AMERICAN HEALTH CONSULTANTS®

Providing Evidence-based Clinical Information for 22 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

Bartonella quintana: What a Lousey Bug!

ABSTRACT & COMMENTARY

Synopsis: *Bacteremia due to B quintana is prevalent among homeless individuals in many cities and is often asymptomatic and chronic or intermittent.*

Source: Foucault C, et al. *Bartonella quintana* bacteremia among homeless people. *Clin Infect Dis*. 2002;35:684-689.

Foucault and colleagues in Marseilles, France, evaluated homeless individuals presenting either to the emergency departments of the University Hospital as well as those admitted to medical facilities at shelters in order to determine the prevalence of *Bartonella quintana* bacteremia. One milliliter of whole blood was plated onto sheep blood agar while the remainder was inoculated into an aerobic blood culture bottle. After 7 days of incubation, 1 mL was removed from the blood culture bottles and plated on sheep blood agar plates, which, like those directly inoculated, were examined weekly for 3 months. Isolates from blood and body lice were identified by PCR methods.

Of the 126 individuals studied, all of whom were HIV-negative, 42 (33%) had *B quintana* bacteremia. Lice were detected on 18 (43%) of the bacteremic and 18 (21%) of the nonbacteremic subjects (OR, 2.75). *B quintana* was detected by PCR in lice more frequently from bacteremic than nonbacteremic individual (56% vs 6%; OR, 21.25). Sixty-five percent of the bacteremic and 20% (OR, 7.66) of the nonbacteremic subjects had elevated antibody titers to *B quintana*.

Approximately one-third of both the bacteremic and nonbacteremic patients were febrile, and the groups were similar in most other characteristics as well, with the exception of a greater frequency of sweats (22% vs 5%) among the former. The WBC was normal in all subjects.

Only one of the serial blood cultures was positive in 22 of the 42 bacteremic homeless subjects, but at least 2 consecutive cul-

VOLUME 22 • NUMBER 7 • JANUARY 1, 2003 • PAGES 49-56

INSIDE

tures obtained at weekly intervals were positive in 16, while 5 had intermittently positive cultures. Bacteremia persisted for 17, 53, and 78 weeks in 1 subject each and was intermittent for periods of 4-58 weeks in another 4.

No evidence of endocarditis was detected in the 14 patients who underwent echocardiography, although a transthorac procedure was performed in only 7 of these.

Six of 8 patients treated with either amoxicillin, amoxicillin/clavulanate, or benzathine penicillin remained bacteremic, as did 2 of 4 treated with doxycycline. None of 4 given gentamicin plus doxycycline had bacteremia at follow-up.

COMMENT BY STAN DERESINSKI, MD, FACP

Pediculus humanus, the human body louse, is the only known vector of *B quintana*, which may cause, in addition to the chronic and often asymptomatic bacteremia described in this study, trench fever, endocarditis and some cases of bacillary angiomatosis. *P humanus* infests only humans and is the vector for at least 2 pathogens, in addition to *B quintana* Rickettsia prowazekii, the agent of epidemic typhus, and the spirochete, *Borrelia recurrentis*, a cause of relapsing fever.[1] High seroprevalence rates indicating *B quintana* infection have been described among homeless in Paris,[2] Baltimore,[3] and Seattle,[4] and the organism has been detected in 12.3% of body lice examined in Russia.[5]

B quintana infects erythrocytes where it may persist for the life of the individual red blood cell and, in addition, may infect endothelial cells.[6-8] Bacteremia may persist for as long as 8 years.[9] In contrast to infection with *Bartonella bacilliformis*, which also infects erythrocytes, *B quintana* infection is not associated with hemolysis. Asymptomatic *B quintana* bacteremia has its counterpart in the domestic cat, a large proportion of which in some locations has chronic asymptomatic bacteremia due to *B henselae*, the agent of cat scratch disease whose vector is the cat flea.[10,11]

A high index of suspicion must be maintained in order to make a bacteriological diagnosis of bloodstream infection with *B quintana* if for no other reason than the difficulty most of us currently have in convincing our microbiology laboratories to do any work over and above the routine minimum. As indicated above, recovery from blood requires prolonged incubation since detectable growth often takes 20-40 days.[12] Serological tests are, of course, less specific than microbiological diagnosis.

Although the data from this study are nonrandomized and very limited, they do suggest that a combination of doxycycline and gentamicin may be a preferred regimen. Others have recommended monotherapy with doxycycline, erythromycin, or azithromycin for 4-6 weeks if the infection is uncomplicated, with the addition of either a third-generation cephalosporin or an aminoglycoside for the first 2-3 weeks in patients with endocarditis.[12]

All of this begs the question of what to do when next confronted with a homeless individual, whether symptomatic or not, in an area where *B quintana* infection is prevalent. In this study, only one-third had a temperature higher than 37.5°C. Reliance on serological screening would also be of limited value; while 65% of the bacteremic patients in this study had an elevated antibody titer to *B quintana* antigens, so did 20% of the nonbacteremic group. On the other hand,

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: Brenda Mooney.

EDITORIAL GROUP HEAD: Glen Harris.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robin Mason.

ASSISTANT MANAGING EDITOR: Robert Kimball.

SENIOR COPY EDITOR: Christie Messina.

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: $20.
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™

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517, or e-mail to robin.mason@ahcpub.com, or **Christie Messina,** Senior Copy Editor, at (404) 262-5413, or e-mail to christie.messina@ahcpub.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Subscriber Information

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

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $145).
Multiple Copies
1-9 additional copies: $215; 10 or more copies: $191.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 45 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.

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, GlaxoSmithKline, and Pharmacia, and does research for Elan, Roche, Merck, Pharmacia, and Becton-Dickinson. Dr. Jenson is on the speaker's bureau of Merck and Aventis. Dr. Donnelly is a consultant for OrthBioTech, and does research for Janssen, Merck, Novartis, Numico, Pharmacia, and Pfizer. Dr. John and Dr. Smilack report no speaker's bureau, research, stockholder, or consulting relationships having ties to this field of study.

the presence of very high titers (> 1:800) was a better discriminator between the groups but was quite insensitive, with only 23% of bacteremic subjects having such a titer.

Furthermore, in the absence of endocarditis, it is unclear that there is any clinical benefit to treatment, which, at any rate, may often fail.

Finally, sending the individuals back to their previous environment is likely to subject them to reinfection. Thus, the question of when to badger our microbiology laboratories to appropriately handle blood cultures in order to detect *B quintana* bacteremia remains, in most circumstances, unclear. ■

References

1. Raoult D, Foucault C, Brouqui P. Infections in the homeless. *Lancet Infect Dis*. 2001;1:77-84.
2. Guibal F, et al. High seroprevalence to *Bartonella quintana* in homeless patients with cutaneous parasitic infestations in downtown Paris. *J Am Acad Dermatol*. 2001;44:219-223.
3. Comer JA, et al. Antibodies to *Bartonella* species in inner-city intravenous drug users in Baltimore, Md. *Arch Intern Med*. 1996;156:2491-2495.
4. Jackson LA, et al. Seroprevalence to *Bartonella quintana* among patients at a community clinic in downtown Seattle. *J Infect Dis*. 1996;173: 1023-1026.
5. Rydkina EB, et al. *Bartonella quintana* in body lice collected from homeless persons in Russia. *Emerg Infect Dis*. 1999;5:176-178.
6. Rolain JM, et al. *Bartonella quintana* in human erythrocytes. *Lancet*. 2002;360:226-228.
7. Seubert A, Schulein R, Dehio C. Bacterial persistence within erythrocytes: A unique pathogenic strategy of *Bartonella* spp. *Int J Med Microbiol*. 2002;291: 555-560.
8. Brouqui P, Raoult D. *Bartonella quintana* invades and multiplies within endothelial cells in vitro and in vivo and forms intracellular blebs. *Res Microbiol*. 1996; 147:719-731.
9. Kostrzewski J. The epidemiology of trench fever. *Bulletin de l'Academie Polonaise des Sciences. (Medecine)*. 1949;7:233-263.
10. Bergmans AM, et al. Prevalence of *Bartonella* species in domestic cats in The Netherlands. *J Clin Microbiol*. 1997;35:2256-2261.
11. Jameson P, et al. Prevalence of *Bartonella henselae* antibodies in pet cats throughout regions of North America. *J Infect Dis*. 1995;172:1145-1149.
12. Ohl ME, Spach DH. *Bartonella quintana* and urban trench fever. *Clin Infect Dis*. 2000;31:131-135.

Staphylococcal Bacteremia: Methicillin Resistance and Mortality Revisited

ABSTRACT & COMMENTARY

Synopsis: *A meta-analysis of 31 published studies of Staphylococcus aureus bacteremia found that MRSA bacteremia was associated with a significantly higher mortality than MSSA bacteremia.*

Source: Cosgrove SE, et al. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: A meta-analysis. *Clin Infect Dis*. 2003;36:53-59.

COSGROVE AND COLLEAGUES REVIEWED STUDIES comparing mortality rates for MSSA and MRSA bacteremia published in the English language literature from 1980-2000. They excluded studies in which the odds ratio of mortality for MSSA or MRSA bacteremia could not be determined, fewer than 2 cases of MRSA bacteremia were reported, the subjects were children, or the data had been previously published. They identified 31 studies meeting criteria, with a total of 3963 cases. Of these, 2603 (65.7%) had MSSA bacteremia and 1360 (34.3%) had MRSA bacteremia. Twenty-four studies (77.4%) found no significant difference in mortality and (22.6%) found significantly higher mortality associated with MRSA bacteremia. No study found a significantly higher mortality associated with MSSA bacteremia. Combining the results of all studies demonstrated a significant increase in mortality associated with MRSA bacteremia compared with MSSA bacteremia (pooled OR 1.93, 95% CI 1.54-2.42, $P < .001$). There was, however, significant heterogeneity among the studies' results ($P = .03$ by the Q statistic), indicating that the different studies may be estimating multiple effects on the association between methicillin resistance and bacteremia mortality.

Cosgrove et al then analyzed the subgroup of 11 studies in which the association between methicillin resistance and mortality was adjusted for potential confounding factors. The pooled OR for this subgroup of studies was 1.88 (95% CI 1.32-2.18; $P < .001$), and there was no significant heterogeneity among results ($P = .16$). They conducted further subgroup analyses, including studies that reported unadjusted mortality, predominantly nosocomial bacteremias, a high proportion of catheter-related infections, endocarditis, and outbreaks

of MRSA infection. In each of the additional subgroup analyses, there was a significant association between methicillin resistance and mortality and minimal or no evidence of heterogeneity of results.

COMMENT BY ROBERT MUDER, MD

The question of whether methicillin resistance is an independent contributor to mortality in *S aureus* bacteremia has been the subject of debate for more than 20 years. Cosgrove et al attempt to answer this contentious issue by use of meta-analysis, a technique that has not been widely used in the field of infectious diseases. This study has several strengths, which include explicit and reasonable inclusion and exclusion criteria for the studies examined, an attempt to identify confounding factors and heterogeneity among studies, and explicit a prior hypotheses. They identified a consistent association between methicillin resistance and mortality whether considering the total number of studies, the studies that were adjusted for potential confounders, the studies that were unadjusted, and in each of several additional subgroup analyses.

One potential weakness in this analysis is the possibility that the studies that attempted to adjust for potential confounders did not completely identify and adjust for all confounding factors. However, the relative consistency of the increase in mortality associated with MRSA bacteremia is striking and suggests that the contribution of methicillin resistance to mortality is a real one.

MRSA strains are not more virulent than susceptible strains. A likely cause for the increased mortality associated with MRSA bacteremia is that vancomycin is intrinsically less active against *S aureus* than are beta-lactam antibiotics.[1,2] The newer antistaphylococcal agents active against MRSA, linezolid and quinupristin/dalfopristin, appear to be clinically equivalent but not superior to vancomycin, when used to treat a variety of *S aureus* infections.[3-5] At present, there are no large randomized trials comparing either agent with vancomycin for the treatment of staphylococcal bacteremia.

Despite the limitations of meta-analyses, Cosgrove et al provide strong evidence for an association between methicillin resistance and mortality in *S aureus* bacteremia. One likely reason is the relatively poor antistaphylococcal activity of antimicrobial agents available for the treatment of MRSA infection. Although new agents with greater activity are clearly needed, they are not likely to be available for the foreseeable future. Improved control of the spread of MRSA within hospitals currently offers the best opportunity for reduction in morbidity and mortality due to MRSA infection. ■

References

1. Small PM, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob Agents Chemother*. 1990;34:1227-1231.
2. Levine DP, et al. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med*. 1991; 115:674-680.
3. Rubenstein E, et al. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: A randomized, double-blind, multi-center study. *Clin Infect Dis*. 2001;32: 402-412.
4. Stevens DL, et al. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis*. 2002;34:1481-1490.
5. Fagon J, et al. Treatment of Gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. *Am J Resp Crit Care Med*. 2001;163:1759-1760.

Caspofungin for Invasive Candidiasis

ABSTRACT & COMMENTARY

Synopsis: *Caspofungin was superior to amphotericin B deoxycholate in the treatment of patients with invasive candidiasis.*

Source: Mora-Duarte J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;347:2020-2029.

MORA-DUARTE AND COLLEAGUES RANDOMIZED 239 patients at multiple centers in the Americas and Europe with invasive candidiasis to receive either caspofungin (70 mg IV, then 50 mg IV qd) or amphotericin B deoxycholate (0.6 - 0.7 mg/kg/d; those with neutropenia received 0.7 - 1.0 mg/kg/d). The study was double-blind and double-dummy.

Four-fifths of the patients had bloodstream infection and one-tenth had intraabdominal infection; approximately one-tenth of each group was neutropenic. *C albicans* accounted for 54% of infections in patients assigned amphotericin B but only 36% of those assigned caspofungin ($P = 0.009$). *C parapsilosis* was recovered from approximately one-fifth in each group, *C tropicalis* from 20% of the amphotericin and 13% of the caspofungin recipients, and *C krusei* from 4% and

1%, respectively.

Patients in both groups received their study drug for an approximate mean duration of 12 days. One-fourth of caspofungin and one-third of amphotericin recipients were given fluconazole after at least 10 days of study drug therapy.

In the modified intention-to-treat analysis of the 224 patients with documented infection and who received at least 1 dose of a study drug, the proportion of patients with a favorable response at the end of intravenous therapy was 73.4% in the caspofungin group and 61.7% in the amphotericin B group. The difference in the proportion of patients with a favorable response was 12.7 percentage points (95.6% CI, 0.7 to 26.0; $P = 0.09$). The outcomes were generally similar in the 2 groups when they were stratified according to the *Candida* species.

In an analysis of patients who met prespecified criteria for evaluation, including receipt of study drug for at least 5 days, 80.7% of the caspofungin-treated patients and 64.9% of the amphotericin B-treated patients had successful outcomes at the end of intravenous therapy. The difference between the treatment groups for this analysis was 15.4 percentage points (95.6% confidence interval, 1.1 to 29.7; $P = 0.03$).

Analysis of patients with candidemia who met these same criteria found that 80.3% of the caspofungin-treated patients and 64.6% of the amphotericin B-treated patients had a successful outcome at the end of IV therapy. In this analysis, the difference was 15.2 percentage points (95% CI, 0.6 to 31.0; $P = 0.06$).

Management of central venous catheters did not differ significantly between the 2 groups; three-fourths in each arm were removed by day 3. Removal or retention did not affect outcomes. The outcome of treatment was not predicted by the base-line minimal inhibitory concentration; all isolates for which the minimal inhibitory concentration of caspofungin exceeded 2 μg per milliliter responded favorably to caspofungin.

There were 39 deaths in the caspofungin group (34.2%) and 38 in the amphotericin B group (30.4%, $P = 0.53$). Five of the caspofungin-treated patients (4.4%) and nine of the amphotericin B-treated patients (7.2%) died from *Candida* infection ($P = 0.57$).

A larger proportion of patients in the amphotericin group had toxic effects requiring a change in therapy ($P = 0.03$). One patient in the caspofungin group (0.9%), as compared with 40 patients in the amphotericin B group (32%), had infusion-related adverse events of moderate or severe intensity.

Significantly more patients in the amphotericin B group had nephrotoxicity effects (24.8% vs 8.4% in the caspofungin group). The death of 1 patient (a patient in the amphotericin B group who had a cardiac arrest) was judged to be drug-related.

An eye examination was performed by an ophthalmologist in 217 of the patients (96.9%); a total of 187 patients (83.5%) underwent a base-line examination, and 155 (69.2%) underwent one or more follow-up examinations. Only 7 patients (3.7%) had *Candida* endophthalmitis at base line; resolution was noted in all patients with follow-up examination. One patient in the amphotericin B group who had normal findings at baseline reported ocular disturbances on day 3. A follow-up eye examination confirmed the presence of endophthalmitis.

COMMENT BY STAN DERESINSKI, MD, FACP

This study has demonstrated that caspofungin is superior to conventional amphotericin B in the treatment of invasive candidiasis. The number of patients with neutrophil counts less than 500/mm^3 was insufficient to make firm statements about the relative efficacy of these drugs in this group. However, to the extent that fungicidal activity is critical in the treatment of invasive candidiasis in the absence of phagocytes, caspofungin would be expected to maintain efficacy in this group since it is candidacidal at concentrations at or close to its MIC.

In contrast to prior trials in the treatment of bloodstream infection with *Candida* and contrary to expectations, early or late removal of central venous catheters did not affect outcome. It is perhaps interesting that caspofungin is active against *Candida* growing in biofilm. While this is true of some lipid formulations of amphotericin, no data regarding amphotericin B deoxycholate have been reported.

The IDSA recommendations state that all patients with candidemia should have a dilated retinal examination, preferably by an ophthalmologist.[1] In this study, however, only 3.7% of such exams at baseline revealed the presence of endophthalmitis and all of these resolved with systemic therapy alone. Thus, while I would not argue against the desirability of a dilated retinal examination in patients with candidemia, the cost effectiveness of an ophthalmological consultation requires further investigation.

Caspofungin is active in vitro against all species of *Candida*, although *C guilliermondi* has relatively elevated MICs. Questions have, however, been raised concerning its activity against *C parapsilosis*. In this study, 5 of the 9 patients with persistently positive cultures on therapy with caspofungin had *C parapsilosis* candidemia. These isolates, however, did not have elevated caspofungin MICs. Furthermore, 4 of these 5 enrolled at the same

institution within a 4-month period and, in addition, 12 of the 14 patients with *C parapsilosis* at other institutions responded favorably to caspofungin therapy, and there was no apparent difference in outcome of infections with this organism between the treatment groups.

This robust study has demonstrated that caspofungin is superior to amphotericin B in the treatment of invasive candidiasis. A study similar in size to this one that compared fluconazole (400 mg qd), a drug with a narrower spectrum of activity against *Candida* spp. than caspofungin, to amphotericin B in nonneutropenic patients found no significant difference in outcomes.[2] These findings raise important questions regarding the optimal treatment of patients with invasive candidiasis. Given the toxicity of amphotericin B, should it be discarded for this purpose? Would lipid amphotericin products fare better in clinical trials such as this one?

While the answer to the second question will require further clinical trials, the answer to the first may already be before us. ■

References

1. Rex JH, et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis*. 2000;30:662-678.
2. Rex JH, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. *N Engl J Med*. 1994;331:1325-1330.

Suggested Reading

1. Deresinski S. Caspofungin: A novel antifungal agent. *Infectious Disease Alert*. 2001;20(13):97-100.

Bites in the Night: A Rabies Immunization Update on People and Animals

CONFERENCE COVERAGE

By Mary Louise Scully, MD

AN EXCELLENT UPDATE ON RABIES WAS PROVIDED BY Charles E. Rupprecht, the Rabies Section Chief of the CDC, during the Symposium, Control of Zoonoses: A Veterinary Perspective at the recent 51st annual American Society of Tropical Medicine and Hygiene meeting in Denver, Colo. The most significant development is that Imovax-ID, the human diploid cell vaccine formulated for pre-exposure intradermal rabies vaccination, is no longer available in the United States. This event occurred in April 2001. The WHO position will remain supportive of the intradermal route for pre-exposure vaccination.

This discontinuation occurs in the setting of otherwise continued expansion of the intradermal route for pre-exposure prophylaxis and postexposure treatment, especially in areas of the world where rabies remains a significant health problem and cell-derived vaccines and rabies immune globulin are in short supply. It is thought that the estimated 50,000 rabies deaths reported per year (India alone reports 30,000 deaths per year) is actually an underestimate.[1] For health care providers in the United States, the discontinuation of Imovax-ID eliminates a less-expensive pre-exposure rabies prophylaxis regimen. However, the human diploid cell vaccine Imovax-IM, rabies vaccine adsorbed (RVA), and purified chick embryo cell vaccine (PCEC) remain available in the United States for intramuscular use.

Rabies is an acute, fatal encephalitis caused by neurotropic RNA viruses in the family Rhabdoviridae, genus lyssavirus. Classic rabies virus (genotype 1) is the type species of lyssavirus. Only 1 viral species was believed to cause rabies, but more recent investigations have showed at least 7 putative genotypes. Classic rabies virus accounts for most cases of rabies, but all lyssaviruses have shown capacity as human or animal pathogens.

Although many carnivorous mammals can serve as hosts, dogs remain the major reservoir and vector of rabies virus. Worldwide, dogs cause the majority of the human deaths due to rabies. Although domestic and wild cats do not seem to act as reservoirs for rabies, cats are effective vectors of transmission; hence, cats should be vaccinated despite the small relative risk of sarcoma.

In the United States, adequate canine and livestock vaccination has largely eliminated rabies from domestic animals, and the majority of animal rabies occurs in wild terrestrial animals such as raccoons, which accounted for 37.7% of all animal rabies cases in 2000. Skunks, foxes, and other mammals, including mongooses, groundhogs, bobcats, coyotes, badgers, and opossums, accounted for the remainder. Small mammals and rodents such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, rabbits, and hares are not important in the epidemiology of rabies, and bites from these animals rarely require rabies prophylaxis.

Bats account for a relatively small proportion of the

animal rabies cases reported in the United States (16.8% in 2000), but in the last 20 years variants of bat rabies have become the most common causes of human death from rabies.[2] Six of the 7 lyssavirus genotypes have been isolated from bats. Of the 39 cases of bat-associated rabies deaths in the United States during the last 50 years, only 9 (23%) reported a definite history of a bite, even though 20 (51%) reported contact with bats.[3] Since bats have small teeth, their bites might have gone unnoticed. Therefore, bat encounters in which a patient awakens to find a bat in the room, finding a bat in the room of an unattended child, or seeing a bat near a mentally impaired or intoxicated person warrant postexposure rabies prophylaxis.[4]

The resurgence of raccoon rabies that began in the Mid-Atlantic states in the late 1970s has spread so that raccoon rabies is now enzootic in all of the eastern coastal states as well as Alabama, Pennsylvania, Vermont, and West Virginia. Oral rabies immunization of free-ranging wildlife using vaccine-laden baits has shown promise in Europe, and similar efforts are under way to limit the expansion of raccoon rabies in the United States. More than 2 million doses of an oral vaccinia-rabies glycoprotein (V-RG) bait vaccine have been distributed in Ohio alone in the last 2 years. Additional states are expected to implement V-RG in the future as well. The hope is to make an immune barrier spanning the country from the shores of Lake Erie in Ohio south to the Gulf of Mexico in Alabama, preventing further westward spread of raccoon rabies.[5] Unfortunately, these types of control measures are less applicable to limiting bat rabies.

A practical question from the audience raised the issue of an allergic reaction in a patient after the third dose of a postexposure series. Rupprecht suggested trying another rabies vaccine formulation. The decision to continue the series should be based on the exposure history. A titer in the midst of the series should not be used to decide if the patient is protected. If a patient has had significant rabies exposure, every effort should be made to complete the recommended postexposure treatment.

Two recent companion reviews referenced above deserve special mention as outstanding papers on the past, present, and future of rabies.[2,3] ■

References

1. Rabies vaccines. WHO Weekly Epidemiological Record. 2002;77(14):109-119.
2. Hemachudha T, et al. Human rabies: A disease of complex neuropathogenetic mechanisms and diagnostic challenges. *Lancet Neurol*. 2002;1:101-109.
3. Rupprecht CE, et al. Rabies re-examined. *Lancet Infect Dis*. 2002;2:337-353.
4. CDC. Human rabies prevention-United States, 1999: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 1999;48(No.RR-1).
5. Krebs JW, et al. Rabies surveillance in the United States during 2000. *J Am Vet Med Assoc*. 2001;219: 1687-1699.

Dr. Scully is on the editorial board of Travel Medicine Advisor.

CME Questions

1. **Which of the following is correct?**
   a. *B quintana* is transmitted by fleas.
   b. *B quintana* bacteremia is invariably associated with high fever and shaking chills.
   c. Serological tests for *B quintana* bacteremia are reported to have both high sensitivity and specificity, with each > 90%.
   d. *B quintana* infects red blood cells where in which it persists for the life of the erythrocyte.

2. **Which of the following is correct?**
   a. MSSA is associated with lesser mortality than is MRSA bacteremia.
   b. Vancomycin is intrinsically more active against MSSA isolates than are beta lactams such as nafcillin.
   c. MRSA strains are demonstrably more virulent than MSSA strains.

3. **Which of the following is correct?**
   a. Caspofungin is more nephrotoxic than is amphotericin B deoxycholate.
   b. Caspofungin causes infusion-related toxicity as frequently as does amphotericin B deoxycholate.
   c. Caspofungin is inferior to amphotericin B deoxycholate in the treatment of invasive candidiasis.
   d. Caspofungin is active in vitro against all clinically important species of Candida.

In Future Issues:

West Nile Virus—Not Just Mosquitoes!

UPDATES

By Carol A. Kemper, MD, FACP

MRSA Hits Footballers Hard in Texas

Source: ProMED-mail post. November 14, 2002; www.promedmail.org.

Since the beginning of the school year, about 50 kids attending a local district high school in Pasadena, Texas, have developed infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). The outbreak has hit the football team particularly hard, and at least 1 football player has missed 13 days of school because of recurrent skin boils. Infections began occurring in the school about 2 weeks into the school year and are probably being transmitted by the close contact of the kids, especially those on the sports teams.

Close contact sports, such as football, have been blamed for outbreaks of various infections for many years, including herpes simplex, molluscum contagiosum, trichophyton, Hepatitis B, group A strep, as well as *S aureus*.

While many "community-acquired" cases of MRSA are still believed to have their origins in hospitals, there is increasing evidence that true community-acquired MRSA is occurring with greater frequency. Interestingly, such cases may be more likely to result in toxic shock syndrome. Recent evidence presented in abstract form at the 2001 ICAAC suggested that community isolates are more likely to express staphylococcal toxins B and C compared with nosocomial isolates.[1] In addition, community isolates are more likely to have isolated resistance to the penicillin-binding proteins, but retain susceptibility to other non-beta-lactam agents, such as clindamycin, trimethoprim-sulfamethoxazole, and quinolones. In contrast, nosocomial isolates are more frequently broadly resistant to a variety of agents. ■

Online Pharmacies Cater to Special Interests: Cipro and Anthrax

Source: Tsai AC, et al. *Am J Med.* 2002;113:424-427.

On-line pharmacy retailing and mail-order prescriptions continue to grow briskly, in part due to the aging baby boomer generation's need for drugs.

One technology consultant estimates that consumers will buy $2.8 billion worth of prescription drugs online this year, plus $900 million worth of vitamins and over-the-counter drugs. While some of this business is limited to web sites designated by health care plans, smaller sites successfully turn a profit by nimbly responding to consumer whims and filling unusual niches. Of concern, many (possibly illegal) sites provide poor-quality information and inadequate consumer safeguards, and some sell foreign unapproved versions of various drugs as highlighted by the jump in the number of web sites selling ciprofloxacin in the wake of the anthrax scare last fall.

In October 2002, Tsai and associates identified 59 web sites selling ciprofloxacin, 23 of which were created within 2 weeks of the first anthrax report October 4. Forty-eight of the sites (81%) were registered to US addresses, but the rest operated around the globe or their address could not be identified. Half of the sites (49%) sold only ciprofloxacin; The remaining sites sold other drugs (usually Viagra®). Interestingly, while most of the sites specially advertised ciprofloxacin for anthrax "prophylaxis" or treatment, only two-thirds specified the appropriate duration of post-exposure prophylaxis (60 days). Several sites sold a 3- or 7-day "package" at discount. Side effects and contraindications were not provided by 28% of sites, and 19% did not require a completed medical questionnaire in order to purchase a drug. The median cost per tablet was $6.95 (range, $5.67-11.36), a 50% mark-up over the wholesale cost in the United States at that time.

During the next 12 months, many of the sites stopped selling ciprofloxacin or vanished from the net (presumably as demand lessened); almost 1 year later, only one-fifth of the original sites were still selling ciprofloxacin. Tsai et al maintain that US regulators are ill-equipped to adequately police such fly-by-night online retailers. While the FDA did attempt to halt private shipments of ciprofloxacin into the country last year and sent "cyber" letters to 11 overseas web sites selling non-US-approved versions of drugs, these warnings are apparently largely disregarded. While 3 of the sites selling ciprofloxacin received these warning letters, 2 were still in operation 1 year later. ■

PHARMACOLOGY WATCH

FDA Approves Claritin For OTC Use For Seasonal Rhinitis

After years of legal wrangling, the FDA has approved loratadine (Claritin, Schering-Plough) as an over-the-counter (OTC) product for the treatment of seasonal rhinitis. Loratadine is considered a nonsedating antihistamine, and its OTC approval was linked with the FDA's work with the National Transportation Safety Board to improve public awareness about the concerns of drowsiness while driving associated with older antihistamines. The OTC switch also comes within months of loss of patent protection for loratadine and the entry into the market of generic equivalents. The OTC switch applies to all 5 formulations of Claritin, and at least 1 generic house plans to market "Reditabs." Meanwhile, Schering-Plough continues to aggressively market desloratadine, the active metabolite of loratadine under the trade name Clarinex, in an attempt to protect its $3 billion Claritin market.

Simpler Atrial Fibrillation Management

Management of atrial fibrillation (AF) may be simpler in the future based on the results of 2 studies published in the December 5, 2002, *N Engl J Med*. The larger of the 2 studies (AFFIRM) enrolled more than 4000 patients in the United States and Canada with AF and at least 1 other risk factor for stroke such as hypertension, coronary artery disease, diabetes, congestive heart failure, or age older than 65. Patients were randomized to a rhythm control strategy with cardioversion followed by amiodarone, sotalol, propafenone, or older antiarrhythmics such as procainamide or quinidine; or a rate control strategy with digoxin, beta-blockers, and/or calcium channel antagonists. All patients in both groups were anticoagulated with warfarin. The primary end point was overall mortality. The 5-year death rate was 23.8% in the rhythm control group and 21.3% in the rate control group (P = 0.08). Rhythm control was associated with more hospitalizations and more adverse drug effects. In the second study from The Netherlands, 522 patients with persistent AF after electrical cardioversion were randomized to treatment aimed at rate control or rhythm control. Both groups received oral anticoagulation, and the composite end point was death from cardiovascular causes as well as bleeding, implantation of a pacemaker, or severe adverse effects of drugs. After a mean duration of nearly 2.5 years, the primary end point occurred in 44 patients in the rate control group (17.2%) and 60 patients in the rhythm control group (22.6%) (P = 0.11). Although both studies showed trends toward adverse outcomes with rhythm control, neither study reached statistical significance. The authors of both studies suggest that a rate control strategy for the treatment of AF is at least as good as the rhythm control strategy. In an accompanying editorial, Michael D. Cain, MD, states that "on the basis of these data, rate control can now be considered a primary approach to the treatment of atrial fibrillation." He also suggests that nonpharmacologic treatments for AF will still be pursued with the goal toward maintaining

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. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. 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.

sinus rhythm (*N Engl J Med*. 2002;347:1825-1833; 1834-1840; 1883-1884).

Oral Anticoagulation Vs Aspirin in AF

In a related study, oral anticoagulation was found to be superior to aspirin in preventing stroke in patients with atrial fibrillation (AF) or paroxysmal AF. The study was a pooled analysis of 6 trials of more than 4000 patients who were randomized to receive therapeutic doses of oral anticoagulant or aspirin with or without low-dose oral anticoagulants. Patients receiving oral anticoagulation were significantly less likely to experience stroke (2.4 vs 4.5 events per 100 patient years; hazard ratio [HR], 0.55), ischemic stroke (HR, 0.48), or cardiovascular events (HR, 0.71) but were more likely to experience major bleeding (2.2 vs 1.3 events per 100 patient years; HR, 1.71). Anticoagulant therapy also showed benefit on all-cause mortality but only after 3 years of therapy. Interestingly, more benefit was seen for anticoagulation vs aspirin in patients younger than 75 compared to those 75 years or older. A lesser benefit was also seen for women compared to men. The authors suggest that oral anticoagulation is more effective than aspirin in decreasing the risk of stroke and other cardiovascular events in patients with nonvalvular AF (*JAMA*. 2002;288:2441-2448).

Immunization Does Not Cause Autism

A new study should put an end to concern regarding the MMR (measles, mumps, and rubella) vaccine and its possible link to autism. Researchers in Denmark looked at the records of all children born between January 1991 and December 1998, representing a cohort of almost 540,000 children. Of those, 82% (440,655) received the MMR vaccine. In the cohort, 316 children were diagnosed with autism and 422 were diagnosed with other artistic spectrum disorders. After adjustment for potential confounders, the relative risk for artistic disorder in the vaccinated children compared to the unvaccinated was 0.92 (95% CI, 0.68 to 1.24). The relative risk for other artistic spectrum disorders was 0.83 (95% CI, 0.65 to 1.24). The authors also looked for a possible association between age at the time of vaccination, the time since vaccination or the date of vaccination, and development of artistic disorder and found no relationship. They also found no temporal clustering of cases of autism at any time after immunization (*N Engl J Med*. 2002;347:1477-1482).

Statins May Lower CRP Levels

C-reactive protein (CRP), an inflammatory marker, has shown to be a strong predictor of cardiovascular events, perhaps even more predictive then LDL cholesterol levels (*N Engl J Med*. 2002; 347:1557-1565). Most physicians have looked at these studies with interest but have been unsure what to do with an elevated CRP level in an individual patient. Perhaps even more importantly, it is unclear whether lowering CRP affects cardiovascular outcomes. Until an answer is found to this important question, an increasing body of evidence is suggesting that statins may lower CRP levels.

Simvastatin Reduced CRP Plasma Levels

A recent study reviewed the use of simvastatin in 130 patients with mixed hyperlipidemia and 195 patients with hypertriglyceridemia in a placebo-controlled, double-blind trial. After 6 weeks of treatment with simvastatin 20, 40, and 80 mg, significant reductions in CRP plasma levels were noted vs placebo ($P < 0.05$) (*Am J Cardiol*. 2002;90:942-946). CRP lowering by statins appears to be a class effect with multiple reports of benefit with various statins in the last 2 years.

FDA Actions

Roche's pegelated interferon alfa-2a (Pegasys) has been approved for use in combination with a ribavirin for the treatment of hepatitis C. The drug was approved in October 2002, but Roche has been eagerly awaiting the approval for combination treatment in order to compete with Schering-Plough's Peg-Intron/ribavirin combination for the same indication.

Eli Lilly has received approval to market atomoxetine (Strattera) for the treatment of attention deficit hyperactivity disorder (ADHD). Unlike other drugs for this indication, atomoxetine is not a stimulant and is not listed as a controlled substance. Rather, the drug is a selective norepinephrine reuptake inhibitor, which seems to play a role in regulating attention, impulsivity, and activity levels. Strattera is approved for treatment of ADHD in children, adolescents, and adults.

Eli Lilly has also received approval to market teriparatide injection (Forteo) for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture. Teriparatide is a portion of human parathyroid hormone, which stimulates new bone formation in the spine and hip. The drug is given by daily injection in the thigh or abdomen. ■

AMERICAN HEALTH CONSULTANTS®

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

VOLUME 8, NUMBER 1 PAGES 1-2 JANUARY 2003

Effects of Losartan on Cardiovascular Morbidity and Mortality in Patients with Isolated Systolic Hypertension and LVH

Source: Kjeldsen SE, et al. *JAMA*. 2002;1491-1498.

Since the early 1990s it has been recognized that left ventricular hypertrophy (LVH) is an important prognostic indicator for cardiovascular morbidity and mortality. More recently, it has been suggested that angiotensin receptor blockers (ARBs) might exert a particularly favorable effect upon LVH, perhaps even independent of blood pressure (BP) effects. The LIFE (Losartan Intervention for Endpoint Reduction) study was designed to test the hypothesis that losartan (LSN) exerts preventive cardiovascular effects, beyond simply controlling BP. To this end, a randomized, controlled trial (n = 1326) of LSN vs atenolol (ATN) was initiated in persons with isolated systolic hypertension and LVH, with a primary composite end point of cardiovascular death, stroke, and MI.

Despite the fact that BP reduction was equal in both groups (28/9 mm Hg), there was a 25% relative risk reduction in the primary end point (CV death, stroke, MI) in favor of losartan. Additionally, LVH reduction was much more vigorously achieved by LSN than ATN. Stroke reduction was particularly favorably affected by LSN, in which a 40% reduction compared to ATN was seen. Lastly, LSN demonstrated a more favorable tolerability profile than ATN: discontinuations due to drug-related events were half as frequent in recipients of LSN than ATN. ■

Increase in Nocturnal Blood Pressure and Progression to Microalbuminuria in Type 1 Diabetes

Source: Lurbe E, et al. *N Engl J Med*. 2002;347:797-805.

It has been noted that among persons with type 1 diabetes (DM-1), hypertension (HTN) often develops concomitantly with occurrence of microalbuminuria (MAU). Closer investigation with ambulatory BP monitoring (ABPM) suggests that nocturnal blood pressure elevations (NBP) are particularly associated with MAU; however, whether the NBP causes the MAU (or they are concomitant) has been uncertain.

Lurbe and associates prospectively studied ABPM in adolescent DM-1 patients (n = 75) who were normoalbuminuric and normotensive at enrollment. Subjects were periodically monitored by ABPM and urinary albumin measurements for more than 5 years. MAU developed in 19% of study subjects, and was preceded by a modest elevation in BP, but it was only the NBP in which change was manifest. Over time, in the group that ultimately developed MAU, the NBP increased by 5 mm Hg compared to baseline; in the normoalbuminuric group, NBP did not change. The subtlety of these findings is reflected by the fact that neither office BP, nor mean daytime BP predicted MAU. Hence, ABPM may detect modest BP patterns, which lead to early prediction of target organ damage. ■

HRT, Lipid, and Glucose Metabolism in Diabetic and Nondiabetic Postmenopausal Women

Source: Crespo CJ, et al. *Diabetes Care.* 2002;25:1675-1680.

Like cardiovascular diseases, type 2 diabetes (DM-2) increases in postmenopausal women. Prospective randomized interventional trials have not shown a benefit for hormone replacement therapy (HRT) in improving cardiovascular outcomes. The effect of HRT upon lipids and glucose among diabetic populations has been little studied. Crespo and colleagues evaluated subjects (n = 2786) in the Third National Health and Nutrition Examination Survey (NHANES III) seeking the relationship between HRT, diabetes, and lipids.

In diabetic women, total cholesterol and non-HDL levels were significantly lower in women who used HRT than never users, but there was no difference in HDL levels. In contrast, in nondiabetic women HDL levels were higher in HRT users than

nonusers. Fasting glucose levels (FBS) in diabetic women were significantly lower in HRT recipients than never users (112 mg/dL vs > 150 mg/dL). Crespo et al conclude that menopausal HRT is associated with improved FBS, total cholesterol, and non-HDL in diabetics. The fact that these findings are observational in nature suggests cautious interpretation until their clinical relevance is ascertained through interventional trials. It may be that other, undetected factors in women who choose to use HRT are influencing lipid and glucose metabolism. ■

Effects of Long-Term Treatment With ACE Inhibitors in the Presence or Absence of Aspirin

Source: Teo Koon K, et al. *Lancet*. 2002;360:1037-1043.

Both angiotensin converting enzyme inhibitors (ACEI) and aspirin (ASA) have a proven valuable track record in a variety of cardiovascular preventive and therapeutic areas. One of the mechanisms by which ACEI are believed to confer benefit is the production of vasodilatory prostaglandins, including PGI-2 and PGE-3. Since ASA can blunt production of prostaglandins, it is conceivable that the combination of the 2 might "cancel out" beneficial effects. To date, evaluation of large clinical trials in which both ASA and ACEI were used have provided conflicting data. Hence, Teo and associates undertook a systematic review of long-term randomized trials in which ACEI and ASA were coadministered (n = 22,060) for meta-analysis.

ACEI treatment in these trials (including the SOLVD treatment, SOLVD prevention, SAVE, AIRE, TRACE, and HOPE studies) produced overall a 22% reduction in major clinical outcomes. Concomitant use of ASA was not associated with a statistically significant diminution of benefit. Based upon this information, Teo et al suggest that for persons who are receiving either ACEI or ASA, if the other agent is indicated, clinicians may feel confident that the combination will not reduce beneficial effects. ■

Long-Term Risks Associated with Atrial Fibrillation: 20-Year Follow-up of the Renfrew/Paisley Study

Source: Simon S, et al. *Am J Med*. 2002;113:359-364.

Most of the studies of atrial fibrillation (AF) that address cardiovascular (CV) consequences provide only short-term or intermediate-term insight (6 months-24 months). Long-term consequences of AF are much less studied. Simon and colleagues evaluated CV outcomes (including hospitalizations and deaths) over a 20-year follow-up in 15,000 persons enrolled in Renfrew and Paisley, Scotland. The population was middle-aged (45-64 years) at enrollment.

At entry enrollment (1972-1976), 100 persons had AF. During the extended follow-up, women manifest a 5-fold increase in cardiovascular hospitalization or death, and risk in men was 2-fold increased. Lone AF (AF in the absence of discernible cardiovascular disease) did not confer a statistically significant increase in cardiovascular risk. The increase in CV risk associated with AF was expressed primarily as stroke and heart failure. This new information indicates substantial long-term risk from AF. Simon and colleagues suggest that strategies to prevent CHF, as well as those already commonly practiced for stroke prevention, may be of benefit in persons with AF. ■

Olfactory Impairment in Older Adults

Source: Murphy C, et al. *JAMA*. 2002;288:2307-2312.

Despite widespread attention to the demographics and management of hearing and visual impairments in older adults, there has been little study of olfactory impairments (OLF). Olfactory impairment can results in aggravation of nutritional problems, inability to respond promptly to risk situations such as fire or gas leaks, and reduce quality of life. To better determine the prevalence of OLF, Murphy and colleagues examined data from participants in the Epidemiology of Hearing Loss Study (n = 2491), a cross-sectional study of adults aged 53-97.

Initially, self-report of OLF was assessed by asking the question, "Do you have a normal sense of smell (compared to other people)?" Then, testing for OLF was performed using the San Diego Odor Identification Test (SDOIT), which uses natural home odors such as coffee and chocolate. OLF was defined as inability to identify at least 6 of 8 odorants.

One fourth of the tested population manifested OLF by SDOIT. On the other hand, only 9.5% of the population self-reported deficits in smell. A multiple logistic regression model determined that smoking, nasal congestion, stroke history, and epilepsy were associated with increased risk of OLF. ■

Clinical Briefs in Primary Care™ is published monthly by American Health Consultants. Copyright © 2003 American Health Consultants. **Vice President/Group Publisher:** Brenda Mooney. **Editorial Group Head:** Glen Harris. **Editor:** Stephen Brunton, MD. **Managing Editor:** Robin Mason. **Assistant Managing Editor:** Rob Kimball. **Senior Copy Editor:** Christie Messina This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information

Customer Service: 1-800-688-2421

E-Mail Address: neill.larmore@ahcpub.com

World Wide Web: http://www.ahcpub.com

Address Correspondence to: American Health Consultants 3525 Piedmont Road, Building Six, Suite 400 Atlanta, GA 30305.

THOMSON™
AMERICAN HEALTH CONSULTANTS