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INSIDE

Financial Disclosure:

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Gardening Can Kill You

ABSTRACT & COMMENTARY

David A. Stevens, MD, FACP.

Chief, Division of Infectious Diseases, Department of Medicine, Santa Clara Valley Medical Center, San Jose, CA; Professor of Medicine, Stanford University Medical School

Dr. Stevens reports no financial relationship relevant to this field of study.

Synopsis: *A patient developed acute respiratory failure and died after exposure to dust while mulching in his garden. While attributed by the author to invasive disease by aspergillus, other considerations, such as extrinsic allergic alveolitis must be considered.*

Source: Russell K, et al. Gardening can seriously damage your health. *Lancet*. 2008;371:2056.

As mentioned in the article by Russell et al, a patient was admitted to the hospital in the United Kingdom after a week's febrile respiratory illness; he had previously been in good health. Admission chest radiograph showed many nodules. His illness progressed to respiratory failure, with a radiographic picture of consolidation; he died a few days after admission. His history revealed his symptoms had started less than 24 hours after mulching in his garden, where he was exposed to clouds of dust. Sputum cultures in the hospital had grown Aspergillus fumigatus, and serum testing revealed a high serum Aspergillus galactomannan level and "significant" Aspergillus antibodies. He was given intravenous amphotericin B as a result of these findings.

This report was given attention in international media because of the implication of gardening causing aspergillosis. Russell et al stated that "inhalation of spores" can cause disease that "can be acute and invasive," and suggested that their patient had invasive disease ("Unlike most patients with acute, invasive aspergillosis, our patient did not seem to be immunosuppressed. . ."). However, Russell et al provide no evidence that their patient had invasive disease; the definitive basis for this would be documentation of tissue invasion, and suggestive support could be provided by radiographic evidence of cavitation or clinical evidence of hemorrhage. They indicate, cor-

VOLUME 27 • NUMBER 11 • AUGUST 2008 • PAGES 121-132

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rectly, that "acute aspergillosis, after contact with decayed plant matter," may occur and "may be considered an occupational hazard for gardeners," but I believe may incorrectly juxtapose this with their implication of "invasive disease." Of note, corticosteroids were apparently not given, which would be consistent with a working diagnosis of invasive aspergillosis.

■ COMMENTARY

Most forms of acute aspergillosis that occur "after contact with decayed plant matter" are allergic forms of the disease, usually acute provocation of asthma. I believe the best pathophysiologic explanation of this patient's illness is as a variant of extrinsic allergic alveolitis. The pathophysiology is presumed similar to that entity when there is massive inhalation of Aspergillus spores, usually in farm environments. Symptoms are classically present within 24 hours, as was the case in this patient, and granulomas are found on biopsy. The classical entity of extrinsic allergic alveolitis is an unusual form of Aspergillus lung disease, and has been most associated with *Aspergillus clavatus* in malt workers. The patients develop dyspnea and fever four hours after exposure, and the clinical picture resembles the better-known "bird-fancier's lung" or "farmer's lung" (due to other allergens); diffuse micronodular infiltrates may be present at the time of symptoms. The patients have lgG precipitins and cell-mediated immune reactions against Aspergillus antigens, and granulomas are present on biopsy. Eosinophilia is not a feature. The scratch test is negative, though an intradermal test produces a reaction in four hours, with immunoglobulins and complement present on biopsy. Bronchial challenge, with antigen, as can be reproduced in the pulmonary function test laboratory, produces a reaction in four hours, with systemic symptoms and a restrictive defect, but without airway resistance. The entity can progress to irreversible fibrosis. Treatment of the acute or chronic form is uncertain, but corticosteroids have been used, and might be expected, to ameliorate inflammation, granulomas, and the cell-mediated component. It would be expected that antifungals would have no role in an allergic entity, but occasional cases have been described (*Am Rev Resp Dis*. 121:63), with a histopathology of granulomas with purulent microfoci, suggesting a tissue response to invasion; with a recommendation to use antifungals if the patient is unresponsive to steroid therapy.

Another possible explanation of this patient's illness is that he was a heterozygote for the congenital immunodeficiency, chronic granulomatous disease (CGD), or had one of its genetic variants. A syndrome has been described in such persons (*Clin Infect Dis*. 45:673) of hypoxia, fever, and pulmonary infiltrates following inhalation of lots of Aspergillus from mulch. It is usually adult-onset, unlike the invasive pulmonary Aspergillus disease seen in children with classical CGD; the immunodeficiency may have been unknown prior to the exposure. The immunodeficiency is related to granulocyte failure to fire its NADPH oxidase enzyme, resulting in no effective cellular respiratory burst. In this type of "overwhelming mulch pneumonitis," the case fatality rate is 50%. The pathophysiology is suspected to be due to neutrophil damage from an ineffectual, but intense infiltration into the lung. Histopathology reveals dense neutrophil infiltration and pyogranulomas. Cavitation, vascular invasion, and hemorrhage do not occur and, as described, the serum galactomannan test is negative. The recommended therapy is corticosteroids and antifungals, and therapy with steroids must be sustained; premature tapering has been associated with exacerbations. The elevated galactomannan in the patient described could have been a false positive, such as from antibacterials given during the hospitalization.

These unusual entities need to be considered in the differential diagnosis of acute pneumonitis presenting after exposure to large quantities of Aspergillus spores. ■

Infectious Disease Alert, ISSN 0739-7348, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MARKETING PRODUCT MANAGER: Shawn DeMario.
MANAGING EDITOR: Leslie Hamlin
GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Infectious Disease Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Tuberculosis Screening in Internationally Adopted Children: Test Twice

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

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

Dr. Jenson is on the speaker's bureau for Merck.

Synopsis: *A high proportion of internationally adopted children arriving in the United States have an initial false-positive tuberculin skin test. All internationally adopted children with an initially negative tuberculin skin test should have a repeat tuberculin skin test after three months in the United States. This should be the standard of care for identifying latent tuberculosis infection and preventing tuberculosis disease in these children.*

Source: Trehan I, et al. Tuberculosis screening in internationally adopted children: the need for initial and repeat testing. *Pediatrics*. 2008;122:e7-e14.

A cohort of 549 internationally adopted children ≥ 3 months of age (mean age, 22.9 months; range, 1.2 200 months) was evaluated at Cincinnati Children's Hospital between 1999 and 2004, with a post-adoption health visit within two months (mean, 12 days) after arrival in the United States. Children arrived from 29 different countries, with 81% coming from Russia, China, Guatemala, Kazakhstan, and South Korea; none of the children tested positive for HIV infection.

The initial tuberculin skin test (TST) was read at 48-72 hours in 527 children (96%) and was positive (³ 10 mm induration) in 111 children (21%). Of the 416 children with a negative initial TST, 92% had no induration and 8% had 1-9 mm of induration. In these 416 children, a second post-adoption TST was performed at least three months later in 203 children and read at 48-72 hours in 191 (94%). The repeat TST was positive in 38 children (20%). All of the children had normal physical examinations and chest radiographs and were diagnosed with latent tuberculosis infection (LTBI). They begun the recommended nine--month course of isoniazid; there was no apparent association of positive repeat TST and country of birth.

The majority (81%) of children had evidence of BCG vaccination, except for children from South Korea, with only 15% having evidence of BCG vaccination. Only eight children had documentation of multiple BCG vaccinations. Children with evidence of BCG vaccination were more likely to have a positive TST result than children with evidence of BCG vaccination (OR: 15.3; 95%CI 3.3 70.1; $p = 0.0004$).

The median age (14.8 vs 13.1 months) and institutionalization history of children with a positive TST was not significantly different from children with a negative TST. The TST was positive 19.7% of the time for children who had lived in an orphanage or hospital at any time, 19.5% for children who had lived in an orphanage at least six months, and 24.1% for children who had resided in a foster home. Malnutrition (defined as a weight-for-age z score less than 2.0) was present in 158 (30%) children. The median (range) z score for children with a positive TST result, 1.13 (5.40-1.31), was slightly higher than for children with a negative TST result, 1.38 (7.00-3.94), $p = 0.06$. Children with an initially negative TST result were more likely to be malnourished compared to children with an initially positive TST result (31% vs 22%, $p = 0.06$).

■ COMMENTARY

Over 20,000 children are adopted into the United States each year, many from areas of high tuberculosis endemicity. The initial health screening guidelines include testing for tuberculosis using the TST for all immigrants from high-prevalence countries. Consensus guidelines recommend that TST results be interpreted without consideration of the BCG vaccination history, and that the TST be repeated once the child is better nourished, if malnutrition is initially suspected.

Because of the long incubation period of tuberculosis infection, the TST has poor sensitivity following recent exposure and during early developing infection. Other factors that may contribute to anergy and false-negative TST results include undernourishment, recent live virus vaccine administration, concomitant infections, and immunosuppression.

Tuberculosis remains a major global public health threat. This study demonstrates that many additional cases of LTBI can be identified among internationally adopted children by repeat TST after a few months in the United States. It is unlikely that these children represent acquisition of tuberculosis infection in the United States, but rather that the ability to mount an appropriate delayed hypersensitivity response to TST occurs after nutritional status has improved. Although not statistically significant, the results of this study showed that malnourished children were less likely to have a positive TST result at the initial visit. A history of BCG vaccination is not a contraindication to placement of a TST, and the interpretation of the TST result should not be influenced by a history of BCG vaccination. ■

Femoral vs Jugular Venous Catheterization and Risk of Infection

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor, Stanford University School of Medicine

Dr. Winslow serves as a consultant for Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *In this study, 750 severely ill patients requiring initial hemodialysis were randomized to receive either jugular or femoral vein catheterization. Jugular catheterization significantly increased the incidence of catheter colonization in patients with body mass index (BMI) < 24.2, whereas jugular catheterization decreased the incidence in patients with BMI > 28.4. Across all BMI strata, there was no significant difference in catheter-related blood stream infections in patients who underwent femoral vs jugular catheterization.*

Source: Parienti JJ, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA*. 2008;299:2413-2422.

In France, 750 patients from 12 hospitals participated in a concealed, randomized, multicenter, evaluator-blinded, parallel-group trial (the Cathedia study) conducted between 2004 and 2007. Severely ill, bed-bound adults with BMI < 45, who required first catheter insertion for renal replacement therapy, (RRT) were enrolled and randomized to femoral vs internal jugular (IJ) access. Morbidly obese patients with BMI > 45, local skin infection, volume overload precluding Trendelenburg position, presence of an AV fistula, thoracic contraindications, and those patients with only one site available were excluded. All operators were experienced, and employed appropriate sterile technique at both sites. Seldinger technique was used at both sites. Ultrasound guidance was recommended for IJ insertion, but was not required. Catheter colonization was defined as catheter tip culture with > 10^3 CFU/mL. Catheter-related bloodstream infection was defined as catheter tip colonization plus at least one peripheral blood culture yielding the same organism within 48 hours of catheter removal.

Jugular catheters were more difficult to insert and required longer insertion times, and insertion resulted in more failures on one side and more crossovers to the femoral site and more hematomas. Two patients in the jugular group had severe respiratory distress due to compressive hematoma; they required intubation.

The overall incidence of catheter colonization was similar between the femoral vs jugular groups (40.8 vs 35.7/1000 catheter-days). Colonization of the catheter with Gram-positive organisms (mostly *Staphylococcus epidermidis*) was seen in 41 femoral vs 51 jugular catheterizations and Gram-negative organisms in 30 femoral vs 15 jugular catheterizations. Catheter-related BSI incidence was 1.5/1000 catheter days in the femoral vs 2.3/1000 in the jugular group, but this difference was not statistically significant. Subgroup analysis was remarkable for significant differences in catheter colonization incidence by BMI tercile. Patients in the lowest BMI tercile (< 24.2) experienced catheter colonization incidence of 23.7/1000 catheter days with femoral catheters vs 45.4/1000 with jugular catheters (HR 2.10). Patients in the highest BMI tercile (> 28.4) experienced catheter colonization incidence of 50.9/1000 by femoral vs 24.5/1000 by jugular route (HR 0.40).

■ COMMENTARY

It has been axiomatic since I began training in the early 1970s that the femoral site should be avoided in all adults for venous catheter insertion due to the perceived increased risk of BSI associated with the femoral route; either the IJ or subclavian sites were favored. However a critical look at the literature suggests that this perception had largely been based on anecdotal data. This important study shows fairly conclusively that in patients with normal or low BMI that the risk of catheter colonization and infection is greater with IJ vs femoral site catheterization. Only in obese patients was catheter colonization increased with femoral vs IJ catheterization. This study does not address the relative rate of catheter colonization and BSI in subclavian vein catheterization, which may be superior to both the femoral and IJ sites. The increased risks of vascular complications associated with IJ insertion (and of both iatrogenic pneumothorax and vascular complications associated with subclavian insertion) need to be considered as well. These data suggest that, except in very obese patients, the femoral site may be appropriate for venous access,

when necessary, especially when the expected duration of catheter placement at the femoral site is likely to be short term. ■

Epidemiology of Invasive Group B Streptococcal Disease in the United States

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *In an active population-based surveillance study conducted between 1999 and 2005 in 10 states, 14,573 cases of invasive group B streptococcal (GBS) disease were identified. The incidence of invasive GBS among infants from birth through 6 days of age decreased; incidence remained stable in infants aged 7-89 days and in pregnant women. Among persons 15 years of age or older, the incidence of invasive GBS also increased during the period of the study. All 4882 isolates for which antimicrobial susceptibility test results were available, remained susceptible to penicillin, ampicillin, and vancomycin, though some were resistant to erythromycin and clindamycin respectively.*

Source: Phares CR, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*. 2008;299:2056-2065.

This active, population-based, surveillance study was conducted by the CDC, in collaboration with state health departments and universities in 10 states participating in the Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network. Neonatal cases were categorized as early onset if GBS was isolated from infants younger than 1 week and as late onset if infants were 7-89 days old.

From 1999-2005, surveillance identified 14,573 cases of invasive GBS disease. Age groups included: early-onset neonatal (1232 with 83 deaths), late-onset neonatal (1036 with 48 deaths), children 90 days-12 months (143 with 4 deaths), 1-14-years-old (90 with 11 deaths), 15-64-years-old (6496 with 472 deaths), ≥ 65-years-old (5576 with 730 deaths).

Among 2056 case individuals identified in 2005, 54% were white, 28% were black, 2% were Asian/Pacific Islander, < 2% were Native American, and 14% were of unknown race. Incidence of invasive GBS was 12.8/100,000 among blacks, 6.5/100,000 for whites, and 5.1/100,000 for other races combined. Overall incidence among blacks was two times higher than among whites. Also, the proportion of patients who died, among individuals with early onset neonatal infection and in patients > 45-years-old, was significantly higher for blacks than whites.

In this study, 1232 cases of early-onset disease were identified. After the 2002 release of early-onset GBS disease prevention guidelines (which utilize antepartum screening of the mother and intrapartum administration of parenteral penicillin), disease incidence decreased 27%, from 0.47/1000 live births to 0.34/1000. Interestingly, small increases in the incidence of early-onset GBS disease occurred in 2004 and 2005, with the incidence being 0.52/1000 in 2003 to 0.89/1000 in 2005. This increase was driven primarily by black infants. The most common syndromes seen in early-onset disease were non-focal bacteremia (83%), pneumonia (9%), and meningitis (7%). Of the 1036 cases of late-onset disease, median age at first positive culture was 37 days. Meningitis was more common (27%) than in the early-onset disease group. The risk of death for pre-term infants was more than three times that of term infants. Only 233 cases of invasive GBS infection were identified in children (90 days-14 years). Of children > 1 year of age, underlying conditions (including neurologic disorders, immunosuppression, cancer, asthma, and renal disease) were present in 44%.

There were 6087 cases of invasive GBS infection identified in adults 15-64-years-old and 5576 among those older than 65. Among adults aged 15-64, the incidence increased from 3.4/100,000 population in 1999 to 5.0/100,000 in 2005. Among patients older than 65, the incidence increased from 21.5 to 26.0/100,000. The most common clinical syndromes among all 11,663 adults were bacteremia without focus (48%), bacteremic cellulitis (22%), pneumonia (11%), osteomyelitis (9%), arthritis (9%), peritonitis (3%), and abscess (3%). Underlying conditions included diabetes (41%), heart disease (36%), and malignancy (17%).

Serotype distribution for early-onset neonatal disease revealed a predominance of serotypes Ia, III, V, and II. In late-onset disease serotype III accounted for half the cases followed by Ia and V. In non-pregnant pediatric and adult cases, serotype V predominated, followed by Ia, II, and III. All 4882 isolates submitted for susceptibility testing were susceptible to penicillin, ampicillin, and vancomycin; 32% were resistant to erythromycin and 15% were resistant to clindamycin.

■ **COMMENTARY**

This is an important review of a major clinical problem. Some insights from this study include the demonstration that black Americans of all ages bear a disproportionate burden of cases of invasive GBS infection. The reasons for this are unclear. While intrapartum prophylaxis appears to have reduced the incidence of early-onset infection, this strategy will have little effect in preventing infection in children of women who go into pre-term labor. Further development and use of a pentavalent conjugate vaccine, including the most common serotypes, could potentially prevent up to 96% of neonatal disease and 88% of pediatric and adult disease. The large number of cases in adults was surprising to me, and seems largely reflective of the increased numbers of aging adults with diabetes and other underlying conditions. Despite increased use of prophylactic penicillin, it was reassuring that isolates have retained susceptibility to penicillin over time. However, the identification of the large proportion of isolates with reduced susceptibility to erythromycin and clindamycin highlight the importance of susceptibility testing of isolates obtained from pregnant women who are at risk for penicillin anaphylaxis before administration of erythromycin or clindamycin for intrapartum prophylaxis. ■

Types of Cancer Among HIV-infected Persons

ABSTRACT & COMMENTARY

By Dean L. Winslow, MD, FACP, FIDSA

Synopsis: *A total of 54,780 HIV-infected persons enrolled in two large cohort studies followed from 1992-2003, and 334,802 patients from 13 population-based cancer registries, were studied. Standardized rate ratios (SRRs) were used to compare cancer incidence in the HIV-infected population with cancer incidence in the general population. The following non-AIDS-defining cancers were seen with excess incidence in the HIV-infected population: anal, vaginal, Hodgkin's lymphoma, liver, lung, melanoma, oropharyngeal, leukemia, colorectal, and renal. The incidence of prostate cancer was lower among HIV-infected patients than in the general population.*

Source: Patel P, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Int Med*. 2008;148: 728-736.

Data on cancer incidence in the HIV-infected population were derived from the CDC-sponsored Adult and Adolescent Spectrum of HIV Disease Project (ASD) conducted in 11 geographic areas, as well as from the HIV Outpatient Study (HOPS) conducted in eight US cities. The Surveillance, Epidemiology, and End Results Program (SEER) is an active and passive cancer surveillance system which collects data from 13 population-based cancer registries in the United States. The SEER program includes HIV-infected patients who probably represent fewer than 1% of the total population studied.

Important longitudinal data from this study show some important trends, including the progressive reduction in incidence of AIDS-defining cancers from 1992-1995 until 2000-2003. Kaposi sarcoma fell from SRR 197.0 to 112.1, and non-Hodgkin's lymphoma fell from 79.4 to 17.0, although cervical cancer SRRs remained stable at 11.8 and 10.1 across these time periods.

In contrast, the incidence of most of the traditionally non-AIDS-defining cancers remained significantly elevated or increased over the time periods of the study. Anal cancer SRRs increased from 31.4 to 59.4, Hodgkin's lymphoma from 11.7 to 17.9, and melanoma from 1.3 to 3.0. The following non-AIDS-defining cancers were shown to be increased in incidence compared to the general population over time, but their incidence remained relatively stable: liver 9.3 and 7.0, lung 3.5 and 3.6, oropharyngeal 2.5 and 3.0, colorectal 2.5 and 2.4, and breast 0.7 and 1.1 during both time periods, respectively. The incidence of prostate cancer was less frequent in HIV patients vs the general population, with SRRs of 0.3 during 1992-1995 and 0.7 during 2000-2003.

■ **COMMENTARY**

This study provides an important update to our understanding of cancer in HIV-infected patients. It highlights the importance of non-AIDS-defining cancers in HIV-infected patients, which in contrast to AIDS-defining cancers, have not been significantly reduced in frequency due to HAART. In particular, due to the fact that HAART does not alter the incidence or progression of either cervical cancer or anal neoplasia, efforts to detect and treat these HPV-related malignancies at earlier stages in HIV-related patients should continue. These data also reinforce the importance of tobacco cessation efforts and colorectal cancer screening in HIV-infected patients. ■

The Risk of Infection after Nasal *Staphylococcus aureus*

ABSTRACT & COMMENTARY

By Joseph H. John, MD, FACP, FIDSA, FSHEA

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Dr. John is a consultant for Cubist, Genzyme, and bioMerieux, and is on the speaker's bureau for Cubist, GSK, Merck, Bayer, and Wyeth.

Synopsis: *Another study confirms that MRSA nasal colonization is associated with a higher rate of infection than MRSA colonization. Separately, it is reported that individuals with perennial allergic rhinitis have an increased prevalence of nasal colonization with* S. aureus*, but that nasal mupirocin treatment does not reduce the frequency of nasal symptoms.*

Sources: Safdar N, Bradley EA. The risk of infection after nasal colonization with *Staphylococcus aureus*. *Am J Med*. 2008;121:310-315; Zeldin Y, et al. Efficacy of nasal *Staphylococcus aureus* eradication by topical nasal mupirocin in patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. 2008;100:608-611.

Recently, authors from the University of Wisconsin Medical School asked what is the risk of infection associated with nasal colonization with *Staphylococcus aureus*. Using some statistical methods that only statisticians can understand, the authors queried 528 studies, and found 113 potentially relevant. They wanted to review data of both methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. So, they ended up with only 31 studies which included both MSSA and MRSA; from those, only 10 met the authors' inclusion criteria. From a group of 3381 patients who were screened for colonization, the studies included 791 patients colonized by MSSA and 379 by MRSA. Rectal swabs were used with nasal swabs in two studies.

The findings were surprising: MRSA colonization was associated with a four-fold higher risk of infection following the colonization, significant at a $p = 0.007$. The authors conducted a sensitivity analysis to test heterogeneity in colonization and infection, and showed that no one study biased the analysis.

The focus of the second study, by Zeldin et al from Israel, was to see if nasal mupirocin reduced the frequency of attacks due to perennial allergic rhinitis. There were 60 patients, ages 5-60 years of age, in the treatment group and 55 in the control group. Sensitivity to dust mites was much higher (100% vs 13%) in the rhinitis than in the control group.

The results showed *S. aureus* carriage in 38% of the rhinitis group compared to 15% of the control group ($p = .004$). No distinction was made between MRSA and MSSA. Eradication of *S. aureus* carriage worked well with self-administered mupirocin in both groups. The allergist investigators were most focused on whether eradication of *S. aureus* carriage was associated with reduced frequency of perennial symptoms of rhinitis or if it was not. Changes in rhinitis symptom scores, measured at five weeks, compared to baseline varied very little in the carrier and non-carrier groups.

■ COMMENTARY

Well, there you have it: Infection is more likely to follow MRSA carriage than MSSA carriage. For old timers who have followed staphylococcal infection for decades, this may come as a surprise. Certainly we always have had plenty of infection due to *S. aureus,* and infection is generally related to the carrier state. The increased intensity of focus over the past decade on MRSA has been, in my opinion, overdone in relation to the relative preoccupation with MSSA. Yet, when a good review analysis, like the one by Safdar and Bradley, considers only the studies that truly studied the link between MSSA/MRSA carriage, and subsequent infection, MRSA wins.

Yes, we do need to emphasize that focus on MRSA carriage, and those organizations both abroad and in the United States that are trying to limit carriage through surveillance studies and other means are well justified to do so. The Dutch enterprise "Search and Destroy" to make MRSA a nearly national enemy has resulted in extremely small rates of MRSA in Dutch hospitals like the large facility at Erasmus University in Rotterdam.

There may be subsets of patients who are more likely than not to carry MRSA. There have been a few studies in HIV patients that suggest they are at greater risk. Now we see in the study by Zeldin et al that one subgroup, those with perennial allergic rhinitis, have a higher rate of *S. aureus* carriage when compared to controls. The Zeldin study also found that eradication carriage of *S. aureus* carriage did result in fewer rhinitis attacks. Yet, the implications for staphylococcal infection pathogenesis may be more interesting, namely, that the rhinitis group had a higher carriage rate of *S. aureus* than the control group, a fact that may enter into future studies concerned with identifying risk factors in subgroups for *S. aureus* carriage. ■

Importation of Vaccine-Preventable Diseases

ABSTRACT & COMMENTARY

By Corryn S. Greenwood, MD, and Philip R. Fischer, MD

Dr. Greenwood is a resident in the Department of Pediatric and Adolescent Medicine at the Mayo Clinic in Rochester, MN. Dr. Fischer is a Professor of Pediatrics, Division of General Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Greenwood and Dr. Fischer report no financial relationships related to this field of study.

This article originally appeared in the June 2008 issue of Travel Medicine Advisor. It was edited by Frank Bia, MD, and peer reviewed by Phillip Fischer, MD, DTM&H. Dr. Bia is Professor of Medicine and Laboratory medicine; Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN. Dr. Bia is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson, and Dr. Fischer reports no financial relationships relevant to this field of study.

Synopsis: *Recent reports of imported measles and mumps serve as reminders that all travelers should be fully current with routine childhood immunizations.*

Sources: Takahashi H, Saito H. Measles exportation from Japan to the United States, 1994 to 2006. *J Travel Med* 2008;15:82-86; Dayan GH, et al. Recent resurgence of mumps in the United States. *N Engl J Med* 2008;358:1580-1589; Polgreen PM, et al. The duration of mumps virus shedding after the onset of symptoms. *Clin Infect Dis* 2008;46:1447-1449.

Over the past several years, Japan has been chief source of measles importation into the United States. A total of 63 cases of measles were imported to the United States from Japan during the past 22 years. Individuals of almost all age groups were affected (median 17 years, range 9 months-53 years). Ninety percent of such cases occurred in citizens of Japan, and cases identified in the United States reflected common destinations of Japanese visitors (27 in Hawaii, 15 in California, and six in New York). Seven of the infected individuals were known to have transmitted measles to other people in the United States, one of them initiating an outbreak that involved 33 high school students in Alaska. The majority of subjects with known vaccine histories had not been vaccinated against measles.

The largest US outbreak of mumps in the past two decades occurred in 2006 when there were 6,584 cases. A total of 85 subjects were hospitalized, but no fatal cases were identified. Eighty-five percent of cases occurred in eight contiguous Midwestern states, and cases were often associated with outbreaks on college campuses. Orchitis was the most common complication. Sixty-three percent of infected patients overall (and 84% of those aged 18 to 24 years) had received two doses of mumps vaccine. Interestingly, the main mumps virus genotype, G, was identical to the strain isolated from the 2004-2006 outbreak in the United Kingdom that affected more than 70,000 individuals.

Post-outbreak analysis suggests that 8%-15% of mumps patients were still shedding virus more than five days after the onset of symptoms. The new data suggest that infected patients should be isolated for nine days after the onset of symptoms rather than the currently recommended five days.

■ COMMENTARY

It's summer time. Children, adolescents, and young adults are flying around the world for vacations. Microbes, too, are being flown around the world.

Already this year, there have been measles outbreaks in Wisconsin, Arizona (apparently imported from Switzerland), Virginia (from India), and New York (from Israel).[1] Several lessons from these outbreaks are relevant to travel medicine practitioners.

Imported measles is not simply originating from developing countries. In fact, trips to Japan, Switzerland, and Israel (or the United Kingdom, as seen with the mumps outbreak) rarely prompt pre-travel consultations. All physicians should seek to ensure that all their patients, traveling or not, are current on "routine" vaccines against childhood illnesses. What, however, constitutes "current?" In the United States, it is recommended that everyone born after 1956 have two measles-mumps-rubella vaccines. (Older individuals are thought to have high likelihood of having had natural immunity from illness exposure in the pre-vaccine era.) In Canada, it is birth after 1970 that prompts the recommendation of two measles-mumps-rubella vaccines. For pre-travel consultations, illness visits, and health maintenance visits, the recent outbreaks provide fresh reminders for physicians to emphasize the need for compliance with routine vaccination schedules.

The mumps outbreak, however, reminds us that even compliance with vaccination recommendations does not fully protect patients. The vaccines are expected to be 95% effective, but this still leaves a significant number of at-risk individuals who are especially susceptible when in close quarters in col-

lege dormitories and classrooms. Isolation recommendations have been modified to help protect non-immune individuals from exposure to patients who might still be shedding infective virus more than a week after the onset of illness. Concern about vaccine failures has also stimulated discussion of developing improved vaccines against the recently common virus genotypes.

Vaccine recommendations, especially for children and adolescents, change frequently. Medical practitioners should consult up-to-date sources[2] as they seek to keep all travelers up-to-date on all routine vaccines. With hepatitis A vaccine and meningococcal vaccine now routine immunizations on childhood schedules, vaccines once considered to be unique to the practice of travel medicine currently are used broadly. Nonetheless, adolescent travelers might not have received these vaccines, since the vaccines were not "routine" at the time present-day adolescents were young children. New routinely scheduled vaccines, such as the one against human papillomavirus, can also be given prior to international trips when the traveler has not yet been vaccinated and when there is risk of transmission.

Several of the patients in the mumps outbreak were younger than the 12-month age at which the measles-mumps-rubella vaccine is usually given. When infants are traveling and might incur increased risk of vaccine-preventable diseases, "accelerated" schedules may be used. Levels of trans-placentally acquired maternal anti-bodies are waning between six and 12 months of age. Measles-mumps-rubella vaccine, for example, may be given during the first year of life, especially after six months of age, when the risk of disease is felt to outweigh the cost and inconvenience of vaccination. Potential "accelerations" in vaccine scheduling are available in the published literature.[3] ■

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MRSA in the United States and Beyond

ABSTRACT & COMMENTARY

By Maria D. Mileno, MD

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This article originally appeared in the June 2008 issue of Travel Medicine Advisor. It was edited by Frank Bia, MD, and peer reviewed by Phillip Fischer, MD, DTM&H.

Synopsis: *Before 1975, infections due to methicillin-resistant* Staphylococcus aureus *(MRSA) were uncommon. Slowly but steadily, increased reporting of MRSA nosocomial infections occurred through the 1980s and '90s and now presents an additional risk for travelers.*

Sources: Popovich KJ, et al. Are community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains replacing traditional nosocomial MRSA strains? *Clin Infect Dis.* 2008;46:787-794; Wang JL, et al. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*. *Clin Infect Dis.* 2008;46:799-806; Boyce JM. Community-associated methicillin-resistant *Staphylococcus aureus* as a cause of health care-associated infection. *Clin Infect Dis.* 2008;46:795-798.

By 1998, COMMUNITY-ACQUIRED (CA) CASES APPEARED among young children and are now widely documented, representing 15%-74% of *Staphylococcus aureus* skin and soft-tissue infections in US emergency departments. Still, they had not gained great attention until the St. Louis Rams made headlines in the *New England Journal of Medicine*.[1] Two articles and an excellent editorial in the March 15th issue of *Clinical Infectious Diseases* describe MRSA acquired from the community and the similarities in risk factors, outcomes, and behavior of the hospital-acquired strains.

Popovich et al report a method for using molecular typing methods and antimicrobial susceptibility patterns of MRSA isolates responsible for hospital-onset bloodstream infections (BSI). They classify the isolates as either community genotypes or hospital genotypes. Over a seven-year period, the community genotype increased from 24% to 49%; this is significantly higher than the healthcare-associated infections reported at 16%-22% by other authors

recently. There has been a statistically significant decrease in resistance to clindamycin, ciprofloxacin, and gentamicin among hospital-onset MRSA BSI isolates in parallel with an increase in number of BSI isolates showing community genotypes.

The article by Wang et al examined clinical features and outcomes of adults with CA-MRSA bacteremia compared to those with CA-MSSA (methicillin-sensitive *S. aureus*) bacteremia in Taipei, Taiwan. Thirty patients with CA-MRSA and 185 patients with CA-MSSA infections were studied. Increased numbers of patients with CA-MRSA bacteremia were documented over time. Cutaneous abscesses and necrotizing pneumonia were independent predictors of CA-MRSA bacteremia; endovascular infection was the only independent predictor of CA-MSSA bacteremia. The same mortality rates occurred in patients with CA-MRSA as with CA-MSSA. In this cohort only four of the 30 patients with CA-MRSA bacteremia received empirical agents active against MRSA within the first 48 hours of hospitalization. Shock, advanced age, and thrombocytopenia were all predictors of mortality

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In summary, clone USA 300 and similar strains of virulent MRSA have taken off like wild fire on a worldwide basis. CA strains have pulse field gel electrophoresis patterns that differ from hospital-acquired strains. Panton-Valentine Leukocidin (PVL) may provide the organisms with an ability to cause necrotizing skin and soft-tissue infections including necrotizing fasciitis, as well as necrotizing pneumonia, and with the capacity to spread rapidly. Showing slight molecular differences, similarly virulent community-acquired strains are spreading in Europe, Taiwan, and Australia. Although staphylococcal infections can occur at home or abroad, it may be important to alert travelers about the risk of MRSA clone USA 300. Travelers can be warned also that necrotizing skin infections from virulent MRSA can look like spider bites, although a study of spiders concluded that house spiders do not carry MRSA.[2] ■

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CME Questions

28. How much more likely is MRSA carriage to result in subsequent infection than MSSA carriage?

a. None
b. Two times
c. Three Times
d. Four times

29. Which of following is correct?

a. Femoral vascular catheter placement is associated with a significantly greater risk of catheter colonization than jugular vascular catheter placement.
b. Jugular vascular catheter placement is associated with a greater risk of life-threatening hematoma formation than is femoral vascular catheter placement.
c. High BMI increases the risk of jugular catheter colonization.
d. Low BMI increases the risk of femoral catheter colonization.

30. Which country has been the chief source of measles importation into the United States over the past several years?

a. Myanmar
b. Lichtenstien
c. Japan
d. Bourkina Fasso

Answers: 28. (d); 29. (b); 30. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases adn new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy. ■

In Future Issues:

MRSA Colonization

UPDATES

By Carol A. Kemper, MD, FACP

Which do You Treat First — HCV or HIV?

Source: Labarga P, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-Infected patients. *J Infect Dis*. 2007;196:670-676.

REDUCTION OF TREATMENT-RELATED toxicities have direct bearing on the decision when to initiate antiretroviral therapy. Clinicians may opt to delay antiretroviral therapy or avoid certain agents because of quality-of-life issues and the risk of treatment-related toxicity. Fears of hepatotoxicity may drive decisions regarding treatment, especially in patients with higher CD4 counts (eg, with the use of nevirapine) or in patients with chronic HCV.

Labarga et al determined the risk of antiretroviral treatment-related toxicity in 132 patients with HCV/HIV co-infection, who had received a full course of interferon therapy. Most patients had early HIV disease (the mean CD4 for the group was > 600), allowing for a reasonable delay in HIV treatment. A sustained HCV virologic response (SVR) was achieved in 33%. Despite treatment with interferon, 40% had advanced liver fibrosis (using a composite endpoint of liver disease). Following completion of interferon therapy and initiation of HAART, liver toxicity events were recorded, including symptomatic elevations in liver enzymes, all grade 3 and 4 elevations in transaminases (> 5-fold the upper limit of normal or > 3.5-fold baseline values, if already elevated), and events resulting in discontinuation of drug or a change in the regimen. A total of 49 episodes of liver toxicity occurred during a mean follow-up of 35 months (~9.7% per year). The majority of these episodes were attributed to either dideoxynucleoside analogues (i.e. didanosine and stavudine) (40%) or nevirapine (30%), while liver toxicity from efavirenz (11%) and protease inhibitors (8%) was less frequent. About one-fourth of patients had symptomatic elevations in liver enzymes that did not achieve grade 3 or 4, and about 4% resulted in discontinuation of drug or a change in the regimen.

Liver toxicity was significantly less frequent in patients who achieved a SVR compared with those who did not (3.1% vs 12% per year, $p < .001$). The proportion having a grade 3 or 4 elevation in ALT was significantly lower in patients achieving SVR than those who did not (6.9% vs 27.3%, $p = .007$). Hepatotoxic events occurred in 23% and 54% of those without and with advanced liver disease (7.6% vs 11.6% per year, $p = .003$), respectively.

Logistic regression analysis showed that the lack of SVR and the use of dideoxynucleosides were the only predictors of liver toxicity.

For patients in the developed world, these findings may not be that relevant, as the use of dideoxynucleosides has all but vanished. Patients in the developing world are, however, still receiving these agents, and for these patients, these data may be helpful in recognizing the risk of treatment in patients with HIV/HCV. Such patients seldom have access to interferon therapy for HCV.

For patients in the developed world, the question remains whether to reasonably delay initiation of HAART in those who could first be treated for HCV. For those asymptomatic patients with higher CD4 counts, this may be reasonable. However, since most hepatotoxicity can be managed with little long-term sequela, and most events are not life-threatening (and only 4% resulted in a change in therapy), the presence of HCV should not dissuade physicians from initiation of ART as soon as is reasonable.

Toxoplasmosis in Marine Animals

Source: Massie G, et al. 108th American Society of Microbiology General Meeting, June 6, 2008.

TOXOPLASMOSIS IS GENERALLY understood to be a disease of meat-eaters. *T. gondii* has a predilection for muscle and brain, where it encysts — waiting to be eaten by the next carnivore. Most humans acquire toxoplasmosis from undercooked meat, although garden produce contaminated with cat feces may also be a significant source of infection. Cases of acute toxoplasmosis, in my practice, have included a middle-aged woman on an eco-tour of Costa Rico, where she ate deer cooked over an open barbecue, and one patient who dined on elk tartar. Lately, I cannot but wonder about the homemade venison sausage we get from home every Christmas, previously considered a real treat.

But how did the otters off the coast of California become such frequent victims of toxoplasmosis? They don't exactly eat elk. While it is conceivable cat feces have contaminated local water run-off into the ocean, the worldwide spread of toxoplasmosis in marine life seems too extensive for this explanation. Although sea otters off the California coast have been hard hit (17% of sea otter deaths are currently being attributed to toxoplasmosis), tox-

oplasmosis has now been reported in beluga whales, dolphins, sea lions, and seals, extending from one end of the globe to the other.

A graduate student at CalPoly may have an answer: according to a preliminary paper presented at ASM this year, northern sea anchovies, which are considered "filter feeders", are able to filter *T. gondii* oocysts. Anchovies are a favorite food of sea otters. If anchovies prove to harbor infectious oocysts, it could explain the spread of toxoplasmosis to marine mammals.

Response to Therapy for Strongyloides

Source: Boscolo M, et al. Evaluation of an indirect immunofluorescence assay for Strongyloidiasis as a tool for diagnosis and follow-up. *Clin Vaccine Immunol*. 2007;14:129-133.

Sometimes patients ask the greatest questions. A middle-aged woman, who had traveled extensively as a younger woman, presented with a two-year pruritic rash. Her husband has occasional respiratory symptoms, and her 24-year-old daughter (who had been dragged along on the family sojourns to 21 different countries) had occasional pruritus and abdominal pain. My patient had been to several dermatologists, biopsies were nonspecific, and topical steroidal creams were of no benefit. Serologies for strongyloides stercoralis were positive in three of four family members — only a younger sibling who had missed all of the fun was seronegative. Antibody tests for Schistosoma were negative, and multiple stool specimens in each were negative. All three received ivermectin 200 µ/kg daily for two days, and again two weeks later.

Since the goal of therapy is a cure, how does one assess response to therapy, other than possibly based on a symptomatic response? Serological testing for strongyloides may have varying degrees of sensitivity, the cut-offs are not well-defined, and they frequently cross-react with other helminthes. One smaller study found that antibody levels declined in only one of eight patients following treatment.

Boscolo et al followed changes in *S. stercoralis* antibody titers in a group of 155 patients at ~4 months post-treatment. Symptoms were common (84%), and included pruritus (59%), abdominal pain (48%), skin rash (25%), respiratory symptoms (14%), and diarrhea (10%). Patients received either thiabendazole or a single dose of ivermectin 200 µ/kg. Antibodies were measured using an indirect immunofluorescence antibody test (IFAT) for *S. stercoralis*, which has the advantage of providing a quantitative result of the specific antibody titer. Based on assessment of patients with confirmed stool diagnosis of *S. stercoralis* vs those admitted to Italian hospital for other reasons, the sensitivity and specificity of the assay was determined to be 97% and 98%, respectively.

Four months following treatment, 60% had an apparent response to treatment, based on antibody response, with either seroreversion (36%) or a decrease in antibody titer (24%). Seventeen percent had only a one-fold reduction in antibody titer, while 23% had a stable or increased antibody titer. Patients with higher antibody titers were more likely to respond to therapy.

A second study from the Queensland Institute for Medical Research assessed antibody titers before and after treatment in a group of 79 seropositive Aboriginals living in an area of Northern Australia endemic for strongyloides.[1] During the initial study period, patients received albendazole 400 mg daily for 3 days as directly observed therapy in the clinic; if they remained seropositive, therapy was repeated. Once ivermectin was available for use in 2000, seropositive patients received a single dose of ivermectin 200 µ/kg. Most patients received multiple courses of therapy with either or both agents, although 19 received a single dose of ivermectin. Four patients failed to return to clinic to complete their DOT therapy (three received a single dose of albendazole and one received several single-day courses of albenazole). Antibody was measured using an IgG ELISA test at least three months following treatment; the median interval between the pre-treatment and follow-up antibody tests was about one year.

Seroreversion occurred in 68% of patients receiving a single dose of ivermectin, and 83% of patients receiving multiple course of ivermectin eventually experienced seroreversion. A three-day course of albendazole resulted in 40% response antibody response, whereas none of five patients receiving a single dose of albendazole seroreverted. Overall, seroresponses were observed in 70% of patients received one or more three-day courses of albendazole.

Despite repeated courses of therapy, 22% remained seropositive. In contrast to Boscolo et al, poorer seroresponses were observed in patients with higher antibody titers, although titers in a few patients were more suggestive of re-infection than failure. Whether the presence of persistent antibody in the remaining patients indicates treatment failure or a serofast state, is not clear. However, the observation of seroresponse in those receiving repeated courses of therapy suggests that antibody levels can be used to assess response to therapy. ■

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PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Bird Flu Vaccine Looks Promising

In This Issue: Baxter Bioscience has developed a whole-virus, two dose vaccine against avian flu; warning label now on antipsychotics regarding an increased risk of mortality in elderly patients treated for dementia-related psychosis; vitamin D for men with heart disease on horizon? A new oral anticoagulant may soon be available for prevention of thrombotic complications of hip or knee surgery; FDA Actions

An effective two dose vaccine has been developed against the avian flu (H5N1 virus) according to a recent study in the *New England Journal of Medicine*. Researchers from Baxter Bioscience have developed a whole-virus vaccine that was tested on 275 volunteers between the ages of 18 and 45 years. Four different strengths of the vaccine were tested with and without adjuvant. The most effective regimen was a dose of either 7.5 µg or 15 µg of hemagglutinin given without adjuvant 21 days apart. The vaccine was effective at inducing neutralizing antibody response against three different viral strains. Mild pain at the injection site and headache were the most common adverse effects. The authors conclude that a two dose vaccine regimen of either 7.5 µg or 15 µg induced neutralizing antibodies against diverse H5N1 viral strains in a high percentage of subjects (*NEJM*. 2008;358:2573-2584).

Boxed warning now required for antiphychotics for elderly with dementia

The FDA is requiring a boxed warning for conventional antipsychotics regarding an increased risk of mortality in elderly patients treated for dementia-elated psychosis. This expands the warning on the newer atypical antipsychotics which was issued in April 2005 to include the older, more conventional antipsychotics. The new warning includes medication such as haloperidol (Haldol), thioridazine (Mellaril), and chlorpromazine (Thorazine). The warning specifically states that elderly patients with dementia-related psychosis treated with conventional or atypical antipsychotic drugs are at increased risk of death. Antipsychotic drugs are not approved for the treatment of dementia-related psychosis, and physicians who prescribe antipsychotics for elderly patients with dementia-related psychosis should discuss this risk of increased mortality with their patients, patient's families, and caregivers. It was previously thought only the newer, atypical antipsychotics were associated with increased mortality; however, multiple studies have now shown that the older antipsychotics also increase the risk. The warning can be found on the FDA web site at www.FDA.gov.

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) 262-5431. E-mail: iris.young@ahcmedia.com.

Vitamin D for men with heart disease?

Men may be asking about prevention of heart disease with vitamin D based on this reports of recent studies. In a follow-up from the Health Professionals Follow-up Study (HPFS) from the Harvard School of Public Health, plasma 25-hydroxyvitamin D levels were measured on over 18,000 male health-care professionals age 40 to 75 years, who were free of diagnosed cardiovascular disease at blood collection. In 10 years of follow-up, 450 men had nonfatal myocardial infarction or fatal coronary heart disease. After adjustment for matched variables, and men deficient in 25-hydroxyvitamin D (≤ 15ng/ml) were at increased risk of MI compared to those considered to be sufficient (≥ 30ng/ml) (RR 2.42; 95% CI, 1.53-3.84; *P* <.001 for trend). After adjustment for family history and multiple risk factors, the relationship remains significant. Even those with levels 22.6 to 29.9 ng/ml were at higher risk than those with levels over 30 ng/ml. The authors conclude that "low levels of 25-hydroxyvitamin D are associated with a higher risk of myocardial infarction in a graded manner even after controlling for factors noted to be associated with coronary disease." The mechanism for this relationship is unclear but may be related to vitamin D, its effect on vascular smooth muscle proliferation, inflammation, vascular calcification, and blood pressure. Whether vitamin D supplementation reverses these findings remains be seen, but it is clear that men with low vitamin D levels will require more than the current recommended daily allowance of 200-600 IU/d, perhaps even as much as 3000 IU/day (*Arch Int Med*. 2008;168:1174-1180). Another study with similar conclusions was recently published (*Arch Intern Med*. 2008;168:1340-1349).

New oral anticoagulant tested for patients with hip or knee surgery

A new oral anticoagulant may soon be available for prevention of thrombotic complications of hip or knee surgery. Rivaroxaban is an oral direct inhibitor of factor Xa that is in phase 3 trials by Bayer and Ortho-McNeil Pharmaceutical. The drug has the advantage of being highly bioavailable when given orally and has a standard 10-mg dose given once a day. In 3 recent trials, rivaroxaban was compared to subcutaneous enoxaparin after total hip arthroplasty and total knee arthroplasty. Over 7000 patients were randomized to receive rivaroxaban 10 mg daily beginning after surgery or subcutaneous enoxaparin 40-mg once daily beginning the day before or the day of surgery. A third study compared long-term use of rivaroxaban with short-term use of enoxaparin. The primary outcomes included deep venous thrombosis, pulmonary embolism, and all cause mortality. In all 3 studies thromboprophylaxis with rivaroxaban was significantly more effective than enoxaparin, while toxicity, specifically major bleeding, was the same in both groups. The authors conclude that a once-daily 10-mg oral dose of rivaroxaban is significantly more effective than a 40 mg subcutaneous dose of enoxaparin in preventing thrombotic complications in patients undergoing total hip or total knee arthroplasty (*NEJM.* 2008;358:2765-2775, 2776-2786. *Lancet* 2008 published early online 25 June 2008). While rivaroxaban is not yet approved in this country, the prospect of an orally active direct Xa inhibitor that could take the place of parenteral heparin compounds and perhaps even warfarin is exciting to clinicians.

FDA Actions

The FDA has approved a new pentavalent vaccine for children age 6 weeks through 4 years. The new vaccine combines diphtheria, tetanus, pertussis, poliomyelitis, and Haemophilus influenza type b. It is given as a 4 dose series at 2, 4, 6 and 15-18 months of age. The vaccine is marketed by Sanofi Pasteur as "Pentacel." GlaxoSmithKline has also received approval for a combination vaccine with diphtheria, tetanus, acellular pertussis, and polio for children 4 to 6 years old who require their fifth DTaP and fourth polio shot. The combination vaccine may prevent additional injections for these children. This four vaccine combination will be marketed as "Kinrix."

The FDA has issued warning letters to 23 US companies and two foreign individuals regarding the marketing of fake cancer cures on the Internet. The products which include tablets, tonics, black salves, and creams are fraudulently promoted, claiming to prevent and cure cancer. The products contained in treating such is bloodroot, shark cartilage, coral calcium, cesium, Cat's Claw, herbal tea and mushrooms. A complete list of companies and individuals concluded and the warning can be found at www.fda.gov/cder/news/fakecancercures.htm. ■