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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

Uncomplicated Pure Cellulitis: No Need to Cover for MRSA?

By Richard R. Watkins, MD, MS, FACP
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Dr. Watkins reports no financial relationships in this field of study.

SOURCE: Pallin DJ, et al. Clinical Trial: Comparative Effectiveness of Cephalexin Plus Trimethoprim-Sulfamethoxazole Versus Cephalexin Alone for Treatment of Uncomplicated Cellulitis: A Randomized Controlled Trial. *Clin Infect Dis* 2013 Apr 1. [Epub ahead of print]

Uncomplicated cellulitis, defined as cellulitis without abscess, is most often caused by streptococci. The widespread dissemination of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has led to increased prescribing of antibiotics for cellulitis with activity against the organism (e.g.

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Infectious Disease [ALERT]

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trimethoprim-sulfamethoxazole, doxycycline, clindamycin, and linezolid). This is despite the fact that CA-MRSA is associated with purulent cellulitis and abscesses, and optimal management is incision and drainage, not antibiotic therapy.[1] Pallin and colleagues sought to determine if treating uncomplicated cellulitis with antibiotics targeting CA-MRSA and streptococci would lead to better outcomes compared to therapy against streptococci alone.

The study was a double-blind, randomized, multicenter, placebo-controlled trial conducted between June 2007 and December 2011. Participants were enrolled from one of three emergency departments in an area considered endemic for CA-MRSA. The diagnosis of cellulitis was made during routine clinical care by attending physicians. Most of the participants were generally healthy and were enrolled if they had uncomplicated cellulitis or if <1 cc of pus was observed or reported by the patient. A total of 146 subjects were included in the intent-to-treat analysis. All received cephalexin, while 73 also received trimethoprim-sulfamethoxazole (intervention group) and 73 were given placebo (control group). Participants were told to stop taking the antibiotics 3 days after they believed the infection to be cured, for a minimum of 7 days and a maximum of 14. Compliance was monitored by a log filled out by the participants. The primary outcome was the risk difference for cure, which was determined by an in-person exam at 2 weeks and a follow-up telephone interview and review of medical records at 1 month. Failure was defined as subsequent hospitalization, altering of antibiotics, drainage of an abscess, or recurrence of infection within 30 days. The secondary outcome was the association of nasal MRSA carriage at enrollment with clinical response.

The investigators found no significant benefit from the addition of trimethoprim-sulfamethoxazole, including those participants with purulence. Clinical cure was obtained in 62 of the 73 (85%) in the intervention group vs. 60 of 73 (82%) in the control group (P = 0.66). Five participants in each group had progression to abscess (P = 1.0). Seven of 142 (4.9%) for whom data were available were colonized with MRSA, and this was not associated with response to therapy (P = 0.67). There was a high rate of adverse events among the participants (51%) which was similar in intervention group (49%) vs. control group (53%) (P = 0.62). Most of the adverse events were minor (e.g. diarrhea, nausea, vomiting) but one participant in the control group developed *C. difficile* infection.

■ COMMENTARY

This study is timely and has important clinical implications. Given the current epidemic of CA-MRSA, it seems biologically plausible that targeting this organism when treating cellulitis would be advantageous. Indeed, the

investigators noted they expected to find a benefit in the intervention group. That no benefit was found with the addition of trimethoprim-sulfamethoxazole seems to support the current MRSA treatment guidelines from the Infectious Disease Society of America (IDSA), which recommend not targeting CA-MRSA in nonpurulent cellulitis.[2] The study included 19 subjects (13% of the total) with purulence, of whom 8 received anti-MRSA therapy and 11 did not. It was somewhat surprising that no difference was found between their outcomes. However, it is possible that the small number of patients prevented the detection of a significant difference.

The study had a few limitations. The researchers chose to exclude diabetics, and whether the findings can be extrapolated to these patients (most likely they can) requires further investigation. The diagnosis of cellulitis itself is subjective and open to interpretation. Also, since not all patients colonized with MRSA have positive nasal swabs, perhaps if axilla and groins had been collected a correlation between colonization and treatment response would have been observed. Should we abandon empiric coverage for CA-MRSA in uncomplicated cellulitis? The IDSA guidelines say yes and now there is evidence-based data to support this recommendation. However, I still recommend caution in patients with a previous history of MRSA or who are colonized, especially if purulence is present. A larger study that addresses these two scenarios would be beneficial.

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2. Liu C, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52:e18-55. ■

ABSTRACT & COMMENTARY

Zoster Vaccine Works — If People Get It

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Hospital Epidemiologist, Sequoia Hospital, Redwood City, CA, Editor of Infectious Disease Alert.

SYNOPSIS: In a 5% random Medicare sample to examine the uptake and efficacy of the herpes zoster vaccine in the general population, including immunocompromised individuals — the adjusted vaccine efficacy for protection against herpes zoster was 0.48 (95% CI, 0.39 to 0.56). Among individuals who were immunocompromised, vaccine efficacy was 0.37 (95% CI, 0.06 to 0.58). Protection against the development of post-herpetic neuralgia was also demonstrated by a vaccine efficacy of 0.59 (95% CI, 0.21 to 0.79)

SOURCE: Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS Med* 2013 Apr 9; 10:e1001420.

Randomized trials in the U.S. have demonstrated that Zostavax, a high titer live attenuated varicella zoster vaccine reduced the risk of herpes zoster by approximately one-half and the risk of post-herpetic neuralgia by approximately two-thirds. The Centers for Disease Control and Prevention recommends

that, in the absence of contraindications, all individuals >60 years of age should receive the vaccine. Although it also has received FDA approval for individuals 50-59 years of age, CDC has not made a recommendation for this cohort. Despite the recommendation for those >60 years of age and coverage by Medicare Part D, the use of the vaccine has appeared to be limited. Langan and colleagues have now used a 5% random Medicare sample to examine the uptake and efficacy of the vaccine in the general population, including immunocompromised individuals.

Of the 766,330 participants, only 3.9% had been vaccinated during the study period(2007-2009). Vaccination rates were especially low in the oldest patients, in African-Americans (0.3%), and in those in the lowest socioeconomic groups (0.6%). Herpes zoster occurred during the study period in 13,112 individuals. The incidence rate per 1000 person-years in vaccinated individuals was 5.4 (95% CI, 4.6 to 6.4) and 10.0 (95% CI, 9.8 to 10.2) in those who had not received the vaccine. As a consequence, the adjusted vaccine efficacy for protection against herpes zoster was 0.48 (95% CI, 0.39 to 0.56). Among individuals who were immunocompromised, vaccine efficacy was 0.37 (95% CI, 0.06 to 0.58). Protection against the development of post-herpetic neuralgia was also demonstrated by a vaccine efficacy of 0.59 (95% CI, 0.21 to 0.79).

■ COMMENTARY

This very large population-based study confirms the results of randomized trials in more selected populations, with evidence of significant protection against both shingles and post-herpetic neuralgia. Furthermore, the vaccine was also effective in immunocompromised individuals, a group for whom CDC still recommends against vaccination.

In addition to confirming the efficacy of the vaccine, this study also confirms its lack of use. Herpes zoster affects a million individuals yearly in the US, many of whom develop post-herpetic neuralgia and, as a consequence, it has serious health, quality of life, and cost consequences. Barriers to greater use of Zostavax include lack of prescriber and patient knowledge, cost, lack of Medicare eligibility for most before age 65 years, and lack of coverage by some third party payers and state Medicaid systems. We need a medical care system in the United States. ■

ABSTRACT & COMMENTARY

Leptin may Mediate Severe Infection in Obese Patients with Pandemic Influenza A

By Dean L. Winslow, MD, FACP, FIDSA

Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, Associate Editor of Infectious Disease Alert.

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: High levels of circulating leptin contribute to the development of severe lung injury by Influenza A(H1N1) pdm09 in mice with diet-induced obesity.

SOURCE: Zhang AJX, et al Leptin mediates the pathogenesis of severe 2009 pandemic influenza A (H1N1) infection associated with cytokine dysregulation in mice with diet-induced obesity. *JID* 2013; 207: 1270-80.

In a mouse model of diet-induced obesity obese mice infected with pandemic influenza A (H1N1) (pdm09) had significantly higher pulmonary viral titers and mortality compared with age-matched lean mice. Obese mice had heightened proinflammatory cytokine and chemokine levels and more severe pulmonary damage and this was associated with higher preexisting serum leptin levels and lower adiponectin levels. Recombinant leptin increased IL-6 mRNA in single-lung-cell preparations. Administration of anti-leptin antibody improved survival in obese mice and was associated with reductions in pulmonary levels of the pro-inflammatory cytokines IL-6 and IL-1B, but did not affect pulmonary viral titer.

■ COMMENTARY

During the 2009 influenza pandemic, obesity was unexpectedly seen to be an independent risk factor which increased the likelihood of hospitalization, admission to the ICU, and death. The mechanisms responsible for this association are not clear. The adipokines leptin and adiponectin are known to regulate the inflammatory response and leptin is pro-inflammatory and is associated with chronic systemic inflammation in obese individuals. In addition to being secreted by adipose tissue, leptin is secreted by bronchial epithelial cells, type II pneumocytes and lung macrophages. Higher leptin levels in bronchoalveolar fluid have been associated with higher mortality in patients with acute respiratory distress syndrome.[1,2] Other studies have shown that higher leptin levels are associated with more severe asthma and COPD.[3,4]

This study conducted in a mouse model of obesity induced by diet sheds some light on possible pathogenic mechanisms responsible for the severity of pandemic influenza A seen in obese patients. It seems likely that the pro-inflammatory effect of leptin (likely mediated by increased transcription of inflammatory cytokines by lung macrophages and epithelial cells) is causal. In addition, the low levels of the anti-inflammatory cytokine adiponectin (which induces production of the anti-inflammatory cytokines IL-10 and Il-1 receptor antagonist) may contribute to the severity of disease as well.

While these mouse studies must be extrapolated carefully to human disease, the effectiveness of anti-leptin antibody in reducing mortality (without decreasing pulmonary viral load) in mice suggests that modulation of the immune response in severe influenza may improve survival in obese patients with influenza, especially in patients who present more than 48 hours after symptom onset when antiviral treatment may be less effective.

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ABSTRACT & COMMENTARY

Inhibition of Telomerase Activity by NRTI's may Contribute to Accelerated Aging in HIV Patients

By Dean L. Winslow, MD, FACP, FIDSA

Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, Associate Editor of Infectious Disease Alert.

Dr. Winslow is a consultant for Siemens Diagnostic. Abstract and commentary by Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: Nucleoside and nucleotide analogues inhibit telomerase activity and leads to shortening of telomere length (TL) in activated PBMC's in culture.

SOURCE: Leeansyah E, et al. Inhibition of telomerase activity by human immunodeficiency virus (HIV) nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated aging. *JID* 2013;1157-65.

Telomerase activity and telomere length (TL) were measured by quantitative PCR in vitro in activated peripheral blood mononuclear cells (PBMC's) cultured with NRTI's and in PBMC's from uninfected patients as well as PBMC's from HIV-infected patients receiving NRTI-containing cART. Lamivudine, abacavir, emtricitabine, and tenofovir all significantly inhibited telomerase activity in activated PBMC's in vitro. Tenofovir (TDF) was the most potent telomerase inhibitor and caused the greatest telomere shortening at clinically-achievable concentrations (0.3uM). PBMC's from patients receiving NRTI's had significantly lower telomerase activity than PBMC's from HIV-uninfected patients. In HIV-infected patients receiving non-NRTI-containing cART, TL was inversely associated with age and total duration on any NRTI in the past. TL in PBMC's from uninfected controls did not appear to be related to age.

■ COMMENTARY

I always look forward to reading papers from the Australian group since they seem to consistently do such careful and interesting translational research in the field of HIV. This paper is no exception.

Over the last several years there has been increasing attention paid to non-AIDS-defining illnesses in HIV patients including malignancy, cardiovascular disease, and bone disease. A cellular correlate of human aging is progressive shortening of telomere length with cell division. Telomeres are located at the ends of chromosomes and consist of short, tandem, G-rich hexanucleotide repeats. During mitotic cell division, telomere DNA is not duplicated by DNA polymerase and undergoes progressive shortening until a critical length is reached and the cells enter replicative senescence. Several studies have shown a correlation between TL in PBMC's and diseases of aging including cardiovascular disease and dementia. TL is maintained by telomerase (a ribonucleoprotein enzyme complex containing a telomerase RT subunit). AZT, ddI, and abacavir have previously been shown to inhibit telomerase activity in replicating cell lines in vitro and cause accelerated shortening of TL. This has been felt to be due to NRTI inhibition of telomerase RT activity (TERT) via chain termination, similar to their mechanism of action against retroviral RT. However, other mechanisms may play a role as well. This study demonstrates that the newer NRTI's have similar effects on telomerase activity and TL in PHA-activated PBMC's, which may be more relevant than effects observed in T-cell lines.

This study is thought-provoking for several reasons. Despite the wonderful impact of HAART on reversing immunosuppression, reducing the prevalence of classic AIDS-defining infections and malignancies and prolonging life in patients infected with HIV, it is clear that cART does not completely prevent all of the complications seen in HV-infected patients. Despite cART, patients with

HIV still experience greater risk of cardiovascular disease than HIV-negative individuals, experience more rapid progression of HBV and HCV-related disease, and an increased prevalence of many cancers including Hodgkin lymphoma and HPV-related cancers. Many clinicians believe that some of these effects are related to "accelerated aging." However the relative contributions of increased inflammatory cytokines (probably related to increased gut microbial translocation despite effective cART), HIV itself, and the effects of antiretroviral therapy are not clear. The demonstration that one of our preferred NRTI's (tenofovir) may directly contribute to "accelerated aging" by its effect on inhibition of telomerase bears further study. ■

Coccidioidomycosis – Update

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University, Hospital Epidemiologist, Sequoia Hospital, Redwood City, CA, Editor of Infectious Disease Alert.

In the last issue of *Infectious Disease Alert*, we summarized a recent report demonstrating the increasing risk of coccidioidomycosis, especially in California and Arizona. The comment ended by pointing out the large number of cases of this fungal infection that occurred during construction of Interstate 5 down the spine of the highly endemic central valley of California and warning about the construction of high speed rail along a similar path in the near future. Since that issue, the problem has been highlighted by reports of two additional events.

The Central Valley of California is nothing if not sun drenched (except during episodes of tule fog — dense ground fog that has been the cause of huge traffic accidents on Interstate 5). An outbreak of coccidioidomycosis involving 28 workers at solar power construction plants in San Luis Obispo county in central California is under investigation by county and state public health personnel, as well as by CalOSHA. The two plants are the California Valley Solar and Topaz Solar Farm, located on the Carrizo Plain in the eastern portion of the county bordering the Central Valley, a semi-arid grassland at a mean 700 m elevation with only 230 mm rain annually features typical of the Lower Sonoran Life Zone that is loved by Coccidioides. The problem leading to the outbreak is, of course, the disruption of the soil with release of dust containing arthroconidia into the air and their subsequent inhalation. Another project, the Antelope Valley Solar Ranch was recently ordered to cease construction because of dust blowing from the construction site to the nearby California town of Lancaster.

But that's not the only problem recently presented by this dimorphic fungus. Pappagianis, in 2007, reported that two state prisons, the Pleasant Valley State Prison (PVSP) near Coalinga and Avenal State Prison (ASP) near Avenal on the western side of the San Joaquin Valley, had been hit hard by coccidioidomycosis as early as 2005 - 2006.[1] In 2005, serologic testing identified 150 new cases from PVSP as well as 30 from ASP. In 2007-2010, the average annual incidence rates at ASP and PVSP were 1156/100,000 and 374/100,000, respectively.[2] These rates were 16-fold and 123-fold greater than in their respective counties (Kings and Fresno). The relative risk for death in males due to coccidioidomycosis in adult institutions was 9.7 (95% CI 6.2 to 15.1) when compared to adult males statewide.

These and additional data have now led J. Clark Kelso, a federal receiver monitoring health in California's overburdened

correctional system, to request assistance from the Centers for Disease Control and Prevention in the investigation of deaths caused by coccidioidomycosis in state inmates.[3] More drastically, he has also ordered the transfer of about 40% of the more than 8,200 inmates from the two state prisons. Those ordered to be transferred include patients known to be at risk for severe outcomes of coccidoidal infection, including Filipinos, African-Americans, individuals with immunocompromising disease or illness, and those >55 years of age, and those with signicant other selected comorbidities.

The problem with coccidioidomycosis among prison inmates housed in an endemic area brings to mind an occurrence in relation to World War II, by the end of which there were more than 400,000 enemy prisoners of war held within the U.S.[4] More than 10,000 were housed in a prison in Florence, Arizona, which is located midway between Phoenix and Tucson. Unfortunately, coccidioidomycosis became epidemic among the prisoners, including those who were sent there for the climate because they had tuberculosis — a significant proportion of whom also developed the fungal infection. Concerned that they would be accused of violating the Geneva Conventions, authorities transferred inmates to other sites — a harbinger of the solution to be imposed in California more than seven decades later.

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ABSTRACT & COMMENTARY

Is Your Smart Phone Spreading Infection in the ICU?

By David J. Pierson, MD, Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle.

Dr. Pierson reports no financial relationships in this field of study.

SYNOPSIS: Bacteria were present on the cell phones of all hospital clinicians studied, with potentially pathogenic microorganisms isolated from 29% of them. Contamination with pathogens was found more commonly with smart phones than with non-smart phones, and by multivariable analysis no other factor was associated with this difference.

SOURCE: Lee YJ, et al. Contamination rates between smart cell phones and non-smart cell phones of healthcare workers. *J Hosp Med* 2013;8: 144-147.

Lee and colleagues administered questionnaires and performed bacterial cultures on the cellular phones of 203 clinicians (39% physicians, 52% nurses, 9% medical assistants) working in three university-affiliated teaching

hospitals in Seoul. The questionnaire included data on participant demographics (age, gender, occupation) as well as behavior regarding cell phone use (type of cell phone, frequency and reasons for use, and cleaning of cell phones). The investigators touched the anterior and posterior surfaces of the phones onto blood agar plates and classified the recovered bacteria according to pathologic potential. Among probable pathogenic microorganisms, representative drug-resistant strains such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus, and imipenem-resistant Acinetobacter baumannii were categorized as drug-resistant pathogens. The participants' mean age was 29 years and 79% were women. A total of 115 (57%) were smart phone users and 88 (43%) used non-smart phones. The smart phone users were slightly younger (28 vs 29 years, P = 0.03), but this was the only significant difference between the groups. Only a minority of all cell phone users reported taking special measures to clean them.

All 203 cell phones had positive cultures: 4% had a single organism recovered, 19% had two organisms, and 76% had three or more. The most commonly cultured microorganism was coagulase-negative staphylococci, isolated from 96% of the phones. Gram-positive bacilli and Micrococcus species were also frequently recovered. Probable pathogenic bacteria were isolated from 58 cell phones (29%). S. aureus was the most common of these, and it was MRSA in 8 of the 50 instances. *Acinetobacter baumannii* was recovered from five phones. Probable pathogens were isolated more often from smart phones (35% vs 20% of non-smart phones, P = 0.03). The total colony count of probable pathogens from smart phones was also higher (average, 5.5 vs 5.0 from non-smart phones, P = 0.01). Among all the factors examined for possible association with phone contamination, only the phone's being a smart phone was found to be a risk factor for contamination by bacteria with pathogenic potential (adjusted odds ratio [OR] 4.02; 95% confidence interval [CI], 1.43-11.31; P = 0.01). Using the cell phone more than 10 times during working hours appeared to be associated with pathogen contamination; however, this correlation failed to reach statistical significance (OR, 2.9; 95% CI, 0.9-9.3; P = 0.07).

■ COMMENTARY

This study found that health care workers' smart phones were more frequently contaminated with potentially pathogenic bacteria than non-smart phones. The authors postulate two reasons for this — that smart phones have larger surfaces that are more often touched by the user's fingers, and that they may be used more times during the day, since clinicians can use them for more work-related tasks than non-smart phones.

Other studies have documented frequent bacterial contamination of the cell phones of health care workers — along with their stethoscopes and various parts of their attire — as well as of the bed rails, monitors, bedside curtains, computer keypads, and other features of the patient's immediate environment. Direct linkage between such contamination and specific cases of hospital-acquired infection has generally been lacking, although it is hard to ignore the possibility of this or measures aimed at avoiding it. Cell phones are now carried by virtually all health care workers. Today, more and more of these are smart phones, which are increasingly being integrated into clinical and administrative aspects of critical care. How concerned we should be about their contamination with potential pathogens is not entirely certain, but we should be aware of the fact that such organisms are present not only on our hands but also on the things we carry around with us in the ICU. ■

Updates

By Carol A. Kemper, MD, FACP

Risk of TB in older persons

Hochberg NS, et al. Prevention of tuberculosis in older adults in the United States: Obstacles and opportunities. *CID* 2013;(56):1240-1247.

While the absolute number of cases of tuberculosis (TB) in the United States have declined over the last decade, the risk for reactivation TB in the elderly remains disproportionately high. Some of this risk is the result of an aging immigrant population, longer life-span, and the higher prevalence of co-morbidities in older adults (i.e., diabetes, chronic kidney disease). Older adults (> 65 years of age) living in long-term care facilities have the highest rates of TB in the U.S. (39.2 cases/100,000 persons) – more than 400% greater than that for all age groups. Between 1993 and 2008, 9% of all patients diagnosed with TB in the U.S. resided in a long-term care facility.

These authors examined rates and risk factors for TB in older adults in the U.S. From 1993-2008, 61,124 adults > 65 yrs of age were diagnosed with TB (21.9% of all TB cases in the U.S.). The average yearly rate for persons > 65 yrs or older was 10.9 cases /100,000 compared with 7.3 cases/100,000 for persons aged 21-64 yrs of age – but for persons 85 yrs of age or older, the rate nearly doubled that of the general population (14.2 cases/100,000). Not only did rates of TB increase with advancing age, but in the older population, rates were significantly higher in men, Asian Americans (where the rate was 94.6 cases/100,000 cases), American Indians/ Alaska Natives, and in residents of long term care facilities.

From 1998 to 2008, 21% of older persons (including 42% of older patients residing in skilled nursing facilities died while receiving treatment for tuberculosis compared with 7% of younger persons.

The prevention of TB in older patients before they get too much older is therefore especially important. While I believe there generally needs to be a bigger push in this country for chemoprophylaxis of all persons with latent TB, older people — especially those born in countries with endemic TB — should be routinely screened and treated for latent TB as soon as feasible. Though waning immunity in older people may lead to falsely negative PPD/TSTs, limited data suggests that the interferon-gamma release assays may be less affected by age than PPD/TST results, and most older persons are able to mount an adequate immune response for Tb Quantiferon testing. ■

Non-cocci cocci

Brillhante RS, et al. Coccidioidomycosis in armadillo hunters from the state of Ceara, Brazil. *Mem Inst Oswaldo Cruz* 2012;(107):813-815.

Infection with Coccidioides posadasii, another endemic pathogenic soil fungi found in certain areas of Texas, Mexico and South America, may provide an alternate explanation for patients at risk for pneumonia not responding to antibacterials. *C. posadasii* is far less common, and certainly less recognized than its cousin *C. immitis*, but may result in a similar illness — both in animals and in humans. While it generally causes a self-limited flu-like illness, with fever, sweats, fatigue, cough and chest discomfort, it can result in severe progressive pulmonary and extra-pulmonary disease, with potential dissemination to bones and joints, brain and skin, similar to *C. immitis*. The recent report above documents an outbreak of infection due to *C. posadasii* in Armadillo

hunters in Northeastern Brazil — the diagnosis of which was delayed while patients received antibacterial therapy.

C. posadasii and *C. immitis* appear morphologically the same, but are genetically distinct species (first recognized in 2002). *C. posadasii* also has a much larger range, and is found outside the San Joaquin Valley and areas recognized as "cocci country" — including the semi arid areas of Texas, the southern desert of Mexico, and parts of South America. It is quite hardy, much more draught tolerant than its cousin, and tolerates soils with high salinity and highly variable pH. So if you are seeing what looks like a cocci case without the appropriate epidemiology — you might be correct. Cultures of clinical material still represent a biohazard for laboratory workers — but real time PCR assays used for the detection of *C. immitis* in clinical specimens do not distinguish between the two species. ■

A new "App" for your mobile phone

Bogosh II, et al. Short Report: Mobile phone microscopy for the diagnosis of soil-transmitted helminth infections: A proof of concept study. *Am J Trop Med Hyg* 2103;88:626-629.

Nowadays, mobile phones can go almost anywhere in the world — and compared to bulky cameras and light microscopes, are cheap and easy to carry. These authors conducted a proof of concept study to assess whether a mobile phone could be modified to detect intestinal parasites in stool.

Stool samples were collected from school aged children in Tanzania over a 5-day period, and were processed using the Kato-Katz technique. The thick smears were evaluated by a trained technician using conventional light microscopy, with the number of *Ascaris* and *Trichuris* spp. eggs and the number of hookworms tabulated, and compared with the results obtained using a mobile phone "microscope."

A mobile phone was transformed into a microscope using a 3 mm ball lens and a piece of double-sided tape. A small aperture was created in the tape, into which the lens was inserted; and two extra little bits of tape were placed on either side of the lens — in order to give some "depth" to the field, and creating a 1 mm space between the slide and the lens. The phone was placed over the stool slide, and illuminated by a hand-held flashlight (using a AA battery). The authors estimate the whole contraption took about 5 minutes to assemble and cost $15. While the estimated magnification was about 50-60 x, the resolution was not as good as hoped — apparently the smaller 1 mm lens had better resolution but a narrower field of view, so they had opted for the 3 mm lens, hoping it was adequate.

A total of 199 thick smears were compared. For any helminth, the sensitivity of the mobile phone microscope, compared with the conventional light microscopy results, was 69%. The best results obtained using the mobile phone were observed for A. lumbricoides eggs (81%) followed by T. trichuria eggs (79%); the worst result was observed for the detection of hookworms (14%), possibly because hookworms quickly clear on smears. Heavy eggs burdens were easier to detect (93% sensitivity).

Since the resolution with the mobile phone microscope was not as good as hoped with the 3 mm lens, several false-positives were observed, leading to a lower specificity (61%). The authors believe, however, their low-tech approach was nearly adequate, and could likely be improved upon with a better lens – yielding an inexpensive, small portable tool for use in developing countries with limited laboratory access and resources. Since one simple approach in such countries is "see an egg, treat an egg", accuracy may not be paramount, as detection of any egg in stool could be used as a basis for broader anti-helminthic treatment. ■

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?

A. Uncomplicated non-purulent cellulitis is most often caused by Staphylococcus aureus.

B. Cephalexin is effective in the treatment of MRSA infections.

C. The addition of trimethoprim-sulfamethoxazole cephalexin improves outcomes in the treatment of uncomplicated non-purulent cellulitis.

D. Cephalexin alone is effective in the treatment of non-purulent cellulitis.

2. Which of the following is correct?

A. Leptin is pro-inflammatory.

B. Adiponectin is pro-inflammatory.

C. Leptin is only produced by fat cells.

D. Obesity is protective against severe influenza virus infection.

3. Which of the following is correct?

A. Telomerase acts to shorten telomere DNA.

B. Inhibition of telomerase leads to lengthened telomere DNA.

C. When a threshold telomere DNA length is exceeded, cells enter senescence.

D. Tenofovir inhibits telomerase.

CME OBJECTIVES

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

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latent 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]

Azithromycin – The Heart of the Matter Redux: Preexisting Risks Tell the Tale

Infection Risks of Pandemic H1N1 Flu, Measles during Air Travel

Early use of Daptomycin Compared to Vancomycin for MRSA Bacteremia

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.*

Do Perioperative Beta-Blockers Reduce Mortality?

In this issue: Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95%CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were "unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders" (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95%CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that "statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class" (*Ann Intern Med* 2013;158:526-534). ■

FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product "has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)." The agency's refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■

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, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

Source: Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

The prevailing 5-year tamoxifen regimen for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years (n = 3418) or 10 years (n = 3428) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

Is There More Pro than Con in Probiotics in Critically Ill Adults?

Source: Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

The technical definition of probiotic offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU) setting, ultimately netting 13 clinical trials, all published after 2002 (n = 1439). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

Source: Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

The recognition of obstructive sleep apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

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At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

Inhaled Steroids Increase Risk of TB in COPD Patients

Source: Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

Reactivation of tuberculosis (TB) is an ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients (n = 620) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States, these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

The ASH Position Paper on Orthostatic Hypotension

Source: Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

Standing from a seated or supine position is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may OH improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■