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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

Cephalexin vs. Clindamycin for Pediatric Skin Infections — Perhaps Drainage Is All That's Needed

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: Two hundred patients from 6 months to 18 years of age with uncomplicated skin and soft tissue infections (SSTIs) were randomly assigned to cephalexin (Keflex) vs. clindamycin. Spontaneous drainage or a drainage procedure was performed in 97% of patients. By 48-72 hours, 94% of patients in the cephalexin arm and 97% of patients in the clindamycin arm were improved. By day 7 all patients had improved.

SOURCE: Chen AE, et al. Randomized controlled trial of cephalexin versus clindamycin for uncomplicated pediatric skin infections. Pediatrics 2011;127;e573-e580.

Two hundred patients from 6 months to 18 years of age with uncomplicated purulent SSTIs not requiring hospitalization were enrolled from 2006 through 2009. The infections included abscesses (with or without surrounding cellulitis), furuncles, or carbuncles. Patients were randomized to 7 days of cephalexin vs. clindamycin. Primary endpoints included clinical improvement at 48-72 hours and at 7 days. Cultures were obtained and isolates were tested for antimicrobial susceptibility, pulsed-field gel electrophoresis (PFGE) type, and Panton-Valentine leukocidin

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Infectious Disease [ALERT]

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(PVL) production. Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in 69% of patients. Most of these were USA300 strains by PFGE typing, were positive for PVL, and were clindamycin-susceptible (91%). Nineteen percent grew methicillin-susceptible *S. aureus* (MSSA), 8% grew other organisms, and 5% were sterile. Spontaneous drainage occurred or patients underwent a drainage procedure in 97% of cases. Improvement by 48-72 hours occurred in 94% of cephalexin-treated patients and in 97% of clindamycin-treated patients. By day 7 all patients had improved with complete resolution demonstrated in 97% of cephalexin-treated patients and in 94% of clindamycin-treated patients. Fever and age < 1 year (but not initial erythema > 5 cm) were associated with early treatment failures in both antibiotic treatment groups. Four patients required hospitalization after enrollment, but in only two cases was this due to worsening of their initial infection. No serious adverse events related to study treatment were encountered. One 13-month-old child developed mild diarrhea with stool positive for *Clostridium difficile* toxin 1 week after completing study treatment with clindamycin, but this resolved without treatment and follow-up stool specimens were negative for *C. difficile* toxin.

■ COMMENTARY

This large randomized trial performed in Baltimore is an important addition to the medical literature. The study illustrates a number of important points including the demonstration that two-thirds of SSTIs in inner city children in an East Coast U.S. city were due to MRSA. The study, most importantly, emphasizes the teaching point that the most important element of successful treatment of uncomplicated SSTIs is adequate drainage and that antimicrobials play a secondary role in their management. The essentially equivalent outcomes between clindamycin and what is essentially a placebo vs. MRSA (cephalexin), suggests that antimicrobials should be withheld in most cases of uncomplicated SSTIs as long as appropriate drainage and wound care is performed. Future, larger studies may determine whether the addition of an effective antibiotic may reduce the risk of recurrences or of transmission to close contacts, including family members. ■

ABSTRACT & COMMENTARY

Exposure to Environment Microorganisms and Childhood Asthma

By Hal B. Jenson, MD, FAAP

Professor of Pediatrics, Tufts University School of Medicine, and Chief Academic Officer, Baystate Medical Center, Springfield, MA

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

SYNOPSIS: Children living full-time on family-run farms were exposed to a wider spectrum of indoor microbes, which may account for the relationship between growing up on a farm and the reduced risk for developing childhood asthma.

SOURCE: Ege MJ, et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med 2011;364:701-709.

Two separate, cross-sectional studies involving 6,843 and 9,668 children 6-13 years of age in South Germany randomly compared children living on farms with reference groups for the prevalence of asthma relative to the exposure to and diversity of indoor microorganisms. The first study screened 489 samples of mattress

dust for bacterial DNA using single-strand conformation polymorphism (SSCP), which detects environmental bacteria that cannot be cultured. In this first study population, 52% of children lived on farms and had an 8% prevalence of asthma. The second study screened settled dust collected over 14 days by electrostatic dust collectors from 444 children's rooms for bacteria and fungi using quantitative cultures. In this second study population, 16% of children lived on farms with an 11% prevalence of asthma.

Children living full-time on family-run farms were classified as members of the farm group, and all other children were classified as members of the reference group. Asthma was defined as physician-diagnosed asthma on at least one occasion, or "wheezy bronchitis" on more than one occasion. In both studies, children who lived on farms were exposed more frequently and to a greater variety of environmental microorganisms, and had lower prevalences of asthma and atopic disease. The diversity of microbial exposure was inversely related to the risk of asthma (odds ratio [OR] for the first study, 0.62; 95% confidence interval [CI], 0.44 0.89; OR for the second study, 0.86; 95% CI, 0.75-0.99), but not to the risk of atopy, independent of farming. Exposure to certain species was also inversely related to the risk of asthma, including exposure to species in the fungal taxon eurotium (adjusted loves ratio, 0.37; 95% CI, 0.18-0.76) and to a variety of bacterial species including *Listeria monocytogenes*, *Bacillus*, corynebacterium, and others (adjusted OR, 0.57; 95% CI, 0.38-0.86).

■ COMMENTARY

In this study, children living on farms had exposure to a greater diversity of environmental microorganisms than children who did not live on farms. A greater diversity of indoor environmental microbial exposure was inversely related to the risk of asthma, but not to atopy. It is possible that the indoor microbial diversity for children living on farms in these studies was a marker for exposure to even greater outdoor microbial diversity.

These results are consistent with the "hygiene hypothesis," which states that reduced childhood exposure to environmental microorganisms actually increases the risk of childhood asthma and atopic disease, presumably by affecting the natural development of certain aspects of immunity. Exposure to nonpathogenic microbes in early life might promote tolerance by triggering the innate immune system and activating signaling pathways that induce T cells. Activation of type I helper T cells may promote immunologic tolerance and counterbalance the predominance of type 2 helper T cells, which are more characteristic of asthma. Another hypothesis might be that low-level and continuing exposure to a broad range of microorganisms may prevent colonization with bacteria and fungi that increase the risk of asthma.

The studies used state-of-the-art methods for microbiological detection, though the methods are relatively crude and did not permit identification of specific protective pathogens, only broad families of species within microbial taxa. It is intriguing to consider that future studies using much more advanced technologies could identify specific microbes that confer protection to developing childhood asthma. The studies could also shed light on the mechanism of the protective benefit of exposure to microbial diversity. ■

ABSTRACT & COMMENTARY

STD Management — What's New?

By Stan Deresinski, MD, FACP, FIDSA

SYNOPSIS: The 2006 Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) guidelines have been updated.

SOURCE: Workowski KA, Berman S; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1-110.

The latest iteration of the CDC guidelines on the treatment of STDs was finally published at the end of 2010 after finishing a process that began in 2008. The more than 100 pages of text are too voluminous to fully summarize here (and would resist useful summarization at any

rate). I will instead focus on some of the changes from the 2006 document. Two areas of change in the guidelines, genital warts and sexual assault, will not be discussed here.

PREVENTION

An extensive section of the current document deals in detail with approaches to the prevention of STDs, including: education and counseling; identification of both symptomatically and asymptomatically infected individuals; effective diagnosis, treatment, and counseling of infected individuals and their partners; and vaccination of at-risk individuals. Education and counseling begins with evaluating risk via questions assessing "The Five P's": Partners, Prevention of pregnancy, Protection from STDs, Practices (i.e., sexual practices), and Past history of STDs — as well as questions regarding risk for HIV infection and viral hepatitis such as a history of injection drug use. Prevention methods discussed include abstinence and reduction in the number of partners, pre-exposure vaccination (HPV, HBV, HAV), male and female condoms, cervical diaphragms, topical microbicides and spermicides, non-barrier contraception including surgical sterilization and hysterectomy, emergency contraception, male circumcision, post-exposure prophylaxis, pre-exposure prophylaxis, and retesting to detect repeat infections.

SPECIAL POPULATIONS

Preventive, diagnostic, and therapeutic management of special populations is discussed at length. These groups include pregnant women, adolescents, children, men who have sex with men (MSM), women who have sex with women, and individuals confined to correctional facilities.

CERVICITIS, TRICHOMONIASIS

Women with cervicitis should be evaluated for evidence of pelvic inflammatory disease and tested for the presence of infection with *Chlamydia trachomatis* and *Neisseria gonorrheae* using a nucleic acid amplification test (NAAT), as well as for trichomoniasis and bacterial vaginosis. If microscopy fails to detect *Trichomonas vaginalis*, further testing, such as culture, should be performed. While infection with *Mycoplasma genitalium* is possible, commercially available tests for this pathogen are not available.

BACTERIAL VAGINOSIS

Symptomatic women with bacterial vaginosis should be treated with one of three regimens: metronidazole 500 mg orally twice daily for 7 days; metronidazole gel 0.75% intravaginally once daily for 5 days; or clindamycin cream 2% intravaginally at bedtime for 7 days. Alternative regimens utilize orally administered tinidazole or clindamycin or intravaginal clindamycin ovules. Options for treatment of women with multiple recurrences include the use of metronidazole gel for 4-6 months or oral metronidazole followed by intravaginal boric acid and long-term suppression with metronidazole gel.

CHLAMYDIA TRACHOMATIS

The treatment of chlamydia infections during pregnancy has been challenging since doxycycline and fluoroquinolones are contraindicated. While amoxicillin has previously been recommended for the treatment of *C. trachomatis* infection in pregnant women, clinical experience suggests that azithromycin may be safe and effective when administered as a single 1 g oral dose. Repeat testing by NAAT should be performed 3 weeks after completion of therapy and, in those infected in the first trimester, again 3 months later. Those with risk of reinfection should be retested during their third trimester.

[Education and counseling begins with evaluating risk via questions assessing "The Five P's": Partners, Prevention of pregnancy, Protection from STDs, Practices (i.e., sexual practices), and Past history of STDs — as well as questions regarding risk for HIV infection and viral hepatitis such as a history of injection drug use.]

LYMPHOGRANULOMA VENEREUM

Doxycyline 100 mg twice daily for 21 days is recommended for the treatment of LGV infection, with erythromycin as an alternative. In addition, "Although clinical data are lacking, azithromycin 1 g orally once weekly for 3 weeks is probably effective based on its chlamydial antimicrobial activity. Fluoroquinolone-based treatments might also be effective, but extended treatment intervals

are likely required." In MSM with anogenital chlamydia infection and either proctitis (as determined by proctoscopic examination and the presence of > 10 white blood cells upon high-power field examination of an anorectal smear specimen) or with HIV coinfection, treatment for LGV with 3 weeks of doxycycline can be considered.

MYCOPLASMA GENITALIUM

M. genitalium accounts for 15%-25% of cases of non-gonococcal urethritis (NGU) in the United States. While both doxycycline and azithromycin are effective for the treatment of chlamydial urethritis, azithromycin (a single 1 g dose) is more effective than the tetracycline derivative for *M. genitalium* infection. Moxifloxacin (400 mg daily for 7 days) also is effective against this infection and is among the acceptable alternative therapies in individuals with recurrent NGU.

ANTIBIOTIC-RESISTANT NEISSERIA GONORRHEAE

The emergence of fluoroquinolone resistance in *N. gonorrheae* is now widespread in the United States and, as a consequence, this class of drugs has not been recommended for the treatment of gonococcal infections since 2007. The only class of acceptable agents at this time are cephalosporins. Resistance to cephalosporins remains rare, as is failure of treatment, especially with ceftriaxone. Approximately 50 cases of failure of oral cephalosporins (cefixime is recommended for oral therapy in the United States) have been reported, with most having occurred in Asia. One possible case of failure of cefixime therapy in Hawaii has been reported. To ensure appropriate antibiotic therapy, clinicians should ask patients with gonorrhea about recent travel to and sexual activity in countries where resistance and treatment failure have been reported.

INDICATIONS FOR CEREBROSPINAL FLUID (CSF) EXAMINATION FOR NEUROSYPHILIS

Patients with apparent latent syphilis who demonstrate any of the following should have a prompt CSF examination: compatible neurologic or ophthalmologic signs or symptoms, findings suggestive of tertiary syphilis, or serological treatment failure. Quantitative non-treponemal serologic tests should be repeated at 6, 12, and 24 months. "A CSF examination should be performed if 1) titers increase fourfold, 2) an initially high titer (≥ 1:32) fails to decline at least fourfold (i.e., two dilutions) within 12-24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In such circumstances, even if the CSF examination is negative, retreatment for latent syphilis should be initiated. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might fail to decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear."

HIV infection may be associated with an increased risk of central nervous system involvement by *Treponema pallidum*. In coinfected patients, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count ≤ 350 cells/mL and/or an RPR titer ≥ 1:32. Despite this association, in the absence of neurologic symptoms or signs, CSF examination in this setting has not been associated with improved clinical outcomes. However, all HIV-infected persons with evidence of syphilis and who have neurologic symptoms and/or signs should undergo immediate CSF examination. In addition, if there is evidence of failure of treatment of non-CNS or CNS syphilis, repeat CSF examination, as outlined above, is warranted.

AZITHROMYCIN-RESISTANT TREPONEMA PALLIDUM

Azithromycin as a single 2 g oral dose has been effective in the treatment of early syphilis, but chromosomal mutations in *T. pallidum* associated with treatment failure have now been identified in the United States. As a consequence, azithromycin should be used with caution and only when treatment with penicillin or doxycycline is not feasible. It should not be used in MSM or pregnant women.

SEXUAL TRANSMISSION OF HEPATITIS C VIRUS

Recent data indicate that sexual transmission of HCV, especially among HIV-infected persons, is more frequent than previously believed. One in 10 individuals with acute HCV infection report contact with a known HCV-infected sex partner as their only risk for infection. Studies of HCV transmission in heterosexual or homosexual couples have yielded somewhat conflicting results, but generally have identified low but increased rates of HCV infection in partners of persons with HCV infection compared with those whose partners are not HCV-infected. The risk appears to rise in parallel with increasing number of sex partners among both heterosexuals and MSM and this risk is further increased if partners are HIV-infected. Transmission clusters have been identified in HIV-infected MSM, often associated with serosorting (i.e., HIV-infected men having sex with one another), group sex, and the use of cocaine and other non-intravenous drugs during sex. ■

ABSTRACT & COMMENTARY

The Enigma of Bedbugs

By Alan D. Tice, MD, FACP
Infectious Disease Consultants, John A. Burns School of Medicine, University of Hawaii, Honolulu
Dr. Tice reports no financial relationship to this field of study.

SYNOPSIS: Bedbugs have been a global problem for centuries, but recently have had a resurgence in prosperous countries, where they had been relatively dormant for years. Despite the nature of this pest, they have not been identified as a vector for any infections, though the potential risk cannot be completely ignored.

SOURCE: Delaunay P, et al. Bedbugs and infectious diseases. Clin Infect Dis 2011;52:200-210.

A group of investigators in France undertook an exhaustive review of bedbugs and found evidence of them in the tombs of Egypt 3,500 years ago. They found them to be a common problem in developing countries throughout history, although there apparently was some decline with DDT. The dominant strains affecting humans are *Cimex lectularius* and *Cimex hemipterus*, although there are other strains that affect animals as well. The bans of DDT use in the United States in 1972 and globally in 2001 have been blamed for the recrudescence, but are probably not responsible for the resurgence of this hematophagous arthropod, as many are resistant to DDT and other pesticides, especially in countries with limited resources.

Bedbugs are unusual creatures that feed primarily on humans and reproduce by traumatic insemination, whereby the male penetrates the female through her cuticle instead of her reproductive tract, which is often fatal to the female. However, the survivors usually produce 200-500 eggs in a lifetime, which become larva within about a week and molt with each new blood meal until they become adults. They can live for a year without feeding — and longer in colder climates.

These tiny insects are nocturnal and hide out in dark places such as beds, mattresses, clothes, and luggage. When a person or animal becomes available, they inflict a bite or blood collection with the help of an anesthetic and anticoagulants in their saliva. The wounds generally become apparent the next day, with itching and then a cluster of papules at the dinner table. These papules vary with the host; they may be small and itch a bit, but urticaria and bullae and even anaphylaxis have been reported.

With this history and the ability to crawl around, it seems only logical that they could spread a variety of infections. In fact, a large number of curious investigators have studied these bugs over the years and have been able to isolate as many as 45 different potential pathogens from them. Upon further investigation, however, the role of this worldly arthropod is questionable, especially when rigorous criteria are applied, such as vectorial competence (e.g., acquisition, maintenance, and transmission) and vectorial capacity (e.g., reasoning and detection in the wild). Many of the possible pathogens have been inoculated into bedbugs, but they do not even perpetuate themselves.

While a role in transmission on a limited level cannot be excluded, there have not been any outbreaks of human pathogens documented or even associated. Among the front-runners for apparent infections to consider are *Coxiella burnetti*, Wolbachia, *Aspergillus* species, *Tripanosoma cruzi*, hepatitis B, and HIV.

■ COMMENTARY

The resurgence of bedbugs is a curious phenomenon. They are an irritant to travelers, a headache to hoteliers, and have created a media frenzy, especially with eradication programs, which have briefly closed some very fashionable clothing stores.[1] We are fortunate, however, that they are not vectors or carriers for what could be much more virulent organisms. Why this arthropod has not become a vector for disease over the years is unclear and a bit of a surprise given the role of so many other insects such as mosquitoes and fleas. Perhaps they are able to suppress the growth of intruders through immune or other mechanisms — a defense for themselves as well as the hosts they feed on.

The question now becomes what to do about these annoying pests. The authors refer to a simple and prompt test that is being used to detect this parasite: A dog trained to recognize the obnoxious odor the bedbugs produce simply snifs around the infested room or luggage or clothing. Once bedbugs are detected, the next step is to clean up all materials

that may harbor these bugs and vaccum the premises thoroughly. Clothing that may be infested should be put into sealed plastic bags until washed and then dried in a hot machine drier. They are often resistant to common pesticides. Fumigation is often not effective because of resistance and failure to penetrate their hiding places in beds, bedding, clothing, furniture, and luggage. Spray pesticides may help reach into the dark depths of their existence where fumigation usually cannot, but resistance is a problem there as well. Another route of elimination is to super-heat the infested rooms for a day or so, which apparently kills them off.[2]

So, beware of the potential for bedbugs wherever you travel and beware of their potential to cause disease, although secondary transmission may not be a problem, yet. ■

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1. Manuel J. Invasion of the bedbugs. Environ Health Perspect 2010;118:A429.
2. How YF, Lee CY. Effects of temperature and humidity on the survival and water loss of Cimex hemipterus (Hemiptera: Cimicidae). J Med Entomol 2010;47:987-995.

ABSTRACT & COMMENTARY

Norovirus — It's Here to Stay

By Stan Deresinski, MD, FACP, FIDSA

SYNOPSIS: Noroviruses are the major single cause of gastroenteritis outbreaks throughout the world and the leading cause of foodborne disease in the United States.

SOURCE: Centers for Disease Control and Prevention. Updated Norovirus Outbreak Management and Disease Prevention Guidelines Recommendations and Reports. Morb Mortal Wkly Rep 2011;60(RR03):1-15. Available at http://cdc.gov/mmwr/preview/mmwrhtml/rr6003a1.htm?s_cid=rr6003a1_w. Accessed March 14, 2011.

Ten years after their original publication, the Centers for Disease Control and Prevention (CDC) has updated their recommendations for the prevention of norovirus infection and the management of outbreaks due to this non-enveloped, single-stranded RNA member of the Calciviridae family. Since 2001, a single norovirus genotype GII.4 has emerged as the major cause of infections throughout the world. Its emergence is evidence of the ability of the virus to evolve in response to the selective pressure of host immune systems, thus allowing its escape from immune suppression. The success of this virus is also the result of the fact that prior exposure to the virus does not provide lasting protection. While pre-existing homologous antibody is protective, this protection appears to be lost after 2-6 months. These facts, combined with an estimated infectious dose as low as 18 virions — when a gram of feces collected during the period of peak viral shedding is estimated to contain 5 billion infectious doses — help frame the problem. To make matters worse, while peak shedding is reached 2-5 days after symptom onset, viral excretion persists during and after convalescence, lasting for an average of 4 weeks after infection. In addition, as many as approximately one-third of infections are asymptomatic and, while such infections are associated with lower levels of fecal shedding, the very small infectious dose necessary for transmission makes these asymptomatic individuals a potential source of transmission.

Noroviruses are the predominant cause of outbreaks of gastroenteritis throughout the world, being responsible for approximately one-half of those investigated in Europe and the United States. In the United States, approximately one-third of norovirus outbreaks occurred in long-term care facilities, another approximately one-third were from restaurants, parties, and events, and one-fifth were vacation-related, including cruise ships. Thirteen percent arose in schools and communities. Noroviruses are the leading cause of foodborne disease outbreaks in the United States.

The preferred diagnostic method for diagnosis of norovirus infection is reverse transcriptase (RT)-PCR of stool or vomitus. While some laboratories offer such testing, there is no FDA-approved commercial kit for this purpose.

CDC recommendations for investigation and response to norovirus outbreaks in any setting, including acute and long-term care facilities, are as follows:

- Initiate investigations promptly, including collection of clinical and epidemiologic information, to help identify predominant mode of transmission and possible source.
- Promote good hand hygiene, including frequent washing with soap and running water for a minimum of 20 seconds. If available, alcohol-based hand sanitizers (≥ 70% ethanol) can be used as an adjunct in between proper handwashings, but should not be considered a substitute for soap and water handwashing.
- Exclude ill staff in certain positions (e.g., food, child care, and patient care workers) until 48-72 hours after symptom resolution. In closed or institutional settings (e.g., long-term care facilities, hospitals, and cruise ships), isolate ill residents, patients, and passengers until 24-48 hours after symptom resolution. In licensed food establishments, approval from the local regulatory authority might be necessary before reinstating a food employee following a required exclusion.
- Reinforce effective preventive controls and employee practices (e.g., elimination of bare-hand contact with ready-to-eat foods and proper cleaning and sanitizing of equipment and surfaces).
- After initial cleaning to remove soiling, disinfect potentially contaminated environmental surfaces using a chlorine bleach solution with a concentration of 1,000-5,000 ppm (1:50-1:10 dilution of household bleach [5.25%]) or other Environmental Protection Agency (EPA)-approved disinfectant. In health care settings, cleaning products and disinfectants should be EPA-registered and have label claims for use in health care; personnel performing environmental services should adhere to the manufacturer's instructions for dilution, application, and contact time.
- Collect whole stool specimens from at least five persons during the acute phase of illness (≤ 72 hours from onset) for diagnosis by TaqMan-based real-time RT-PCR, perform genotyping on norovirus-positive stool specimens, and report results to CDC via CaliciNet (CDC's electronic norovirus outbreak surveillance network).
- Report all outbreaks of acute gastroenteritis to state and local health departments, in accordance with local regulations, and to the CDC via the National Outbreak Reporting System. ■

ABSTRACT & COMMENTARY

Orbital Cellulitis in Children

By Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: A retrospective review of 94 children treated at a children's hospital between 2004 and 2009 for orbital infections was performed. A true pathogen was recovered from 31% of patients. Streptococcus anginosus was most commonly identified (14 patients). Staphylococcus aureus was present in 8 patients with methicillin-resistant Staphylococcus aureus (MRSA) in 1 case. Other pathogens encountered in > 1 case included Group A streptococci, Streptococcus pneumoniae, Haemophilus influenzae, and Fusobacterium species.

SOURCE: Seltz LB, et al. Microbiology and antibiotic management of orbital cellulitis. Pediatrics 2011;127:e566-e572.

A retrospective chart review of all patients admitted to a tertiary care children's hospital in Denver between 2004 and 2009 with orbital infections confirmed by CT scan was performed. Patients with preseptal cellulitis, preceding surgery or trauma, malignancy, and immunodeficiency were excluded. Ninety-four children's records met criteria for inclusion. The median age of children in the series was 72 months. Ophthalmoplegia and proptosis were documented in 48% and 38% of patients, respectively. Median hospital stay was 4 days.

A true pathogen was identified in 31% of patients. *Streptococcus anginosus* group was isolated in 14 patients, *Stapholococcus aureus* in 8 (including 1 with MRSA). Other pathogens present in ≥ 2 cases each included Group A streptococci, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Fusobacterium* species. Single cases of infection due to seven other pathogens were seen.

A variety of antibiotics were used in the inpatient setting to treat these infections, including ampicillin/sulbactam in 34% of cases, two- or three-drug combination therapy was used in 80% of patients, vancomycin was used in 36% of children with increasing frequency of vancomycin use observed between 2004 and 2008. Surgical procedures performed included sinus drainage procedures and drainage of subperiosteal and orbital abscesses. Isolation of a true pathogen was more common in patients who underwent surgery. Serious complications observed included residual visual impairment (3 patients), recurrent orbital cellulitis (1 patient), and death (1 patient, after presenting with meningitis, subdural empyema, and cerebral edema). Numerous antibiotic regimens were selected to be continued at the time of discharge from the hospital.

■ COMMENTARY

While retrospective studies have many obvious limitations, a large case series such as this from an excellent tertiary care children's hospital is a useful addition to the literature and should be helpful to clinicians who manage this common serious infection seen in children. Some obvious factors influenced the results of the study. One of these factors is the likelihood that pathogens such as *Streptococcus pneumoniae* (which are likely to be susceptible to empiric antibiotics) probably are under-represented in the series. However, notorious pus-forming pathogens like *Streptococcus anginosus/milleri* group organisms would seem to be more likely to cause serious infections, which would require surgical drainage and, therefore, yield a pathogen on culture. While only one microbiologically confirmed case of orbital cellulitis due to MRSA was seen, it is possible that several early cases of orbital cellulitis due to this pathogen may have been adequately treated with effective empiric antibiotics. It certainly seems prudent to continue to include coverage of MRSA in addition to streptococci, *Haemophilus influenzae*, and anaerobes when empiric antibiotics are chosen to treat this disease. ■

BRIEF REPORT

Once-Daily Pill Yields Higher ART Adherence

Study looked at marginalized populations

Even HIV-infected individuals who have the greatest challenges in adhering to their antiretroviral therapy (ART) can achieve high adherence on a regimen of one pill taken daily, research shows.

"When we looked at one pill taken once a day, adherence was just short of 90%," says **David Bangsberg**, MD, MPH, director of the Massachusetts General Hospital Center for Global Health and associate professor at Harvard Medical School in Cambridge, MA. Bangsberg was a lead author on the study, which was presented at the 2010 Conference on Retroviruses and Opportunistic Infections (CROI).[1]

The one pill, once-daily regimen consisted of a combination of efavirenz, emcitrabine, and tenofovir.[1]

The study looked at individuals recruited from single room occupancy (SRO) hotels, free meal programs, and homeless shelters. They were within 6 months of treatment initiation, and adherence was determined for 6 months using unannounced pill counts at usual places of residence.[1]

"This population had all the risk factors for poor adherence," he says. "Indeed, this is an exceptionally high level of adherence in any population."

A near 90% adherence rate is high by ART historical perspective, particularly for a population that is homeless and has drug use and depression issues, Bangsberg notes.

The high level of adherence on ART was associated with good rates of viral suppression.

"Therapy in 1996 was quite complex with 20 pills a day, and it has become much simpler and more potent now with the availability of once-daily, one pill treatment," he explains.

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Updates

By Carol A. Kemper, MD, FACP

Utility of Pneumococcal Urinary Antigen

SOURCE: Sordé R, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med 2011;171:166-172.

Community acquired pneumonia "bundles" often include the use of the pneumococcal urinary antigen assay, but how useful is it for streamlining antibacterial use?

Sordé and colleagues prospectively examined 474 sequential episodes of community-acquired pneumonia in 464 patients. A diagnosis was made in 269 (57%) cases; 171 (36%) were due to pneumococcus based on the results of cultures of blood (53), pleural fluid (5), and/or sputum (38), or exclusively by urinary antigen (75). Of those with a positive culture for *Streptococcus pneumoniae*, pneumococcal urinary antigen tests were obtained in 50, yielding 39 (78%) positive results. The sensitivity of the assay was therefore 78%, with a specificity of 96%, and a positive predictive value of 88.8%-96.5%.

The median time to obtaining a pneumococcal urinary antigen test result and physician modification of antibiotics was about 2 days, and occurred in 41 patients (8.6%). The use of the urinary antigen test helped to identify an additional 44% of pneumococcal pneumonia infections, providing further opportunity for antibiotic reduction. The concurrent use of the *Legionella pneumophila* urinary antigen test also identified 14 cases of legionella pneumonia — important information when rendering therapeutic decisions. ■

Histoplasmosis in Travelers

SOURCE: Buitrago MJ, et al. Histoplasmosis and paracoccidioidomycosis in a non-endemic area: A review of cases and diagnosis. J Travel Med 2010;18:26-33.

Twice in the past 2 years I've encountered pulmonary histoplasmosis in travelers returning from Central America (Mexico and Costa Rica), and both times the diagnosis proved challenging. One case, in particular, was a 60-year-old man who had traveled to Costa Rica for one week and then presented with fever, persistent dry cough, malaise, and complaints of memory loss. Only a biopsy of lung tissue confirmed the diagnosis of carcinoid tumor, bronchiolitis obliterans, and histoplasmosis (based on histopathology; cultures were negative).

These authors at the Spanish Mycology Reference Laboratory in Madrid, Spain, describe their experience with the laboratory detection of histoplasmosis and paracoccidioidomycosis (PCM) in returning travelers and immigrants, including the use of a novel PCR-based technique based on DNA amplification of the internal transcriber spacer region of *H. capsulatum* var. *capsulatum*, *H. capsulatum* var. *duboisii*, and *P. brasiliensis*. Precipitating antibodies were detected using immunodiffusion assay.

Since 2006, histoplasmosis was diagnosed in nine returning travelers and 30 immigrants; most had come from South America (83%), Africa, or both. The nine travelers had no underlying disease, and were diagnosed with probable histoplasmosis based on positive immunodiffusion test results. The organism was not cultured in any of these patients. RT-PCR was positive in five, including three of seven serum specimens, two of three lung biopsies, and one of one sputum specimen.

In contrast, all 30 immigrants were diagnosed with disseminated histoplasmosis; 97% of these were HIV-infected and the remaining patients had a hematologic malignancy. Of these, 97% were diagnosed with proven histoplasmosis based on a positive culture or visualization of the organism in tissue specimens; only one patient was diagnosed based on the results of RT-PCR alone. Immunodiffusion testing was performed in 20 patients, and was positive in eight (40%), whereas RT-PCR was positive in 24 of 27 patients tested (89%; this included plasma or serum, bone marrow biopsy, or other tissue biopsy). Three patients from Africa were found to have *H. capsulatum* var. *duboisii* based on RT-PCR results.

Six patients, all immigrants from South America, were diagnosed with PCM; all six had positive immunodiffusion assays for PCM (which were weakly positive in three), and all six had a positive RT-PCR of plasma or serum, bronchoalveolar lavage, lung biopsy, or other biopsy.

Pulmonary histoplasmosis should be suspected in any traveler returning from Central or South America with fever, headache, malaise, dry cough, and chest discomfort (especially if

they have visited caves), although confirming the diagnosis may be challenging. Immunodiffusion assays are helpful in many patients, but it may be necessary to obtain tissue. ■

HIV Transmission and Premastication of Food

SOURCE: Centers for Disease Control and Prevention. Premastication of food by caregivers of HIV-exposed children — nine U.S. sites, 2009-2010. Morb Mortal Wkly Rep 2011;60:273-275.

HIV transmission generally is not believed to occur from contact with saliva (it has been estimated that there is approximately one HIV particle in a gallon of saliva) although patients with dental or gingival disease may transmit virus through close contact, such as deep kissing or oral sex. Approximately 13% of pediatric HIV infection is believed to occur through mechanisms other than perinatal exposure. It was only recently discovered that transmission in three children had occurred because they were being fed food pre-chewed by their HIV-infected mothers. Prompted by this discovery, the Centers for Disease Control and Prevention (CDC) conducted a survey of pediatric HIV clinics at nine centers throughout the United States. These clinics included both HIV-infected and non-HIV-infected children born to HIV-infected mothers.

Caregivers of pediatric patients attending the clinics were surveyed regarding the practice of pre-chewing food fed to small children. Since children younger than 6 months are more likely to be bottle-fed, the survey focused on those 154 primary caregivers with children ≥ 6 months of age. Amazingly, 48 (31%) reported that they or someone in the household fed their child pre-chewed food; most (79%) of these were the biological HIV-positive mothers, and the rest were other members (possibly HIV-infected) of the household. Premastication was more common among younger mothers and non-Hispanic black women. Two-thirds of the respondents reported this was a common practice, and occurred at least once per week. Common reasons for this practice included the child wanted "adult food," they were afraid the child would "choke on real food," and because it was common practice in their family. Premastication may, in fact, be a part of certain cultures.

Based on these results, the CDC recommends that caregivers in pediatric HIV clinics be counseled about the risk of pre-chewing food for their young children. Other infections that may be transmitted through this practice include HSV, group A Strep, *Helicobacter pylori*, and other enteric pathogens — as well as syphilis *(see* Infectious Disease Alert, *May 2009)*. Syphilis has been reported in two infants as the result of transmission from the parent (or grandparent) with secondary syphilitic oral lesions.[1] ■

Reference

1. Zhou P, et al. Nonvenereal transmission of syphilis in infancy by mouth-to-mouth transfer of prechewed food. Sex Trans Dis 2009;36:216-217.

Hospital-Acquired Vibrations

SOURCE: Rothberg MB, et al. Phantom vibration syndrome among medical staff: A cross sectional survey. BMJ 2010;341:c6914.

Infectious diseases may be the most heavily curb-sided specialty *(see* Infectious Disease Alert, *November 2010)*. There are times when I am glued to the phone with "beeper paralysis," and check my pager "just in case." The term "phantom vibration" was first described in 2007 in a survey of cell phone behavior, where two-thirds of cell phone users described phantom rings. The term has become increasingly popular, moving on to the Net and Facebook.

Rothberg and colleagues wondered how often this phenomenon might affect medical personnel who carry cell phones and pagers. They conducted a survey of 176 hospital medical staff (including 160 attending physicians, residents, and medical students) who regularly carried a pager in hospital. Phantom vibrations occurred with 68% of cell phones users and 69% of those with pagers. The majority had been carrying their pagers for at least 1 month, and 99% used their device ≥ 6 hours per day; one-third used their device ≥ 12 hours per day. Nearly half (46%) received an average of five or more pages per hour, and nearly half (46%) indicated their maximum number of pages per hour was in the range of 11-15. One-fourth received a maximum of 15 or more calls or pages per hour.

Phantom vibrations occurred daily (13%), weekly (39%), or monthly (49%). Risk factors associated with phantom vibrations included younger age, being a resident or medical student, frequency of use, and keeping the device in a breast pocket. Most respondents agreed the sensation was not at all or "only a little" bothersome, but 2% found the sensation bothersome or "very bothersome" (worse than being paged?). Strategies to reduce the sensation included turning the device off or removing the pager — (!) — but moving it to another location sometimes helped.

Because younger age was more frequently associated with this phenomenon, the authors likened it to "new mom syndrome" (listening for the baby crying), but I imagine the hyperacute state (and, at times, sheer anxiety) of taking primary hospital call is more likely to trigger the sensation. ■

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"When we looked at adherence in the population receiving more complicated therapy we historically have seen adherence in the high 60s, low 70s."

HIV-infected individuals in the cohort receiving more complicated therapy had an adherence rate of about 70%, Bangsberg says.

Researchers recruited HIV patients who mostly were receiving routine care at publicly funded HIV clinics in the Tenderloin mission areas of San Francisco, Bangsberg says.

"With their permission and informed consent, we would go to their usual place of residence, sometimes an SRO or homeless shelter, sometimes on the street, and on a random day we would count their pills to see how many they had in their possession," Bangsberg says. "We did that every month for 6 months."

The study's results clearly demonstrate that excellent adherence results can be achieved with a single pill, once-daily ART regimen even among a challenging population that has many risk factors for poor adherence, Bangsberg says. ■

Reference

1. Bangsberg D, et al. A one-pill, once-daily fixed-dose combination of efavirenz, emcitrabine, and tenofovir disoproxil fumarate regimen is associated with higher unannounced pill count adherence than non-one-pill, once-daily regimens. Abstract presented at the 17th Conference on Retroviruses and Opportunistic Infections (CROI); Feb. 16-19, 2010, in San Francisco, CA. Abstract:1000.

CME Questions

1. Bedbugs:

a. are still sensitive to DDT.
b. are responsible for transmission of *Coxiella burnetti*.
c. produce an odor.
d. infest only humans.

2. Which of the following is recommended by the CDC as a possible therapy for *Chlamydia trachomatis* infection during pregnancy?

a. Doxycycline 100 mg twice daily for 7-10 days
b. Azithromycin 1,000 mg as a single dose
c. Moxifloxacin 400 mg daily for 7-10 days
d. Levofloxacin 500 mg daily for 7-10 days

3. Which of the following regarding norovirus is *correct?*

a. A single norovirus infection produces life-long immunity.
b. Peak fecal shedding occurs 2-5 days after symptom onset and stops as soon as symptoms resolve.
c. The infectious dose is approximately 100,000 viral particles.
d. It is the leading cause of foodborne outbreaks in the United States.

Answers: 1. c, 2. b 3. d.

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]

Chikungunya infections in the United States

New IDSA guidelines for treating uncomplicated UTIs in women

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.*

Apixaban and Rivaroxaban Near Approval for Nonvalvular AF

In this issue: Apixaban and rivaroxaban near approval for nonvalvular atrial fibrillation; fidaxomicin for *C. difficile* infections; guideline for intensive insulin therapy; and FDA Actions.

Dabigatran for stroke in patients with nonvalvular atrial fibrillation

Dabigatran, a direct thrombin inhibitor, recently was approved for prevention of stroke in patients with nonvalvular atrial fibrillation. The evidence for its benefit is strong enough that the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society recently upgraded their atrial fibrillation guidelines to include dabigatran (*Circulation* published online February 14, 2011). Meanwhile, the direct factor Xa inhibitor rivaroxaban is working its way through the FDA approval process for the same indication, with approval expected later this year. The latest player in the field is apixaban, also a direct factor Xa inhibitor. Apixaban was studied in a double-blind Phase 3 study of 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. Patients were randomized to receive apixaban 5 mg twice daily or aspirin 81-324 mg per day with a mean follow-up of 1.1 years. The primary outcome was occurrence of stroke or systemic embolism. The study was terminated early because of a clear benefit in favor of apixaban. There were 51 events (1.6 % per year) in the apixaban group vs 113 events (3.7% per year) in the aspirin group (hazard ratio with apixaban 0.45, 95% confidence interval 0.32-0.62; P < 0.001). The death rate was 3.5% in the apixaban group vs 4.4% in the aspirin group (P = 0.07). The rates of major bleeding or intracranial hemorrhage were similar; however, the risk of first hospitalization for cardiovascular causes was significantly lower with apixaban. The authors suggest that apixaban is more effective than aspirin. In indirect comparisons, apixaban is more effective than aspirin plus clopidogrel and at least as effective as warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation (*N Engl J Med* published online February 10, 2011). Apixaban is currently being studied head-to-head with warfarin in the ARISTOTLE trial. If the data from that trial looks favorable, it is likely that both apixaban and rivaroxaban also will be approved for this indication in the not-too-distant future. Dabigatran and apixaban are both dosed bid while rivaroxaban is a once-a-day drug. The extent to which these drugs gain general usage at the expense of warfarin in large part will be due to patient preference and cost. ■

Fidaxomicin for *C. difficile* infections

A new option may soon be availiable for treating *Clostridia difficile* infections. Fidaxomicin (not yet approved in this country) is a non-systemic (poorly absorbed) narrow spectrum macrolide antibiotic that is bacteriocidal against *C. difficile* infections. It recently was compared to vancomycin in a head-to-head Phase 3 noninferiority study of 629 adults. Patients with a positive stool toxin test to *C. difficile* were randomized to

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fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. The primary endpoint was clinical cure and the secondary endpoint was recurrence within 4 weeks and global cure (no recurrence). Fidaxomicin was noninferior to vancomycin in both the intention-to-treat (88.2% cure rate with fidaxomicin vs 85.8% with vancomycin) and per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients had recurrence with fidaxomicin in both groups (15.4% vs 25.3%, $P = 0.005$ intention-to-treat, and 13.3% vs 24.0%, $P = 0.004$ per protocol) although the lower rate of recurrence was in the less virulent strains. For the more virulent strains, the recurrence rate was about 25% for both drugs. Fidaxomicin was associated with a higher rate of hyperuricemia and elevated transaminases (*N Engl J Med* 2011;364:422-431). An accompanying editorial points out that the incidence and virulence of *C. difficile* infections is increasing at an alarming rate in this country. Fidaxomicin inhibits vegetative forms of *C. difficile* while preseving intestinal flora, a combination that holds promise, and if borne out "this new agent could become a recommended therapy for *C. difficile* infection" (*N Engl J Med* 2011;364:473-475). ■

Guideline for intensive insulin therapy

A guideline from the American College of Physicians (ACP) recommends against aggressively controlling blood glucose in hospitalized patients. Intensive insulin therapy (IIT) is no longer recommended for patients in intensive care units, regardless of whether they have diabetes. Specifically, the ACP recommends not using IIT to strictly control blood glucose or even normalized blood sugar in surgical ICU or medical ICU patients, and recommends a target blood glucose level of 140-200 mg/dL if insulin therapy is used. The recommendation is based on multiple studies that show no reduction in mortality with a blood glucose target of 80-180 mg/dL compared with higher targets using a variety of intensive insulin regimens. This includes treatment of patients with myocardial infarction, stroke, acute brain injury, or those under perioperative care. The guideline further recommends that avoiding targets less than 140 mg/dL should be a priority because harm is likely with lower blood glucose targets (*Ann Intern Med* 2011;154:260-267).

FDA actions

The FDA is warning against the use of terbutaline for prevention or prolonged treatment of preterm labor in pregnant women. The drug, which is approved for treatment of asthma, has been used off label for treatment of preterm labor and uterine hyperstimulation; however, the agency has received postmarketing reports of serious adverse reactions, including heart problems, and even maternal deaths, associated with the drug. The FDA has added a Boxed Warning and Contraindication to the labeling of the drug warning against these uses. This extends to both the IV and oral forms of terbutaline.

The FDA has approved hydroxyprogesterone caporate injection to reduce the risk of preterm delivery before 37 weeks of pregnancy in a pregnant woman with a history of at least one spontaneous preterm birth. The drug is not intended for use in women with a multiple pregnancy, such as a twin pregnancy, or other risk factors for preterm birth. The drug was approved under the FDA's accelerated approval regulations, and, as such, additional studies will be required after approval to show that the drug does indeed have clinical benefit. Hydroxyprogesterone caproate is given once a week by injection into the hip beginning at week 16 and no later than week 21. The drug is marketed by Hologic Inc. as Makena.

The FDA has issued a drug safety alert regarding the risk of serious liver injury with dronedarone (Multaq). The drug — which is approved for prevention of atrial fibrillation/flutter — has been associated with multiple cases of severe liver injury, including two cases that required liver transplantation. Dronedarone previously was found to double the risk of death in patients with severe heart failure and was approved with a REMS designed to prevent its use in that patient population. Physicians are reminded to advise patients to contact a health care professional immediately with any signs of hepatic injury or toxicity. All patients on dronedarone should get periodic hepatic serum enzymes especially during the first 6 months of therapy.

The FDA has approved a new treatment for head lice. Spinosad is an insecticide originally derived from a naturally occurring soil bacterium. The 0.9% topical suspension was shown to be effective in two Phase 3 active-control, randomized studies in which 86% of patients treated with the active drug were lice free after 14 days compared to 44% of controls. The product should not be used in children under 6 months of age because it contains benzyl alcohol. Spinosad is applied as a single 10-minute application which may be repeated in one week if lice are seen. It will be marketed by ParaPro LLC as Natroba. ■