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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

Diagnosis and Treatment of Influenza: Rapid Tests and Antiviral Options

By Stan Deresinski, MD, FACP, FIDSA

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

SOURCES: Chartrand C, et al. Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med* 2012; 156:500-11.
Hsu J, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med* 2012; 156:512-24.

Recent ACIP recommendations for the management of influenza virus infections include: "1) early antiviral treatment of suspected or confirmed influenza among persons with severe influenza (e.g., those who have severe, complicated, or progressive illness or who require hospitalization); 2) early antiviral treatment of suspected or confirmed influenza among persons at higher risk for influenza complications; and 3) either oseltamivir or zanamivir for persons with influenza caused by 2009 H1N1 virus, influenza A (H3N2) virus, or influenza B virus or when the influenza virus type or influenza A virus subtype is unknown; 4) oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated; 5) local influenza testing and influenza surveillance data, when available, to help guide treatment decisions; and 6) consideration of antiviral treatment for outpatients with confirmed or suspected influenza who do not have known risk factors for severe illness, if treatment can be initiated within 48 hours of illness onset."[1]

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Infectious Disease [ALERT]

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Editorial E-Mail:
gary.evans@ahcmedia.com

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These recommendations raise at least two important questions: how is the diagnosis of influenza virus infection best made; and what is the evidence that current antiviral therapies are effective? The role of point-of-care antigen detection tests was addressed in a metanalysis by Chartrand and colleagues. These investigators examined 159 studies involving 26 rapid immunochromatographic diagnostic tests (RIDT) designed to detect influenza antigens. The pooled specificity of the tests was excellent (98.2%; 95% CI, 97.5% to 98.7%), as was the positive likelihood ratio (38.1). In contrast, however, the sensitivity (62.3%; 95% CI, 57.9% to 66.6%), and negative likelihood ratio (0.38) were each unacceptably low. The sensitivity was higher in children than adults and higher for influenza A than for influenza B.

Having made the diagnosis, how effective are currently available antivirals? Hsu and colleagues examined 74 observational studies that compared single antiviral therapy with no therapy or with other antiviral therapy, or that had no comparator, in patients with influenza or influenza-like illness. Their metaanalysis was designed to determine whether the available evidence demonstrated benefit from therapy with amantadine, rimantidine, oseltamivir, or inhaled zanamivir of patients with influenza or influenza-like illness. The included studies were, in general, not of the highest quality and were generally limited by potential confounding, selection bias, and publication bias. There was low to very low confidence in the estimates of effect. The investigators, nonetheless, concluded that oseltamivir "may provide net benefit by reducing mortality and the duration of symptoms and complications from influenza". Thus, when compared to no treatment, the odds ratio (OR) for mortality for oseltamivir was 0.23 among high risk patients, while that for need of hospitalization was 0.29. Oseltamivir was associated with a mean reduction in duration of symptoms of 33 hours. Zanamavir administered by inhalation was associated with reduced hospitalizations and a mean 23 hour reduction in duration of symptoms, but with a greater number of complications compared to no treatment. Analysis of direct comparisons of oseltamivir to zanamivir found no apparent differences in outcomes. No study included in this metaanalysis involved the use of rimantidine and a single study suggested that amantadine therapy was associated with a reduction in mortality and pneumonia due to influenza A.

■ COMMENTARY

These valuable metanalyses represent an enormous amount of work and, to the clinician, there conclusions may be considered somewhat disappointing, albeit not surprising. The conclusions one can reach from these analyses are several. First, in agreement with previous CDC statements, RIDTs can "rule in", but they cannot rule out the presence of influenza virus infection. The gold standard for influenza diagnosis is now RT-PCR and, in circumstances where its use is feasible, this method of testing should be made available to the clinician. Second, treatment with either oseltamivir or inhaled zanamivir is likely to provide clinical benefit to patients with influenza infection caused by susceptible virus. The potential benefit is maximized by early initiation of therapy.

A more general conclusion was articulated by Hsu and colleagues: "We need high-quality evidence from randomized trials that address patient-important outcomes and include

hospitalized patients with influenza". They point out that such trials will require collaboration among organizations caring for large numbers of patients together with preparedness to initiate such trials when epidemic infection is first recognized. ■

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Lessons from the 2009 Pandemic Flu Experience

By Stan Deresinski, MD, FACP, FIDSA,

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

SYNOPSIS: Hospitalized patients infected with the 2009 pandemic influenza virus who developed pneumonia frequently required intensive care, mechanical ventilation, and many died.

SOURCE: Jain S, et al; for the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Influenza-associated pneumonia among hospitalized patients with 2009 pandemic influenza A (H1N1) Virus — United States, 2009. *Clin Infect Dis* 2012; 54:1221-1229.

Jain and colleagues at the U.S. CDC evaluated the characteristics of 195 hospitalized patients with laboratory-confirmed influenza influenza A pdm09 (pH1N1) infection who had pneumonia, comparing them to hospitalized flu patients without pneumonia. Those with pneumonia were more likely to have been ill for >2 days prior to hospitalization and to have a preexisting neurological condition, but less likely to have other underlying medical conditions, including asthma or chronic obstructive lung disease.

Admission white blood cell counts were normal in one-half of those with pneumonia while leukopenia and leukocytosis were each present in one-fourth. Bacterial infection was diagnosed in 3 patients without and 13 patients with pneumonia (including 7 patients with positive blood cultures - 5 with Staphylococus aureus). Two of the 3 bacteria-infected patients without pneumonia were bacteremic, both with *S. aureus*. Approximately four-fifths of patients with and without pneumonia received antiviral therapy, most often (91%) oseltamivir, but those with pneumonia were less likely to have received antiviral therapy within 48 hours of illness onset. Patients with pneumonia were significantly more likely than patients without pneumonia to receive antibiotics (93% vs. 67%). Approximately one-half of pneumonia patients were admitted to an intensive care unit compared to one-sixth of those without evident lower respiratory tract infection. Mechanical ventilation was required in 39% of pneumonia patients; 34 (17%) of the patients with pneumonia died.

The pH1N1 virus was resistant to amantadine and rimantidine, leaving orally administered oseltamivir and inhaled zanamivir (neither of which had received FDA approval for complicated infection) as the only readily available therapeutic options. The lack of a commercially available drug that could be parenterally administered was believed to be problematic for at least some critically ill patients. Two investigational products became available — peramivir, which was provided under an Emergency Use Authorization (EUA) through the CDC, and a formulation of zanamivir (which maintains activity against viruses containing the H275Y mutation) — each suitable for intravenous administration associated with oseltamivir resistance.

The EUA required that all medication errors, selected adverse events (AE), serious adverse events, and deaths occurring during peramivir therapy be reported to the FDA within 7 calendar days. Sorbello and colleagues reviewed reports on 344 patients of the "at least" 1274 who were provided peramivir.[1,2] The most frequently reported serious AEs were death (15%), H1N1 influenza (8%), respiratory failure (8%), acute renal failure (7%), and acute respiratory distress syndrome (7%). Skin

rash was the only AE attributed to peramivir.

No assessment of the efficacy of peramivir could be made — a critical shortcoming of the emergency system (one of many). As pointed out in an accompanying editorial by Andrew Pavia, it is essential that better planning for data collection in similar situations be put in place before the event.[3] This, together with the development of a funded national collaborative clinical trials system, would go a long way toward resolving some of the collosal shortcomings in accurate therapeutic data in the field of infectious diseases. ■

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ABSTRACT & COMMENTARY

Staphylococcus aureus Virulence — how the Alpha Hemolysin Damages the Host

By Dean L. Winslow, MD, FACP, FIDSA

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

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Staphylococcal a-hemolysin (Hla) is a major virulence factor in *S.aureus* pneumonia. It activates the nucleotide-binding domain and leucine-rich repeat containing gene family, pyrin domain containing 3 (NLRP3) inflammasome inducing production of IL-1B and programmed cell death.

SOURCE: Kebaier C, et al. *Staphylococcus aureus* a-hemolysin mediates virulence in a murine model of severe pneumonia through activation of the NLRP3 inflammasome. *Jrl Infect Dis* 2012; 205(5): 807-17.

A wild type Newman strain of *S.aureus* and the hemolysin-deficient Newman strain hla::erm were studied in wild-type mice and Nlrp3-/- and IL1r1-/- mice. In addition, pyrogen-free purified hemolysin was used in several intratracheal challenge experiments. An established murine pneumonia model was employed using viable *S.aureus*, heat-killed *S.aureus* (HKSA) or hemolysin. Bronchoalveolar lavage (BAL) with determination of cell counts in BAL fluid, lung mechanics and histology were all assessed.

Heat-killed *S. aureus*, Hla, and HKSA+Hla did not induce IL-1 secretion in Nlrp3-/- mice. In contrast, Hla with or without HKSA induced high levels of IL-1 in wild type, but not in Nlrp3-/- mice. In a similar fashion, the histology of lungs in wild type mice challenged with HKSA+Hla showed marked neutrophil infiltration, vasculitis, vascular extravasation, epithelial sloughing and necrosis whereas histopathologic changes seen in similarly-challenged Nlrp3-/- mice were minimal. At 60 hours 80% of challenged Nlrp3-/- mice survived compared to only 30% of wild type mice.

In mice challenged with live *S. aureus* wild type Newman strain, mortality was higher in the wild type mice than it was in the Nlrp3-/- mice. Pulmonary function abnormalities were more severe in wild type surviving mice treated with vancomycin than observed in Nlrp3-/- mice. These differential effects were not related to *S. aureus* burden since *S. aureus* CFU/mL in BAL fluid were the same in wild type and Nlrp3-/- mice. As in the studies done with HKSA and HKSA+Hla, mortality and histopathological abnormalities were correlated with IL-1 and neutrophil levels in BAL fluid, but not with TNF in BAL fluid.

In mice challenged with hemolysin-deficient *S. aureus* there were no differences in neutrophil counts in BAL fluid in wild type vs. NLRP3-/- mice. In IL1r1-/- mice challenged with live *S.aureus* mortality was indistinguishable from that seen in wild type mice. Finally, experiments in CD11b+ cells, hemolysin induced NLRP3-dependent programmed necrosis in these cells as shown by release of the marker HMGB1.

■ COMMENTARY

All *S.aureus* produce secreted exotoxins including the cytolysins a-hemolysin, hemolysin, and bicomponent leukocidins.[1] Moreover, a-hemolysin has emerged as a key virulence factor in a murine model of *S. aureus* necrotizing pneumonia.[2] Purified hemolysin has also been shown to induce pulmonary inflammation in rats and rabbits.[3-5]

The NLRP3 inflammasome is signaling complex which activates procaspase-1, processing and secretion of IL-1B and IL-18, and the initiation of programmed cell necrosis. The NLRP3 inflammasome is activated in response to a number of pathogen-derived molecules and *S. aureus* hemolysin has recently been shown to induce NLRP3-mediated signaling in cultured cells.[6]

The elegant studies reported in this paper conclusively demonstrate that hemolysin almost certainly causes pulmonary damage through activation of NLRP3 inflammasome-mediated signaling and that this effect is independent of IL-1 expression. While mice lacking NLRP3 are not completely protected from hemolysin-producing *S. aureus* this suggests that hemolysin promotes virulence through both NLRP3-dependent and NLRP3-independent mechanisms. The authors postulate that targeting the NLRP3 inflammasome might someday be a potential therapeutic strategy in not only *S. aureus* pneumonia, but also in bacterial pneumonias due to other pathogens including *Streptococcus pneumoniae* in which pore-forming toxins including pneumolysin have also been shown to activate NLRP3 signaling. ■

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Streptococcus suis a Cause of Human Meningitis: Another Emerging Pig Pathogen

By Ellen Jo Baron, Ph.D., D(ABMM)

Professor Emerita, Stanford University School of Medicine
Director of Medical Affairs, Cepheid

Dr. Baron is Secretary-Treasurer of the NGO Diagnostic Microbiology Development Program (www.dmdp.org)

SYNOPSIS: The number of cases of pig-associated meningitis and sepsis caused by *Streptococcus suis* has been increasing dramatically in Southeast Asia, with recent increases seen also in Spain and UK. The initial diagnosis is often incorrectly determined to be *Streptococcus pneumoniae*. One particular clone, Sequence Type 1, is responsible for much of this recent expansion. In contrast to *S. pneumoniae*, ceftriaxone resistance is not uncommon with this species. Several cases have been reported in the U.S. and new reports of first cases (Korea; Cambodia) highlight the growing recognition of this syndrome.

SOURCES: Sekizaki, T. *Streptococcus suis:* An Emerging Biothreat. *Jrl Disaster Research* 2012;7:303-312.
Choi, S.M. et al. Meningitis Caused by *Streptococcus suis:* Case Report and Review of the Literature. *Jrl Clin Neurol* 2012; 8:79-82.

In addition to increasing the risk of acquiring swine flu, kissing pigs could now be associated with another serious disease. *Streptococcus suis* meningitis is considered an emerging infectious disease, although cases of systemic infection have been described since 1954 in veterinarians. The first human meningitis cases other than in veterinarians were reported in Denmark in 1968, and a 2009 review noted that published cases worldwide increased from slightly more than 400 in 2007 to >700 cases in just 2 years.[1] Perhaps it is still considered emerging because we in the U.S. are just discovering it. The first case report in a U.S. patient was in 2006 and a second case from a California hospital was described in 2008.[2-3] Only one additional case has been reported in the U.S.[4] In fact, it is possible that microbiology laboratories may be failing to identify *S. suis*, calling it "viridans streptococcus," which may suggest that it is a contaminant rather than a pathogen in the cerebral spinal fluid or the blood. To confuse unfamiliar microbiologists even more, the isolate may be positive for Lancefield type D, a hallmark of both enterococci and viridans streptococcal strains in the *S. bovis* family.

My first encounter with the organism was when the rural hospital microbiology laboratory for which I consult (and which is supported by the NGO Diagnostic Microbiology Development Project) in Kampong Cham, Cambodia, reported a viridans streptococcus from a woman patient with meningitis. I read the microbiology report: "Gram positive cocci in pairs and short chains, catalase negative, alpha-hemolytic colonies on sheep blood agar, bile soluble, and optochin resistant" and told the laboratory technician that she must have made a mistake. I said, "Viridans streptococci do not cause meningitis, so this must be *S. pneumoniae* and your optochin disk must have expired and lost potency."

Readers may remember from medical school training that the antimicrobial compound optochin should inhibit *S. pneumoniae* and thus display a rather large zone of inhibition. *S. pneumoniae* are soluble in sodium deoxycholate (bile), a usually fail-safe rapid test. In addition, because the isolate was intermediate for ceftriaxone, another anomalous result, it was sent to the Naval Medical Research Unit (NAMRU-2) in Phnom Penh for confirmatory testing.

To my surprise, an API 20 Strep strip (abbreviated biochemical test panel) and, eventually, molecular sequencing identified the strain as *Streptococcus suis*. Based on the Gram stain result, the patient's regimen was changed from the original anti-malarial empiric therapy to penicillin, and 5 days later she left the hospital in relatively good condition. This was the first identification of this species in Cambodia, although nearby Vietnam had been experiencing outbreaks for years.[5] In fact, S. suis is the most common cause of meningitis in Vietnam. Virtually all cases subsequently seen in Cambodia (our laboratories are up to around 20) and those in Southeast Asia, Europe, and the few reported in the U.S. are associated with exposure to pigs. Patients have eaten pork, handled sick pigs or worked with pork meat. The first case from Korea was reported this year although the patient had no known pig exposure.[6] An unusual risk factor is a practice seen only among a few young Chinese men, eating raw pig liver and kidney as a proof of manliness. This reminds me of a recent report about 2 young men from Wyoming who acquired *Campylobacter* enteritis after castrating lambs with their teeth.[7] A few of the lambs were said to have diarrhea. Don't ask.

In the U.S. *S. suis* disease is most likely to be seen in patients who have recently visited Asia and had close contact with pigs or eaten undercooked pork. *S. suis* is an important cause of infection in pigs and piglets, but it is usually carried asymptomatically in the oropharynx. Although rates of colonization among pigs may reach 80% (50% in Japan), only a small proportion of pigs and piglets become ill.[8] Pigs carry many serotypes but almost all human infections worldwide are caused by serotype 2. In addition to pigs, other animals including cattle, deer, horses, cats, and dogs, can carry the organism asymptomatically.

A virulence factor associated with this serotype and apparently less common in pig strains than in human strains is the polysaccharide capsule of serotype 2. Drug resistance is carried on integrative conjugative elements (ICEs). It is postulated that massive use of antibiotics

in the livestock industry contributes to the acquisition and spread of the ICEs.[9] Similarly, *S. suis* — with its easily mobile genetic elements — may be the source of resistance genes in more common human streptococcal pathogens, another illustration of unintended consequences of the animal husbandry industry in the U.S. Multilocus sequence typing (MLST) is the major tool used to track the epidemiology of *S. suis*. Among human isolates, MLST sequence type 1 (ST1) is most common. Independent of the sequence type, the serotype 2 capsule seems to be the major virulence factor; mutations in the gene for the capsule are avirulent.

Human disease may present with fever, headache, dizziness, nausea, vomiting, nuchal rigidity, and a unique symptom — hearing loss. As many as 66% of patients may exhibit this finding, many of whom do not ever recover full hearing capacity. CSF has all the signs of meningitis, and organisms are often seen on direct Gram stain. Organisms are usually susceptible to penicillin, but they variable susceptibilities for tetracycline (many are resistant), macrolides, clindamycin, and now a few are intermediate to third generation cephalosporins. Strains resistant to other beta-lactams, trimethoprim-sulfa, aminoglycosides, chloramphenicol, and fluoroquinolones have been reported. A large outbreak in China that occurred in 2005 heralded the new finding of a toxic shock-like syndrome associated with *S. suis* rather than the regular presentation of meningitis. All cases were due to a single ribotype which was the ST7 MLST type. This outbreak, with a total of 215 cases and 39 deaths (within a median of 25 hours), started with goat exposure, not pigs, although pig-associated cases occurred later.[10]

S. suis meningitis and potentially toxic shock syndrome may increase in the U.S. with the increasing globalization of our food sources and our human population. Clinicians and microbiologists should be aware that patients with meningitis — especially associated with hearing loss — seem to yield only "viridans streptococci" from their CSF cultures. ■

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ABSTRACT & COMMENTARY

Iron Deficiency Protects against Severe Malaria

By Dean L. Winslow, MD, FACP, FIDSA,

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

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: 785 Tanzanian children living in an area of intense malaria transmission were enrolled at birth and monitored for malaria parasitemia until age 3. Iron deficiency (ID) at routine visits decreased the odds of parasitemia and severe malaria as well as all-cause mortality.

SOURCE: Gwamaka M, et al. Iron deficiency protects against severe Plasmodium falciparum malaria and death in young children. *CID* 2012; 54: 1137-44.

785 Tanzanian children living in an area of high malaria endemicity were intensely monitored for parasitemia and other illness from birth to 3 years of age. The degree of parasitemia was determined by number of parasites/200 WBC's on thick smear. Severe malaria was defined by WHO criteria. Iron deficiency was defined as ferritin concentration < 30 ng/mL when CRP was < 8.2 ug/mL or ferritin < 70 ng/mL when CRP was > 8.2 ug/mL. Iron deficiency at well-child visits decreased the odds of subsequent parasitemia (23% decrease) and severe malaria (38% decrease). When sick visits were also included in the analysis, iron deficiency was associated with a reduced prevalence of parasitemia, hyperparasitemia and severe malaria.

■ COMMENTARY

Both malaria and iron deficiency are common in sub-Saharan Africa. While malaria and diarrheal disease are the leading causes of mortality in young children in sub-Saharan Africa, iron deficiency in children is associated with impaired cognition, motor development, growth velocity and anorexia in addition to anemia. International guidelines currently recommend iron and folic acid supplementation in children < 2 years of age. However, children in a malaria-endemic region of Tanzania randomized to receive iron supplementation suffered from 15% increased all-cause mortality.[1] This study is of great interest since it specifically addresses malaria outcomes in a population of children from a malaria-endemic region who did not generally receive iron supplementation. From the standpoint of pathogenesis the results of this study are intriguing, yet it is unclear whether iron deficiency limits parasite density due to parasite or host-specific effects. Malaria parasites acquire iron through a transferrin-independent pathway and iron chelation reduces parasite growth.[2,3] In the host, iron chelation increases cellular nitric oxide (NO) production and parasite killing in cell culture.[4] Iron has also been shown to inhibit NO synthase (iNOS), therefore iron supplementation may impair iNOS-mediated macrophage-mediated cytotoxicity against malaria parasites.

These data show that interventional studies are needed which are designed to ascertain the benefits and risks of iron supplementation in children in malaria-endemic regions, but only in conjunction with effective malaria control measures. ■

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Conjugate Pneumococcal Vaccine and Adults

By Stan Deresinski, MD, FACP, FIDSA,

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

SYNOPSIS: While Prevnar 13 has received FDA approval for use in adults aged 50 years and older, the CDC recommends continued use of the 23-valent polysaccharide pneumococcal vaccine until further information becomes available.

SOURCE: CDC. Licensure of 13-valent pneumococcal conjugate vaccine for adults aged 50 years and older. *MMWR* 2010; 59:1102-6.

Prevnar 13 (PCV13), a 13-valent pneumococcal conjugate vaccine, which had been available for pediatric use since 2010, was approved at the end of 2011 by the FDA for the prevention of pneumonia and invasive disease caused by included serotypes in adults 50 years of age and older. Although not yet recommended by the Advisory Committee on Immunization Practices (ACIP), PCV13 is available for use among adults in this age group.

This approval was not based on a demonstration of protective efficacy but rather on the demonstration of immunogenicity comparable to that observed with the 23-valent pneumococcal vaccine, Pneumovax 23. Confounding this approach is that, while it is agreed that the latter is protective against invasive pneumococcal disease, a consensus regarding its ability to prevent nonbacteremic pneumococcal pneumonia is lacking. Furthermore, the antibody response that correlates with protection remains unknown. PCV13 serotypes currently account for approximately one third of cases of invasive pneumococcal disease among adults aged 65 years and older. In addition, 11 serotypes that account for 25% of invasive pneumococcal disease cases in adults aged 65 years and older are included in PCV23 but not in PCV13. Thus, there remains a degree of uncertainty regarding the efficacy of PCV13 in adults. However, the ability to prevent pneumococcal pneumonia is currently being evaluated in a trial involving 85,000 individuals aged 65 years and older who had never received PPSV23 in the Netherlands.

The availability of PCV13 for adults 50 years of age and older has raised the question of whether clinicians should switch to its use in place of PCV23, not only in the outpatient setting, but also as part of obligatory vaccination of targeted inpatients. The following is the current recommendation:

"ACIP will continue to review evidence as it becomes available to guide development of a recommendation regarding routine use of PCV13 in adults aged 50 years and older. In the meantime, health-care providers should continue to administer PPSV23 in accordance with current recommendations." ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

HIV Risk Triples in Women with an STD

1. Mlisana K, et al. Symptomatic vaginal discharge is a poor predictor of sexually transmitted infections and genital tract inflammation in high-risk women in South Africa. *J Infect Dis* 2012;206:6-14.

2. Classical sexually transmitted diseases drive the spread of HIV-1: Back to the future. *J Infect Dis* 2012;206:1-2.

Studies of stable, heterosexually active HIV/non-HIV discordant couples demonstrate a favorably low risk of HIV transmission (estimated at 1/500 to 1/1000 episodes of coitus, depending on various factors). I find myself counseling discordant couples with the occasional condom breakage that the risk of HIV transmission is reassuringly low. Some couples have even taken advantage of this low risk, successfully risking pregnancy without transmission. So why is there an estimated 50,000 new cases of HIV occurring in the United States every year? Is there that much sex occurring out there?

Mlisana and colleagues shed light on an uncomfortable reality *(see the lead article and accompanying editorial)*. Most cases of HIV are not occurring in otherwise healthy individuals in a stable discordant relationship. And the risk of HIV acquisition is much greater than previously recognized for a woman with an STD or cervicovaginal inflammation, even in the absence of vaginal discharge or STD symptoms.

They prospectively followed 242 South African non-HIV-infected women at high risk for HIV infection, examining them every 6 months for

2 years for the presence of vaginal discharge, STDs, cervical inflammation, and the acquisition of HIV. The women were described as having a single, stable sexual partner (33%) or multiple stable partners (57%), although additional questions revealed that at least 95% reported at least one casual sex partner in the previous 3 months, and 79% described themselves as sex workers. Regular 6-month evaluations consisted of serologies for syphilis and HIV, cervical and vaginal swabs for Bacterial vaginosis, DNA testing for gonorrhea and chlamydia trachomatis, and (in-house) PCR testing for HSV, trichomonas vaginalis, mycoplasma genitalum; as well as measurements of 42 cytokine concentrations in cervicovaginal secretions. Additional studies were performed if genital ulcers were visualized, including PCR testing for syphilis, chlamydia spp. including lymphogranuloma venereum strains, and Calymmatobacterium granulomatis.

Testing at entry to study revealed STDs in a number of the women, including trichomonas (20%), gonorrhea (5.4%), chlamydia (4.2%), and mycoplasma genitalum (1.2%). HSV-2 antibodies were present in 86%, and active HSV-2 shedding was present in 3.7%.

During the two-year follow-up, 204 were women were diagnosed with at least one STD, only 25 (12.3%) of which resulted in a symptomatic vaginal discharge. At the 6 and 12 month screening visit, respectively, 18.5% and 24% were diagnosed with one or more STDs. However, only 1.5% and 4.8% respectively, reported symptoms/vaginal discharge.

Twenty-eight women (11.6%) became HIV-infected during the 2-year study. The presence of an STD was associated with a 3-fold increased risk for HIV-infection. Among the STDs, gonorrhea, chlamydia and Mycoplasma genitalum were statistically associated with an increased risk of HIV transmission. In multivariate analysis, adjusting for various factors, gonorrhea remained significantly associated with a risk of acquiring HIV (> 7-fold unadjusted risk), presumably as the result of the significant cervical inflammation associated with this infection. HSV-2, bacterial vaginosis and vaginal discharge by itself were not statistically significant.

Sexually active sub-Saharan women are at significantly higher risk for acquiring HIV in the presence of an STD, especially gonorrhea, even if those infections are asymptomatic or do not result in clinical vaginal discharge. While aggressive screening and treatment for STDs may decrease this risk, these study authors found that even with routine 6 month screening and treatment, 11.6% of women nonetheless acquired HIV infection. ■

Reactivation of HBV with Chemotherapy

Lok ASF, et al. Reactivation of hepatitis B during immunosuppressive therapy: potentially fatal yet preventable. *Ann Intern Med* 2012;156:743-745.

Approximately 1 in 300 adults in the United States are infected with Hepatitis B virus (HBV) with a positive Hepatitis Bs Ag, and 1 in 20 may be seropositive for HBV core antibody/ seronegative for HBV surface antigen. With the increasing use of anti-TNF-alpha inhibitors and more potent chemotherapeutic agents with immunosuppressive potential, reactivation of HBV infection is a real risk in the oncology and rheumatology populations. HBV reactivation is especially a problem in persons with lymphoproliferative/ hematologic malignancy, but has also been reported in persons receiving chemotherapy for solid tumors, those receiving long-term corticosteroids, and those receiving anti-TNF alpha inhibitors. And yet, based on survey data, the CDC estimates that only 13% to 19% of oncologists routinely screen patients for HBV.

These authors reviewed 14 studies of HBV reactivation, including 2 randomized clinical trials, which included a total of 550 Hepatitis Bs ag-positive patients receiving chemotherapy. For those patients not receiving prophylactic antivirals, fully one-third (36.8%) had reactivation HBV infection, 13% developed liver failure and 5.5% died. Unfortunately, even if antiviral treatment is provided to these patients, the success rate is not good: severe hepatitis may still occur in 13% to 36% despite initiation of antiviral treatment. In contrast, the use of antiviral prophylaxis (e.g., lamivudine) can reduce the risk of reactivation HBV infection in patients with positive surface Ag by 79% to 100%.

While patients seropositive for HBV surface antigen are at the greatest risk for reactivation, data also suggest that Hep Bs ag-negative/Core Ab-positive persons are at risk for reactivation, especially if receiving rituximab or other anti-TNF alpha inhibitors. Rheumatologists and oncologists should screen their patients for Hepatitis Bs Ag and B core Ab (as well as a TB test and Strongyloides Ab in those at risk) and consider offering HBV antiviral prophylaxis to both groups of patients. ■

A Pox on You !

Viner K, et al. Transmission of varicella zoster virus from individuals with herpes zoster or varicella in school and day care settings. *J Infect Dis* 2012; 205: 1336-41.

Suspicions have previously been raised about the higher than expected risk of transmission of varicella zoster virus from patients with Herpes zoster (shingles) under ordinary circumstances. VZV has been detected in ventilation units used for patients hospitalized with zoster, suggesting that airborne virus is occasionally found in the rooms of patients with dermatomal zoster. Salivary samples for VZV DNA from patients with dermatomal zoster are frequently positive, and VZV DNA can be found in 18% of salivary samples at 2 weeks of antiviral therapy. Potentially infectious varicella virus was even found in the saliva of a young woman with prodromal pain who had not yet developed dermatomal lesions. Another report documented the occurrence of a small outbreak of varicella in a long-term healthcare facility, following a case of herpes zoster 15 days earlier. Laboratory investigation confirmed that 18 of 26 (69%) environmental samples taken from the bedframes, rooms, lockers, and community areas of the facility were PCR-positive for VZV identical to that isolated from 4 cases.

These reports demonstrate that patients with dermatomal zoster may be infectious in a nosocomial setting, especially to patients with a prior history of varicella with waning immunity. Virus may be shed or aerosolized from zoster lesions, and infectious virus may be present in the saliva of patients with active zoster.

Viner and colleagues examined the risk of acquisition of VZV from person with dermatomal zoster in schools and day care facilities in their community from 2003-2010.
They focused on cases of varicella occurring within 10-21 days of a reported case of dermatomal zoster or a sporadic case of varicella within the same facility. A sporadic case of varicella was defined as occurring >6 weeks after or at least 10 days before another case of varicella.
The cases were stratified based on vaccine status and disease severity. Tertiary cases occurring within 10-21 days of a secondary case were also included.

During the 8-year period of observation, 2296 cases of Herpes Zoster and varicella were reported by schools or day cares. Of these, 1648 were considered primary cases, including 1358 cases of sporadic varicella. For the HZ cases, 27 (9%) were associated with the occurrence of 84 secondary cases of varicella within the same institution; 70% of these were considered mild. In contrast, 15% of the sporadic cases of varicella were associated with the occurrence of 564 cases of secondary varicella within the same institution. About 72% of these were considered mild. Most of the children (>90%) with secondary varicella had previously received at least one dose of vaccine.

Thus the risk of secondary VZV infection appeared similar, regardless of whether the index case had dermatomal zoster or varicella. In addition, transmission from either a case of zoster or varicella similarly resulted in a single case of varicella about half the time, in 2-4 secondary cases about one-third the time, and outbreaks with multiple infections 14% of the time. One case of shingles was associated with 30 secondary varicella cases over a 3-month period at one facility; and, at another facility, a single case of chickenpox resulted in 35 secondary cases over a 7-month period.

Environmental samples collected from doorknobs, computers, and desks were positive for VZV DNA from 3 of 9 elementary schools surveyed.

The authors believe the gradual reduction in naturally occurring varicella infection as the result of pre-school vaccination is leaving an environmental niche for increased transmission from persons with dermatomal zoster. It is likely that this low-grade transmission has existed forever, resulting in natural re-priming of individuals with pre-existing immunity at low

risk for symptomatic re-infection — only now it is occurring in previously vaccinated children with obviously less robust immunity.

At a minimum, this represents a low cost approach to re-priming immunity at relatively low risk, in contrast to broad revaccination booster programs. All I know is that I am a whole lot more confident in my own naturally-acquired immunity. ■

CME INSTRUCTIONS

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

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

CME QUESTIONS

1. Which of the following is correct regarding commercial antigen tests for the detection of influenza virus in respiratory specimens?

A. They are sensitive but not specific.
B. They are specific but not sensitive.
C. They have a high negative predictive value.
D. Their sensitivity is higher in testing adults relative to children and in detecting influenza B than influenza A.

2. Which of the following is correct regarding *Streptococcus suis*?

A. It is beta-hemolytic.
B. It can cause a toxic shock-like syndrome.
C. It has never been identified in the U.S.
D. In most cases it is resistant to beta lactam antibiotics.

3. Which of the following is correct with regard to Prevnar 13, the 13-valent pneumococcal conjugate vaccine?

A. It has been approved for use by the FDA in adults 50 years of age and older.

B. It has been demonstrated in clinical trials to prevent non-bacteremic pneumococcal pneumonia in adults.
C. It has been recommended by the Advisory Committee on Immunization Practices (ACIP).
D. It contains antigens of pneumococcal serotypes that account for 90% invasive pneumococcal infections in adults 65 years of age and older.

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]

Guidelines for Improving Antiretroviral Adherence for Persons With HIV

Zinc as Adjunct Treatment in Infants with Probable Serious Bacterial Infection

Evaluation of the National 'Cleanyourhands' Campaign to Reduce *Staphylococcus aureus* bacteremia and *Clostridium difficile* infections in UK hospitals

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.*

Does Azithromycin Cause Cardiovascular Death?

In this issue: Azithromycin and cardiac risk; warfarin and heart failure; aspirin and VTE; effectiveness of long-acting contraceptives; and FDA actions.

New study finds increased risk

Is azithromycin proarrhythmic? Macrolide antibiotics are associated with an increased risk of sudden cardiac death, but azithromycin (Zithromax), the popular "Z pack" macrolide, has been considered safe. That may change based on the results of a new study from Vanderbilt. Researchers reviewed the records of patients in the Tennessee Medicaid cohort to detect an increased risk of death related to short-term cardiac effects of azithromycin and several control antibiotics. Patients with serious noncardiovascular illness and hospitalized patients were excluded. Over the study period, there were almost 350,000 patients who took azithromycin, 1.35 million patients who took amoxicillin, 265,000 patients who took ciprofloxacin, nearly 200,000 patients who took levofloxacin, and nearly 1.4 million control patients. Five days of therapy with azithromycin compared to no antibiotics significantly increased the risk of cardiovascular death (hazard ratio [HR] 2.88, confidence interval [CI], 1.79 to 4.63; $P < 0.001$) and death from any cause (HR 1.85; 95% CI, 1.25 to 2.75; $P = 0.002$). Use of amoxicillin was not associated with increased risk of death. Relative to amoxicillin patients, patients taking azithromycin were at 2.5 times higher risk of cardiovascular death and 2 times higher risk of death from any cause, although the absolute risk was low with an estimated 47 additional cardiovascular deaths per million courses. Patients at risk for cardiovascular disease were at higher risk, with an estimated 245 additional cardiovascular deaths per 1 million courses. Cardiovascular death risk was higher with azithromycin compared to ciprofloxacin, but the death rate from levofloxacin was roughly the same. The authors conclude that 5 days of azithromycin was associated with a small but absolute increased risk of cardiovascular death, which was most pronounced in patients with a high baseline risk for cardiovascular disease (*N Engl J Med* 2012;366:1881-1890). Soon after this study was published, the FDA issued a statement urging patients to continue taking azithromycin unless instructed otherwise by their health care professional. The FDA will review the results of the study and will communicate any new information on azithromycin, including the potential risk of QT interval prolongation, to health care professionals and the public. Health care professionals are urged to report any adverse effects related to the use of azithromycin to the FDA's MedWatch Safety program. ■

Warfarin doesn't prevent death

Warfarin is no more effective than aspirin in preventing mortality in patients with heart failure who are not in atrial fibrillation (AF), according to a new study. More than 2300 patients with a left ventricular ejection fraction less than 35% (average 25%) and a mean age of 61 years were randomized to warfarin with a target INR of 2.0-3.5 or

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.

aspirin 325 mg per day. The primary outcome was ischemic stroke, intracerebral hemorrhage, or death from any cause. Patients were followed for up to 6 years with a mean follow-up of 3.5 years. There was no difference in the primary outcome (7.47 events per 100 patient years for warfarin, 7.93 for aspirin; HR with warfarin 0.93, CI, 0.79 to 1.10, $P = 0.40$). Warfarin was associated with a significant reduction in the rate of ischemic stroke but was associated with a higher rate of hemorrhage. The authors conclude that among patients with heart failure who are in sinus rhythm, there was no difference in outcome between warfarin and aspirin, but note that since warfarin was associated with a lower risk of ischemic stroke, the choice between the two drugs should be individualized (*N Engl J Med* 2012;366:1859-1869). An accompanying editorial asks, "Could there be some patients with heart failure who would benefit from warfarin?" Those with AF, a history of cardioembolic stroke, history of left ventricular thrombus, and perhaps those with atherothrombotic coronary artery disease may benefit, but in general, warfarin cannot be recommended for patients with heart failure who are not in AF (*N Engl J Med* 2012;366:1936-1938). ■

Aspirin and venous thromboembolism

Aspirin may be protective in patients who have had an unprovoked venous thromboembolism (VTE) to prevent recurrence after they finish oral anticoagulant therapy. In a double-blind study, patients with first-ever unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment were randomly assigned to aspirin 100 mg daily or placebo for 2 years. The primary endpoint was recurrent VTE with major bleeding being the primary safety outcome. Recurrent VTE occurred in 6.6% of patients on aspirin and 11.2% of patients on placebo (HR 0.58; 95% CI, 0.36 to 0.93). One patient in each group had a major bleeding episode. The authors conclude that aspirin reduces the risk of recurrence in patients with unprovoked VTE after they have finished anticoagulant therapy, with no apparent increase in risk of major bleeding (*N Engl J Med* 2012;366:1959-1967). This study is important because about 20% of patients with unprovoked VTE have a recurrence within 2 years. It also shows that taking low-dose aspirin safely reduces that risk by nearly half. An accompanying editorial points out that a similar but larger study is currently ongoing in Australia and New Zealand with results due later this year (*N Engl J Med* 2012;366:2028-2030). ■

Long-acting contraceptives are better

Long-acting contraceptives, such as IUDs and implants, are up to 20 times more effective than oral contraceptives and other short-acting contraceptive methods, according to a new study. In a large, prospective cohort study, women participants were provided with the reversible contraception of their choice at no cost for 3 years. The endpoint was failure of long-acting reversible contraception (IUDs and implants) compared with commonly prescribed contraceptive methods, including oral contraceptive pills, transdermal patches, contraceptive vaginal rings, and depot medroxyprogesterone acetate injection (DMPA). In the nearly 7500 women participants, there were 334 unintended pregnancies. The failure rate among participants who used pills, patch, or ring was 4.55 per 100 participants years as compared with 0.27 among participants using long-acting reversible contraception (HR after adjustment for age, educational level, and history with respect to unintended pregnancy 21.8; 95% CI, 13.7 to 34.9). The rate for DMPA was also low at 0.22. Younger women (< 21 years) who used a short-acting contraceptive had a pregnancy rate almost twice as high as older participants. The pregnancy rate among women who used DMPA, an IUD, or implant were similarly low regardless of age. The authors conclude that the effectiveness of long-acting reversible contraception is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents or young woman (*N Engl J Med* 2012;366:1998-2007). This study not only points out the reliability of long-acting contraceptives, but also the surprisingly high failure rate of short-acting contaceptives, especially in young women. ■

FDA actions

In the biggest generic launch since last year's atorvastatin (Lipitor), the FDA has approved generic clopidogrel (Plavix). The popular antiplatelet drug, with sales of more than $9 billion last year, will be available from seven generic manufacturers in the 75 mg strength and four manufacturers in the 300 mg strengths. The immediate "multisource" status of the generic approval should result in dramatic cost reductions for patients, from an average of $200 per month to about $40 per month. The drug is approved for treatment of acute coronary syndrome and prevention of thrombotic events in patients who have had a recent myocardial infarction, recent stroke, or peripheral artery disease. ■