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Seaweed Poultices and *Vibrio* Infection

By Carol A. Kemper, MD, FACP

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Dr. Kemper does research for Abbott Laboratories and Merck. This article originally appeared in the December 2011 issue of Infectious Disease Alert. At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.

Source: ProMED post, Oct. 20, 2011. Available at: promedmail.org.

This report details the occurrence of an infected, cellulitic lower extremity wound infection in a 70-year-old British woman secondary to an unusual *Vibrio* species, *V. alginolyticus*. The woman was otherwise in good health, and she liked to take a daily swim in the sea off Guernsey (near the Channel Isles). She first injured her leg on a pot in the garden, and for 2 weeks had applied a home-made seaweed poultice to the wound, which she had created by extracting the alginate gel from the receptacles (knobby bladder-like organs at the end of fronds) of a local seaweed called spiral wrack. The wound had initially seemed to heal and crust over, then broke open, becoming weepy, swollen, and erythematous. The organism was recovered from both the wound and from seaweed samples collected from the beach near her home. She responded well to doxycycline.

Popular opinion holds that sea bathing and saltwater promote wound healing, and seaweed preparations have a long history as a home-based remedy. Commercial products increasingly incorporate alginate gels, which are absorbent and appear to promote wound healing. Unfortunately, home-based remedies do not use sterilized material, and seaweed can be contaminated with bacteria.

Changes in ocean temperature raise concerns that microbial flora in seawater and seaweed may be changing. Reports from Northern Europe suggest there has been an increase in serious infections from *Vibrio* spp. *V. alginolyticus* is a salt-tolerant (halophilic), Gram-negative bacilli found in more temperate seawater, such as coastal areas and estuaries. While unusual, infections occur more commonly in the summer months, when the water is warmer. Infections from this organism generally result in superficial wound infection, and external and middle ear infection, but can occasionally result in severe cellulitis, necrotizing fasciitis, bacteremia, and sepsis. Home-based seaweed poultices should be discouraged. ■

Moxifloxacin for Odontogenic Infection

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostic. This article originally appeared in the November 2011 issue of Infectious Disease Alert. At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.

Synopsis: *In a randomized, double-blind clinical trial, treatment with moxifloxacin was as effective as clindamycin in the treatment of dental abscess and superior to clindamycin in the treatment of odontogenic inflammatory infiltrates.*

Source: Cachovan G, et al. Comparative efficacy and safety of moxifloxacin and clindamycin in the treatment of odontogenic abscesses and inflammatory infiltrates. *Antimicrob Agents Chemother* 2011;55:1142-1147.

Outpatients with a diagnosis of either dentoalveolar or periodontal abscess or a diagnosis of gingival inflammatory infiltrates were randomized to receive either moxifloxacin 400 mg daily or clindamycin 300 mg QID, both for 5 days, in a prospective, randomized, placebo-controlled, double-dummy clinical trial design. The primary efficacy endpoint was percent reduction in pain on a visual analogue scale (VAS) at days 2-3 from baseline. (This endpoint has been shown historically to be a useful endpoint for dental intervention studies.)

Among gingival infiltrate patients, the 21 patients randomized to moxifloxacin (MXF) experienced a 61% median reduction in pain at days 2-3 vs. 23% in the 19 patients receiving clindamycin (CLI) (P = 0.006). Among abscess patients, the 15 patients receiving MXF had a 56% reduction in pain vs. 43% in the 16 patients receiving CLI (P = 0.358). Objective evidence of infiltrate and abscess resolution by day 5-7 of treatment also favored MXF.

While not reaching statistical significance, MXF appeared to be better tolerated than CLI with lower incidence of diarrhea and nausea (1 in the MXF arm vs. 8 in the CLI arm).

■ COMMENTARY

Clindamycin is commonly prescribed for treatment of odontogenic infection in both the inpatient and outpatient setting. While generally effective, clindamycin requires TID or QID dosing and is commonly associated with diarrhea (including *Clostridium difficile* colitis). Moxifloxacin, while also occasionally associated with *C. difficile* disease, is generally well-tolerated, has the advantage of once daily dosing, and has in vitro activity against most of the pathogens implicated in odontogenic infections.

This study nicely demonstrates that MXF is superior to CLI for treatment of dental inflammatory infiltrates and at least equal to CLI as adjunctive treatment of odontogenic abscess. MXF appeared to have fewer side effects than CLI. ■

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Lyme Meningitis in Children with Aseptic Meningitis

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Dr. Jenson reports no financial relationship to this field of study. This article originally appeared in the December 2011 issue of Infectious Disease Alert. At that time it was peer reviewed by Timothy Jenkins, MD, Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Jenkins reports no financial relationship to this field of study.

Synopsis: *The prevalence of Lyme meningitis among children with nonspecific aseptic meningitis occurring from April through December in the years 2006 through 2009 in an endemic area for Lyme disease was 13.3% (95% confidence interval [CI], 6.3%-25.1%).*

Source: Garro AC, et al. Prevalence of Lyme meningitis in children with aseptic meningitis in a Lyme disease-endemic region. *Pediatr Infect Dis J* 2011;30:990-991.

A DESCRIPTIVE STUDY ENROLLED CHILDREN 2-18 YEARS OF age presenting to a pediatric emergency department in Rhode Island during the months of April through December of 2006-2009. Children were enrolled who had pleocytosis, defined as white blood cell count of > 8/mm^3 in the cerebrospinal fluid (CSF), in the absence erythema migrans rash, cranial neuropathy, papilledema, a positive Gram stain, antibiotic use within 2 weeks, chronic neurologic disease, or an indwelling ventricular shunt. Serum *Borrellia burgdorferi* studies were recorded if ordered by the referring physician, though this testing is not standard of care and was not required for study participation. CSF *B. burgdorferi* ELISA studies were performed if there was sufficient CSF.

Confirmed Lyme meningitis was defined by positive 2-tier *B. burgdorferi* serologic studies using the Centers for Disease Control and Prevention (CDC) criteria (ELISA followed by Western blot of positive or equivocal samples, with Western blot IgM positive for at least 2 of 3 proteins at 23, 39, and 41 kD; and IgG positive for at least 5 of 10 proteins at 23, 28, 30, 39, 41, 45, 58, 66, and 93 kD). Probable Lyme meningitis was defined by positive CSF *B. burgdorferi* ELISA, which is not diagnostic for Lyme meningitis but suggestive in the presence of pleocytosis.

Of the 104 children who were screened, a total of 60 children were enrolled. Among the excluded cases were 10 children with erythema migrans, which is diagnostic of Lyme disease, and 9 children with cranial neuropathy without erythema migrans, which in the presence of pleocytosis indicates a high probability of Lyme meningitis. The median age was 10 years (range, 2.8-18.0 years), 57% were male, 56% were non-Latino white, 26% were Latino, 10% were black, and 8% were other ethnicity.

Among the 60 children there were 30 children with tier-2 *B. burgdorferi* serologies available, which showed 8 confirmed cases (8/60) for a minimum prevalence of Lyme meningitis of 13.3% (95% CI, 6.3%-25.1%). Of these 8 cases, 7 had sufficient CSF for ELISA and 6 were positive. CSF ELISA of the remaining 30 children identified 1 case of probable Lyme meningitis. The minimum prevalence of confirmed or probable cases (9/60) was 15.0% (95% CI, 7.5%-27.1%). None of the 9 children had a history of Lyme disease.

■ COMMENTARY

This interesting report probably underestimates the prevalence of Lyme meningitis in children because serum *B. burgdorferi* studies are not standard of care and in this study were obtained in only half of the cases. CSF B. burgdorferi ELISA may be performed but may be negative, as occurred in 1 case in this series, because the intrathecal antibody response is usually detectable after at least 2 weeks of neurologic symptoms.

The results indicate that clinicians should perform serum *B. burgdorferi* studies for children presenting with undifferentiated aseptic meningitis in Lyme disease-endemic regions during appropriate seasons. Lyme meningitis is very amenable to treatment and failure to diagnose may permit progression and delay resolution of symptoms. ■

Use of Newer Assays for Syphilis

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Source: Park IU, et al. Screening for syphilis with the treponemal immunoassay: Analysis of discordant serology results and implications for clinical management. *J Infect Dis* 2011;204:1297-1304.

Clinical laboratories in North America are increasingly switching to the newer treponemal-specific assays, such as the enzyme immunoassay (EIA) or chemiluminescence immunoassay (CIA) for syphilis testing. Because these assays are automated, they are cost-effective for clinical laboratories compared with the traditional RPR/VDRL testing. But whether they are cost-effective for clinical purposes is uncertain. While the EIA/CIA assays are highly sensitive (95%-99%) and specific (98%-99%), they may result in a larger number of false-positive or discordant results in a low prevalence population, which arguably increases the cost for treatment and follow-up, as well as potential over-treatment. Furthermore, data are lacking on the management of patients with discordant test results (CIA-positive/RPR-negative). The CDC presently recommends the use of a second treponemal test (e.g., FTA or TP-PA) for discordant specimens. Data suggest that, in a low-prevalence population, approximately 40% of these discordant specimens will be negative by a second treponemal-specific test; treatment may not be necessary for these individuals. For those who test positive by a second-treponemal-specific assay, physical findings and clinical risk factors should be assessed, and patients with risk factors should be offered antibiotic therapy, if not previously treated.

Researchers at Kaiser Permanente in San Francisco and Oakland, CA, examined the clinical characteristics of patients with discordant serology, who would not be identified by standard screening methods (i.e., CIA-positive, RPR-negative). A total of 21,623 assays were performed between August 2007 and October 2007, 439 (2%) of which were CIA-positive. Of these, 255/439 (58%) were RPR-negative. Of these 255 CIA-positive/RPR-negative discordant specimens, 184 (72%) were TP-PA-positive and 71 (28%) were TP-PA-negative. The CIA-positive/RPR-negative/TP-PA-positive group was significantly more likely to be male, men having sex with men (MSM), and HIV-positive compared with the TP-PA-negative group (all $P < 0.001$). They were also more likely to be African-American, and to have received previous treatment for syphilis (57% vs. 9%). However, even after excluding patients with history of syphilis, discordant TP-PA-positive patients were still more likely to be male, MSM, HIV-positive, and African American compared to those who were TP-PA-negative.

In addition, the median CIA test quantitative index was significantly higher in the CIA-positive/RPR-negative/TP-PA-positive group compared with the TP-PA-negative group (9.8 vs. 1.6), suggesting that the CIA index may be potentially useful in treatment decisions. Two-thirds of the TP-PA-negative patients had CIA index values ≤ 2, whereas only 9% of the TP-PA-positive patients had a result ≤ 2.

Several additional interesting observations were made from these data. One individual was initially CIA-positive/RPR-negative/TP-PA-negative but subsequently TP-PA-positive on follow-up testing, suggesting that he may have been in the "window period" and seroconverted the CIA test earlier than the TP-PA. On the other hand, 6 of 31 (23%) patients with discordant results who were initially TP-PA-negative, and who were followed with repeat testing, "seroreverted" their CIA result, suggesting their initial CIA test was falsely positive. Of the 28 pregnant woman identified with discordant serology, 12 (43%) were CIA-positive/RPR-negative/FTA-positive; 5 of these had a history of syphilis. Of the remaining 16 women who were CIA-positive/RPR-negative/TP-PA-negative, none had a prior history of syphilis.

Of the 255 patients with discordant serology, 100 (39%) were HIV-positive; most (86%) of these were CIA-positive/RPR-negative/TP-PA-positive. The use of the tests and interpretation of discordant test results in HIV-positive individuals presents a difficult challenge. Current guidelines recommend a lumbar puncture (LP) for HIV+ patients with latent syphilis of uncertain duration or late latent disease (although neurosyphilis is less likely in patients with an RPR titer ≤ 1:16). Because the CIA quantitative results are often masked, it is uncertain whether all of these patients require an LP. Further study is required to examine the utility of the CIA as a quantitative index. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Rivaroxaban Now Approved for Stroke Prevention

In this issue: New indication for rivaroxaban; new study on warfarin testing; medications causing adverse drug events; niacin as an add-on therapy; and FDA actions.

Rivaroxaban for atrial fibrillation patients

Rivaroxaban (Xarelto), Janssen Pharmaceutical's once-a-day oral Xa inhibitor, has been approved for reducing the risk of stroke in patients with atrial fibrillation. The drug was previously approved for prophylaxis of deep vein thrombosis in patients undergoing hip or knee replacement. Rivaroxaban is the second "non-warfarin" oral anticoagulant to be approved for this indication after the direct thrombin inhibitor dabigatran (Pradaxa). The approval was based on the ROCKET AF trial, a double-blind, randomized, noninferiority comparative trial with warfarin, which showed a rate of stroke or systemic embolism of 2.1% per year for rivaroxaban and 2.4% per year for warfarin. The study looked at 14,000 patients over 700 days of follow-up. Rates of major and non-major bleeding were the same with the two drugs, although the rate of intracranial hemorrhage was lower for rivaroxaban while the rate of GI bleeding was lower with warfarin. ROCKET AF showed noninferiority of rivaroxaban vs warfarin but not superiority (*N Engl J Med* 2011;365:883-891). The approval sets up a major marketing showdown between Janssen and Boehringer Ingelheim, the manufacturer of dabigatran, for this multibillion dollar market. Meanwhile, Pfizer and Bristol-Myers Squibb are jointly developing a third drug — apixaban, also a factor Xa inhibitor — which is undergoing an "accelerated review" by the FDA with approval likely in March 2012. All three drugs have the potential disadvantage of the lack of an antidote, a problem that seems to be plaguing dabigatran with more than 250 fatal bleeding episodes reported worldwide since the drug was approved in 2010. A recent report suggests that prothrombin complex concentrate may be an effective reversal agent for rivaroxaban but not dabigatran (*Circulation* 2011;124:1573-1579). ■

Warfarin testing every 12 weeks?

One of the major disadvantages of warfarin over the newer anticoagulants is the need for frequent prothrombin time monitoring and dose adjustment. Most guidelines recommend a maximum interval of 4 weeks between testing. A new study suggests that stable patients may be safely tested at 12-week intervals. A total of 226 patients who were on a stable dose of warfarin for at least 6 months were assigned to testing every 4 weeks, while the other half had blood tests done every 4 weeks, but sham INRs within the target range were reported for two of the three 4-week periods. The percentage of time in the therapeutic range was 74.1% in the 4-week group compared with 71.6% in the 12-week group (noninferiority $P = 0.020$ for a 7.5% point margin). Patients in the 12-week group had fewer dose changes and secondary outcomes, including major bleeding, thromboembolism, and death that were no different between the two groups. The authors conclude that assessment of warfarin dosing every

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12 weeks seems to be safe and noninferior to assessment every 4 weeks, although they recommend further study (*Ann Intern Med* 2011;155:653-659). This study is important given the marked cost differential between warfarin and dabigatran or rivaroxaban. Some patients, especially if they pay for their own medications, may opt to remain on warfarin if they are on a stable dose, especially if they only require testing four times a year. ■

Adverse drug events in the elderly

Although low cost, warfarin remains one of the most dangerous medications in common usage. In fact, hospitalizations for adverse events in the elderly are much more likely to be caused by commonly used medications, such as warfarin, rather than medications classified as high risk in the elderly, according to a new study from the CDC. Researchers used a national database of adverse drug events from 2007-2009 to estimate the frequency and rates of hospitalization after emergency department visits for adverse events in older adults to assess the risk of specific medications causing this hospitalization. It is estimated that adverse drug events led to nearly 100,000 hospitalizations during the 2-year period with nearly half among adults 80 years of age or older. Nearly two-thirds of the hospitalizations were due to unintentional overdoses. Four medications or medication classes were implicated alone or in combination in 67% of hospitalizations including warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% of hospitalizations. The authors suggest that efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to our older patients (*N Engl J Med* 2011;365:2002-2012). This study points out that we may be spending too much effort in managing "high-risk" medications in the elderly, while warfarin alone is responsible for a third of medication-related hospitalizations. ■

Is it time to retire niacin?

An editorial published online in the *New England Journal of Medicine* asks, "Niacin at 56 Years of Age — Time for an Early Retirement?" Retirement may be the logical next step after publication of the AIM-HIGH trial (see *Pharmacology Watch* July 2011), the National Heart Lung and Blood Institute's trial comparing niacin plus intensive statin therapy with intensive statin therapy alone in patients with established cardiovascular disease. The study was halted early when it was found that the addition of 1500-2000 mg of niacin per day to simvastatin, despite significantly raising HDL levels an average of 7 points, had no effect on the primary endpoint, which was a composite of the rate of death from coronary artery disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (primary endpoint 16.4% niacin group, 16.2% placebo group; $P = 0.79$) (*N Engl J Med* published online November 15, 2011). The accompanying editorial suggests there is lack of evidence to support niacin as an add-on therapy in patients with cardiovascular disease who have well-controlled LDL cholesterol levels. Additionally, long-acting niacin is relatively expensive and frequently causes flushing — two additional factors that argue against continued use of the drug except, perhaps, in patients who are intolerant of statins (*N Engl J Med* published online November 15, 2011). ■

FDA actions

The news isn't much better for fenofibrate. The FDA has issued a safety communication for the cholesterol lowering medication stating that the drug may not lower the risk of major cardiovascular events based on data from the ACCORD Lipid trial. ACCORD (similar in design to AIM-HIGH) evaluated the efficacy and safety of fenofibrate plus simvastatin vs simvastatin alone in patients with type 2 diabetes. There was no significant difference in the risk of experiencing a major adverse cardiac event between the two groups, and women may have even experienced an increase in the risk for major adverse cardiac events with combination therapy vs simvastatin alone. The FDA is requiring the manufacturer of Trilipix brand fenofibric acid to conduct a clinical trial to evaluate the cardiovascular effects of the drug in patients at high risk for cardiovascular disease who are already taking statins (www.fda.gov/Drugs/DrugSafety/ucm278837.htm).

The FDA has approved a new formulation of zolpidem for treatment of insomnia in patients who wake up in the middle of the night and have difficulty returning to sleep. Zolpidem, originally marketed as Ambien and now available as a generic, is a short-acting hypnotic. The new product is a lower dose sublingual formulation that comes in a 1.75 mg dosage recommended for women and 3.5 mg for men. The lower dose for women is recommended because women clear the drug more slowly than men. It can be used if the patient has at least 4 hours of bedtime remaining. Zolpidem sublingual is marketed by Transcept Pharmaceuticals as Intermezzo. ■