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Infectious Disease [ALERT]

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

Avian H7N9 Flu Emerging in China, U.S. Cases May Be Recent Travelers

By Stan Deresinski, MD, FACP, FIDSA

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

SOURCES: World Health Organization. Global Alert and Response. Human infection with avian influenza A (H7N9) virus in China – update. http://ow.ly/kdWMq

Centers for Disease Control and Prevention. CDC Health Advisory. Human infections with novel influenza A (H7N9) viruses. http://ow.ly/kdWVX

A novel avian influenza A virus, H7N9, had caused, as of 18 April 2013, 87 laboratory confirmed cases of human infection, with the first case having an onset of illness on February 19. H7N9 had never previously been demonstrated to infect any mammalian species. The cases occurred in 4 adjacent provinces of China: Henan, Jiangsu, Zhejiang, and Anhui, as well as in Shanghai Beijing municipalities. Shanghai and Zhejiang together have accounted 59 cases and 13 deaths.

The fact that infected avians generally appear well together with the recent observation of asymptomatic human infection complicates surveillance efforts.

To date, there has been no clear evidence of human-to-human transmission, although familial occurrence has been observed and hundreds of close contacts of confirmed cases are being closely monitored. Some cases have had no known direct contact with avians. The

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Editorial E-Mail:
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virus appears to be susceptible to neuraminidase inhibitors, but resistant to the adamantanes.

Other avian influenza viruses have recently caused human disease. The highly pathogenic avian influenza A (H7N3) virus in Jalisco, Mexico caused illness in 2 poultry workers in 2012. H5N1, a highly pathogenic avian virus, has caused human disease in Egypt and several Asian countries. Other novel viruses have been associated with swine contact as in 16 individuals who developed H3N2v infection in the U.S. in the summer of 2012.

Examination of the gene sequences of the first 3 isolated viruses indicate changes seen in viral strains with high virulence in mammals. The virus is a triple assortment with all genes of avian origin 1. As a "novel," i.e., a "non-human" virus, H7N9 has the potential to cause a pandemic in a virgin human population — if it acquires the capacity for facile human-to-human transmission.

China reported slaughtering 20,358 birds in response to detection of the virus in pigeons in the Huhai live bird market in Shanghai. The Centers for Disease Control and Prevention has started the process of making a seed virus in anticipation of the possible need for vaccine production.

The CDC can provide testing for novel influenza A (H7N9) virus infection, and is also developing a test kit for use by state laboratories. At this time, no human cases of H7N9 have been detected in the United States. Clinicians should consider the possibility of H7N9 virus infection in persons with respiratory illness who also meet either of the exposure criteria below:

- Patients with recent travel to countries where human cases of novel H7N9 virus infection have recently been detected, especially if there was recent direct or close contact with animals (such as wild birds, poultry, or pigs) or where H7N9 viruses are known to be circulating in animals. Currently, China is the only country that has recently reported novel H7N9 human cases.
- Patients who have had recent contact with confirmed human cases of infection with novel H7N9 virus.

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ABSTRACT & COMMENTARY

Infections may Play a Role in Cognitive Decline, Dementia

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH.

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

SOURCE: Katan M, et al. Infectious burden and cognitive function. *Neurology* 2013;80:1209-1215.

Do latent infections cause dementia? While certain chronic illnesses (e.g. peptic ulcer disease, Burkitt's lymphoma and cervical cancer) have known infectious etiologies, mainstream research has not elucidated a significant role for microbes in cognitive decline. But emerging data suggest an association between some viruses and bacteria and Alzheimer dementia (AD). Moreover, the detrimental neurocognitive effects of HIV infection are well established. Dementia represents an enormous financial burden on the healthcare system, comparable to heart disease and cancer.[1] Katan and colleagues present epidemiologic evidence of an association between infectious burden (IB) and dementia from a large multiethnic cohort.

The Northern Manhattan Study (NOMAS) was a multiethnic stroke-free cohort that enrolled 3,298 participants ≥ 40 years of age between 1993 and 2001. Of these, 1,625 subjects (65% women, mean age 69 years, 58% Hispanic) had serologic measurements taken for *Chlamydia pneumoniae*, Helicobacter pylori, cytomegalovirus, and herpes simplex virus type 1 and type 2. Cognitive status was assessed at baseline using the mini-mental state exam (MMSE) and then annually by a telephone interview. A subset also had the number of APOE*4 alleles (known to increase risk for AD) identified. IB was used as the main predictor, which was determined by the relationship of individual serologic test results to the risk of stroke using estimates from Cox proportional hazard models. In a post hoc analysis, the investigators created a viral burden index (VIB) and also tested its association with cognition in the same manner as the overall IB index.

The results of the study were that the IB index was higher in black and Hispanic subjects, those with less than a high school education, no alcohol intake, and without cardiac disease. Furthermore, the IB index was associated with greater odds of having MMSE ≤ 24 compared to MMSE > 24 (unadjusted odds ratio = 1.58). The effect of the IB index on MMSE did not differ by APOE genotype. The association between IB index and MMSE was prominent among subjects who were physically inactive, women, had Medicaid or no insurance, and had less than a high school education. However, no relation was found between IB and change in cognition over time based on the annual telephone interviews, either unadjusted or adjusted for demographics and risk factors (P = 0.13). Moreover, findings were similar with both the IB and VIB in that the VIB index was associated with MMSE ≤ 24 (adjusted odds ratio = 1.22; P = 0.04) but not with change over time during follow up interviews (P = 0.24).

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There were several limitations to the study. While prior research supports a possible role for several of the infections that were tested (i.e. CMV, HSV-1), it is possible that other common viruses, like Epstein-Barr virus, Hepatitis B and C, can also lead to cognitive decline, although this remains theoretical. Furthermore, the authors did not test for HIV and its potential impact on the cohort is unknown. Because of the cross-sectional nature of the study, definitive conclusions about the direction of the associations (i.e. which came first, the infection or the dementia) cannot be determined with certainty. It was not possible to examine the relationship between infections and specific forms of cognitive impairment, such as AD and vascular dementia. Testing for syphilis, a known infectious etiology of dementia in late illness, was not performed. Finally, the role of threshold effect on the study (i.e. the damage is already done so there is no further decline) may have reduced the ability to detect an association between IB and cognitive decline over time.

The microbe-dementia hypothesis is intriguing because it implies that dementia could be reversible with antimicrobial agents. If true, it would signify a major paradigm shift in our understanding of cognitive decline. The present study by Katan and colleagues extends previous findings of the association between chronic infections and cognitive decline. It is somewhat surprising that the IB index did not correlate with cognitive decline over time. As the authors hypothesized, this could be due to the relatively advanced stage of cognitive impairment at the time the subjects were enrolled, which would have limited the ability to detect further decline. The mechanism behind the association is uncertain but might be from the inflammatory response elicited by chronic infection. This inflammation, combined with other risk factors, then leads to atherosclerosis, subclinical stroke, and dementia. The close (essentially identical) correlation between the IB and VIB in the study

supports the notion that most of the effect on cognition is mediated by viral rather than bacterial infections.

Although the study showed an association between IB and cognitive performance, association does not always equal causality. As noted in an accompanying editorial, only a randomized controlled trial would be definitive.[2] Currently there are no published clinical trials in humans on treating AD with antimicrobials. In a recent study, investigators administered minocycline to transgenic mice predisposed to AD-like amyloid pathology.[3] They found the drug down-regulated inflammatory markers that correlated with a reduction in amyloid precursor protein levels and amyloid precursor protein-related products. Minocycline has known anti-inflammatory properties and most likely did not exert a direct anti-microbial effect. Following an initial animal trial, the next step could be a randomized controlled trial in patients with AD using valacyclovir over an extended duration, perhaps 6 months or longer, to treat reactivations of herpesviridae. Study endpoints would have to be chosen carefully and would likely require detailed and comprehensive neurocognitive testing. Anti-inflammatory therapy could also be given and APOE ε4 genotype determined. Such a study could produce solid evidence-based medicine that determines the validity of the microbe-dementia hypothesis.

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Coccidioidomycosis — a Growth Industry

By Stan Deresinski, MD, FACP, FIDSA

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

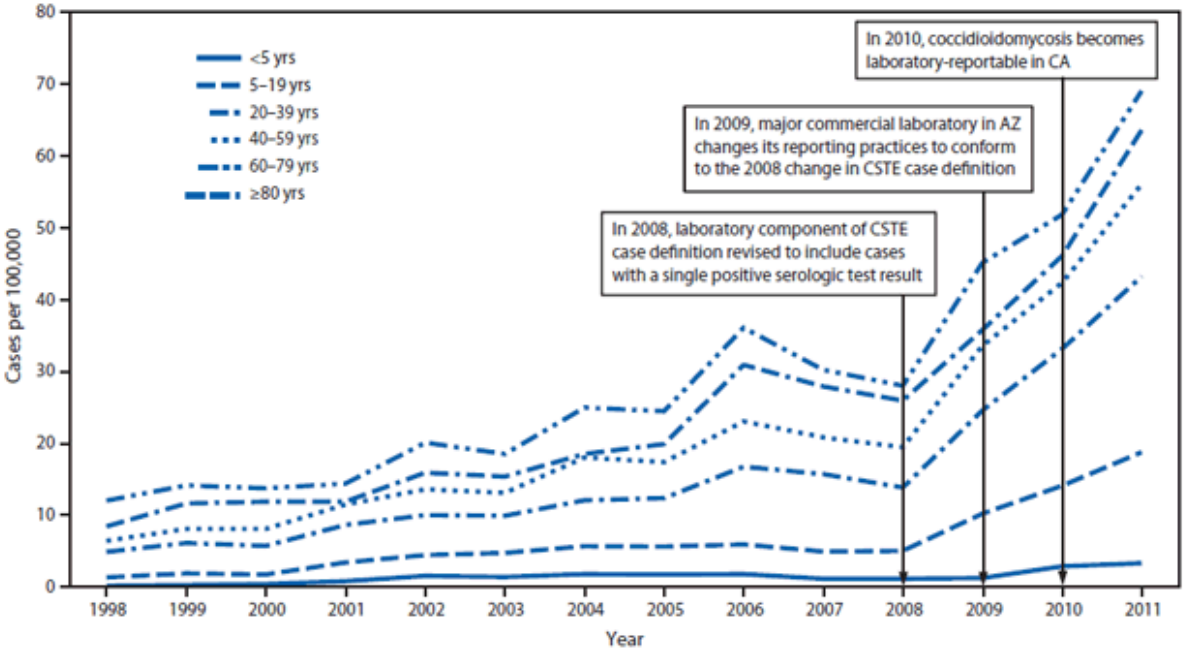
SYNOPSIS: There was an 8-fold increase in the incidence of coccidioidomycosis in endemic states from 1998-2011 – with more to come.

SOURCE: Centers for Disease Control and Prevention (CDC). Increase in reported coccidioidomycosis - United States, 1998-2011. *MMWR* 2013; 62:217-21.

Clinicians in California and Arizona have been aware of an apparent increase in their number of encounters with patients with coccidioidomycosis over the last decade and this has been confirmed in several publications. In addition to these 2 states, however, areas of endemicity exist in Nevada, New Mexico, and Utah, as well as in western Texas (but, unfortunately, coccidioidomycosis is not reportable in Texas). The CDC provides a broad picture of the changing epidemiology of coccidioidomycosis in the U.S. by analyzing data from the National Notifiable Diseases Surveillance System (NNDSS) for the years 1998–2011.

During that period, a total of 111,717 cases were reported to CDC from 28 states and the District of Columbia. Overall, the incidence of reported coccidioidomycosis increased from 5.3 per 100,000 population in the endemic area states of Arizona, California, Nevada, New Mexico, and Utah in 1998 to 42.6 per 100,000 in 2011. Of the cases, 66% were from Arizona, 31% from California, 1% from other endemic states, and <1% from states not considered endemic for this infection. Combining data from Arizona, California, Nevada, New Mexico, and Utah, it was found that the number of cases increased from 2,265 in 1998 (age-adjusted incidence rate [aIR]: 5.3 per 100,000 population) to 8,806 in 2006 (18.0 per 100,000). It has not, however, been a steady trend: there was a decreased number of cases in 2007 and 2008 followed by an increase in 2009 (12,868 cases; 25.3 per 100,000), which continued into 2010 and 2011 (42.6 per 100,000). The incidence increased in all

FIGURE. Coccidioidomycosis incidence per 100,000 population, by age group — Arizona, California, Nevada, New Mexico, and Utah, 1998–2011



Abbreviations: CSTE = Council of State and Territorial Epidemiologists; AZ = Arizona; CA = California.

Alternate Text: The figure above shows Coccidioidomycosis incidence per 100,000, by age group, in Arizona, California, Nevada, New Mexico, and Utah during 1998-2011. Incidence in coccidioidomycosis-endemic states increased among all age groups during 1998-2011. During this period, incidence typically was highest among the 40-59 year age group in California but was consistently highest among persons aged ≥60 years in Arizona and other coccidioidomycosis-endemic states.

SOURCE: Centers for Disease Control and Prevention

age groups with those 40-59 years having the highest rates in California while in Arizona, this distinction was held by those >60 years of age (Figure). In 2011, the incidence of coccidioidomycosis in Arizona was 381.1 per 100,000 among persons aged 60–79 years and 385.2 per 100,000 among those persons ≥80 years of age.

In Arizona alone, the number of cases increased from 1474 in 1998 to 16,467 in 2011 accounting for a growth in aIR from 30.5 to 247.7 per 100,000 population — an increase of approximately 16% per year. The rate of growth was similar in California with the number of cases increasing from 719 in 1998 (aIR: 2.1 per 100,000) to 5,697 in 2011 (aIR: 14.9 per 100,000) for an average annual increase of 13%. The number of cases reported in Nevada, New Mexico, and Utah combined increased from 72 in 1998 (aIR: 1.4 per 100,000) to 237 in 2011 (aIR: 3.1 per 100,000) ($p<0.001$). In nonendemic states there was an increase in reported cases from 6 to 240 during the period of study.

■ COMMENTARY

In 2011, coccidioidomycosis was the second most commonly reported nationally notifiable condition in Arizona and the fourth most commonly reported in California. While some of this increased incidence described by CDC may be related to improved diagnosis, it is likely that the numbers still represent an underestimate of the extent of the problem. Despite the fact that studies have shown that coccidioidomycosis may account for approximately one in 5 cases of community acquired pneumonia in urban areas of Arizona, a very large proportion of these go undiagnosed — hardly an advertisement for diagnostic acumen.[1] Despite the increase in reported cases,

overall U.S. coccidioidomycosis mortality rates have remained fairly stable at approximately 0.6 per 1 million person-years during 1990–2008[2], suggesting that the most severe life-threatening cases are being identified by clinicians and are being appropriately treated.

New foci of infection are still being identified as in the case of the description of 3 cases of coccidioidomycosis in which the infection appeared to have been acquired in eastern Washington state.[3] In addition, the human population in endemic areas is expanding and, in the process, disrupting the source of Coccidioides species, the soil. The construction if Interstate 5 running the length of the central valley of California was almost disrupted as a result of a large number of cases of coccidioidomycosis in workers. California is about to begin construction on its "bullet train" system, with the first portion to be built in the San Joaquin Valley, from Merced ("Gateway to Yosemite") to the San Fernando Valley and Los Angeles. Arizona is also considering construction of a high speed rail system. These activities will guarantee business for physicians expert in the management of coccidioidomycosis.

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Illness in Returned Travelers 2007-2011

By Dean L. Winslow, MD, FACP, FIDSA

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

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: 42,173 ill returned travelers were seen between 2007 and 2011 at 53 travel or tropical disease sites. Asia and sub-Saharan Africa were the most common regions where illnesses were acquired.

SOURCE: Leder K, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Int Med* 2013; 158: 456-468.

GeoSentinel sites are 53 specialized travel or tropical medicine clinics located in 24 countries (21 North America, 17 Europe, 10 Australasia, 3 Latin America, 1 in South Africa, and 1 in the Middle East). This consortium maintains a large database and has done so since the founding of this consortium in 1995 by the International Society of Tropical Medicine and the CDC. 42,173 ill travelers were seen during the latest 5 year period of this report (2007-2011).

Asia (33%) and sub-Saharan Africa (27%) were the regions where illnesses were commonly acquired. 34% of illnesses were gastrointestinal, 23% were febrile illness, and 20% were dermatologic. Only 41% of returning ill travelers reported pretravel medical visits. As in previous studies, travelers visiting friends and relatives in countries of origin made up a disproportionate number of serious febrile illnesses and only 18% of these patients sought pretravel advice.

Breakdown by region of acquisition of specific pathogens was interesting and will be helpful to clinicians prioritizing a differential diagnosis in an ill returning traveler. From sub-Saharan Africa, among the 4222 patients returning with febrile illness, *P. falciparum* was by far most common with rickettsial disease, dengue and *P.vivax* next most common. In South Asia, among 1535 travelers with febrile illness, enteric (Typhoid) fever was most common followed by dengue, *P.vivax*, chikungunya, and extrapulmonary TB. In Latin America and the Caribbean febrile returning travelers were most likely to have dengue followed by *P. vivax.* From the Middle East and North Africa hepatitis A followed by *P. falciparum*, brucellosis, enteric fever, dengue, and Q fever were seen. Travelers from Southeast Asia were most likely to have febrile illness due to dengue followed by *P. falciparum*, *P.vivax*, chikungunya, enteric fever, and leptospirosis.

Among gastrointestinal pathogens in all regions, Giardia, Strongyloides, Campylobacter, Salmonella and Shigella were commonly seen. Among dermatologic conditions Cutaneous larva migrans was commonly seen in most regions. *Cutaneous leishmaniasis* was seen in patients returning from South Asia, Latin America, Middle East and North Africa. A surprisingly large number of patients visiting all regions sustained animal bites necessitating rabies post-exposure prophylaxis. Among respiratory illnesses coming to medical attention influenza was seen in returning travelers from all regions and pulmonary TB was next most commonly seen.

■ COMMENTARY

This report contains a wealth of information and the reader is strongly encouraged to look up the article and carefully peruse the numerous tables and figures since they provide a wealth of detailed information further broken down by patient demographics and main reason for travel (tourism, visiting friends/relatives, business, missionary, student). Some take home points include the large amount of treatable severe disease in febrile returning travelers (chiefly *Falciparum malaria* and enteric fever) and less common illnesses like spotted fever group rickettsial disease due to *Rickettsia africae* (where a careful physical exam to look for an eschar is important). Many of the serious diseases encountered could also have been prevented if the travelers had availed themselves of a pretravel medical consultation. In addition to the obvious use of malaria chemoprophylaxis, using insect repellant and bed netting could prevent much of the vector-borne diseases, immunization will prevent hepatitis A and to some extent enteric fever, and common-sense behavioral and dietary precautions will prevent many of the other diseases reported. ■

Is it Q Fever? High Index of Suspicion may be Needed

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Q fever is prevalent in farm animals, which are the prime source of infection. The diagnosis of Q fever generally requires a high index of suspicion and a depth of knowledge of serological and other methods of detection.

SOURCES: Georgiev M, et al. Q fever in humans and farm animals in four European countries, 1982 to 2010. *Euro Surveill* 2013 Feb 21;18(8). Centers for Disease Control and Prevention. National Center for Emerging and Zoonotic Infectious Diseases. Diagnosis and Management of Q Fever - United States, 2013: Recommendations from CDC and the Q Fever Working Group. *MMWR* 2013; 29:62(RR-03):1-30.

Q fever, caused by the Gram-negative obligate intracellular rickettsia-like Coxiella burnetii, is a zoonotic disease acquired in humans most often by inhalation of air contaminated by the excreta of infected animals, usually cattle, sheep, or goats. Close contact is not necessary. Thus, in the large recent Netherlands outbreak, living within 2 km of an affected farm was a risk factor for infection and, in one outbreak, cases were documented in individuals living 10 miles of an affected farm. Additional means of acquisition of infection include tick bites and ingestion of contaminated unpasteurized dairy product. Human-to-human transmission is rare. Sexual transmission and trans-placental infection have been reported.

The large outbreak of Q fever in the Netherlands that raged between 2007 and 2010 certainly caught the attention of many in Europe. Georgiev and colleagues have now examined available reports to assess the extent of this infectious disease in the Netherlands and 3 additional European countries (Bulgaria, France, and Germany) between 1982 and 2010.

The first report of Q fever in Europe involved cases in soldiers in the Balkans, including Bulgaria, in 1940, just a few years after the disease had first been identified in slaughterhouse workers in Australia. The first cases in Germany were identified shortly after World War II, followed by the Netherlands in 1956. Studies of farm animals reported that the within-herd seroprevalence of *C. burnetii* in cattle ranged

from 15% to 21% in the 4 countries, while the prevalence of seropositivity in goats ranged from 2.5% (Germany) to 88.1% (France) and that for sheep ranged from 3.5% (Netherlands) to 56.9% (Bulgaria). There were 2354 notified cases in the Netherlands in 2009, in the midst of their infamous outbreak.

Studies in humans reported that the seroprevalence rates in blood donors was 1%-4% in France, 12.2%-24.0% in the Netherlands, 22.0% in Germany, and 38.0% in Bulgaria. There were 29 outbreaks in humans recorded with (in 1964-2006) from 121 to >1000 serologically confirmed cases per outbreak and with a much larger number of cases in the 20087-2010 Netherlands epidemic.
Acute infection is symptomatic in approximately one-half of cases, with complaints of fever and other non-specific symptoms, including headache, which can be severe. Pneumonia is frequent and 85% have elevated serum hepatic transaminase levels; a variety of other manifestations are less frequent. Untreated, the fever lasts a median of 10 days, but resolves rapidly with administration of doxycycline (although doxycycline resistance has been reported). Infection during pregnancy is associated with an increased risk of miscarriage and preterm delivery.

Fewer than one in 20 patients with acute infection go on to develop chronic Q fever, with the highest risk in those with valvular heart disease, aortic aneurysm, or a vascular graft. Infective endocarditis due to *C. burnetii* may occur in 40% of patients with cardiac valve disease who develop acute Q fever. The usual small size of the vegetations in cases of Q fever endocarditis makes their detection by echocardiography difficult. Infection during pregnancy is associated with an increased risk of chronic illness. Persistent fatigue in the absence of evidence of active infection has been reported in some patients after acute Q fever.

Serum antibody to *C. burnetii* phase II antigens initially becomes detectable in most patients by the 3rd week of illness. Most cases of acute infection are diagnosed by serological testing, but to be definitive, this requires paired sera with a four-fold rise in phase II IgG antibody titer. *C. burnetii* DNA may be detected in blood by PCR during the first 2 weeks of illness and before antibiotic administration. The diagnosis of chronic Q fever requires a phase I antibody titer >1:1024 together with an identifiable site of infection, such as a heart valve. The need for clinical evidence beyond antibiody results is necessary because some patients with acute Q fever may develop serologic profiles consistent with chronic Q fever but that eventually regress. Thus, treatment should not be given based on increased titers alone. The organism can be detected in infected tissue by PCR, culture or immunohistochemistry.

Acute infection is treated with doxycycline for 14 days, except in pregnancy, when more prolonged trimethoprim-sulfamethoxaxole therapy is recommended. Chronic Q fever is treated with prolonged administration (18 months for endocarditis) with a combination of doxycycline and hydroxychloroquine.

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Q-VAX, a human Q fever vaccine registered in Australia but not in Europe, was made available in the Netherlands in July 2010 to people at risk from chronic Q fever, including those with cardiac valve disease, aortic aneurysms, and vascular prostheses. The vaccination program, however, was first initiated in January 2011, after the outbreak had subsided. Q-VAX has been used in Australia since 1989 in humans whose occupation puts them at high risk of developing *C. burnetii* infection. It consists of a killed strain of a phase I strain of the organism. Studies suggest a high degree of efficacy, but with a significant risk of severe local reactions in individuals previously exposed to *C. burnetii*. As a consequence, potential vaccinees undergo prescreening that includes antibody and skin testing.

Q fever is uncommon in the U.S., but is undoubtedly under-diagnosed. In the absence of an obvious occupational exposure, testing for this infection is seldom done in patients with febrile respiratory illness. Testing for Q fever is part of the evaluation for culture negative endocarditis, but the detection of endocarditis itself may be difficult because of the relative insensitivity of echocardiography in this disease due to the frequently diminutive vegetations. The finding that *C. burnetii* may be detected in some abdominal aortic aneurysms in the absence of systemic evidence of infection is another example of the difficulties involved. On the other hand, over-diagnosis also occurs due to incorrect interpretation of antibody testing. This is why we need expert consultants.

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Ampicillin plus Ceftriaxone for Enterococcal Endocarditis

By Dean L. Winslow, MD, FACP, FIDSA

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

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: A nonrandomized, observational, comparative multicenter cohort study was conducted at 17 European medical centers. Patients treated with ampicillin+ceftriaxone (AC) were generally more ill at baseline than patients treated with ampicillin+gentamicin (AG). Despite this there was no difference in mortality or treatment failure between the groups. Interruption of treatment due to adverse events was more frequent in the AG-treated patients, mainly due to new-onset renal failure.

SOURCE: Fernandez-Hidalgo N, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. *Clin Infect Dis* 2013; 56: 1261-8.

This large multicenter observational study reports on the results of treatment of patients with *Enterococcus faecalis* infective endocarditis (IE) with either AC (n=159) or AG (n=87). Primary outcome measures were death during treatment or at 3 month follow up, treatment failure, relapse, and adverse events requiring treatment withdrawal. A larger proportion of AC-treated patients had previous chronic kidney disease (CKD) than AG treated patients (33% vs. 16%) and cancer (18% vs. 7%). There were no differences in mortality on treatment between the groups (22% vs. 21%) or at 3 months after treatment (8% vs. 7%), treatment failure (1% vs. 2%) or in relapses (3% vs. 4%). However treatment interruption due to adverse events was much more frequent in AG-treated patients than in patients receiving AC (25% vs. 1%). This was almost entirely due to new onset renal failure (>= 25% increase in serum creatinine above baseline; 23% vs. 0%).

■ COMMENTARY

IE due to Enterococcus remains one of the most challenging infections encountered by ID specialists. The organism itself (in contrast to most streptococci and staphylococci) is inhibited but not efficiently killed by cell wall-active antibiotics, rendering these agents essentially bacteriostatic against enterococci. It was shown by Bob Moellering in the 1960's that aminoglycosides (which are not active by themselves at achievable serum concentrations vs. streptococci) result in synergistic bacterial killing when combined with cell wall-active agents. Since bacteria trapped in the dense fibrin-platelet matrix of the vegetation are protected from phagocytosis by neutrophils, the mainstay of therapy of IE due to enterococci has been penicillin, ampicillin or vancomycin in combination with an aminoglycoside, administered for 4-6 weeks. While cure rates are high with these regimens, the nephrotoxicity and ototoxicity of these aminoglycoside-containing regimens is considerable.

Recently some data have suggested that as little as 2 weeks of combination therapy followed by 2-4 weeks of single agent therapy with a cell wall active agent result in high cure rates. However the toxicity of just 2 weeks of aminoglycoside treatment is significant. In addition, aminoglycosides only are effective in synergy with cell wall-active agents if the isolate of enterococcus does not display high-level resistance to that particular aminoglycoside. In vitro data suggest that certain B-lactam agents (including ceftriaxone) in combination with penicillin or ampicillin result in enhanced killing vs. enterococci. A small case series of patients with IE due to high-level aminoglycoside-resistant enterococcus suggested that ampicillin plus ceftriaxone provides effective therapy in vivo as well.[1] This large non-randomized trial suggests that ampicillin plus ceftriaxone is as effective as traditional aminoglycoside-containing regimens with significantly less toxicity for all cases of *E. faecalis* IE. Clearly prospective randomized trials are in order.

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Updates

By Carol A. Kemper, MD, FACP

Crossing the border with highly resistant TB

Tuberculosis, XDR – USA: Texas ex Nepal. A ProMED-mail post, March 1 2013; www.promedmail.org

This ProMED-mail alert describes the world-wending saga of a man from Nepal with smear-positive extremely-drug resistant tuberculosis (XDR-Tb), who arrived in the United States in late November 2012. In order to enter the United States (illegally), he traveled thru 13 different countries over a 3-month period, including an 8-hour air flight to Brazil, before crossing the border from Mexico into the U.S. near McAllen, Texas. It is not possible to reconstruct his journey nor adequately identify and screen the thousands of people exposed during his journey, but the CDC and WHO have been notifying affected countries. Twelve border patrol agents who were exposed have all tested negative for infection.

This man, who has not been identified, is the first individual with XDR-Tb detained by U.S. immigration authorities. A total of 4 cases of XDR-Tb were reported in the U.S. for 2011 (all of them were foreign born).

XDR-Tb is by definition resistant to at least 3 classes of drugs, including isoniazid, rifampin and/or rifabutin, fluoroquinolones, and at least one injectable agent (e.g., streptomycin). This man has a strain of tuberculosis resistant to at least 8 of 15 drugs tested.

We were involved with a similarly scary case in December 2012 at our hospital in Mt. View, CA, when a 30-year old Nepalese man with smear-positive Tb required hospitalization. He worked as an aide at a local academic medical facility. Thought to possibly be an XDR case, based on preliminary resistance data, his isolate proved resistant to isoniazid, rifampin, rifabutin and streptomycin but was sensitive in vitro to fluoroquinolones (making him only MDR-TB). Quite frustrated with his 4-week hospitalization, he attempted to elope from the hospital one afternoon, and was practically tackled by my colleague in the hall. On examining the family, the local public health department found that his sister had 4+ smear-positive pulmonary disease and both children had abnormal chest radiographs. Concurrently, I was also asked to consult in the clinic on a young woman recently arrived from India with smear-positive pulmonary disease, who also proved to have 4-drug resistant MDR-TB. Their strains were genetically different.

Physicians must be on guard for the increased potential for multi- and extremely-drug resistant TB, especially in foreign born persons from India and Nepal. Both countries have seen a dramatic increase in drug-resistant strains. While Nepal (which reported 35,000 cases of MTb in 2011) has made good public health efforts to control the disease, they are faced with the highest rates of multi-drug resistant disease (up to 48%). ■

Fecal Transplant Centers are growing in 'poopularity'

Jiang Z, et al. Physician attitudes toward the use of fecal transplantation for recurrent Clostridium difficile infection in a metropolitan area. *Clin Infect Dis* 2013; 56: 1059-1060.

On the heels of last month's "poopular" fecal transplant article, these authors from the University of Texas and Baylor Medical School in Houston, Texas conducted a survey of local physicians' attitudes towards fecal transplant. The survey was intended to determine whether there was local community physician support for a fecal transplant treatment center in the area. Two-hundred-and-four local gastroenterologists and ID specialists were queried, only 33% of whom responded. The majority of physicians who responded were in favor of fecal transplant treatment (65% of gastroenterologists and 69% of ID specialists). A significant percent of these indicated they would be willing to refer patients to a local fecal transplant center for treatment, if one were available (89% of gastroenterologists and 81% of ID specialists).

The authors suggest that academic medical facilities develop local treatment programs for fecal transplantation , employing the latest techniques

and emerging technologies (e.g., frozen fecal material from a single donor, synthetic fecal products that mimic fecal microbiota), to assist the community in managing patients refractory to other *C difficile* treatments. ■

Bedbug Detection Squad

Vaidyanathan R and Feldlaufer MF. Bed bug detection: Current technologies and future directions. *Am J Trop Med and Hyg* 2013;88:619-625.

Remember that scene in Doc Martin when he travels to London for a conference, and while his lady awaits his affection in a tiny negligee, he methodically strips the bed looking for bed bugs ? How many of us make that a habit now when traveling ?

Detection and control of bedbugs has become a busy industry the past decade, as estimates suggest 100-fold increase in the bed bug population. Bed bug bites vary from a few annoying bites to dramatic infestations, sometimes resulting in severe allergic reactions, delayed hypersensitivity reactions and even anemia. I've seen patients come in with hundreds of bites, desperate for information and relief.

There are a number of methods and technologies to detect (and possibly control) bed bug infestations, including newer technologies pending patent. Visual inspection of beds and furniture for bugs, exuviae and fecal droplets is cheap and easy — but you have to know what you're looking for and accuracy drops off with lesser infestations. It is also time-consuming (having to remake all those beds). There are a number of passive methods used, most of which employee glue or adhesive "traps", which vary in price from a few cents to $30 for a 12-pack. These are undoubtedly better than passive inspection, especially if you are staying in a place for more than one night. But the traps must be manually removed and inspected, and they often have a mix of live and dead bugs stuck to them — and the traps are not specific for bedbugs so can attract other insects (some people might object to this). Another passive method is a coaster trap for furniture and bed legs, which can be left for a week at a time, and reportedly trap 6-7 times the bed bugs of other passive traps. But they too need to be removed and inspected, and are also non-specific for bed bugs. They cost anywhere from $34 to $80 for a 12-pack.

Active traps can employee a number of methods, including heat and CO2, which are the two most effective attractants, bringing in bugs at night wanting to feed. Traps based on CO2 productions are, however, more costly, varying in price from $400 to $999, and require refillable CO2 cartridges. In addition to cost, these systems also require visual inspection and removal of traps with live bugs and their feces, and operators often complain about the bulky cartridges, mechanical problems with the dispersal systems, and the constant hissing sound of the carbon dioxide being dispersed. One study found that a homemade passive trap using dry ice was more successful than more expensive commercial traps using CO2 — the homemade dry ice system caught as many bugs in one day as the more expensive traps caught in a week.

Newer active trap systems, based on an increased understanding of bed bug interactions and chemical communication, are being developed. Two "alarm" pheromones have been identified, specific to bed bugs, and have been incorporated into active traps. They can also be used in part as a control strategy, because they are more effective at attracting bugs. Bedbugs have also been found to use another pheromone to signal gregarious behavior (called a kairomone), which seems to promote aggregation behavior, thereby possibly allowing better control of infestations. Such systems are advertised for $30 for a 90 day supply.

Pest control companies have also used trained canines for bed bug detection. While it is not entirely clear what the dogs are smelling, they presumably are responding to some combination of volatile pheromones or chemicals in bug excrement. These authors found that a trained dog identified live bed bugs, filter paper with a mix of the two alarm pheromones, and cast skins 100% of the time, although they commented that this was in a clean, well appointed office building. Lower detection rates have been reported when dogs are used in crowded urban settings. One issue with the use of dogs is they may not be able to detect a current infestation from a past infestation, and the dogs can only detect the presence of bed bugs — not reduce their numbers. Newer technologies based on antigens from digested human blood in bed bug feces are also being explored — but again have the disadvantage of not being able to detect current from past infestations. Other technologies based on mass spectrometry, DNA analysis and electronic noses are accurate but impractical for commercial home use. ■

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 with regard to the incidence of coccidioidomycosis in the U.S. from 1998-2011?
   A. It has increased almost 2-fold.
   B. It has increased almost 4- fold
   C. It has increased almost 6-fold
   D. It has increased almost 8-fold

2. Which of the following is correct?
   A. Q fever is caused by a Gram-negative obligate intracellular organism.
   B. Seroprevalence studies demonstrate that *Coxiella burnetii* infection is very rare in Europe.
   C. Among symptomatic cases of Q fever, elevation of serum transaminases is rare.
   D. Serum antibodies to C. burnetii initially appear by the end of the first week of illness in almost all patients.

3. Which of the following is correct with regard to novel H7N9 influenza virus that recently emerged in China?
   A. Genetic analysis indicates it originated in swine.
   B. It appears to be susceptible to oseltamivir.
   C. It appears to be susceptible to amantadine.
   D. It is readily transmitted from human-to-human.

CME OBJECTIVES

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

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

[IN FUTURE ISSUES]

Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis: The BAT Randomized Controlled Trial

Management of human immunodeficiency virus infection in advanced age

Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: A randomized trial.

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By Louis Kuritzky, MD

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

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Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

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Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.

Subscriber Information
Customer Service: 1-800-688-2421
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Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

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.*

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

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.

Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■