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Infectious Disease [ALERT]

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

ABSTRACT & COMMENTARY

Pertussis in Infants in California

By Dean L. Winslow, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine
Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

SYNOPSIS: A total of 32 infants younger than age 3 months with pertussis were hospitalized at Children's Hospital of Orange, CA (CHOC). Compared to infants hospitalized with viral respiratory infections, patients with pertussis were more often afebrile, had more visits before admission, and had longer hospital stays.

SOURCE: Nieves DJ, et al. Clinical and laboratory features of pertussis in infants at the onset of a California outbreak. *J Pediatrics* 2011; Epub ahead of print.

A total of 32 infants younger than age 3 months with pertussis hospitalized at a large children's hospital in Southern California were compared to 92 control patients hospitalized with RSV or influenza virus infections. Of the infants hospitalized with pertussis, 81% were Hispanic, 16% were white, and 1 infant was Vietnamese. PCR was positive in 27 of 27 patients studied with this diagnostic method, 20 of 28 were positive by culture, and 3 of 3 were positive by DFA.

Admission at first outpatient visit for the acute illness occurred in 27% of pertussis patients and in 53% of controls. Seven pertussis patients had three or more outpatient visits prior to hospital admission compared to no control patients. Pertussis patients had a longer duration of symptoms prior to admission vs. control patients (mean, 11 days vs. 3.4 days, respectively) and were also less likely to have fever or congestion than the controls. Paroxysmal coughing, post-

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tussive emesis, and apnea or seizure were also more likely in the pertussis patients than in controls. Mean WBC and absolute lymphocyte count were higher in pertussis patients. Average length of hospital stay was significantly longer in pertussis patients than in controls (mean, 8.9 days vs. 3.5 days, respectively). PICU admission was more common in the pertussis patients. Household coughing contacts were reported for 75% of pertussis patients and 71% of the pertussis patients had not received pertussis immunization.

■ COMMENTARY

This is an important large case series, which highlights some of the clinical features of infants with pertussis who were ill enough to require hospitalization. Despite the fact that pertussis became epidemic in California in 2010, it is clear that many pediatricians/primary care practitioners did not think of this diagnosis when first seeing a sick infant with paroxysmal cough. It is also likely that the frequent absence of fever in younger children with pertussis contributed to delayed diagnosis. Unrecognized pertussis in adult and adolescent household contacts of these infants was the source of infection in virtually all cases.

"Cocoon" vaccination of household contacts of infants too young to receive pertussis immunization is critically important as a control strategy for prevention of this severe disease. This should include state-mandated Tdap prior to middle school entry, administration of Tdap to pregnant women, and aggressive administration of this vaccine to virtually all adults and adolescents. Successful implementation of these measures will require ongoing education efforts directed to both patients and health care providers. ■

ANTI-INFECTIVE UPDATE

No More Xigris®

By Stan Deresinski, MD, FACP, FIDSA

Xigris® (drotrecogin alfa [activated]), a recombinant form of human activated protein C, received FDA approval in November 2001 for the reduction of mortality in adult patients with severe sepsis with a high risk of death. This approval was largely based on the PROWESS trial, in which Xigris administration was associated with a significant reduction in 28-day all-cause mortality relative to placebo administration.[1] In practice, however, its use was often limited by its cost and a significant risk of serious bleeding episodes, as well questions about study design, the results achieved in some subsets of patients, and disputes about the amount of benefit associated with its use. These considerations, together with a European Union regulatory commitment, led Eli Lilly and Company to perform the PROWESS-SHOCK trial, another randomized, multinational, placebo-controlled, double-blind study to assess the effectiveness of drug in adults with septic shock.[2]

While the trial results are as yet unpublished, there was no apparent survival benefit associated with the use of Xigris. Results based on preliminary analyses done by Eli Lilly and Company and submitted to the FDA showed a 28-day all-cause mortality rate of 26.4% (223/846) in Xigris-treated patients compared to 24.2% (202/834) in placebo-treated patients, for a relative risk of 1.09 (95% confidence interval, 0.92-1.28; $P = 0.31$, not statistically significant).[3]

It is possible that both the earlier and the current results were correct for their times. Thus, the advances in management of sepsis and septic shock may have led to improved outcomes that could not be further advanced by Xigris. Nonetheless, as a consequence of this result, Eli Lilly and Company has voluntarily removed Xigris from the world-wide market.[3] ■

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3. FDA. FDA drug safety communication: Voluntary market withdrawal of Xigris [dtrotrecogin alfa (activated)] due to failure to show a survival benefit. Available at: www.fda.gov/Drugs/DrugSafety/ucm277114.htm. Accessed Nov. 11, 2011.

ABSTRACT & COMMENTARY

Streptococcus bovis Group Organisms and the Association with Colon Cancer: Pinning the Tail on the Donkey

By Brian G. Blackburn, MD

Clinical Assistant Professor of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine

Dr. Blackburn reports no financial relationship to this field of study.

SYNOPSIS: Among *Streptococcus bovis*-infected patients who underwent gastrointestinal evaluation, 60% had colorectal adenomas or carcinomas, which appeared to be more common than in the general population. Those infected with *S. bovis* biotype I (*Streptococcus gallolyticus*) were 7.3 times more likely to have colorectal adenomas or carcinomas than those infected with other *S. bovis* biotypes.

SOURCE: Boleij A, et al. Clinical importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: Systematic review and meta-analysis. *Clin Infect Dis* 2011;53:870-878.

The association between *S. bovis* group infection (particularly endocarditis) and concurrent colorectal neoplasia has been known for some time.[1,2] In recent years, better delineation of the different biotypes of the *S. bovis* complex has occurred, with a recent proposal to re-classify the complex based on molecular characteristics.[3] Using this system, *Streptococcus gallolyticus subsp. gallolyticus* (formerly *S. bovis* biotype I), commonly referred to as *S. gallolyticus*, appears to be emerging as the pathogen most strongly associated with colorectal neoplasia; conversely, this association may be less strong for the other three *S. bovis* biotypes that are regarded principally as human pathogens (*S. infantarius*, *S. lutiensis*, and *S. pasteurianus*). Given the heterogeneity in the nomenclature of the organisms that comprise the *S. bovis* complex, and this possible differential association among biotypes with colorectal neoplasia, the authors undertook a meta-analysis to better delineate this association.

The meta-analysis predominantly consisted of 11 retrospective case series. Among *S. bovis*-infected patients who underwent evaluation of the gastrointestinal tract, 60% had colorectal adenomas or carcinomas; more than one-quarter of these were carcinomas. Although only one study in the meta-analysis reported colorectal neoplasia rates in age-matched controls, the colorectal neoplasia prevalence rates in this study were 56% in patients with *S. bovis* infections, and 27% in controls; however, the absolute numbers and a statistical comparative test were not reported.

In the subset of studies that determined *S. bovis* biotypes, patients infected with *S. gallolyticus* (biotype I) were significantly more likely than patients infected with other biotypes to have colorectal neoplasia (odds ratio [OR], 7.3; 95% confidence interval [CI], 3.9-13.4). *S. gallolyticus* (biotype I)-infected patients were also more likely to have endocarditis than patients infected with other biotypes (OR, 16.6; 95% CI, 8.9-31.2).

Conversely, patients whose *S. gallolyticus* infection was endocarditis were more likely to have colorectal neoplasia than those patients whose infection was not endocarditis (OR, 3.7; 95% CI, 2.0-6.8).

■ COMMENTARY

Although there are some limitations to this study (including the inconsistent naming of *S. bovis* biotypes in the studies included in the meta-analysis, the inconsistent screening of patients for colon cancer, and the retrospective nature of the studies), these data provide evidence that patients infected with *S. gallolyticus* have a high prevalence of colorectal neoplasia (both adenomas and carcinomas), probably above that of the general population. This association was particularly strong for those patients who had endocarditis caused by *S. gallolyticus*. This association was stronger than the associations seen with other *S. bovis* biotypes, for which the associations with colorectal neoplasia may not have been stronger than that of the general population.

The biologic mechanism underlying this association between *S. gallolyticus* infection and colorectal neoplasia may be the high affinity that this organism has for binding to collagen I/IV, which is overexpressed in colorectal polyps and cancers. This likely results in a higher carriage rate of this organism in the colon of patients with these lesions, and places them at higher risk for invasive infection with *S. gallolyticus*. Binding to type I collagen (which is present on heart valves) may also explain the affinity this organism has for causing infectious endocarditis.

Because many clinicians are not yet familiar with the new terminology involving these organisms, increasing awareness of this new nomenclature regarding different biotypes in the *S. bovis* complex is an important implication of this study, as is increasing awareness of the high risk *S. gallolyticus*-infected patients have of a concomitant colorectal neoplasm. Systematic screening of such patients with colonoscopy might lead to earlier diagnosis of such lesions. Microbiology laboratories should also consider attempting to identify *S. bovis* infections to the biotype level (using molecular methods) on a more routine basis, given the important clinical ramifications an *S. gallolyticus* infection has compared to other biotypes and the need for infected patients to undergo colonoscopy. ■

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ABSTRACT & COMMENTARY

Lyme Meningitis in Children with Aseptic Meningitis

By Hal B. Jenson, MD, FAAP

Dean, Western Michigan University School of Medicine, Kalamazoo, MI

Dr. Jenson 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 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. ■

SPECIAL FEATURE

What's New in the HIV Treatment Guidelines?

By Stan Deresinski, MD, FACP, FIDSA

SYNOPSIS: Most of the changes in the guideline deal with the choice of antiretroviral therapy in the previously treatment-naïve patient.

SOURCE: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 14, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. Accessed Nov. 8, 2011.

A revision to the Jan. 10, 2011, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents was published on Oct. 14, 2011. This update focuses on the choice of an initial regimen for antiretroviral treatment-naïve HIV patients: "What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient." The changes recommednded by the Panel are summarized here.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI)-BASED REGIMENS

- **Rilpivirine** (RPV) was added as an alternative NNRTI option for initial therapy in treatment-

Table. Rating scheme for recommendations.

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

Source: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 14, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf. Accessed Nov. 8, 2011.

naïve patients.

Background: On the basis of clinical trial results and safety data, the Panel recommends that efavirenz (EFV), RPV, or nevirapine (NVP) may be used as part of an initial regimen. In most instances, EFV is preferred, based on its potency and tolerability. RPV may be used as an alternative NNRTI option in treatment-naïve patients (B; *see Table, above for rating scheme for recommendations*), whereas NVP may be used as an acceptable NNRTI option (C) in women with pretreatment CD4+ counts ≤ 250 cells/mm^3 or in men with pretreatment CD4+ counts ≤ 400 cells/mm^3.

Although RPV demonstrated overall non-inferiority to EFV, among participants with higher pre-treatment HIV RNA (> 100,000 copies/mL), virologic failure occurred more frequently in those randomized to receive RPV. Subjects with virologic failure on RPV were also more likely to have genotypic resistance to other NNRTIs (EFV, ETR, and NVP) and to have resistance to their prescribed NRTIs. For those reasons, the guideline indicates that RPV should be used with caution in patients with pre-treatement HIV RNA > 100,000 copies/mL.

The drug interaction tables were also updated to include information regarding RPV. Table 14 indicates that the following should not be coadministered with this NNRTI: rifamycins, proton pump inhibitors, St. John's wort, other NNRTIs, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin. Table 15b indicates that antacids may be administered at least 2 hours before or 4 hours after RPV, and H2 antagonists may be given at least 12 hours before or 4 hours after. The use of proton pump inhibitors is totally contraindicated, as are carbamazepine, phenobarbital, phenytoin, rifampin, and rifabutin. Because of a likely interaction with clarithromycin, azithromycin is recommended as an alternative in patients receiving RPV. More than a single dose of dexamethasone is contraindicated in patients on the NNRTI.

Dosing of RPV was also addressed. Appendix B, Table 2 recommends a daily 25 mg dose (alone or as part of Complera®, which also contains emtricitabline and tenofovir). It was noted that RPV is a CYP3A4 substrate with serum half-life of 50 hours and that the adverse events most commonly associated with its use are rash, depression, insomnia, and headache. In addition, Appendix B, Table 7 indicates that no dosage adjustment is indicated in patients with renal insufficiency, including those undergoing chronic peritoneal dialysis or hemodialysis. Finally, no dosage recommendation is indicated for patients with Childs Class A or B hepatic impairment, while no recommendation is made for those in Childs Class C.

- **All nevirapine-based regimens** were reclassified as acceptable options for treatment-naïve patients (females with pretreatment CD4+ count < 250 cells/mm^3 or males with pretreatment CD4+ count < 400 cells/mm^3). Previously, "nevirapine + zidovudine/lamivudine" was classified as an alternative regimen and "nevirapine + abacavir/lamivudine" and "nevirapine + tenofovir/emtricitabine" were recommended as regimens that may be acceptable but should be used with caution.

Background: Patients who experience CD4+ count increases to levels above the thresholds indicated above in response to NVP-containing therapy can safely continue therapy without an increased risk of adverse hepatic events. At the initiation of NVP, a 14-day lead-in period at a dosage of 200 mg once daily should be instituted before increasing to the maintenance dosage of

400 mg per day (as an extended-release 400 mg tablet once daily or 200 mg immediate-release tablet twice daily). Some experts recommend monitoring serum transaminases at baseline, at 2 weeks, then 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit.

PROTEASE INHIBITOR (PI)-BASED REGIMENS

- **"Ritonavir (RTV)-boosted darunavir (DRV) + abacavir/lamivudine"** was reclassified as an alternative regimen (BIII). This regimen had previously been recommended as one that may be acceptable, although more definitive data were needed (CIII).

Background: The Panel uses the following criteria to distinguish between preferred vs. alternative PIs in ART-naïve patients: 1) demonstrated superior or non-inferior virologic efficacy when compared with at least one other PI-based regimen, with at least published 48-week data; 2) RTV-boosted PI with no more than 100 mg of RTV per day; 3) once-daily dosing; 4) low pill count; and 5) good tolerability. Using these criteria, the Panel recommends atazanavir (ATV)/r (once daily) and DRV/r (once daily) as preferred PIs.

The ARTEMIS study compared DRV/r (800/100 mg once daily) with LPV/r (once or twice daily), both in combination with tenofovir (TDF)/emtricitabine (FTC), in a randomized, open-label, non-inferiority trial. At 96 weeks, virologic response to DRV/r was superior to response to LPV/r. Based on these data, the Panel recommends DRV/r + TDF/FTC as a preferred PI-based regimen (AI). No randomized controlled trial exists to evaluate the efficacy of DRV/r with the other two-NRTI combinations. A small retrospective study suggested that DRV/r + ABC/3TC may be effective in treatment-naïve patients for up to 48 weeks. Based on this preliminary information, the Panel recommends this combination as an alternative PI-based regimen (BIII).

- Regimens with **unboosted fosamprenavir** were removed as PI options for treatment-naïve patients because they have inferior potency compared with other PI-based regimens and because of the potential for selection of mutations that confer resistance to darunavir in patients who experience virologic failure while on these regimens.

RALTEGRAVIR-BASED REGIMENS

- **"Raltegravir + abacavir/lamivudine (RAL)"** was reclassified as an alternative regimen (BIII). This regimen was previously classified as a regimen that may be acceptable, but more definitive data are needed (CIII).

Background: Comparisons of RAL-based regimens with other regimens in ART-naïve subjects have not yet been reported, and experience with RAL is less than with EFV or boosted PIs for initial therapy. In addition, RAL must be administered twice daily, a potential disadvantage when compared with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial.

DUAL-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI) OPTIONS

- **"Zidovudine + lamivudine"** was reclassified from an alternative dual-NRTI option to an acceptable option because the combination has greater toxicities compared with tenofovir/emtricitabine and abacavir/lamivudine and requires twice daily dosing. However, zidovudine + lamivudine remains as the preferred dual-NRTI for pregnant women receiving antiretroviral therapy for prevention of perinatal transmission of HIV.

- **"Didanosine + lamivudine"** was removed as a dual-NRTI option for initial therapy because the combination has the least clinical trial experience and greater toxicity compared with other available dual-NRTI options.

- Discussion on the **association between abacavir use and the risk of a cardiovascular event** was updated.

Background: The D:A:D observational study found that recent (within 6 months) or current use of abacavir, but not TDF, was associated with an increased risk of myocardial infarction, particularly in participants with pre-existing cardiac risk factors. Since this study, however, multiple studies have explored this association and come to varying conclusions. To date, no consensus has been reached either on the association of abacavir use with myocardial infarction risk or a possible mechanism for the association. ■

ABSTRACT & COMMENTARY

New Malaria Recommendations for Greece — October, 2011

By Mary-Louise Scully, MD, FAAP

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Dr. Scully reports no financial relationship to this field of study. This article originally appeared in the December 2011 issue of *Travel Medicine Advisor*. At that time it was peer reviewed by Lin H. Chen, MD, Assistant Clinical Professor, Harvard Medical School; Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA. Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex.

SYNOPSIS: Due to ongoing evidence for malaria transmission in the Laconia (Lakonia) district of Greece, the Centers for Disease Control and Prevention (CDC) is now recommending that travelers to this area take anti-malarial chemoprophylaxis. The enhanced use of personal protection measures against mosquito bites in this and other agricultural areas of Greece is also recommended.

SOURCE: CDC Alert. New Malaria Recommendations for Greece. Available at: www.cdc.gov/malaria/malariagreece.htm. Accessed Nov. 5, 2011.

Greek health authorities recently published findings of 36 cases of *Plasmodium vivax* malaria in Greece occurring between May 2011 and September 2011.[1] Twenty of these malaria cases had no travel history outside of Greece and the remaining 16 cases were in persons from malaria-endemic countries where local transmission vs. importation could not be determined (migrant cases). The majority of all the cases occurred in the southern agricultural area of Evrotas, Laconia. Other areas included the Evia/Euboea (island east of Central Greece region), Eastern Attiki, Viotia, and Larissa districts *(see map, page 33)*. All 36 cases were confirmed as *P. vivax* by both PCR and microscopy identification.

The median age of reported cases was 36 years, but the median age in migrant cases was lower (24 years) and migrant cases were all male. All cases were hospitalized, treated, and recovered except for one fatality in a patient with underlying cardiac and pulmonary disease who developed acute respiratory distress syndrome. Most were treated with a 3-day course of chloroquine followed by a 14-day course of primaquine. Only one case had glucose-6-phosphate dehydrogenase (G6PD) deficiency and, therefore, did not receive primaquine.

The Laconia (Lakonia) district is an agricultural plain that lies in the delta region of the Evrotas River. The authors note that this area has fresh-water springs, irrigation and drainage channels, and coastal wetlands that provide ideal breeding grounds for the 15 species of *Anopheles* mosquitoes found in Greece, of which five species are considered to be potential malaria vectors. *Anopheles sacharovi* and *Anopheles claviger* were the most commonly identified species in the areas of outbreaks.

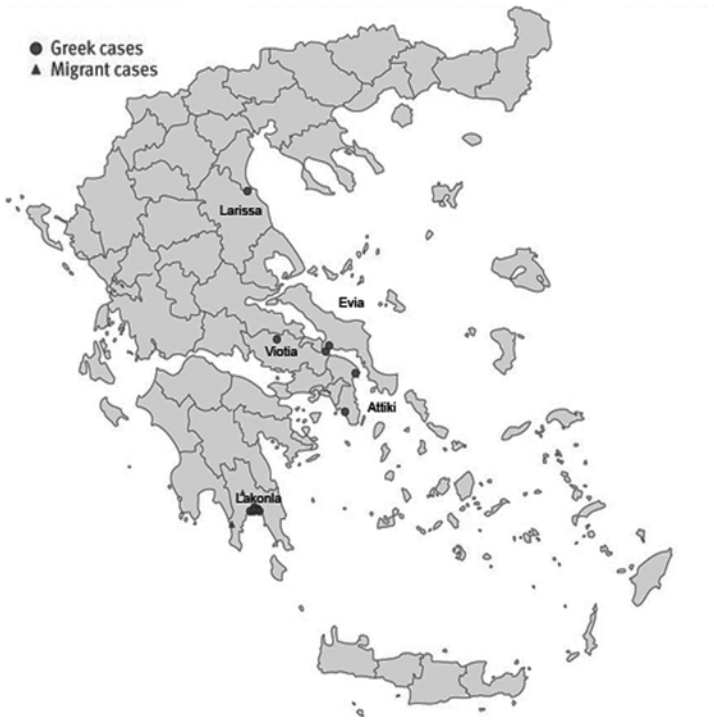
In the Evrotas area, it is estimated that migrant farm workers make up 2,000-4,000 of the total population of 4,485 depending on the time of year. Approximately 80% of migrant workers in this area are from Pakistan, about 15% from Romania, and the remaining are from Morocco. In the other outbreak areas of Greece there were also high numbers of migrant workers from malaria-endemic countries, especially the Indian subcontinent. These areas of Greece are not typically visited by tourists.

In light of the ongoing malaria transmission in the Laconia district of Greece, the U.S. CDC now recommends that travelers to this destination take malaria chemoprophylaxis. Appropriate anti-malarials (U.S. CDC) include atovaquone-proguanil (Malarone®), chloroquine, doxycycline, mefloquine, or primaquine. Primaquine use requires prior testing for G6PD deficiency.

■ COMMENTARY

Malaria was eradicated from Greece in 1974, though occasional sporadic cases of local mosquito-borne transmission have occurred throughout the years. This outbreak is unique both in the number of cases and the sustained transmission that is ongoing. The combination of ideal climate, close proximity of human and mosquito populations, and increasing numbers of

Table. Distribution of malaria cases in Greece, October 2011.



migrant workers from malaria-endemic countries are contributing to the outbreak.

All the cases were secondary to *P. vivax*, for which full treatment requires presumptive anti-relapse therapy (PART) with primaquine to eradicate the hypnozoite forms that remain dormant in the liver. The dose is 30 mg/day for 14 days. Primaquine is contraindicated in persons with G6PD deficiency and pregnant females, so testing is necessary before its use. The most prevalent G6PD variants are G6PD A- and G6PD Mediterranean. These variants can result in severe hemolysis by the sudden destruction of older, more enzyme-deficient red blood cells after exposure to drugs like primaquine, nitrofurantoin, sulfamethoxasole, or foods such as fava beans.[2]

In addition to the recommended use of anti-malarials in travelers to the Laconia district of Greece, clinicians globally should be aware of this outbreak and include malaria in the possible differential diagnosis of any febrile patient returning after travel to Greece. ■

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CASE REPORT

Seaweed Poultices and *Vibrio* Infection

By Carol A. Kemper, MD, FACP

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Dr. Kemper does research for Abbott Laboratories and Merck.

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 *continued on page 36*

Updates

By Carol A. Kemper, MD, FACP

Serologies for Congenital Toxoplasmosis

Source: Olariu TR, et al. Severe congenital toxoplasmosis in the United States: Clinical and serological findings in untreated infants. *Pediatr Infect Dis J* 2011;30:1-6.

Congenital toxoplasmosis occurs exclusively in infants born to mothers who acquire primary infection during their pregnancy. Unfortunately, many of these infections occur without clinical signs or symptoms, and the mothers go untreated. It is estimated that approximately 500-5,000 infants are born annually in the United States with congenital toxoplasmosis, some of which are never recognized as such; and the diagnosis, especially in later months or years of life, can be difficult to confirm.

The Palo Alto Medical Foundation Toxoplasma Serology Laboratory has been doing research on toxoplasma serologic studies for more than 20 years. They examined clinical and serological findings for 164 infants (0-180 days old) diagnosed with congenital toxoplasmosis in the United States between 1991 and 2005, whose mothers had not received treatment during pregnancy. The utility of IgM and IgA toxoplasma-specific antibody in infants with suspected or confirmed congenital toxo was examined. All infants in this study had confirmed congenital toxoplasmosis, defined as a positive Sabin Feldman IgG antibody test, plus at least one other laboratory finding (presence of IgM or IgA antibody, persistence of IgG through 12 months of life, presence of IgM in CSF, and a positive PCR on amniotic fluid, blood, CSF, or urine).

More than half (56%) of the children were diagnosed within the first month of birth. One or more severe clinical findings were identified in 116 (84%) of the infants, including eye disease (92%), cerebral calcifications (80%), and hydrocephalus (68%). All three of these findings were observed in 61% of the infants. Other clinical findings included hepatosplenomegaly (29%), jaundice (19.5%), rash or purpurea (10%), microcephaly (6%), and cerebral atrophy (4%). Thrombocytopenia, CSF pleocytosis, and elevated CSF protein were common.

IgM antibodies were found in 87% of the infants, whereas IgA antibodies were identified in 77%, including 11 infants in whom IgM antibody was not present. Both IgM and IgA antibodies were more commonly found in neonates (< 90 days old) than in older infants (91-180 days old; $P = 0.036$), and decreased with increasing age. Eleven (7%) of the infants did not have detectable IgM nor IgA antibody (and were diagnosed by other means, including persistent of IgG antibody > 12 months or a positive PCR). PCR results were positive in 27/58 (46%) CSF specimens, 5/10 (50%) urine specimens, and 2/7 (29%) whole blood specimens.

These results lend support to the use of both IgM and IgA toxoplasma-specific antibodies in the diagnosis of congenital toxoplasmosis, especially if done within the first 3 months of life. Nearly 11% of infants in this study were IgM-negative but had detectable IgA antibody. ■

Overuse of Antibiotics: Still a Problem

Source: Centers for Disease Control and Prevention. Office-related antibiotic prescribing for persons aged ≤ 14 years — United States, 1993-1994 to 2007-2008. *MMWR Morb Mortal Wkly Rep* 2011;60:1157-1163.

Data derived from the National Ambulatory Medical Care Survey, which is a survey of ~3000 ambulatory care physicians conducted annually by the CDC, were examined for changes in office visits and antibiotic use from 1993-1994 to 1997-1998. Antibiotic prescriptions written for five common acute respiratory infections (ARIs) for children ≤ 14 years of age were compared during this period (including otitis, pharyngitis, bronchitis, sinusitis, and nonspecific upper respiratory infection, e.g., the common cold).

Overall, office visits increased 18% for this age group during the period of study, up from 2,180 visits per 1,000 children in 1993-1994 to 2,581 visits per 1,000 children in 2007-2008. During the same period, office visits for ARIs decreased by 14%. Antibiotic prescriptions for ARIs also decreased 24% during this period (from 300/1,000 visits to 229/1,000 visits). This was largely due to a decrease in antibiotic prescriptions for pharyngitis (-26%) and the common cold (-19%). There was no apparent change in the frequency of prescriptions written for sinusitis, bronchitis, or otitis.

Despite the modest decrease observed in antibiotic prescriptions written for ARIs in 2007-2008, 58% of office visits during that period for children

≤ 14 years of age in which an antibiotic was prescribed were for one of the five ARIs — most of which do not require antibacterial treatment. Arguably, the reduction in treatment for pharyngitis may be due to the introduction of the rapid strep antigen test during this period, and not improvement in prescribing habits. The use of antibiotics for ARIs in the ambulatory care setting remains inappropriately high, despite an ongoing public health campaign against such prescribing habits and an active conversation in the lay press about increasing antibiotic resistance. ■

Use of Newer Assays for Syphilis

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. ■

continued from page 33

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 seawood poultices should be discouraged. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. Which of the following is *correct* regarding rilpivirine?

a. It is a novel HIV-1 protease inhibitor.
b. It is a CYP3A4 substrate.
c. There are no contraindications to the use of any other medication together with rilpivirine.
d. The most frequent associated adverse effect is hyperbilirubinemia.

2. Which of the following is *true*?

a. The strength of the association between all biotypes of the *S. bovis* complex and a co-existent colorectal cancer is equal.
b. Patients with *S. gallolyticus* endocarditis are at no higher risk of having a colorectal neoplasm than patients infected with *S. gallolyticus* at other body sites.
c. Patients infected with *S. gallolyticus* were more likely to have colorectal carcinomas than adenomas.
d. Patients with *S. gallolyticus* endocarditis have a high prevalence of a co-existing colorectal neoplasm.

3. Which of the following statements about recent autochthonous malaria cases in Greece is *true*?

a. Recent malaria cases in Greek migrant workers had high mortality rates.
b. Primaquine should not be used for prophylaxis in travelers to Greece especially among expatriates.
c. G6PD Mediterranean variants are at risk of severe hemolysis with primaquine administration.
d. Malaria cases in Greece were secondary to both *P. falciparum* and *P. vivax*.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

[IN FUTURE ISSUES]

Safety of efavirenz in the first trimester of pregnancy

Accuracy of signs and symptoms of streptococcal pharyngitis in children

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.*

HPV Vaccine Now Recommended for Males

In this issue: New recommendations for HPV vaccine; guidelines for treatment of essential tremor; updates on smoking cessation drugs; and FDA actions.

HPV vaccine and anal cancer risk

The human papillomavirus (HPV) vaccine is routinely administered to adolescent girls; now the CDC's Advisory Committee on Immunization Practices is recommending the vaccine for 11- and 12-year-old boys as well. The vaccine has been approved for use in both adolescent girls and boys to protect them against HPV but has been somewhat underutilized in girls and rarely used in boys. HPV causes genital warts and cervical cancer in women and the vaccine effectively reduces the rate of both. The vaccine is generally recommended for 11 and 12 year olds when they get other routine vaccines, and before they become sexually active. Although the vaccine is approved for boys, the CDC had not made a recommendation on routine use until now. After evaluating data on efficacy in males, the committee felt that the vaccine could protect boys against genital warts, as well as throat and anal cancer caused by HPV, and could help prevent spread of the virus to girls.

In related news, a new study shows the HPV vaccine is effective in preventing anal intraepithelial neoplasia in men who have sex with men. In a double-blind study of 602 men (ages 16-26) who have sex with men, half were randomized to the quadravalent HPV vaccine and half to placebo. The vaccine reduced the risk of anal intraepithelial neoplasia caused by the four subgroups of HPV covered by the vaccine (HPV-6, 11, 16, and 18) by half in the intention-to-treat population and by 77% in the per-protocol population. Anal intraepithelial neoplasia caused by HPV of any type was reduced by 25.7% and 54.9%, respectively. Rates of anal intraepithelial neoplasia per 100 person years were 17.5 in the placebo group and 13 in the vaccine group in the intention-to-treat, and 8.9% placebo vs 4.0% vaccine in the per-protocol population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to HPV subtypes covered by the vaccine was reduced by 54.2% (intention-to-treat) and 74.9% (per-protocol). The vaccine was well tolerated. The authors conclude that the HPV vaccine reduced the rate of anal intraepithelial neoplasia in men who have sex with men and may help reduce the risk of anal cancer (*N Engl J Med* 2011;365:1576-1585). ■

Treatment of essential tremor

The American Academy of Neurology has published its updated guideline for the treatment of essential tremor. Propranolol and primidone remain first options with a Level A recommendation (established as effective). Alprazolam, atenolol, gabapentin as monotherapy, sotalol, and topiramate are graded as Level B (probably effective), while nadolol, nimodipine, clonazepam, botulinum toxin a, deep brain stimulation, and thalamotomy remain as level C (possibly effective). There is not enough evidence to make a recommendation for gamma knife therapy. The new guideline also states that there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozipine. Levetiracetam and 3,4 diaminopyridine are ineffective and flunari-

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zine is probably ineffective. The guideline was published online in *Neurology* October 19, 2011 (doi: 10.1212/WNL.0b013e318236f0fd). ■

Chantix and neuropsychiatric side effects

There is good news for the smoking cessation drug varenicline (Chantix). Following concern about neuropsychiatric side effects, the FDA sponsored two epidemiologic studies that evaluated the risk of neuropsychiatric hospitalizations associated with the drug. Neither study found a difference in risk of neuropsychiatric hospitalization between varenicline and nicotine replacement therapy, although hospitalization was the only endpoint evaluated and they did not rule out an increased risk of other neuropsychiatric events. While reassuring, the FDA is recommending that health care professionals and patients continue to follow the recommendations previously established and monitor for neuropsychiatric symptoms when prescribing or using varenicline. The manufacturer is conducting a large safety study of the drug to assess neuropsychiatric adverse effects but the results will not be available until 2017 (www.fda.gov/Drugs/DrugSafety/). In related news, the inexpensive partial nicotine agonist cytisine is an effective adjunct to smoking cessation, according to a new study in the *New England Journal of Medicine*. Cytisine is extracted from the seeds of *Cysisus laborinum L.* (Golden Rain acacia) and has been available worldwide for years, particularly in Eastern Europe, where it can be purchased for $6-$15 per course. Researchers randomized 740 smokers to cytisine or matching placebo for 25 days along with counseling. The rate of sustained 12 months abstinence was 8.4% in the cytisine group compared with 2.4% in the placebo group ($P = 0.01$). GI side effects were slightly more prevalent in the treatment group. The authors conclude that cytisine was more effective than placebo for smoking cessation and may be "an affordable treatment to advance smoking cessation globally" (*N Engl J Med* 2011;365:1193-1200). ■

FDA Actions

The FDA is continuing to review the association of oral contraceptives and thrombotic risk, particularly oral contraceptives containing drospirenone. On October 27, the FDA issued a preliminary Drug Safety Communication, with the full report due out in early December. Reviewing the records of Kaiser Permanente members in California and state Medicaid programs in Tennessee and Washington, which included 835,826 women receiving contraceptive prescriptions from 2001-2007, an increased risk of venous thromboembolism (VTE), deep venous thrombosis, and pulmonary embolism was noted with several contraceptives, with low estrogen hormonal contraceptives as a reference. Products containing drospirenone had relative risk of VTE of 1.74 (95% confidence interval [CI] 1.42-2.14). The norelgestromin/ethinyl estradiol transdermal patch was associated with relative risk of 1.55 (95% CI 1.17-2.07) and etonogestrel/estradiol vaginal ring was associated with a relative risk of 1.56 (95% CI 1.02-2.37). The risk was higher in younger users then older women (www.FDA.gov./DRUGS/DrugSafety/ucm277346.htm).

The FDA has approved the first generic olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder. The generic carries the same warnings as the brand regarding increased risk of death in elderly people with psychosis or dementia. Generic olanzapine will be available from several manufacturers as tablets and orally disintegrating tabs.

The FDA has announced that drotrecogin alfa (Xigris) is being withdrawn from the market by Eli Lilly & Co. The withdrawal is based on the results of the recently completed PROWESS-SHOCK trial in which drotrecogin alfa failed to show a survival benefit in patients with severe sepsis and septic shock. The FDA is recommending that the drug should be stopped in any patients currently being treated and should not be initiated in new patients. All remaining product should be returned to the supplier.

The FDA has approved tadalafil (Cialis) for the treatment of benign prostatic hyperplasia (BPH) either alone or when it occurs along with erectile dysfunction (ED). The drug was approved in 2003 for treatment of ED. The approval was based on two trials in which men taking tadalafil 5 mg daily experienced significant improvements in BPH symptoms compared with those taking placebo. A third study in which men had both BPH and ED, tadalafil 5 mg daily improved both symptoms of BPH and ED compared to placebo. Tadalafil should not be used in patients taking nitrates or in combination with alpha blockers for the treatment of BPH.

The FDA has approved a combination of sitagliptin and simvastatin for the treatment of adults with type 2 diabetes and hypercholesterolemia. This represents the first combination drug for treating these two conditions. The fixed dose combination is available in three strengths: 100 mg sitagliptin/10 mg simvastatin, 100 mg/20 mg, and 100 mg/40 mg. The approval was based on "substantial experience with both sitagliptin and simvastatin" and is a "convenience combination," according to the FDA. Sitagliptin/simvastatin will be marketed as Juvisync by MSD International GmbH Clonmel in Tipperary, Ireland. ■

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