Providing Evidence-based Clinical Information for 23 Years

INFECTIOUS DISEASE ALERT®

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

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON AMERICAN HEALTH CONSULTANTS

INSIDE

Malaria in Peace and War

ABSTRACT AND COMMENTARY

Synopsis: *Malaria remains a serious threat to both tourists and deployed military personnel. Areas once thought to be relatively risk free may later be associated with transmission of malaria, requiring public health vigilance and regular updating of prophylaxis recommendations.*

Sources: CDC Transmission of Malaria in Resort Areas-Dominican Republic, 2004. *MMWR.* 2005;53:1195-1198; Kotwal RS, et al. An Outbreak of Malaria in US Army Rangers Returning From Afghanistan. *JAMA.* 2005;293:212-216.

KAY AND COLLEAGUES FROM CDC DESCRIBE 3 CASES OF FALCIparum malaria presenting in November 2004 in travelers from the United States returning from resort areas in La Altagracia and Duarte provinces in the Dominican Republic. These areas in the far eastern region of the island of Hispaniola had previously been regarded as nonmalarious. All 3 patients had significant delay in correct diagnosis and suffered severe malaria associated with high level parasitemia, and their clinical courses were complicated by acute respiratory distress syndrome, requiring mechanical ventilation, acute renal failure requiring hemodialysis, and cerebral malaria in at least 1 of the cases. An additional 14 cases of malaria have been reported in European and Canadian travelers returning from La Altagracia Province.

Kotwal et al describe an outbreak of vivax malaria involving 38 soldiers from a 725-man Ranger Task Force which had been deployed to eastern Afghanistan between June and September 2002. Of note, was the delayed presentation of many of these patients with a median duration of 233 days (range, 1-339 days) after return from the malaria endemic region. From a post-deployment survey of 521 members of the task force, it was noted that the self-reported compliance rate was 52% for weekly chemoprophylaxis, 41% for terminal prophylaxis, 31% for both weekly and terminal prophylaxis, 82% for treating uniforms with permethrin, and 29% for application of insect repellant.

COMMENT BY DEAN WINSLOW, MD, FACP

Malaria remains a major infectious disease scourge in the developing world, with up to 500 million estimated cases and several million deaths annually.[1] Malaria is largely ignored by the majority of people in the developed world until it strikes home. This most often occurs when we venture forth to malaria endemic regions as either voluntary civilian tourists or as military armed tourists in the service of our country.

The CDC report is of interest for several reasons. The diagnosis appears to have been significantly delayed in all 3 of the cases occurring in US travelers, resulting in multi-organ system complications. The development of malaria in individuals returning from what had been considered to be non-malarious areas, points out the likely influence of climatic events on changes in the regional epidemiology of this disease. In September 2004, Hurricane Jeanne struck the Caribbean islands on its way northward and caused heavy rains and flooding, markedly increasing the risk of transmission due to providing standing water to facilitate the increased breeding of the Anopheles albimanus mosquitoes, the predominant malaria vector in the Dominican Republic. It is of note that a previous outbreak of malaria in European travelers to the eastern part of the Dominican Republic occurred during July 1999-March 2000 in the wake of hurricanes Mitch and George.[2] At that time, the CDC temporarily expanded its travel recommendations to recommend chloroquine prophylaxis for all areas of La Altagracia Province; this recommendation was rescinded 2 months later after the Dominican Republic Ministry of Health increased surveillance and controlled the outbreak. In November 2004, the CDC again expanded its recommendations for chloroquine prophylaxis to include both La Altagracia and Duarte Provinces.[3]

The outbreak of vivax malaria in US Army Rangers returning from deployment to Afghanistan reported by Kotwal et al raises several practical issues for malaria chemoprophylaxis and physical preventive measures. While most individuals taking a 2-3 week vacation to a malarious area will comply with physical preventive measures and chemoprophylaxis, it is much more difficult to do so when one is deployed for 120 days or more. While not specifically addressed by Kotwal et al, the poor compliance with insect repellant (DEET is issued to US military personnel.) may have been related to odor, which could potentially result in tactical compromise of special operations. Additionally, the necessity of conducting night combat operations would be expected to maximize exposure to the mosquito vector. It is not widely appreciated by either commanders or physicians that chemoprophylaxis is not 100% effective, even with good compliance with medication. An outbreak of falciparum malaria in a total of 80 US Marines deployed to Liberia in September 2003 was recently reported.[4] This earlier outbreak was closely studied by the team at National Naval Medical Center in Bethesda, and a number of potentially important factors were identified. While most individuals had detectable levels of mefloquine in their blood, compliance was not perfect. In addition, since it was originally anticipated that the marines would be ashore for only 2-3 days (rather than the 10-12 nights they ended up spending in Liberia), they did not deploy with bed nets.

Due to the co-existence of chloroquine resistant *P. falciparum* in the Indian subcontinent and immediately adjacent areas including Afghanistan, the US military provides mefloquine for non-flying personnel and doxycycline to flyers deployed to the Afghanistan area of operational responsibility (AOR). (In Eastern Turkey

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.

VICE PRESIDENT/GROUP PUBLISHER:
Brenda Mooney.

EDITORIAL GROUP HEAD: Lee Landenberger.

MARKETING PRODUCT MANAGER:
Schandale Kornegay.

MANAGING EDITOR: Robert Kimball.

ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

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.

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.

THOMSON
AMERICAN HEALTH CONSULTANTS

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@ahcpub.com
E-Mail Address: leslie.hamlin@thomson.com
World-Wide Web: www.thomson.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
(Student/Resident rate: $125).

Multiple Copies
Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 36 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.
AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.
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,
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.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Deresinski serves on the speaker's bureau of Merck, GlaxoSmithKline, Ortho, Bayer, and Pfizer. Dr. John is a consultant for Cubist, Roche, and BioMerieux, is on the speaker's bureau of Merck, Pharmacia, GlaxoSmithKline, Bayer, and Wyeth, and does research for Merck. Dr. Kemper serves on the speaker's bureau of Virologic, GlaxoSmithKline, Pfizer, and Agouron and is involved in research with Chiron, Merck, Agouron, and Virologic. Dr. Schleis is on the speaker's bureau for Aventis and Bayer and is a consultant for FFF Enterprises, Aventis, and Bayer. Dr. Muder does research for Aventis, and Pharmacia. Dr. Tice is a consultant for Roche, Merck, and ZLB and is on the speaker's bureau of Roche, Ortho, GlaxoSmith-Kline, and Pharmacia, and does research for Elan, Roche, Merck, Pharmacia, and Becton-Dickinson. Dr. Jenson is on the speaker's bureau of Merck. Dr. Donnelly is a consultant for OrthBioTech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer. Dr. Smilack reports no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.

Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

and Iraq at least 95% of malaria is vivax, so chloroquine is used in the Iraq AOR.) Unfortunately, mefloquine causes CNS side effects (including dysphoria, dreams, mood changes, and other transient neuropsychiatric reactions) in up to 5% of individuals. From personal experience while deployed with the US Air Force during this latest war, doxycycline malaria chemoprophylaxis, when taken daily for weeks at a time, frequently causes nausea, bloating, and loose stools. If taken on an empty stomach, especially before going to bed, severe esophagitis may occur. In addition, photosensitivity can be a significant problem with doxycycline.

An earlier outbreak of malaria reported among US military personnel returning from Somalia in 1993 is also illustrative of the importance of the use of terminal prophylaxis in areas where vivax (and ovale) malaria risk is high.[5] The major malaria threat in Somalia was judged to be *P. falciparum*, so only chemoprophylaxis with either mefloquine or doxycycline was given in most cases. Terminal prophylaxis with primaquine was rarely given and not supervised after redeployment in the cases where it was prescribed. As a result, of the 83 Army and Marine Corps personnel with documented malaria infections, 77% had vivax, 17% falciparum, 4% had mixed vivax and falciparum infection, and ovale was detected in 1 patient.

These reports remind us of the importance of malaria as a cause of fever and severe illness in travelers. Accurate and up-to-date medical intelligence is critical so that appropriate chemoprophylaxis can be prescribed. Prevention of malaria in travelers and military personnel is, also, more than just compliance with chemoprophylaxis. It is multilayered and must include bed nets and personal protective measures including using DEET, treating uniforms/clothes with permethrin, and such seemingly unimportant measures as keeping sleeves rolled down. ■

References

1. Greenwood B. Malaria Mortality and Morbidity in Africa. *Bull World Health Organ*. 1999;77:617-618.
2. Jelinek T, et al. Falciparum Malaria in European Tourists to the Dominican Republic. *Emerg Infect Dis.* 2000;6:537-538.
3. CDC. Outbreak Notice: Advice For Travelers About Revised Recommendations For Malaria Prophylaxis in Dominican Republic; updated December 17, 2004.
4. Martin GJ. Lack of Preparation Led to Malaria Outbreak Among Marines. US Medicine Information Central 2003; (online citation) December 2003.
5. CDC. Malaria Among US Military Personnel Returning From Somalia, 1993. *MMWR.* 1993;42:524-526.

Corticosteroids in the Treatment of Severe Community-Acquired Pneumonia

ABSTRACT & COMMENTARY

Synopsis: *Hydrocortisone administration to patients with severe community-acquired pneumonia was associated with improved oxygenation, radiographic clearing, hospital length-of-stay, and patient survival.*

Source: Confalonieri M, et al. Hydrocortisone Infusion For Severe Community-Acquired Pneumonia: A Preliminary Randomized Study. *Am J Respir Crit Care Med*. 2005;171:242-248.

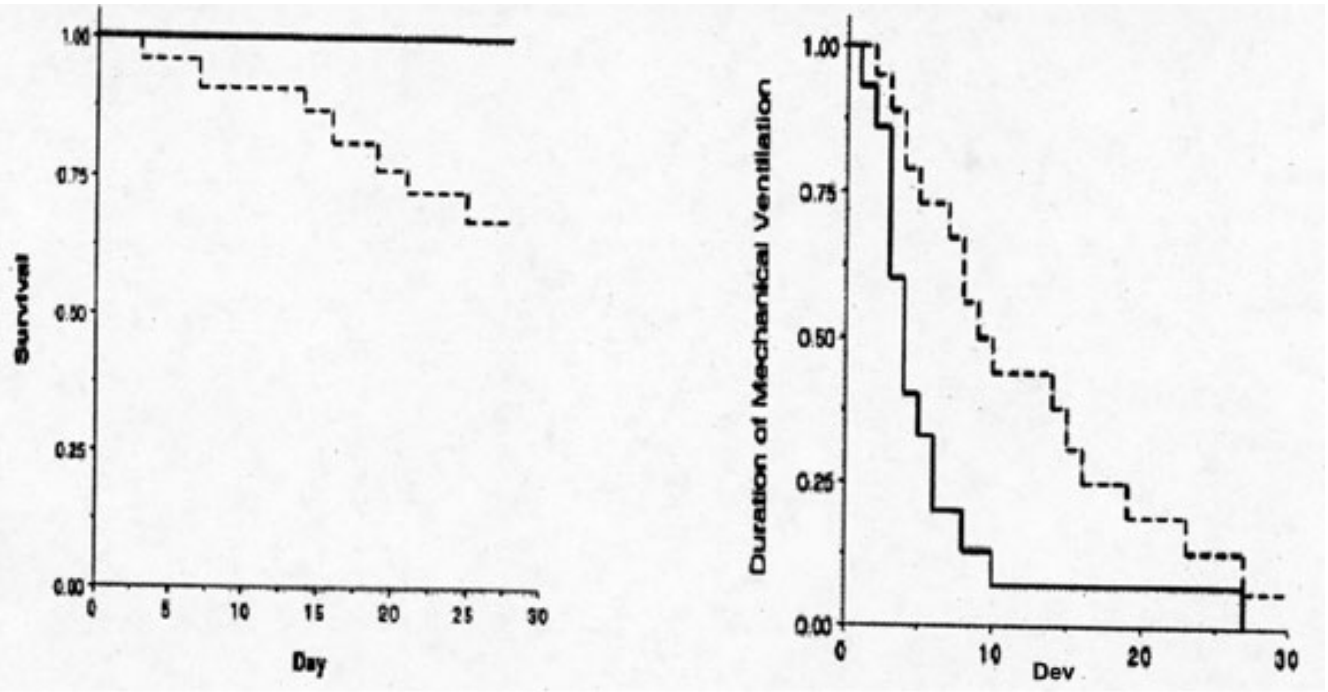
FORTY-SIX PATIENTS WERE ENTERED INTO A PROSPECTIVE randomized, double-blind, placebo-controlled trial conducted at 6 Italian hospitals over a nearly 3-year period. All patients had severe community-acquired pneumonia (as defined by generally accepted criteria, but see comment below); 34 of the 46 required mechanical ventilation. The hydrocortisone a3rm of the study employed a 200-mg initial dose followed by a constant daily infusion of 240 mg over a 7-day period. Most patients received a macrolide, usually in combination with a third- or fourth-generation cephalosporin, fluoroquinolone, anti-pseudomonal penicillin, or aminoglycoside. Antimicrobials were modified in slightly more than half of the patients either because of the patients' failure to improve or because of identification of specific pathogens (such as Staphylococcus aureus or legionella).

At study entry, patients randomized to receive hydrocortisone were sicker, as reflected in lower PaO_2:FIO_2 ratios (141 vs 178) and more extensive radiographic involvement. Primary end points of the study were improvement in PaO_2:FIO_2 ratio to greater than 300 (or an increase of >100 compared with entry into the study) and in multiple organ dysfunction syndrome score, as well as development of delayed septic shock (not specifically defined in the study). Secondary end points included duration of mechanical ventilation, length of intensive care unit and hospital stay, and survival.

Confalonieri and colleagues reported that significant benefit was found in hydrocortisone-treated patients. Oxygenation (measured by the PaO_2:FIO_2 ratio) improved significantly in 87% (compared with 39% of placebo recipients), as did the chest radiograph (91% vs 22%, steroid vs placebo), C-reactive protein levels, mul-

Figure 1

Survival curve (left figure) and time to removal of mechanical ventilation (right figure) in patients randomized to hydrocortisone (solid lines) and placebo (dashed lines).



Source: Confalonieri M, et al. Hydrocortisone Infusion For Severe Community-Acquired Pneumonia: A Preliminary Randomized Study. *Am J Respir Crit Care Med*. 2005;171:242-248.

tiple organ dysfunction score, need for mechanical ventilation (26% vs 65%), and appearance of delayed shock (0% vs 43%). Intensive care unit and overall hospital length-of-stay was shortened, and survival-to-hospital discharge increased (*see Figure 1*).

Although not statistically significant, adult respiratory distress syndrome, nosocomial infection, acute renal failure, and other complications occurred more frequently in the placebo group. No side effects appeared to be related to hydrocortisone therapy.

COMMENT BY JERRY D. SMILACK, MD, FACP

This provocative study by Confalonieri et al adds to accumulating evidence that corticosteroids may have a role in management of critically ill patients. The design and conduct of the study were well conceived and executed, although I might quibble somewhat with inclusion of 1 major criterion for the definition of severe pneumonia: presence of a serum creatinine of 2 mg/dL. This 1 criterion alone could result in classification of an otherwise ordinary pneumonia as severe pneumonia. Confalonieri et al do not indicate how many patients were classified as such solely as a result of this definitional oddity.

Annane and colleagues' seminal study of the use of hydrocortisone and fludrocortisone in patients with septic shock clearly demonstrated a salutary effect of these agents, particularly in the subset with relative adrenal insufficiency.[1] A recent meta-analysis concluded that low-dose hydrocortisone, when given for 5 to 7 days and then tapered over a similar period, increases survival and reverses shock in patients with pressor-dependent shock.[2]

The study by Confalonieri et al, although quite impressive, enrolled only 46 patients. It will be critical to see confirmation of their findings by other investigators studying larger numbers of patients, before concluding that all patients with severe community-acquired pneumonia should be treated with corticosteroids. ■

References

1. Annane D, et al. Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock. *JAMA*. 2002;288:862-871.
2. Minneci PC, et al. Meta-Analysis: The Effect of Steroids on Survival and Shock During Sepsis Depends on the Dose. *Ann Intern Med*. 2004;141: 47-56.

What a Crab to Diagnose and Monitor Invasive Aspergillosis

ABSTRACT & COMMENTARY

Synopsis: *Invasive aspergillosis among neutropenic patients could be reliably diagnosed using a commercial test Fungitell ™ to detect the cell wall component (1->3)-ß-D-glucan of certain fungi, including Aspergillus. However, diagnosis was more accurate when both (1->3)-ß-D-glucan and galactomannan were detected.*

Source: Pazos C, et al. A Contribution of (1->3)-ß-D-glucan Chromogenic Assay to Diagnosis and Therapeutic Monitoring of Invasive Aspergillosis in Neutropenic Patients: A Comparison With Serial Screening For Circulating Galactomannan. *J Clin Microbiol.* 2005;43:299-305.

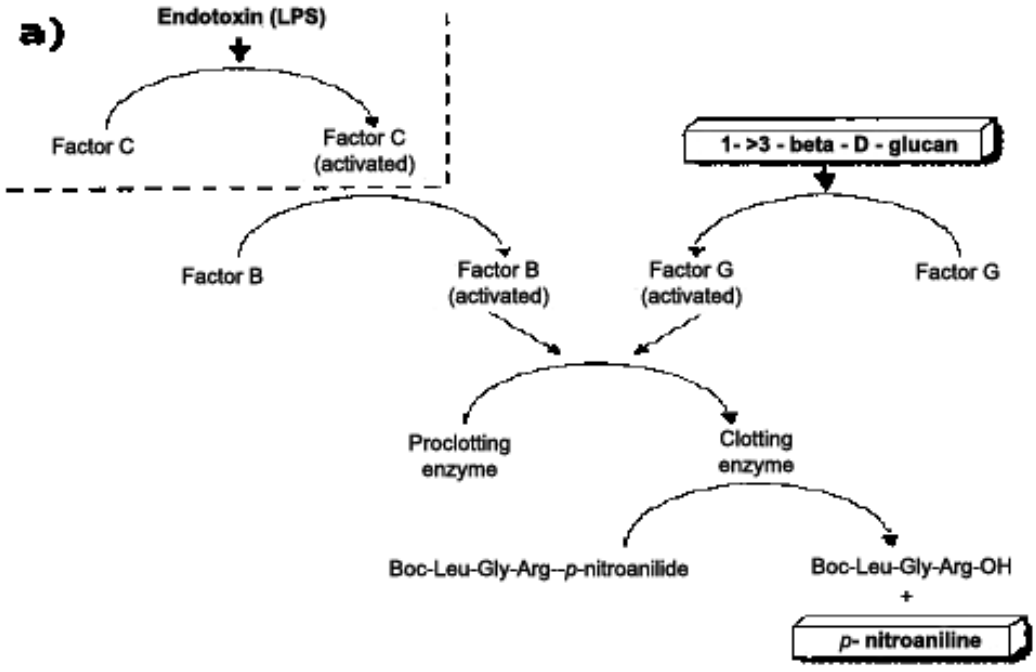
SERUM FROM FORTY NEUTROPENIC PATIENTS WAS USED retrospectively to determine what serum (1>3)-ß-D-glucan (BDG) measurement might contribute to the diagnosis of invasive aspergillosis (IA) among neutropenic patients at high risk of developing invasive aspergillosis (IA).

Pazos and colleagues had already defined 40 of 125 consecutive neutropenia patients at high risk according to the EORTC/MSG definitions as having proven IA (5 cases), probable IA (3 cases), possible IA (3 cases), with their being no evidence of IA found in the remaining cases. The detection of galactomannan was used to provide part of the mycological evidence. The serum left over was stored at -70°C, until tested for BGD using a commercial test Fungitell (formerly known as Glucatell). The assay was first developed as the G-test in Japan over a decade ago and uses amoebocytes from the same hermit crab *Limulus polyphemus* used to detect endotoxin. Removing Factor C allows detection of (1->3)-ß-D-glucan but not endotoxin (*see Figure 2*). As little as 32 ng/L (1->3)-ß-D-glucan can be detected, but a threshold of at least 60 ng/L has been set to eliminate background levels. The test has recently been cleared for diagnostic use by the FDA and is now available in the United States.

Pazos et al found that BGD was detected in the serum of all proven cases, 2 of the 3 probable cases, 1 of the 3 possible cases, and in 3 of the 29 cases without IA. The

Figure 2

Removing C Factor



Source: Pazos C, et al. A Contribution of (1->3)-ß-D-glucan Chromogenic Assay to Diagnosis and Therapeutic Monitoring of Invasive Aspergillosis in Neutropenic Patients: A Comparison With Serial Screening For Circulating Galactomannan. *J Clin Microbiol.* 2005;43:299-305.

course of BDG in serum was similar to that of galactomannan, but BGD was detected earlier and rose sooner. The sensitivity, specificity, and positive and negative predictive values for both BGD and galactomannan tests were also identical, being 87.5%, 89.6%, 70%, and 96.3%, respectively, assuming that only proven and probable cases represented true cases, and that those classified as not having IA did not have the fungal disease. However, performance of both markers could improve diagnostic efficiency when the results were combined, yielding a sensitivity, specificity, and positive and negative predictive values of 87.5%, 100%, 100%, and 96.3%. This was because each test could be used to identify false reactions in the other test. Pazos et al concluded that a proper, prospective evaluation ought now to be done, given the encouraging results of their study.

COMMENT BY J. PETER DONNELLY, PhD

It may seem very odd that after more than a decade in the wilderness, we now have a test for BGD that is commercially available and appears to highly efficient in contributing to the diagnosis of IA in neutropenic patients. Even more surprisingly, combining the test results of BGD detection with those of the galactomannan assay improves the efficiency. But before we get completely carried away, a few observations are worth noting. Firstly, a ratio of =1.5 for the galactomannan was considered positive, whereas, in the United States, the threshold is set at =0.5. Next, only a minority of their patients received any antifungal prophylaxis; 9 of the 40 or 22%, to be exact. In addition, they adopted a threshold of 120 pg/mL for BDG, not the manufacturers level of 60 pg/mL, without saying why. Most importantly, the cases were classified on the basis of the EORTC/MSG criteria, which requires mycological evidence by microscopy, culture, or galactomannan assay of appropriate specimens before a clinically defined case can be upgraded from possible to probable IA. Consequently, failure to obtain such specimens weighs equally with negative results. So, translating these results to other centres demands caution.

Interestingly, the dynamics of BDG were similar to those of galactomannan, indicating that either could be used to monitor treatment. Moreover, twice weekly screening for the presence of both markers appears sufficient. The fact that 1 test helped identify false-positive results with the other test is encouraging, but would add to the cost of screening, which may deter clinicians from ordering either. This would be a pity, since screening of the 2 tests together with an early CT scan might result in lower overall costs by helping better differentiate between those patients who need antifungal therapy and those who don't. Indeed, if there really are so few cases of IA amongst patients at similar high risk (namely 8 of 154 [5%]), as found by Pazos et al, a strategy that efficiently separates proven and probable cases from the rest may prove very cost-effective, if only these patients are treated with antifungal therapy and the remainder were given empirical therapy for not more than a week, whilst the diagnosis is being pursued or better still none at all. Having got this far, it would now be really helpful if this or another group could show the contribution of PCR alongside BGD and GM to the diagnosis of IA.

The test is tailored to detect 1-3 ß-D-glucan by removing Factor C (a). Factor G is activated by BGD, the product and activated factor B help produce the clotting enzyme and this, in turn, cleaves the subtrate Boc-Leu-Gly-Arg-p-nicroanaline to release the yellow coloured. There is thus a direct relationship between the amount of BGD in the sample and the release of of p-nicroanaline. ■

Reference

1. Ascioglu S, et al. Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients With Cancer and Hematopoietic Stem Cell Transplants: An International Consensus. *Clin Infect Dis.* 2002;34:7-14.

Antiretroviral Prophylaxis After Nonoccupational Exposure to HIV

ABSTRACT & COMMENTARY

Synopsis: *Postexposure prophylaxis (PEP) with effective antirtrovirals should be instituted within 72 hours substantial nonoccupational exposure to HIV.*

Source: CDC Antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV in the United States. MMWR 2005; 54(RR02):1-20. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.html

THE CDC PUBLISHED ITS FIRST RECOMMENDATIONS for management of exposure to HIV in the occupational setting in 1990, at a time when the only available antiretroviral was zidvudine.[1] They first addressed the issue of non-occupational exposure in print in 1998, at which time they, however, concluded that the available evidence for or against post-exposure prophylaxis (PEP) in this setting was

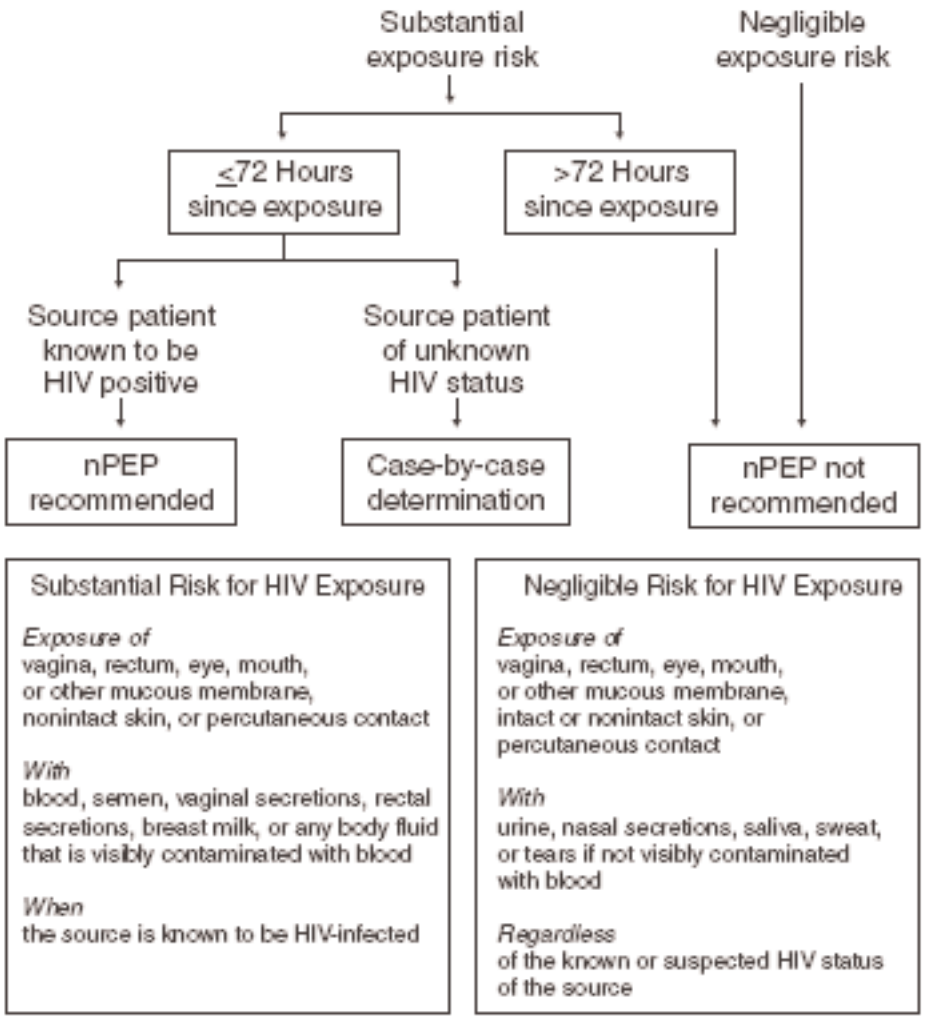
Table 1

Estimated per-act risk for acquisition of HIV

Exposure Route	Risk Per 10,000 Exposures to an Infected Source
Blood transfusion	9000
Needle-sharing	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

Figure 3

Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



Source: www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.html

inadequate to allow them to make a recommendation applicable to the United States.[2] Since then, a great deal of information has become available.

Data from animal and human studies provide clear evidence that the initiation of antiretroviral therapy within 48 to 72 hours after nonoccupational exposure to HIV is likely to reduce the risk of transmission. This document considers a nonoccupational exposure to be "any direct mucosal, percutaneous, or intravenous contact with potentially infectious body fluids that occurs outside perinatal or occupational situations (eg, health-care, sanitation, public safety, or laboratory employment). Potentially infectious body fluids are blood, semen, vaginal secretions, rectal secretions, breast milk, or other body fluid that is contaminated with visible blood."

They recommend prompt institution of PEP within 72 hours after such exposures when the source is known to be HIV infected and the exposure is substantial (*see Figure 3*). The estimated risks of various exposures are listed in *Table 1*.

In cases in which the HIV status of the source is unknown, PEP is not recommended, but clinicians and patients are encouraged "to weigh the risks and benefits on a case-by-case basis." In addition, in instances in which patients seek care more than 72 hours after substantial exposure, clinicians might consider prescribing PEP "if, in their judgment, the diminished potential benefit of PEP outweighs the potential risk for adverse events from antiretroviral medications." In any case, individuals seeking evaluation should be provided counseling in risk-reduction and any other intervention services that are indicated in order to reduce the likelihood of future exposures.

The CDC recommends, as preferred PEP regimens, one of the following:

- Efavirenz plus either lamivudine or emtricitabine plus either zidovudine or tenofovir.
- Lopinavir/ritonavir (Kaletra®) plus either lamivudine or emtricitabine plus zidovudine. PEP should be administered for 28 days.

The potential teratogenicity of efavirenz precludes its use in pregnancy and in women of childbearing age at risk of pregnancy. When efavirenz is prescribed to women of childbearing potential, they should be instructed about the need to avoid pregnancy.

In practice, decisions concerning the level of risk are often quite difficult. A good practice in such circumstances, it seems to me, is to initiate PEP and then reevaluate. PEP can always be discontinued if a conclusion is reached that the risk of exposure was negligible. ■

References

1. CDC. Public Health Service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. *MMWR.* 1990; 39(RR01):1-14.
2. CDC Management of Possible Sexual, Injecting Drug-Use, or Other Nonoccupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy: Public Health Service Statement. *MMWR.* 1998;47:No. RR-17).

Case Study: The Clostridial Connection

ABSTRACT & COMMENTARY

Synopsis: *Physicians in the western United States, where BTH is widely used, should be aware of the potential for WB to occur among IDUs.*

Source: Passaro DJ, et al. Wound Botulism Associated With Black Tar Heroin Among Injection Drug Users. *JAMA.* 1998;279:859-863.

A 46-YEAR-OLD MALE PRESENTED TO A SAN JOSE, California, hospital emergency department with with bilateral diplopia dysphagia, dysphonia, and weakness of his proximal arms. He had been seen in several other medical care facilities over the previous days without diagnosis. The patient regularly self-injected with black tar heroin and had been doing so for 8 years.

On examination he had ophthalmoplegia, mild ptosis, and hypophonia with a nasal quality, as well as mild proximal weakness in both arms. Subcutaneous abscesses were present.

Because of a presumptive diagnosis of wound botulism, the California Department of Health Services was immediately contacted and the CDC promptly provided bivalent A/B antitoxin. The antitoxin was administered within 12 hours of presentation to the Emergency Department. The patient was monitored closely in the intensive care unit, where he was given intravenous penicillin G. He, however, became progressively weaker and required mechanical ventilation. His subsequent course was complicated by the development of pneumo-

nia due to *Enterobacter*. He was extubated after 3 weeks, but required an additional 6 weeks of physical rehabilitation because of his dysphagia and proximal upper arm weakness. He was finally discharged 64 days after admission.

COMMENT BY ALEX STUDEMEISTER, MD

Since the 1990s, black tar heroin use among injection drug users (IDU) has increased, especially in California. Public health officials from the California Department of Health Services have recognized epidemics of 3 types of Clostridium-associated diseases: wound botulism, necrotizing soft tissue infections, and tetanus. These emerging infections and intoxications have been associated with the use of contaminated black tar heroin, an association that has been coined the clostridial connection.

WOUND BOTULISM

Wound botulism, caused by *C. botulinum*, causes acute flaccid paralysis with cranial nerve dysfunction. Botulinum toxin blocks the release of acetylcholine by the presynaptic nerve endings of the peripheral nervous system and cranial nerves leading to muscle weakness. Patients develop descending flaccid paralysis with cranial nerve palsies, but without sensory deficits and with maintenance of a clear sensorium. Untreated, botulism can lead to respiratory paralysis and death.

The number of cases of wound botulism has risen sharply since 1994. Health officials have documented 163 cases since 1988, 156 (96%) of which occurred among IDUs. Of the 163, 142 (91%) injected heroin, and 106 (75%) of these specified the use of black tar heroin. The botulinum toxin was type A in most cases.[1] A case control study identified subcutaneous infection of black tar heroin as a significant factor for wound botulism among IDUs.[2]

Clinicians who suspect botulism should immediately call the emergency 24-hour telephone number at the Department of Public Health in their state. The state health department will contact the CDC to arrange for a clinical phone consultation and, if indicated, release of botulinum antitoxin. The CDC can be directly reached at 404-639-2206 for questions about the use of botulinum antitoxin.

NECROTIZING SOFT TISSUE INFECTIONS

Beginning in the mid-1990s, several California hospitals reported clusters of IDUs presenting with necrotizing soft tissue infections. Subcutaneous injection of heroin, including black tar heroin, was common among reported cases. Wound cultures grew polymicrobial flora with *C. perfringens* and *C. sordelli* as the most commonly isolated Clostridium species.[2]

Clostridial species produce cytotoxins which may cause tissue necrosis and shock. In a 5-month period between 1999 and 2000, 9 cases of necrotizing fasciitis caused by *C. sordelli* were identified in Ventura County, CA. Of the 8 hospitalized patients, 3 died with toxic shock syndrome. Older age, marked leukocytosis, and hemoconcentraion were significantly associated with death.[3]

TETANUS

Since 1994, California has seen an increase in cases of tetanus among IDUs. As in wound botulism and necrotizing soft tissue infections, these cases had in common older age, subcutaneous injection of heroin or black tar heroin, and polymicrobial wound culture results. The distinguishing factors were the predominance of Hispanics, and their lack of immunity to tetanus.[1] Like botulinum, tetanospasmin also blocks the release of acetylcholine at the neuromuscular synapse, but it specifically affects inhibitory motor neurons of the spinal cord, resulting in spastic paralysis and rigidity.

Early management of tetanus includes the use of benzodiazepine to control muscle spasm, and the administration of tetanus immune globulin (TIG) and toxoid. A recent, randomized trial found evidence that intrathecal injection of TIG together with intramuscular delivery, was superior to intramuscular administration alone.[4]

Efforts should be made to ensure that IDUs are up-to-date for tetanus vaccination. Clinicians taking care of IDUs should keep in mind the clostridial connection, and educate IDUs about the potentially severe and often fatal consequences of skin popping of black tar heroin. ■

Dr. Studemeister is an Infectious Disease Specialist with the San Jose Medical Group in San Jose, California.

References

1. Vugia DC, et al. Wound Botulism, Tetanus, and Necrotizing Fasciitis Among Injection Drug Users in California: The Clostridial Connection. In: Scheld WM, Murray BE, Hughes JM, eds. Emerging Infections 6. Washington, DC: *ASM Press.* 2004: 111-120.
2. Passaro DJ, et al. Wound Botulism Associated With Black Tar Heroin Among Injection Drug Users. *JAMA.* 1998 279:859-863.
3. Kimura AC, et al. Outbreak of Necrotizing Fasciitis Due to *Clostridium sordellii* Among Black-Tar Heroin Users. *Clin Infect Dis.* 2004;38:e87-e91.

4. Miranda-Filho, et al. Randomised Controlled Trial of Tetanus Treatment With Antitetanus Immunoglobulin By the Intrathecal or Intramuscular Route. *BMJ*. 2004;328(7440):615.

CME Questions

10. In patients with severe community-acquired pneumonia, physiologic doses of corticosteroids result in one or more of the following:

a. Severe, dose-limiting side effects attributable to the corticosteroid
b. Reduced hospital mortality
c. A statistically insignificant improvement of patients' oxygenation
d. An increased incidence of nosocomial infection
e. Diminution in the need for mechanical ventilation

11. Which of the following is correct?

a. Malaria is absent from the Dominican Republic.
b. Mefloquine may cause central nervous system side effects.
c. Malaria is absent from Afghanistan.
d. Complete compliance with chemoprophylaxis of malaria precludes the need for personal protection, such as use of DEET.

12. Which of the following is correct with regard to the most appropriate recommendation for post-exposure prophylaxis (PEP) of a 23 year old woman who is 3 months pregnant and has had vaginal intercourse with a man known to be HIV infected. Nothing is known about his treatment record.

a. PEP is contraindicated in pregnancy.
b. Immediately begin administration of efavirenz, lamivudine, and zidvoudine.
c. Immediately begin administration of efavirenz, emtricitabine, and tenofovir.
d. Immediately begin administration of lopinavir/ritonavir (Kaletra), lamivudine, and zidovudine.

13. Which of the following is correct?

a. Wound botulism is caused by *Clostridium sordelli*.
b. Both *Clostridium sordelli* and *Clostridium perfringens* each been identified as the cause of necrotizing soft tissue infections in injection drug users.
c. Botulinum antitoxin administration is not indicated in wound botulism, in contrast to food-born botulism.
d. The phrase clostridial connection refers to the association with clostridial infections and the use of methamphetamines.

Answers: 10. (b&e); 11. (b); 12. (d); 13. (b)

In Future Issues:

An Emerging Outbreak of Acinetobacter

UPDATES

By Carol A. Kemper, MD, FACP

Not Your Ordinary Dog Bite

Ngauy V, et al. *J Clin Micro.* 2005;970-972.

THIS UNUSUAL CASE REPORT describes an 82-year old diabetic man who presented with an ulcerated nodule over his first metacarpophalangeal joint. He had been bitten by a dog about 3 months earlier, with initially a small scratch that gradually enlarged and ulcerated with purulent drainage. He failed to respond to separate courses of Augmentin and Keflex, although he did have some response to a 7-day course of levofloxacin. X-rays showed no bone involvement, and a chest radiograph showed only mild bibasilar interstitial disease. Wound culture grew. . . (you'll never guess! A clue: the patient was a WWII POW in the South Seas). *See the next page for the answer. . .*

Wash That *Malassezia furfur* Out of My. . .

Dolk E, et al. *Applied Environ Microbiol.* 2005;71:442-450.

MANY SCIENTISTS NOW BELIEVE that an overgrowth or imbalance of *Malassezia furfur* on the scalp may contribute to dandruff. Usually part of the normal skin flora, greater numbers of *M. furfur* can be found on the scalps of people with dandruff than those without, although whether this is a primary phenomena or a secondary event, remains a matter of some debate. However, treatment with agents active against *M. furfur*, such as ketoconazole, selenium sulfides, and zinc, can decrease the severity of dandruff.

Searching for ways to improve upon existing dandruff shampoos, Dolk and colleagues created a library of single variable domain (VHH) antibodies with a high specificity for cell surface proteins of *M. furfur* (Malf1) that would remain active in various shampoo products. VHHs were investigated because of their physical properties, their antigen specificity, and their ability to inhibit the growth and, perhaps, even neutralize antigens of *M. furfur*. Antibody production was induced by repeated inoculation of a llama with extracts of Malf1. A series of heavy-chain antibodies with a single variable domain (VHH) for antigen binding were subsequently identified from the blood of the llama by polyclonal rabbit anti-llama and swine anti-rabbit immunoglobulins. A library of 107 VHH clones was constructed.

Only those VHHs that highly bound to Malf1 in the presence of various shampoos were deemed acceptable candidates for further investigation. Not surprisingly, most VHHs did not bind to Malf1 well under the harsh conditions of most ordinary shampoos, but a few did. Interestingly, those VHHs that were especially stable in the presence of shampoo were also stable in the presence of denaturants, urea, and guanidine HCL. Stability proved to be related to specific amino acids present at certain positions within the chain. VHHs identified as being particular specific for Malf1 could be further engineered for increased stability, even in the harsh climate of ordinary shampoo. Whether these llama-derived antibodies will prove useful in reducing numbers of *M. furfur* on the scalp and improving dandruff, remains to be seen. (Do we get to ask if the llama's dandruff improved?) ■

Really Hot Cash

ProMED-mail post January 28, 2005; www.promedmail.org.

FEDERAL AUTHORITIES HAVE ISSUED an alert, and are seeking additional information, in a bizarre criminal case in Philadelphia involving the Russian mob and purported drug money possibly contaminated with Staphylococcal exotoxin. Details are sketchy (and no one is talkin'), but during a routine traffic stop, police stumbled upon $250,000 in cash. After the funds were counted, several of the agents became ill and one required hospitalization with severe flu-like symptoms. For unstated reasons, authorities suspect the cash was laced with Staphylococcal exotoxin.

One of a group of agents now believed to function as superantigens, Staphylococcal exotoxin B (SEB) has been investigated as a possible agent of bioterrorism for many years. Various superantigens, including staphylococcal exotoxin A, B, and C, toxic shock syndrome toxin-1 (TSST-1), and streptococcal pyrogenic exotoxin can be detected in up to 42% of patients in septic shock, 31% of septic patients without shock, and 6% of patients with systemic inflammatory response without infection. Streptococcal pyrogenic toxin has been implicated in Kawasaki's syndrome. Similar to toxic shock, patients with low or undetectable levels of antibodies to these superantigens may be at greater risk for more severe inflammatory

response. Patients in the ICU with low levels of antibody to staphylococcal exotoxins and/or TSST-1 have been found to have higher levels of TNF-alpha than those with higher antibody titers.

In contrast, cutaneous and inhalational exposures to staphylococcal exotoxins may produce a different constellation of symptoms. Following laboratory exposure to aerosolized SEB, flu-like symptoms with fever and respiratory symptoms have been reported. In a laboratory accident that occurred in 1964, the US Army reported that 9 laboratory workers exposed to aerosolized SEB variously developed fever, rigors, shortness of breath, cough chest pain, vomiting, loss of appetite, and muscle aches. Fever developed within 12 hours of exposure and lasted an average of 2 days, although chest discomfort and exertional dyspnea was more prolonged. In another incident, ocular exposure resulted in severe conjunctivitis and periorbital swelling, followed by gastrointestinal symptoms. While further information is lacking, authorities have suggested that police agencies handling suspected drug money use appropriate protective gear. ■

Preventing Traveler's Diarrhea

ISTM Travel Medicine List, January 18, 2005

Despite extensive experience in travel medicine and treating traveler's diarrhea, many physicians express frustration at the inability to diminish the frequency of diarrheal illness in travelers. In an upcoming article in *Infectious Disease Clinics of North America*, Dr. David Shlim nicely summarizes the problems in preventing traveler's diarrhea (TD):

1) Travelers make frequent mistakes while eating; >95% of travelers fail to follow current food guidelines while traveling.

2) To some degree, this may not be a problem, as studies suggest no relationship between the type of food eaten and illness; thus, current food precautions and recommendations may not be as effective as hoped.

3) Studies repeatedly demonstrate that eating in hotels and restaurants is not a guarantee against TD. In fact, one investigator observed that eating in restaurants in Mexico is a risk factor for TD.

4) Most restaurants in developing countries lack basic facilities and hygiene, such as sinks in employee bathrooms, adequate storage and refrigeration for food, and clean water and soap.

5) Produce and meat in developing countries is often contaminated with bacteria (even in the United States, meat is contaminated with bacteria). Flies are numerous and efficient vectors of transmission of bacteria. Cross-contamination of foods during preparation and undercooking of meat is common.

6) Since most travelers eat 21 meals per week in restaurants (unless they are fortunate to be staying in someone's home), eating in restaurants is largely unavoidable, and is generally viewed as part of the fun of travelling.

Perhaps the only way to effectively prevent traveler's diarrhea is not to travel! For those willing to risk it, common sense should be the rule of the day. Avoid the most risky types of food and drink, make sure your meat is well cooked, and have ready access to medications for TD. But for all practical purposes, travelers should think of the world as covered by a thin layer of feces. ■

Dog Bite (Answer)

. . .continued from previous page.

Wound culture grew a gram-negative bipolar rod, with creamy colonies on both blood and MacConkey agar. The organism was sensitive to levofloxacin, piperacillin-tazobactam, cefipime, and imipenem, but not aminoglycosides. It was subsequently identified, and later confirmed by PCR, as *Burkholderia pseudomallei.*

The man had been taken as POW in March 1942 by the Japanese and did hard labor building railways in Java, Singapore, Malaysia, and Burma, finally ending up in a labor camp in Thailand for 2 years. After returning to the United States, he lived in Texas and never traveled again.

Meliodosis most often presents with skin and soft tissue infection and pneumonia; acute sepsis occurs in about 20% of patients. Current theory holds that most human infections are acquired through cutaneous inoculation, not inhalation or ingestion. Late presentations are not uncommon, but generally fall into the category of chronic pulmonary disease. Notoriously difficult to treat (meta-analysis suggests that prolonged treatment with cefipime or imipenem is most effective), relapses following treatment are common. Late reactivation is unusual, but has been reported. Two other cases similar to this one have been reported in a Vietnam veteran and a WWII veteran, 18 and 28 years post-exposure. If Ngauy and colleagues are correct, this man's latent infection was acquired about 62 years earlier!

Tsunami-related *B pseudomallei* infections are just beginning to be reported, mostly involving persons with soft tissue injury. Preliminary reports from physicians in Finland have identified 2 patients, returning from tsunami areas, who have been diagnosed with pneumonia, and a third who grew the organism following surgical repair of an Achilles tendon injury. Tsunami-related infections may help to expand our understanding of the distribution of this organism in southeast Asia. ■

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.*

The Risk of Aspirin Withdrawal in ACS Patients

Stopping aspirin may be hazardous to your health, according to recent research. Patients with heart disease who developed acute coronary syndrome (ACS) were questioned to determine whether their aspirin therapy had recently been interrupted. Thirteen percent of patients with recurrent ACS had stopped aspirin within the previous month. The incidence of ST-segment elevation ACS was higher in those who stopped aspirin, compared to those who did not stop aspirin (39% vs 18%; *P*=0.001). The risk of stopping aspirin was particularly high for patients who had uncoated stents. The mean delay between aspirin withdrawal and acute coronary event was 10 days. Patients withdrew from aspirin for a number of reasons including minor surgery, endoscopy, dental treatment, bleeding, and noncompliance. The authors conclude that aspirin withdrawal in patients with coronary disease represents a risk for the occurrence of a new coronary event (*J Am Coll Cardiol.* 2005;45:456-459). The risk of ischemic stroke may be as much as 3 times higher with interruption of aspirin therapy, according to presentation at the International Stroke Conference. Researchers from Switzerland noted that the odds ratio for stroke or TIAs associated with aspirin discontinuation was 3.25 (95% CI). Seventy-seven percent of ischemic strokes related to aspirin discontinuation occurred in the first 8 days after aspirin was stopped, with remaining strokes occurring from day 9 to day 30. The reasons cited for discontinuing aspirin were primarily minor bleeding and minor surgical procedures—many of which can safely be performed (many dental procedures, cataract surgery among others) while patients are taking aspirin (strokeconference.americanheart.org /portal /strokeconference/sc/02.02.05c).

Neuropsychiatric Symptoms of Dementia

Treatment of neuropsychiatric symptoms in patients with dementia represents one of the biggest challenges in primary care. Dementia is diagnosed by the loss of cognitive function, but other symptoms are often more prominent including agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among others. Many classes of psychiatric medications are used to treat neuropsychiatric symptoms in dementia including antidepressants, anxiolytics, anticonvulsants, cholinesterase inhibitors, typical antipsychotics, and atypical antipsychotics. Often these drugs are used in combination, and the cocktail can get confusing and even dangerous for patients and caregivers alike. A new review of the topic in the "Clinician's Corner" section of the February 2nd *Journal of the American Medical Association* helps clarify treatment options. The authors reviewed 29 articles that met their inclusion criteria. Among typical antipsychotics, which

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.

include haloperidol, thiothixene, chlorpromazine, trifluoperazine, and acetophenazine, there was no difference in the efficacy among these drugs in treating neuropsychiatric symptoms. Haloperidol may be somewhat more effective for treating aggression but not agitation. Side effects including extrapyramidal symptoms and somnolence are common with these agents. Antidepressants, including the SSRIs, were also relatively ineffective, except for treatment of depression associated with dementia. The best evidence for efficacy was found in the atypical antipsychotic group, especially risperidone (Risperdal) and olanzapine (Zyprexa). These drugs were found to have a modest effect on agitation/aggression, hallucinations, and delusions. A higher risk of stroke was found in the most recent trial (prompting a "Dear Doctor" letter from Janssen in April 2003). The cholinesterase inhibitors group including galantamine (Reminyl), donepezil (Aricept), and rivastigmine (Exelon) were somewhat disappointing with regard to neuropsychiatric symptoms, with minimal improvement of questionable clinical benefit. Memantine, the relatively new N-methly-D-asparte antagonist was seen to improve cognitive and functional parameters, but also did not improve neuropsychiatric symptoms. The authors stress that the management of neuropsychiatric symptoms in dementia "should always begin with an assessment of the medical (eg, pain and delirium) and environmental causes of the behavior." They also recommend starting with a cholinesterase inhibitor if the patient is not already receiving one, because they are relatively well tolerated and may benefit cognition and function (*JAMA.* 2005;293:596-608).

FDA Actions

Pfizer has received FDA approval to market pregabalin (Lyrica) for the treatment of painful diabetic neuropathy and post-herpetic neuralgia, the 2 most common types of neuropathic pain. Pregabalin was shown to be effective in a company-sponsored study of 338 patients with a 1-5 year history of painful, diabetic, peripheral neuropathy who were randomized to receive the drug at 1 of 3 doses or placebo for 5 weeks. Patients in the 300 and 600 mg/day doses showed improvements in mean pain score vs placebo ($P = 0.0001$), but no improvement was seen at the 75 mg/day dose. The higher doses also resulted in improvements in weekly pain score, sleep interferes score, patient global impression of change, clinical global impression of change, and lifestyle surveys. The most common side effects were dizziness and somnolence (*Neurology.* 2004;63:2104-2110). Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA), and is closely related to Pfizer's gabapentin (Neurontin), which recently lost its patent and is now available as a generic. Pregabalin is currently under review by the FDA for the treatment of partial seizures.

The FDA has also approved palifermin (Kepivance-Amgen) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies undergoing chemotherapy, with or without radiation, in preparation for bone marrow transplantation. The drug, which is the first agent to be approved for this indication, stimulates epithelial cell growth in mucous membranes. It is given prior to fractionated total body irradiation and high dose chemotherapy, and repeated after bone marrow transplantation. The drug's efficacy in non-hematologic malignancies has not been shown.

Citalopram (Celexa) is now available in generic tablets and liquid. The liquid formulation recently joined the tablet formulation for the popular SSRI antidepressant.

Extended release buproprion (Wellbutrin SR) is now available as a generic in the 200 mg strength.

Fosinopril/HCTZ (Monopril) has also joined the generic ranks in 10/12.5 mg and 20/12.5 mg strengths.

The FDA has also approved a generic fentanyl transdermal system (Duragesic) for the treatment of severe chronic pain. The new generic, which is produced by Mylan technologies, provides a constant dose of the drug for 72 hours.

Canada has suspended marketing of Adderall and Adderall XR because of reports of sudden unexplained death (SUD) in children taking the drugs. SUD has been associated with amphetamine abuse and has been reported in children with heart disease taking prescribed doses of amphetamines, including Adderall and Adderall XR. These latest reports of SUD have been in children without structural heart disease who were taking the drugs as prescribed. The FDA is looking at these reports, but “does not feel that any immediate changes are warranted in the FDA labeling or approved use of this drug.” More information is available on the FDA web site at FDA.gov.