of some type. Antibiotic-impregnated beads were used when bony defects were present and were used until delayed bone grafting was performed. Microvascular techniques were used in 27 patients. Acute osteomyelitis occurred in 24.2% of patients but, as of September 2006, only one patient had been diagnosed with chronic osteomyelitis. Bacterial contamination of the wounds by time-of-arrival at San Diego Naval Hospital was common. Organisms isolated from initial bone cultures in patients with acute osteomyelitis included *Acinetobacter baumannii* in nine, Enterobacter species in five, coagulase-negative Staph in four, Enterococcus in three, MRSA in two, and Bacillus species and Klebsiella isolated in one patient each.

■ **COMMENTARY**

During World War II, more than 25% of wounded American servicemen died of their wounds. Due to the advent of helicopter MedEvac and the use of ICUs, the mortality rate fell to less than 20% during the Vietnam War. During Operation Iraqi Freedom, the mortality rate from war wounds has been less than 10%. Factors responsible for this dramatic reduction in mortality include the routine wear of Kevlar helmets, protecting the upper cranium, and individual body armor (IBA), incorporating ceramic plates capable of stopping even assault rifle rounds, protecting much of the torso. Additionally, a wounded American soldier, airman, or marine (often suffering from a severe extremity wound as a result of either a high

velocity gunshot wound or improvised explosive device detonation) receives immediate life-saving care and initial resuscitation in the field by either a combat medic or fellow soldier who has completed rigorous training as a combat life-saver. Following this, the wounded individual is generally no more than 10 minutes by helicopter MedEvac from a Forward Surgical Team (FST), Combat Support Hospital (CSH), an Air Force EMEDS, or even the tertiary care Air Force Theater Hospital (AFTH) in Balad. At any one of these facilities, the wounded individual undergoes immediate life-/limb-saving surgery, and is then generally transported within 48 hours by fixed wing aerovac to Landstuhl Regional Medical Center in Germany, where more definitive surgery, debridement, and washout of wounds is performed. Generally, within 4-7 days, the individual is back at one of the major CONUS military medical centers for definitive care and rehabilitation.

During my own four tours of duty as an Air Force physician in Iraq since March 2003, I saw a steady evolution in the standardization of surgical techniques and confidence shown by US military surgeons in their management of horrific injuries both in theater, at Landstuhl, and at CONUS medical centers. This case series report from the plastic surgery service at San Diego Naval Hospital provides a good review of some of the important lessons learned from this experience. While caring for these brave young people with such devastating injuries is often a heart-breaking experience, it is gratifying to see so many of them survive and be able to eventually return to some type of life with good quality. Fortunately, many of these medical and surgical "lessons learned" from the wars in Iraq and Afghanistan are being transferred to the management of trauma in the civilian world. ■

Acute Mountain Sickness in Children

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Fischer reports no financial relationships relevant to this field of study. This article originally appeared in the February 2009 issue of Travel Medicine Advisor. *It was edited by Frank Bia, MD, and peer reviewed by Mary-Louise Scully. Dr. Bia is Professor of Geographic and Laboratory Medicine, Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Scully works for Sansum-Santa Barbara Medical Foundation Clinic, Santa Barbara, CA. Dr. Bia is a consultant for Pfizer and Sanofi-Pasteur, and receives funds from Johnson & Johnson, and Dr. Scully reports no financial information relevant to this field of study.*

Synopsis: *More than one-third of children traveling to relatively high altitudes experience symptoms of acute mountain sickness, but symptoms are relatively mild and usually self-limited.*

Source: Bloch J, et al. Prevalence and time course of acute mountain sickness in older children and adolescents after rapid ascent to 3450 meters. *Pediatrics* 2009;123:1-5.

FACED WITH LIMITED DATA ABOUT ACUTE MOUNTAIN sickness in children who travelled rapidly to high altitudes, Swiss researchers studied symptoms in 48 children (ages 10-17, mean age 13) who traveled 2.5 hours from low altitude (568 meters) to 3,450 meters (approximately 11,200 feet). During the subsequent two days, 38% developed symptoms of mountain sickness; most of these became symptomatic during the first few hours at altitude. Symptoms were relatively mild and decreased over the days of the study; five of the subjects took acetaminophen for headache, but no further treatment was required. Bloch et al concluded that pharmacologic prophylaxis may not be needed.

■ COMMENTARY

Acute mountain sickness presents as headache, fatigue, abdominal discomfort, dizziness, and/or sleep difficulties in individuals who have ascended to high altitude. Several factors affect the risk of developing acute mountain sickness.

Previous experience suggests that children and adults are equally affected, but that adults older than 50 years are less likely to become symptomatic.[1] Even among pre-verbal children, 22% had acute mountain sickness during their first few hours at an American ski resort at 3,488 meters elevation, while 20% of their adult companions developed symptoms.[2] Nonetheless, a recent study showed that 92% of children, and only 25% of their parents, developed acute mountain sickness after ascending within 24 hours from sea level to 3,500 meters in Chile.[3]

The rate and extent of ascent affect the risk of symptoms, but it is difficult to predict an individual traveler's risk. Bloch et al identified 38% of their pediatric subjects as being symptomatic following ascent

from 568 meters to 3,450 meters during 2.5 hours on a train. This is more than the 22% of pre-verbal children who became symptomatic during a 1.5 hour drive and brief gondola ride from 1,703 meters to 3,488 meters,[2] but less than the 84% of adults who were symptomatic following a one-hour flight from 1,300 meters to 3,740 meters in the Himalayas.[4] It is not always possible to compare results from different studies under different conditions to predict accurately the risk of acute mountain sickness for a specific traveler.

Not all childhood fussiness during vacations is due to high-altitude exposure. Several years ago, symptoms suggestive of acute mountain sickness developed in 28% of children at 2,835 meters and 21% of children vacationing at sea level.[5] Traveling children might benefit from child-friendly scheduling, age-appropriate activity planning, and symptomatic care whether they are at high altitude or not.

Acetazolamide often is used to prevent altitude sickness in travelers, but this product is not approved for this indication by the US FDA for use in children younger than 12 years of age. Bloch et al suggest that preventive medication might not be needed in children since the symptoms were mild in their 48 subjects and diminished over two days. Alternatively, one might argue that acetazolamide is relatively safe when used for brief periods, and that avoiding a day of ill feelings is of great enough benefit to accept the small cost and risk of treatment. (Similarly, antibiotics routinely are used in travelers who develop diarrhea even though antibiotics are relatively safe, and travelers' diarrhea is usually mild and self-limited.) Rather than discourage the use of acetazolamide in children and adolescents, one might suggest that the use of the product be individualized based on personal risk-benefit considerations. Travelers with a previous history of acute mountain sickness are at greater risk of recurrent symptoms and likely would warrant preventive treatment. Pediatric travelers ascending rapidly, becoming active immediately upon arrival, and performing critically important tasks might also be provided appropriately with pharmacologic prophylaxis.

High-altitude pulmonary edema is much less common but much more severe than simple acute mountain sickness. Risk factors for high-altitude pulmonary edema in children include pre-existing viral upper respiratory infection[6] and trisomy 21.[7] It is likely that lower oxygen saturations are involved in triggering symptomatic altitude illness in these and other susceptible individuals. Even normal children have low oxygen saturations at high altitude; an oxygen saturation of 90% should be considered normal at 2,500 meters elevation and 85% is normal at 3,200 meters elevation.[8] (New data suggest that the oxygen saturation in adult mountaineers breathing ambient air at 8,400 meters just after initiating a descent from the summit of Mount Everest is about 54%.[9])

Children living long term at high altitude also face health risks, but several of these risks seem to be moderated by population-specific genetic factors.[10] What else is new for high-altitude travelers? Travelers journeying between Golmud, China and Lhasa, Tibet now can enjoy the comforts of oxygen-supplemented train cars during their 14-hour voyage.[11] ■

References

1. Basnyat B, Murdoch DR. High-altitude illness. *Lancet*. 2003;361:1967-1974.
2. Yaron M, et al. The diagnosis of acute mountain sickness in preverbal children. *Arch Pediatr Adolesc Med*. 1998;152:683-687.
3. Moraga FA, et al. Acute mountain sickness in children and their parents after rapid ascent to 3500 m (Putre, Chile). *Wilderness Environ Med*. 2008;19: 287-292.
4. Murdoch DR. Altitude illness among tourists flying to 3740 meters elevation in the Nepal Himalayas. *J Travel Med* 1995;2:255-256.
5. Theis MK, et al. Acute mountain sickness in children at 2835 meters. *Am J Dis Child* 1993;147:143-145.
6. Durmowicz AG, et al. Inflammatory processes may predispose children to high-altitude pulmonary edema. *J Pediatr* 1997;130:838-840.
7. Durmowicz AG. Pulmonary edema in six children with Down syndrome during travel to moderate altitudes. *Pediatrics* 2001;108:443-447.
8. Subhi R, et al. When should oxygen be given to children at high altitude? A systematic review to define altitude-specific hypoxaemia. *Arch Dis Child* 2009;94:6-10.
9. Grocott MPW, et al. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009;360:140-149.
10. Niermeyer S. Children's health and high altitude living. *Arch Dis Child* 2009;in press but available as doi:10.1136/adc.2008.141838.
11. West JB. A new approach to very-high-altitude land travel: The train to Lhasa, Tibet. *Ann Intern Med* 2008;149:898-900.

CME Questions

19. Which of the following is correct with regard to the CDC study of central line bacteremias?

a. The incidence of central-line-associated MRSA bacteremia decreased while all other central-line-associated pathogens increased.
b. During the same period that the incidence of MRSA central-line-associated bacteremias decreased, the total incidence of healthcare- and device-associated MRSA infections increased.
c. The decrease in central-line-associated MRSA bacteremias was due to the use of nasal mupirocin.
d. The decrease in central-line-associated MRSA bacteremias was due to the use of routine vancomycin prophylaxis.

20. Which of the following is correct with regard to the in vitro activity of tigecylcine?

a. *Mycobacterium abscessus* is suceptible, while *Mycobacterium chelonae* is resistant.
b. *Mycobacterium fortuitum* is suceptible, while *Mycobacterium chelonae* is resistant.
c. *Mycobacterium abscessus* is suceptible, while *Mycobacterium fortuitum* is resistant.
d. *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum* are each susceptible.

21. Which of the following is correct?

a. Children are almost totally non-suceptible to acute mountain sickness.
b. Severe acute mountain sickness is common in children.
c. Acute pulmonary edema is more common than acute mountain sickness in children who ascend to altitude.
d. Because it is generally mild and short-lived, chemoprophylaxis of acute mountain sickness is not routinely warranted in children.

Answers: 19. (b); 20. (d); 21. (d)

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 (e.g., AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

Parenteral Acyclovir Shortage

UPDATES

By Carol A. Kemper, MD, FACP

MRSA at the Zoo

Source: Methicillin-resistant Staphylococcus aureus skin infections from an elephant calf — San Diego, CA, 2008. *MMWR Morb Mortal Wkly Rep*. 2009;58:194-198.

An increasing number of reports document transmission of MRSA between humans and animals, including people and their pets, horse trainers, and farm personnel. Various MRSA genotypes have been found circulating among farm workers, especially among pig farmers. Reports from the Netherlands documented the emergence of a novel clone of non-typable MRSA since 2003-2004, which has since been found in nearly one-fourth of patients hospitalized with MRSA in that country (MRSA in Pig Farmers. *Infectious Disease Alert*. 2008;27: 119.). MRSA also has been found in pig farmers in Ontario, Canada.

This recent MMWR report details the results of an investigation of a number of cases of MRSA infection stemming from contact with a baby African elephant at a San Diego zoo. The mother elephant had complications at birth (though has since recovered) and was unable to nurse, so the calf, which was born two weeks premature, required extensive care and feeding, as well as a central line for total parenteral nutrition. According to the report, the handlers blew air into the calf's nose to stimulate bottle feeding. About three days after the central line was placed, the calf developed cellulitis at the entry site, followed by recurrent skin pustules, all of which were culture positive for MRSA. The development of MRSA infection in several of the animal providers prompted further investigation. In total, 20 individuals were affected by this outbreak, including two with documented MRSA infection, 15 with suspected infection, and three persons with MRSA colonization, all of whom provided care for the animal. All of the isolates were MRSA USA300 by PFGE. Because the mother elephant was culture-negative for MRSA, it is suspected that one of the handlers was previously colonized with MRSA, resulting in infection in the calf.

This is not the first article to suggest that elephants with respiratory infection may present an increased risk of transmissibility. A case of TB in a circus elephant resulted in a number of exposures among circus personnel and other elephants. Their large trunks, with extensive mucous membranes and dripping nostrils, are optimal for transmitting infection, such as nasal colonization with MRSA.

Sadly, the baby elephant failed to thrive and was euthanized. The autopsy showed enterococcal endocarditis.

Implications of Maraviroc in Other Infections?

Roukens AH, et al (Correspondence). AIDS 2009; 23: 000.

It is well-recognized that the chemokine receptor CCR5 functions as a co-receptor for HIV, while the CCR5-32 gene deletion mutation confers resistance to HIV infection in the homozygous state and is associated with a slower progression of HIV infection when in the presence of single allele. Thus, the newer HIV drug, maraviroc, was designed to act as an antagonist for the CCR5 receptor, effectively mimicking the CCR5 32 mutation and slowing the progression of HIV.

Since the discovery of the CCR5-32 mutation, there has been intense interest in the evolutionary implications of this gene deletion. Some theorize this gene deletion may have conferred an evolutionary advantage, as it appears to have emerged (or diverged) in differing populations around the 15th to 16th centuries, perhaps because of epidemics such as the plague during those years.

Roukens et al postulate that antagonism of the CCR5 receptor in patients receiving maraviroc may have other unintended consequences. Epidemiologic and laboratory data suggest that the CCR5-32 mutation may be associated with increased severity of flavivirus infection, such as tick-borne encephalitis and yellow fever. One report described a patient with severe yellow fever vaccine-associated viscerotropic disease, who was heterozygous for the CCR5-32 mutation. Although yellow fever vaccination of HIV+ persons was previously discouraged in the 1990s, HIV-infected persons with CD4 counts > 200 cells/microliter now can be safely immunized per current ACIP recommendations. The use of maraviroc in some HIV-infected patients may prompt rethinking of these recommendations. Although not yet widely used in developing countries where yellow fever is endemic, it is not known whether the use of maraviroc

should be discouraged in those non-immune to yellow fever.

HCV infection also prompts CCR5 chemokine signaling, resulting in gamma interferon production; gene deletion may result in a subtle reduction in that response, the clinical significance of which is not clear. Sub-studies of HIV-infected patients, co-infected with HCV, who are receiving maraviroc, do not appear to have more severe liver impairment or abnormal liver function studies.

Impact of Legalization of Prostitution on Sexual Behavior

Source: Seib C, et al. Commercial sexual practices before and after legislation in Australia. *Arch Sex Behav*. 2008 Dec 30. [Epub ahead of print]

THIS FASCINATING ARTICLE FROM the Schools of Nursing and Public Health in Queensland, Australia, delves into the changes in the sex trade that occurred following the legalization of prostitution in Australia in 1992 and 1999. This legislative change allowed for licensed sex workers to operate as sole proprietors or to work for licensed brothels, though a smaller, illegal (largely street) trade still remains.

Two-hundred female sex workers (ages 16-46 years) were recruited for this cross-sectional survey in 1991, and compared to similar data obtained from 247 female sex workers (ages 18-57 years) recruited in 2003. Most of the female subjects were recruited by word of mouth. In addition, 161 male clients (ages 19-72 years) were recruited from legal establishments for comparison with the female responses, including assessment of what services they would prefer to pay for and what they actually received.

During the intervening 12 years, substantial changes in the sex industry in Australia occurred. Seib et al liken the legal sex trade to any other "mature market economy," with integration of the trade into the business community, the tax system, and with provisions for employee health and safety, and employee rights vs. customer rights. Legally employed sex workers receive compulsory training in safe sex and safe sex negotiation, visual screening for STDs, and training in personal protection. The legal brothels employ strict no smoking/no drugs/no alcohol policies and a compulsory condom policy.

Female workers in 1991 were recruited from escort services (52%), the street (16%) or other sole operators (26%), or from illegally run brothels (16%). By 2003, the sample included woman recruited from licensed brothels (41%), legal sole proprietorships (42%), as well as a lesser number who remained illegal (17%), most of whom worked the street. Workers and clients were surveyed regarding their requested and provided services, sex behaviors, use of condoms, incidence of STDs, substance abuse, marital status, and relationship satisfaction. From 1991 to 2003, fewer of the women were Australian by birth (84% vs. 69%, respectively), fewer were single and never married, and there was an increase in the number of women with children (27% vs. 53%, respectively).

Major differences occurring between 1991 and 2003 included an increase in the diversity of services, especially what would be considered more exotic and dangerous activities, as well as a significant increase in the use of condoms and a reduction in unprotected oral sex (including a reduction in oral sex with ejaculation). Lesbian double acts, cross-dressing, fetish-type activities, and use of sex toys, as well as urination during sex, were significantly increased by 2003, as were bondage, discipline, and submission activities. There was also a trend toward an increase in anal sex and fisting, although more men appeared to request these services than received them. The proportion of sex workers providing the "usual" sexual activities, such as vaginal sex, mutual masturbation, and massage did not significantly change, although there was a slight decline in the proportion who provided only vaginal sex, as well as the number of sex workers who had ever provided oral sex without a condom.

Responses between legal sex workers and clients in 2003 were fairly consistent, indicating that men generally received the services requested, with few exceptions; there did appear to be a greater demand for anal sex, fisting, and urination during sex than available providers.

A significant proportion (70%) of female sex workers reported receiving oral sex from clients in 2003, which Seib et al suggest may be due to a more consistent or assumed personal relationship. By 2003, the number of men having sex with a variety of women had decreased (65% vs. 47%), and the frequency of visits to legal establishments had increased, especially those visiting sole proprietorships.

In contrast, sex activities and provided services did not significantly change for illegal workers between 1991 and 2003. Illegal sex workers were more likely to give unprotected oral sex, as well as anal sex, and least likely to use sex toys or to receive oral sex, suggesting that illegal workers had a more limited ability to negotiate safer sex or specific practices. Interestingly, there was a lower availability of more "dangerous" activities, such as fisting and bondage in the illegal sector. Although this was not specifically addressed by Seib et al, it may be that illegal street workers, with a more tentative hold on their trade, cannot make the investment in equipment, props, and toys that a legal worker, with a stable job and a stable venue, may. ■

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*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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.

0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■