AMERICAN HEALTH CONSULTANTS®

Providing Evidence Based Clinical Information for 20 Years

INFECTIOUS DISEASE ALERT®

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

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

EDITOR
Stan Deresinski, MD, FACP
Clinical Professor of Medicine, Stanford; Director, AIDS Community Research Consortium; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center

CO-EDITOR
Joseph F. John, MD
Professor of Medicine and Microbiology, University of Medicine & Dentistry—New Jersey, Robert Wood-Johnson Medical School

ASSOCIATE EDITORS
J. Peter Donnelly, PhD
Clinical Microbiologist
University Hospital
Nijmegen, The Netherlands
Section Editor, Microbiology

Hal B. Jenson, MD, FAAP
Chief, Pediatric Infectious Diseases, University of Texas Health Science Center, San Antonio, TX

Carol A. Kemper, MD, FACP
Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center
Section Editor, Updates

Robert Muder, MD
Hospital Epidemiologist
Pittsburgh VA Medical Center
Pittsburgh
Section Editor, Hospital Epidemiology

Stephen L. Sacks, MD, FRCP
President,
Viridae Clinical Sciences Inc.
Vancouver, BC
Section Editor, Viral Infections

Thomas G. Schleis, MS, RPh
Director of Pharmacy Services
Infections Limited
Tacoma, WA
Section Editor, Pharmacology

Jerry D. Smilack, MD
Infectious Disease Consultant
Mayo Clinic Scottsdale
Scottsdale, AZ

Alan D. Tice, MD, FACP
Infections Limited, PS
Tacoma, WA
Section Editor, Managed Care

EDITOR EMERITUS
Jeffrey E. Galpin, MD
Clinical Associate Professor of Medicine, USC

Serum Antibody Response and the Clinical Course of *Clostridium difficile*-Associated Diarrhea

ABSTRACT & COMMENTARY

Synopsis: *Patients who fail to mount a serum antibody response to Clostridium difficile toxin A are at high risk for recurrence.*

Source: Kyne L, et al. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. *Lancet* 2001;357:189-193.

Treatment of antibiotic-associated *Clostridium difficile* diarrhea is followed by recurrence in 5-50% of episodes; some patients experience multiple recurrences. Kyne and colleagues prospectively followed 63 patients with nosocomial *C. difficile* diarrhea for up to 60 days. They measured serum IgA, IgG, and IgM concentrations against toxins A and B, as well as nontoxin antigens at three-day intervals. Of 44 patients who survived, 50% had at least one recurrence. Patients with single episodes of *C. difficile* diarrhea had significantly higher serum concentrations of IgM against toxin A by day 3, and significantly higher concentrations of IgG against toxin A at day 12 than did patients who subsequently suffered recurrences. There was no correlation between IgG concentrations against toxin A and age, underlying disease, co-morbidity, or receipt of additional antibiotics.

COMMENT BY ROBERT MUDER, MD

C. difficile diarrhea is a frequent complication of antimicrobial therapy in hospitals and nursing homes. It is associated with significant morbidity, mortality, prolongation of hospital stay, and excess cost. Although most patients respond initially to therapy with metronidazole or vancomycin, recurrent diarrhea occurs in a substantial number of patients, up to 50% in some series. Clinical risk factors for recurrence include advanced age and increased severity of underlying illness.

Kyne et al found a significant association between recurrent disease and lack of antibody response to toxin A. Their observations

Volume 20 • Number 9 • February 1, 2001 • Pages 65-72

NOW AVAILABLE ONLINE!
Go to www.ahcpub.com/online.html for access.

INSIDE

extend previous observations on the role of serum antibody against toxin A and the clinical course of *C. difficile* diarrhea. Kyne et al previously reported that after the onset of colonization with *C. difficile* in patients receiving antibiotics, those who remained asymptomatically colonized had significantly greater increases in anti-toxin A IgG than those who developed diarrhea.[1] There are reports of successful use of intravenous IgG in the treatment of *C. difficile* diarrhea refractory to standard antibiotic therapy,[2] and in the treatment of multiple recurrences.[3] Although these reports are uncontrolled and involve small numbers of patients, they are consistent with a role for serum immunoglobulin response in the clinical course of *C. difficile* diarrhea.

Standard approaches to control of *C. difficile* disease in hospitals and nursing homes has centered on restraint in antibiotic usage, contact isolation, and environmental decontamination. These measures, while theoretically sound, have proven extremely difficult to implement effectively in practice. The preceding observations raise the possibility of development of a vaccine to prevent disease. However, vaccination poses a number of problems. The first is identification of the target population and administration of the vaccine in a timely fashion. Given the near ubiquity of antibiotic administration during hospitalization, immunization at the time of hospital admission could prove to be a cost-effective strategy. The second problem is that the disease, and the severe sequelae of the disease, are more frequent in older, more debilitated patients. This is a population that typically has a suboptimal response to vaccines.

Another potential implication of these observations is the role of immunotherapy in altering the course of *C. difficile* diarrhea. Treatments used in refractory or relapsing disease have included combination antimicrobial therapy, anion exchange resins, administration of non-pathogenic organisms, and enemas of filtered normal stool, to name but a few. A controlled trial of immunoglobin infusion for treatment of severe or relapsing *C. difficile* diarrhea would appear to be a worthwhile undertaking. ❖

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

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.

EDITORIAL GROUP HEAD: Glen Harris.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robin Mason.

ASSISTANT MANAGING EDITOR: Neill Larmore.

GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.

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

Copyright © 2001 by American Health Consultants. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

Back issues: $19.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address: customerservice@ahcpub.com
E-Mail Address: neill.larmore@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$279 per year (Student/Resident rate: $110).

Multiple Copies
1-9 additional copies: $206; 10 or more copies: $183.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 40 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational 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.

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517, or e-mail to robin.mason@ahcpub.com, or **Neill Larmore,** Assistant Managing Editor, at (404) 262-5480, or e-mail to neill.larmore@ahcpub.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 is involved in research with Merck, Sharp & Dohme, Novartis (Systemix), DuPont-Merck, Gilead, Agouron, and Abbott. He also serves as a consultant to Bristol-Myers Squibb, Immunex, and Protein Design Labs and serves on the speaker's bureau of Merck, Sharp & Dohme, Bristol-Myers Squibb, Glaxo Wellcome, Ortho-McNeil, Bayer, and Lederle. Dr. Kemper serves on the speaker's bureau and is involved in research with SmithKline Beecham, DuPont, Merck, Gilead, and Virologics. Dr. Muder does research for Ortho-McNeil and Cubist Pharmaceuticals. Dr. John and Dr. Bia report no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.

References

1. Kyne L, et al. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000;342:390-397.
2. Salcedo J, et al. Intravenous immunoglobulin therapy for severe *Clostrium difficile* colitis. *Gut* 1997;41: 366-370.
3. Leung DY, et al. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by *Clostridium difficile* toxin. *J Pediatr* 1991; 118:633-637.

The Nose Knows: Nosocomial *S. aureus* Bacteremia

ABSTRACTS & COMMENTARY

Synopsis: *Molecular techniques demonstrated the apparent identity between nasal isolates of S. aureus and strains of this organism subsequently causing bacteremia.*

Sources: von Eiff C, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. *N Engl J Med* 2001;344: 11-16; Archer GL, Climo MW. *Staphylococcus aureus* bacteremia—consider the source. *N Engl J Med* 2001;344:55-56.

Staphylococcus aureus (sa) bacteremia causes substantial morbidity and mortality. No vaccine

exists for prevention of this invasive disease. SA colonizes up to 80% of humans at some time during their life. That such an intimate commensal should pack such a pathogenic punch once it invades tissues and blood remains one of the great conundrums of human medicine. The havoc that SA produces in tissue has been a focus of research for more than two decades, along with the process by which the organism escapes from the nose to the blood.

The current study by von Eiff and his German infectious diseases colleagues asks a simple question: are the strains of SA that colonize the nose of patients admitted to the hospital the same strain that becomes bloodborne?

von Eiff et al, thus, undertook two studies to provide data to answer this question. The first study from 1993-1994 featured hospitalized patients in 32 German hospitals. Study patients had a nasal swab done as soon as possible after isolation of SA from blood. They collected 219 SA isolates from blood and 350 isolates from the anterior nares. Only 20 (9.1%) of the 219 bacteremic isolates were methicillin-resistant SA (MRSA), a rate certainly below what we would currently expect for U.S. hospitals now.

Isolates were typed by pulse field gel electrophoresis (PFGE). Most blood isolates (82%) had the same PFGE pattern as the nasal isolate. The association between nasal and blood isolates held true regardless of the time lag between the time the nasal swab was collected and the development of the bacteremia.

These provocative results led to the second study from 1994 through 1999 at a large 1568 patient bed tertiary-care hospital in Münster, Germany. The design of the second study was to collect nasal swabs from patients and compare the pulsed-field gel electrophoresis (PFGE) pattern of isolates subsequently obtained from the blood.

Nasal swabs were obtained from 1278 general medical patients who contributed 1640 SA isolates; only 74 (5.8%) of the nasal isolates were MRSA. Bacteremia developed in 14 study patients, only one of whom had an MRSA strain. The interval between nasal isolation and blood isolation was 6.5 days with a range of 1 day to 60 weeks! Regardless of the interval, the blood isolate PFGE matched the nasal isolate in 85.7% (95% confidence interval, 57.1-98.2%). Only two patients had a nasal strain that differed by PFGE from the blood isolates.

Bacteremia of 258 nonstudy patients did not differ from that of the study patients. The presumed origin of bacteremia in 156 patients studied with bacteremia included catheter-associated infection (46%), skin, soft tissue (27%), pneumonia (11%), urinary tract infection (10%), endocarditis (5%), and other sites (1%).

When all data are analyzed, the most cautionary conclusion is that at least 50% of patients with SA bacteremia are first colonized by an identical SA strain.

COMMENT BY JOSEPH F. JOHN, MD

These studies provide "proof of concept," for the legacy of nasal colonization as a risk for subsequent SA infection. We know that the strains inhabiting the nares will more often than not be the same ones that produce a bacteremia. Because this study uses only a macro restriction of SA chromosomal DNA, we know little about addition, deletion, or mutations that might be related to invasion and have to assume from the data of the study that nasal strains become bloodborne with their genomes relatively unaltered.

The potential clinical implication is that if certain strains can be blocked from colonizing the nose, patients may be much more unlikely to experience bacteremia with that strain. A correlate of this observation is that episodes of SA bacteremia that are classified as "nosocomial," that they occur 48 hours after admission are, in fact, quasi nosocomial since the organism that infected the patient may likely be one that habitually colonizes the patient outside the hospital. Here we see the meshing of community factors (i.e., the selection of strains of SA that preferentially colonize the nose) with nosocomial factors, as well as iatrogenic factors like indwelling IV catheters, bladder catheters, and antibiotic exposure, with both sets of factors combining to place the patient at risk for SA bacteremia.

In fact, one major finding of the study is that strains that patients carry into the hospital may persist (in their nares) for months before giving rise to invasive disease. von Eiff et al conclude that we should develop strategies to reduce systemic disease by interrupting the transmission of SA from the nose to those sites where it gains access to circulation. Furthermore, the concept of interrupting transmission as an emerging infection control strategy should be applied not only to MRSA but also to methicillin-susceptible strains as well.

The comprehensive editorial by Archer and Climo raises several issues with current strategies to limit colonization, including the development of mupirocin resistance where topical use of this agent has been widespread. The most radical inference of Archer and Climo is that we should consider screening for nasal

colonization with SA in all patients admitted to the hospital. We have already advocated this strategy in patients admitted to our MICU, thus protecting them theoretically from subsequent invasive disease and protecting uncolonized patients from becoming colonized with new strains of SA. Patients are kept in isolation until their nares are shown to be free of SA, leaving the choice of decolonizing regimens to the attending physicians. The editorial emphasizes the need for a "rapid diagnostic test," though we have found that the microbiology laboratory identifies presumptive SA in overnight nasal cultures places to blood agar. I agree with the conclusion of the editorial that, "Any real reduction in the incidence of nosocomial infections with *S. aureus* will require widespread aggressive tactics and innovative strategies." The methods to support these strategies, I feel, are currently available. What it takes now is a willful commitment from infection control and hospital administration to implement the methodology. ❖

New Warnings and Alerts in HIV Care

ABSTRACTS & COMMENTARY

Synopsis: *Warnings about adverse reactions to nevirapine and d4T in pregnancy as well as bogus Serostim are discussed.*

Sources: Gangar M, et al. The frequency of rash during initial use and rechallenge with nevirapine and delavirdine. *Ann Pharmacother* 2000;34:839-842; Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures—worldwide, 1997-2000. *MMWR Morb Mortal Wkly Rep* 2001;49:1153-1156; Safety Information Summaries, Jan. 5, 2001; www.fda.gov/medwatch/; Press Release, Serono Statement Regarding Counterfeit Serostim, Jan. 22, 2001; www.fda.gov/medwatch.

Nevirapine used for Postexposure Prophylaxis Causes Life-threatening Hepatitis in Two Health Care Workers

Severe, life-threatening hepatitis has been reported in two health care workers who received nevirapine (NVP) for post-exposure prophylaxis (PEP) for occupational exposure. The first case was that of a 43-year-old female health care worker who received AZT, 3TC, and NVP following a needlestick injury, and developed such fulminant hepatitis and hepatic failure that she required liver transplantation. The second case was of a 38-year-old male physician who received the identical regimen following a mucous membrane exposure, with resulting severe fulminant hepatitis. Both cases occurred last fall.

COMMENT BY CAROL A. KEMPER, MD, FACP

No single antiretroviral regimen has been recommended for use as PEP of sexual exposures and needlestick injuries in health care workers, and clinicians and health care facilities variously use combinations of two or three antiretroviral agents. Some experts advocate the use of protease inhibitors, and others favor the convenience of the non-nucleoside reverse transcriptase inhibitor (NNRTI) NVP (Viramune™, Boehringer Ingelheim/Roxane Laboratories, Inc.). While NVP has not been formally recommended for use in PEP, many clinicians and institutions have included it as part of a combination PEP regimen because of its high level of activity against HIV-1, its known effectiveness as a single dose in the prevention of neonatal transmission, and because it is generally well tolerated and convenient to administer.

The most common side effect observed with NVP is rash, which reportedly occurs in anywhere from 16% to 48% of patients, usually within the first two to six weeks of use. However, in our experience, while cutaneous reactions occurred more commonly after delavirdine administration, those due to NVP were more frequently severe and more frequently resulted in hospitalization. Nearly 40% of cutaneous reactions to NVP in our patient population were moderate to severe in nature (14.6% of the cohort), and fully 7.2% of patients receiving NVP required hospitalization for severe or life-threatening reactions, including angioedema, Steven's Johnson syndrome, and toxic epidermal necrolysis. As a result, the drug was temporarily or permanently discontinued in 28% of our patients receiving NVP. Of course, most PEP regimens are taken for short periods of time, varying from 1-4 weeks, which decreases the risk of adverse events.

Another common potential side effect of the NNRTIs is elevation of hepatic transaminases, which are generally mild and asymptomatic in nature. Serious elevations in liver function tests have been reported, and may be more frequent in patients with underlying hepatitis B or C infection. Because of concerns of increased hepatotoxicity, physicians have been warned to avoid using NVP in combination with interleukin-2.

Following the occurrence of these two cases in

health care workers, the Centers for Disease Control and the FDA surveyed the incidence of serious adverse events due to NVP taken for PEP during the last three years using the MedWatch reporting system. Twelve cases of severe hepatotoxicity were identified, four of whom also had severe skin reactions. One patient developed severe liver failure requiring liver transplantation, seven had clinical hepatitis with fever, abdominal pain, jaundice, and/or hepatomegaly, and four were reported to have elevations in hepatic transaminases. Abnormal liver function tests were obtained a median of 21 days after initiation of NVP for PEP (range, 13-36 days), although symptoms of abdominal pain, fever, malaise, and rash generally occurred sooner. Information on whether NVP was appropriately dose escalated in these patients was not available, but all of the patients received 200 mg either once or twice daily.

No cases of serious hepatotoxicity were identified in the HIV PEP registry at the CDC, which has accumulated 492 cases of PEP for occupational exposures since October 1995. Only 11 health care workers identified in this database received NVP for PEP, one of whom developed a severe cutaneous reaction.

These data suggest that the risk of adverse reactions to NVP administered for occupational PEP far outweighs the potential benefit of this agent for this purpose, especially when one considers that most exposures are associated with a low risk of HIV infection. This is especially the case for mucous membrane exposures. Any one of multiple alternate agents can be used for occupational PEP in lieu of NVP. NVP continues to be recommended for the treatment of HIV infection, although it may be best to avoid the concomitant administration of other agents with potential hepatotoxicity, and clinicians may wish to monitor patients more closely, especially those with underlying hepatitis, at least for the first 4-6 weeks of use.

FDA Warns Against d4T and ddI in Pregnancy

The FDA and Bristol-Myers Squibb are alerting physicians to the potential risk of fatal lactic acidosis in pregnant HIV-infected women receiving a combination of stavudine (d4T) and didanosine (ddI). Three women, who were either pregnant or postpartum, have died. Two of these women were participating in an open-label study of d4T plus ddI, plus either nelfinavir or BMS-232632, an investigational protease inhibitor. The third woman was apparently identified through post-marketing surveillance. Two of the cases were complicated by pancreatitis. Sadly, two of the infants they were carrying also died, one in utero at 32 weeks gestation and one following emergent cesarean section at 36 weeks.

There have also been a number of additional cases of nonfatal pancreatitis, some with lactic acidosis and/or hepatic failure, reported in pregnant women receiving these agents.

COMMENT BY CAROL A. KEMPER, MD, FACP

These agents should be used with extreme caution and only in those pregnant women with no other treatment options. In my experience, this syndrome can occur precipitously and with little warning. Any HIV-infected patient (male or female) receiving these agents with possible pancreatitis, hepatic failure, or jaundice should be immediately evaluated and screened for the presence of lactic acidosis, and aggressively treated in the hospital.

Fake "Serostim" Reported thus far from Seven States!

The biotech firm Serono and the FDA are advising clinicians and consumers about the recent discovery of a look-alike Serostim drug, which is fake. Serostim is an injectable medication used for fighting chronic wasting and myopathy in patients with advanced HIV disease. The first cases of the fake drug were reported in December by consumers in California, and since then the fake version has popped up in six other states, including Ohio, Kentucky, Michigan, New Jersey, Florida, and Missouri. It is not known how widely it is distributed, and the medical advisory did not specify how patients obtained the counterfeit product.

COMMENT BY CAROL A. KEMPER, MD, FACP

The fake product was packaged in a box almost identical to the real thing, with a valid lot number (MNK612A). However, the manufacturer notes that the expiration date on the fake version is August 2002, whereas the proper expiration date for the real product should be August 2001. The composition of the fake product has yet to be determined, but has not been associated with any serious side effects. The only side effect possibly associated with the administration of the fake product has been minor injection sight irritation. Unfortunately, the beneficial effects of this drug are short-lived, and patients who unwittingly discontinue their real Serostim, even for a few weeks, may experience a rapid taper in its apparent effects. ❖

Mycobacterium ulcerans and Buruli ulcer: A Mycobacterium That Doesn't Follow the Rules

ABSTRACT & COMMENTARY

Synopsis: *The recent description of a patient with Buruli ulcer originating from China presents an opportunity to review the somewhat atypical and frankly unusual manifestations of this disease. Its epidemiology, pathology, and even the growth characteristics of the causative organism make this an easily missed infectious disease, with a clear potential for harm to travelers in certain environments.*

Source: Faber WR, et al. First reported case of *Mycobacterium ulcerans* infection in a patient from China. *Trans R Soc Trop Med Hyg* 2000;94:277-279.

A 40-year-old chinese woman, who had been living in Europe for nine years, traveled during July and August to Shan Dong province, People's Republic of China. She walked barelegged in grassy areas near fruit trees, and noted numerous apparent "mosquito bites." Three months later, a pale swelling, with a slightly depressed center, appeared on her left leg. Four months later it was excised while she again visited China, but it ulcerated instead of healing. When she returned to The Netherlands, a Ziehl-Neelson stain showed acid-fast bacteria that had been obtained from a painless 3 × 3.5-cm lesion with undermined borders and ecrotic bed.

Histopathological examination of tissue did not reveal granulomata; instead, there was extensive eosinophilic necrosis and some mononuclear cell infiltrate containing both scattered and clumped extracellular acid-fast bacteria. PCR analysis ultimately demonstrated sequences specific for *Mycobacterium ulcerans*. The causative organism was isolated after 40 days culture but only at 30°C. The organism was later found to be resistant to rifampicin *in vitro* and required additional curative surgery in addition to antituberculous therapy with ciprofloxacin and rifabutin. As the acid-fast organisms were gradually eliminated, tissue biopsies taken from the healing area changed and only then demonstrated a granulomatous reaction at this later stage of her disease.

COMMENT BY FRANK J. BIA, MD, MPH

Recent World Health Organization (WHO) initiatives aimed at stopping the spread of Buruli ulcer disease, particularly in West Africa, underscore the potential importance of this disease, potentially for travelers to countries such as Ghana, Benin, the Ivory Coast, and Togo.[1-5] MacCallum et al established the association between *M. ulcerans* and the Australians noted lesions of Bairnsdale ulcer in 1948. Sir Albert Cook had first described this disease in Uganda as early as 1897.[2] The name, Buruli ulcer, now derives from the 1961 outbreak in Uganda, but the disease has been identified not only in Australia but also in Papua New Guinea, Sri Lanka, Mexico, Peru, and French Guyana. Disease distribution is not even throughout what are considered endemic areas. Rather, it tends to be both focal and intense, at times affecting more than 20% of the population, particularly those residing or working in low lying river and swamp regions, and possibly involving aquatic water insects as vectors living in slow-flowing stagnant water.[4]

Pediatric cases outnumber adults in most series and approximately 70% of cases occur in children younger than 15 years of age. The disease begins as a subcutaneous nodule that appears spontaneously, as opposed to arising from a previous site of traumatic injury. It is not known whether the source of infection is actually either traumatic or due to aerosol transmission of organisms—possibly even inoculated by insect vectors. However, there is no known person-to-person spread of this disease nor association with HIV infections.

In the experimental guinea pig model, areas of fibroblastic cell growth and necrosis within cutaneous lesions are found. The role of mycolactone toxin production in the destruction of subcutaneous tissue is critical.[2] Mycolactone is a nonimmunogenic polyketide-derived macrolide. Once an ulcerative lesion is established, antibiotics alone, without aggressive surgical intervention, will not be curative.

M. ulcerans is a slow growing mycobacteria and may require upward of 6-9 months for primary isolation on solid media. It is analogous to *M. marinum*, being thermosensitive, growing best at 31-33ºC, but not at 37ºC, and like *M. marinum*, causing cutaneous disease. Semret et al reported a better experience isolating *M. ulcerans* with selective liquid media containing antibiotics, supplemented with 10% lysed sheep blood cells and polyoxyethylene stearate.[1] Because of its slow rate of growth on solid media, overgrowth by contaminants is frequently a problem during isolation. Unfortunately, NaOH is used in standard decontamination procedures and it inhibits the growth of *M. ulcerans*. Although a polymerase chain reaction (PCR) test is available in reference laboratories, clinical diagnosis determines therapy in endemic regions of the world.

To understand the evolution of clinical Buruli ulcer

disease, it is critical to realize that the pathogenesis of this infection is quite unlike that of any other mycobacterial disease. Early lesions contain many bacteria and show extensive coagulative necrosis in the lower dermis and subcutaneous fat. Clumps of organisms are visualized, but unlike lepromatous leprosy they are rarely intracellular and there is little inflammatory response or granuloma formation. Disease progression involves both nerves and blood vessels. When epidermal undermining occurs, ulceration follows. During healing, granuloma formation and granulation tissue with epidermal ingrowth become evident. The initial necrosis within skin lesions is found beyond the site of bacterial proliferation, suggesting the macrolide toxin mediated effects are occurring without inducing any inflammatory responses. Sterile filtered supernatants of *M. ulcerans* are capable of producing these cytotoxic and ulcerative effects. Skin test positivity (burulin test) does not occur until patients are well into the healing phase of the disease.

Antibiotics administered without concomitant surgical intervention may not be efficacious and could lead to disfiguring lesions. These may require extensive surgical excision and skin grafting, possibly even amputation. Although the antileprosy agent, clofazimine, has *in vitro* activity against *M. ulcerans*, without surgery, it has not been beneficial. Usually resistant to isoniazid, other agents such as dapsone, streptomycin, rifampicin, and, more recently, clarithromycin have all been shown to have activity against *M. ulcerans*; however, adjunctive surgery appears to be critical for cure. Antibiotic sensitivity patterns alone do not predict clinical responses. Lesions may progress and accelerate with aggressive antimicrobial therapy alone. The role of localized heat application to skin lesions and the topical application of phenytoin to skin ulcers have unclear benefits, if any, for current therapy.[3] (*Dr. Bia is Professor of Medicine and Laboratory Medicine; Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, New Haven, Conn.*) ❖

References

1. Semret M, et al. *Mycobacterium ulcerans* infection (Buruli ulcer): First reported case in a traveler. *Am J Trop Med Hyg* 1999;61:689-693.
2. Thangaraj HS, et al. *Mycobacterium ulcerans* disease: Buruli ulcer. *Trans R Soc Trop Med Hyg* 1999;93: 337-340.
3. van der Werf TS, et al. *Mycobacterium ulcerans* infection. *Lancet* 1999;354:1013-1018.
4. Portaels F, et al. Insects in the transmission of *Mycobacterium ulcerans* infection. *Lancet* 1999; 353:986.
5. Tappero J. *Mycobacterium ulcerans* infection—Buruli ulcer disease: An emerging problem in west Africa. Program and Abstracts of the 38th annual meeting of the Infectious Diseases Society of America. New Orleans, La., Sept. 7-10, 2000;S77:12.

CME Questions

12. Buruli ulcer, associated with infection caused by *Mycobacterium ulcerans*, is characterized by each of the following except one. Which statement regarding Buruli ulcer disease is *false*?

a. The causative organism is thermophilic and grows best at 42ºC in the dark.
b. Most cutaneous lesions appear to arise spontaneously rather than as the direct result of a traumatic injury.
c. Early lesions of Buruli ulcer do not demonstrate a typical granulomatous response.
d. Growth of *M. ulcerans* on solid media is slow and often hindered by competing growth of contaminating microflora.
e. The mainstays of therapy are antibiotics and surgery. Without surgery, antibiotics are unlikely to cure an established skin lesion.

13. Which one of the following is correct?

a. A vigorous antibody response to *C. difficile* toxin A is associated with a high risk of recurrence of associated diarrhea.
b. Clinical risk factors for recurrence of *C. difficile* associated diarrhea include advanced age and increased severity of underlying disease.
c. *C. difficile* associated diarrhea recurs in fewer than 2% of patients after treatment.
d. Multiple recurrences of *C. difficile* associated diarrhea have not been reported.

14. Which one of the following is correct?

a. The combination of ddI and d4T can be administered during pregnancy without significant concern about adverse effects.
b. The use of nevirapine has been associated with the development of severe hepatitis.
c. Nevirapine is indicated as a recommended component of prophylaxis of health care workers after parenteral exposure to HIV.
d. In health care workers in whom nevirapine is contraindicated, it is recommended that no prophylaxis be administered after parenteral exposure to HIV.

In Future Issues:

Antiseptics and Antibiotic Resistance

UPDATES

By Carol A. Kemper, MD, FACP

Delayed HAV Vaccine Boosting

Source: Pappas VJ, Jr. *Vaccine* 2001; 19:339-402.

A question frequently asked of Infectious Disease specialists is whether patients who received a single dose of Hepatitis A vaccine (HAVRIX, SmithKline Beecham Biologicals), but who missed the booster dose within 6-12 months, should repeat the series as recommended or proceed with a single booster dose. Pappas and colleagues assessed whether a delay in the administration of the booster dose of Havrix reduces the response rate. Two groups of patients were selected for study: 124 travelers who received either a single dose of Havrix 1440 IU or two doses of Havrix 720 IU more than 24 months earlier, and a control group of 125 travelers who received the primary dose of Havrix 1440 IU 6-12 months earlier. Subjects were matched by age and gender.

The median duration of time between receipt of their initial vaccine and enrollment was 35 months (range, 24-66 months) for those receiving delayed vaccination compared with nine months (range, 6-14 months) for controls. HAV titers before and 30-40 days following the administration of a single booster dose of vaccine (1440 IU) were compared between groups.

Significantly fewer patients receiving delayed boosting had detectable HAV antibody levels (> 33 m IU/mL) at entry to study compared with controls (68% vs 89%; $P < 0.001$). Nonetheless, both groups responded equally well to a single booster dose of vaccine. There was no statistically significant difference in the geometric mean titers between the two groups in response to boosting. Receipt of a booster dose of Havrix up to 66 months after primary vaccination appears to be as successful as the recommended dosing schedule. Patients who miss their booster dose of Havrix do not have to restart the series. ■

Fewer Unrecognized HCV Infections

Source: Pappas VJ, Jr. *Hepatitis Control Report* 2000;5:3-6.

The hepatitis c lookback program begun by the U.S. Department of Health and Human Services in 1998 has, thus far, identified far fewer cases than anticipated of previously unrecognized hepatitis C virus (HCV) infection. The intent of the program was to trace recipients of contaminated blood products obtained from infected donors before the availability in 1992 of improved HCV screening using the second-generation Chiron assay.

The CDC estimates that 94,906 individuals who donated blood between 1988 and 1992, who subsequently tested positive for HCV infection after July 1992, will have been identified by the program by the end of 2000. Based on this information, ~100,000 recipients of those donated products will be traced and contacted, resulting in the notification of an estimated 1520 individuals who were previously unaware of their HCV infection.

These figures are significantly lower than those originally estimated. Initial calculations suggested that up to 500,000 people could have potentially received blood from infected donors. The actual figures were lower because donors donated less frequently than expected (twice vs estimated 3-5 times/donor), and fewer components were used per donation (2 vs estimated 6-10/donation). In addition, centers that used hepatic transaminase as a surrogate marker were able to screen out a greater number of infected donations than anticipated. These data indicate there are probably far fewer cases of previously unrecognized HCV infection in the United States than public health figures feared—good news for the public but not such good news for the pharmaceutical industry. ■

Quinidine: Check Your Formulary

Source: *MMWR Morb Mortal Wkly Rep* 2000;49:1138-1140.

The availability of newer antimicrobial agents has brought welcome change to many hospital formularies. But, as an Infectious Disease (ID) specialist, how often do formulary changes for cardiac drugs catch your eye?

This report from the Centers for Disease Control indicates that newer antiarrhythmics are, in some hospitals, replacing quinidine gluconate on their formularies. The unintended consequence may be the lack of availability of this critical agent for the treatment of malaria due to *P. falciparum*. Quinidine gluconate is the only parenteral agent in the United States indicated for use in the treatment of patients with complicated or life-threatening malaria, including those who are unable to tolerate oral therapy, who have high levels of parasitemia, and those with altered mental status or renal failure.

ID specialists should check with their hospital pharmacies to ensure ready availability of this agent, or at least have the pharmacist identify a dependable source in case of emergencies. Physicians who have difficulty securing an immediate supply of the drug can contact the Eli Lilly Company (800-821-0538, 24 hours a day), or the CDC malaria hotline (daytime number 770-488-7788; after hours, request the on-call person for malaria be paged). ■