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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Pediatric Coccidioidomycosis in CA: Delayed Diagnosis Increases Severity

By Dean L. Winslow, MD, FACP, FIDSA

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SOURCES: McCarthy JM, et al. Pediatric coccidioidomycosis in central California: A retrospective case series. *Clin Infect Dis* 2013; 56: 1579-85.

A retrospective observational study of all children admitted to Children's Hospital of Central California (Madera, CA) with coccidioidomycosis (coccy) from January 2010 to September 2011 was conducted. Thirty-three children were hospitalized with coccy during this period and ranged in age from 6 months to 17 years. Clinical manifestations included pneumonia (n=28), pleural effusion (n=13), empyema (N=4), lung abscess (n=7), pericarditis (n=2), osteomyelitis (n=5), meningitis/cerebritis (n=2), and vocal cord infection (n=1). Mediastinitis with evidence of purulent/necrotic/abscessed nodes in the mediastinum was present in 7 (21%) and tended to occur in younger children (median age 3 years). Seven patients were admitted to the ICU, 10 required surgical intervention, and one patient died of meningitis. Children with mediastinitis required longer hospitalization (median 130 days) vs. median 43 days for children without mediastinitis. Patients with coccy CF titers >=1:128 required longer hospitalization than those with titers <1:128 (median 130 days vs. 43 days). Overall, 64% of children were Hispanic, 21% were non-Hispanic Caucasian, 9% were Asian, and 6% were African-American.

All patients were treated initially with intravenous liposomal amphotericin B or fluconazole with amphotericin preferentially used in those patients with more severe disease. Overall, 76% of patients responded to initial therapy. Eight patients (47%) failed to respond to initial amphotericin B therapy and had progressive disease. Various salvage therapy regimens were used, including liposomal amphotericin B+an azole in most cases, voriconazole+caspofungin

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in 2 patients, interferon gamma in 3 patients, and intrathecal amphoterician B in one patient. All patients except the one patient who died of meningitis were eventually discharged home on an oral azole.

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This is an important retrospective study which highlights a number of interesting issues for diagnosis and management of coccy in children. Despite the prevalence of coccy throughout much of California, delayed diagnosis of coccy was common in these children and likely contributed to the severity of disease and prolonged hospitalizations observed in many of these patients. None of these children were known to be immunocompromised. The common presentation of mediastinitis with necrotic mediastinal lymph nodes (occasionally resulting in airway compression) was also of note.

Practicing the past 15 years in California has given me a real appreciation for the diverse clinical manifestations of patients with coccy, the problems associated with treatment, and management of complications associated with this disease. I am grateful every day for the wise counsel and expertise of my colleagues at our County hospital (especially David Stevens and Larry Mirels) in managing these patients and I would encourage all of us who care for coccy patients to make liberal use of the advice from experts like these. I am still haunted by the death of a 6-year-old child I cared for about 3 years ago on the Pediatric service at our hospital. This little boy died of complications of coccy meningitis (which included hydrocephalus requiring shunt placement and cerebral vasculitis requiring systemic corticosteroid therapy) despite aggressive treatment with intravenous liposomal amphotericin B, fluconazole, and intrathecal amphotericin B.

Optimal therapy of coccy is still vigorously debated. In this same issue of CID there was another interesting case series describing 9 pediatric patients with refractory coccy who responded to combination therapy with voriconazole and caspofungin.[1] Clearly much work, including large multicenter randomized controlled trials, need to be done to develop more effective therapy of severe coccidioidomycosis in both adults and children.

Reference

1. Levy ER, et al. Treatment of pediatric refractory coccidioidomycosis with combination voriconazole and caspofungin: a retrospective case series. *Clin Infect Dis* 2013; 56: 1573-8. ■

ABSTRACT & COMMENTARY

Increased Risk for Statin Toxicity in the Elderly While on Macrolide Therapy

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: In a large population-based retrospective cohort study, adults > 65 years on statin therapy who received a co-prescription for clarithromycin or erythromycin had an elevated risk for developing statin toxicity. There was no associated risk seen with azithromycin.

SOURCE: Patel AM, et al. Statin Toxicity From Macrolide Antibiotic Coprescription. *Ann Intern Med* 2013;158:869-876.

Drug interactions are ubiquitous in clinical practice. One class of drugs particularly impacted is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly referred to as statins. These medications are

frequently prescribed worldwide for the prevention and treatment of cardiovascular disease and hypercholesterolemia. Statins are metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4). A number of medications inhibit this enzyme, leading to increased statin concentration in the blood. The macrolide antibiotics clarithromycin and erythromycin are two examples of CYP3A4 inhibitors. Of note, azithromycin does not inhibit CYP3A4. Given the large numbers of prescriptions for statins and macrolides especially in the elderly, investigators sought to elucidate the risk of statin toxicity in older patients co-prescribed these two classes of medications.

The study was a population-based, retrospective cohort of adults aged > 65 years in a health care database from Ontario, Canada. Subjects eligible for inclusion in the cohort included those with continuous prescriptions for atorvastatin, simvastatin, or lovastatin and new co-prescriptions for clarithromycin, erythromycin, or azithromycin. Enrollment went from June 2003 to December 2010. A total of 72,591 subjects received clarithromycin, 3,267 received erythromycin, and 68,478 received azithromycin. The baseline characteristics of the groups were similar. Outcomes were determined 30 days after the index date, of which the primary outcome was hospitalization with rhabdomyolysis. Secondary outcomes included hospitalization with acute kidney injury (AKI), hyperkalemia, and all-cause mortality. Absolute risk was quantified as the number needed to harm (1/absolute risk difference), defined as an indicator of how many patients need to receive a co-prescription for clarithromycin or erythromycin to cause harm to one patient who otherwise would not have been harmed.

The median duration of antibiotic therapy was 10 days for clarithromycin or erythromycin and 5 days for azithromycin. Compared to subjects co-prescribed statins and azithromycin, those receiving clarithromycin or erythromycin with a statin had a higher risk for hospitalization with rhabdomyolysis (relative risk [RR], 2.17 [95% confidence interval [CI], 1.04 to 4.53]) and AKI (RR, 1.78 [CI, 1.49 to 2.14]). The risk for hospitalization with hyperkalemia was not significant. The risk for all-cause 30-day mortality was higher with clarithromycin or erythromycin (RR, 1.56 [CI, 1.36 to 1.80]).

When risk was expressed in absolute terms, receiving clarithromycin or erythromycin was associated with a 0.02% (CI, 0.01% to 0.03%) higher incidence of hospitalization with rhabdomyolysis and a 0.25% (CI, 0.17% to 0.33%) higher incidence of all-cause mortality. The corresponding number needed to harm for hospitalization with rhabdomyolysis was 5,870 and for all-cause mortality was 399. Forty percent of the patients had chronic kidney disease at baseline, with a glomerular filtration rate below 60 mL/min per 1.73 m2. Co-prescription of clarithromycin or erythromycin in this group was associated with a high risk for hospitalization with AKI (RR, 2.92 [CI, 1.47 to 5.79]) and hyperkalemia (RR, 11.04 [CI 1.48 to 82.58]).

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The safety of macrolides, in particular their risk for cardiovascular death, has recently been called into question. The subject is controversial however, as different investigators have reported discordant findings.[1,2] The present study by Patel and colleagues brings attention to serious adverse events caused by the interactions of CYP3A4-inhibiting macrolides and statins metabolized by this enzyme. It is reassuring that these adverse events were not associated with azithromycin, which is prescribed for such common conditions as bronchitis and community-acquired pneumonia. Of note, clarithromycin and erythromycin still have important clinical uses, for instance, the former is used in combination therapy for Mycobacterium avium-intracellulare complex (MAC) while the latter is sometimes prescribed for skin infections.

The study had some limitations, the most significant being the observational design which can not prove causality from the associations discovered. Another was the subjects were all > 65 years, making it unclear if the findings can be generalized to younger patients. Clarithromycin and erythromycin are generally prescribed for longer durations than azithromycin which may have also contributed to the observed differences. Finally, the role of other drugs co-prescribed along with the statins and macrolides were not taken into account and may have influenced the outcomes.

How should the results of this study be incorporated into clinical practice? I recommend that if a short course of clarithromycin or erythromycin therapy is needed, a CYP3A4-metabolized statin should be temporarily discontinued. If a longer course is needed (e.g. MAC therapy) then a statin that is not metabolized by CYP3A4 should be used, such as pravastatin which is mostly metabolized in the stomach. Moreover, rosuvastatin should probably be avoided, too, as preliminary data from the study showed an increased risk for AKI when co-prescribed with clarithromycin or erythromycin compared to azithromycin (RR, 1.46). If a clinical situation necessitates that no alternatives to clarithromycin or erythromycin can be given and a CYP3A4-metabolized statin can not be held

(which should be rare), then frequent laboratory monitoring is strongly encouraged. Until data show it is clearly safe to co-prescribe statins with clarithromycin or erythromycin in patients less than 65 years, it is reasonable to avoid the combination in this age group, too.

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ABSTRACT & COMMENTARY

Impact of Vaccination on Maternal Antibody Levels

By Hal B. Jenson, MD, FAAP,

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

SYNOPSIS: As MMR vaccination coverage among mothers increases, compared to mothers with natural immunity the levels of maternal antibodies in offspring at birth decreases and the projected duration of the protection afforded by maternal antibodies among their infants also decreases.

SOURCE: Waaijenborg S, et al. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. *J Infect Dis* 2013;208:10-16.

A large cross-sectional serologic study was conducted in the Netherlands during 2006-2007 to compare kinetics of maternally-acquired antibodies in offspring. A total of 19,781 participants were invited in a nationwide survey of 40 communities selected at random, weighted by their population size. An age-stratified sample of 380-500 participants (less than 80 years of age) was drawn at random from each of these communities, with the sample size dependent on the response rate of each community. For a comparison group, participants were recruited from eight predominantly orthodox Protestant communities where vaccination coverage is low. An age-stratified sample of 380-952 participants (less than 80 years of age) was drawn at random from each of these communities. Vaccination histories of the infant participants were verified by vaccination certificates brought by the mothers and, where possible, a copy of the regional vaccine administration offices archives.
Antibody levels of IgG against measles, mumps, rubella, and varicella were determined by florescent bead-based multiplex immunoassays using Luminex technology (based on complete virus particles).

For measles, there was a large difference in vaccination coverage of women of childbearing age with 51.2% vaccinated in the general population versus 12.6% in the orthodox Protestant communities. Women of childbearing age and infants in the general population had a lower measles antibody concentration than infants and women of childbearing age in the orthodox Protestant communities ($P < 0.0001$). The concentration of maternal antibodies in offspring at birth was 4.13-fold lower in the general population compared to the orthodox Protestant communities. The decay rate for maternal measles antibody was 7.77 per year, which corresponds to a half-life about one month. The projected duration of protection against measles was 3.3 months for newborns in the general population and 5.3 months for newborns in the orthodox Protestant communities.

For mumps, there was a smaller difference in vaccination coverage of women of childbearing age with 25.3% vaccinated in the general population versus 10.1% in the orthodox Protestant communities. There were not statistically significant differences in antibody levels between two groups. The decay rate for maternal mumps antibody was 8.01 per year, which corresponds to a half-life of about one month. The projected duration of protection against mumps was 2.7 months for newborns in both study groups.

For rubella, there was a large difference in vaccination coverage of women of childbearing age with 65.6% vaccinated in the general population versus 17.2% in the orthodox Protestant communities. The concentration of maternal antibodies in offspring at birth was 55.19-fold lower (95% CI, -6.22 to 116.60; $P = 0.0296$) in the general population compared to the orthodox Protestant communities. The decay rate for maternal rubella antibody was 7.01 per year, which corresponds to a half-life of about one month. The projected duration of protection against rubella was 3.9 months for newborns in the general population and also in the orthodox Protestant communities.

For varicella, no participants had been vaccinated and

the level of varicella antibodies did not differ between the two study groups. The decay rate of maternal verso antibodies was 7.36 per year, with the duration of protection against personal of 3.4 months for newborns of both groups.

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This study confirms that infants of vaccinated mothers lose protection from maternal antibodies against measles, mumps and rubella well before 12-15 months of age when the first dose of MMR is recommended. The decay rates of 7.77, 8.01, and 7.01 per year of maternal measles, mumps and rubella antibodies, respectively, implies that each month the concentration of maternally-acquired antibodies is reduced by about half. With the lower level of maternal antibodies of birth, the period of protection decreases by almost 2 months. Indeed, this is evidenced by a shift in the incidence of measles to frequently include children less than 12 months of age.

The comparison of the two groups suggests that as MMR vaccination coverage among mothers increases, compared to mothers with natural immunity the levels of maternal antibodies in offspring at birth decreases and the projected duration of the protection afforded by maternal antibodies among infants also decreases. The basis for this is likely two-fold: MMR vaccine induces lower levels of antibodies than natural infection with measles, mumps, and rubella; and vaccinated individuals are no longer boosted by exposure to wild-type infections.

The optimal timing of the first MMR vaccination is before likely exposure to disease—but a satisfactory immune response is dependent on maturation of the infant's immune system to respond to vaccine antigens, and when the decay of maternal antibodies is sufficient to ensure that they do not interfere and neutralize the live, attenuated vaccine strains. This balance is why the recommended age of MMR vaccination was modified in 1998 to 12-15 months of age (from 15 months of age) to reflect the impact of MMR vaccination and decreased antibody titers among women of child-bearing age. ■

Improved Laboratory Diagnosis of Acute HIV Infection

By Stan Deresinski, MD, FACP, FIDSA

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

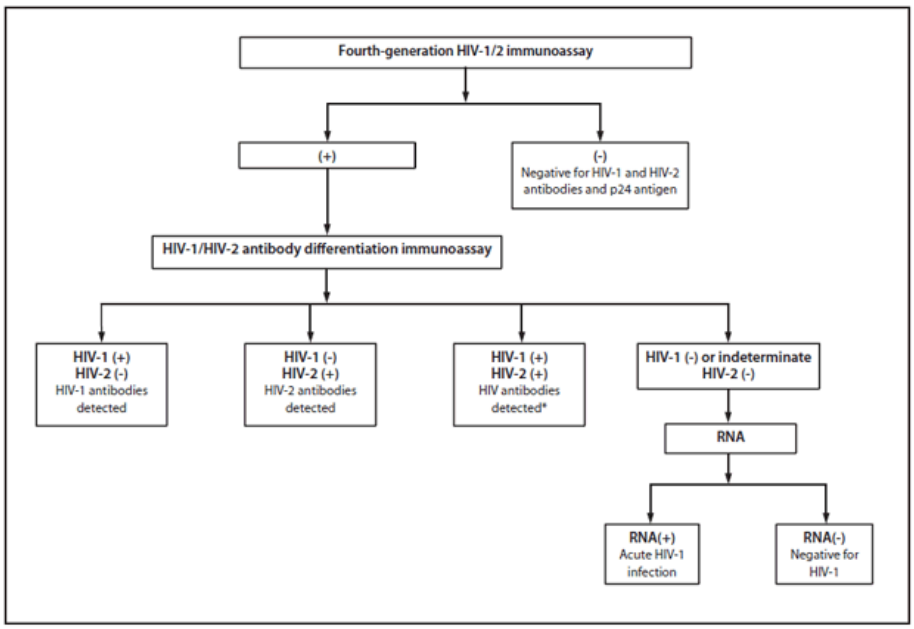
SYNOPSIS: In 2006, the CDC recommended routine, voluntary HIV testing for persons aged 13-64 in all health care settings, with elimination of separate informed consent5 and this recommendation has basically now been adopted by the U.S. Preventive Services Task Force. It is also critical that clinicians be alert to the diagnosis of acute HIV infection. CDC now recommends that current practice be changed to reflect the results of the studies reviewed here.

SOURCE: Centers for Disease Control and Prevention. Detection of Acute HIV Infection in Two Evaluations of a New HIV Diagnostic Testing Algorithm - United States, 2011-2013. *MMWR* 2013;62(24):489-94.

Early treatment of acute or recent HIV infection is associated with improved CD4 cell recovery,[1] as well as additional potential clinical benefits such as a reversal of neuronal inflammation as observed by magnetic resonance spectroscopy.[2] It is also now recognized as a prevention strategy since many transmissions occur during this period of high viral load, often in the absence of symptoms.[3] Unfortunately, most cases of HIV infection are not diagnosed until the infection has become chronic, either because the initial infection was asymptomatic or, in some symptomatic cases, because seroconversion may not have been detected with standard antibody testing.

The current standard HIV diagnostic algorithm consists of performing an immunoassay (IA) which, if initially positive, is repeated. A reproducibly positive IA is followed by use of a supplemental confirmatory test, such as the Western blot (WB) or indirect immunofluorescence assay (IFA). In acute infection, however, currently used IA tests detect HIV infection earlier than supplemental tests. During that interval before the supplemental test becomes positive, a reactive IA in combination with a negative supplemental test may erroneously be interpreted in some patients as indicating an absence of HIV infection. In addition, approximately 60% of HIV-2 infections are misclassified as HIV-1 infection. A recent study in 26 recent seroconverters in the U.S. found that one or more IAs became positive 5-26 days before Western Blot positivity.[4] There has, however, been

Figure 1. New HIV diagnostic testing algorithm evaluated - United States, 2011-2013



Abbreviation: HIV = human immunodeficiency virus.

* Additional testing required to rule out dual infection with HIV-1 and HIV-2.

Alternate Text: The figure above is a flowchart depicting the new human immunodeficiency virus (HIV) diagnostic algorithm, which replaces the Western blot test with an HIV-1/HIV-2 antibody differentiation assay as the supplemental test and includes an RNA test to resolve a reactive immunoassay with a negative supplemental test result.

Source: Centers for Disease Control & Prevention

progressive improvement in HIV testing: 1st and 2nd generation tests, which use viral lysate antigens and either synthetic peptide or recombinant antigens, respectively, and which detect only IgG antibodies, have been largely supplanted by more sensitive tests.

Most laboratories currently use either 3rd generation IAs that detect both IgM and IgG antibodies as well as p24 antigen. The changing technology of HIV testing has led the CDC to evaluate a new HIV diagnostic algorithm utilizing newer tests. In an initial study, in which a sensitive 3rd or 4th generation immunoassay was followed by an HIV-1 and HIV-2 discriminatory test, with discordant results settled by a nucleic acid amplification test, significantly more infections were detected than were with use of the standard algorithm with older tests.[5] Furthermore, a 4th generation test performed better than a 3rd generation test. In contrast, the alternative algorithms performed equally well in patients with chronic HIV infection.

CDC has now extended the study of the alternative algorithm, using a 4th generation IA and replacing the Western Blot with an HIV-1/HIV-2 antibody differentiation assay and uses detection of HIV RNA to resolve cases in which the IA is positive but the supplemental result is negative. In one study in an Arizona emergency department, screening of all adults 18 through 64 years of age identified 37 previously unidentified HIV infections; 12 (32.4%) were acute and would have been missed by current testing practices. Separately, in a multisite study, 56 acute HIV infections would similarly have been missed by current testing practices *[See Figure 1]*.

In 2006, the CDC recommended routine, voluntary HIV testing for persons aged 13-64 in all health care settings, with elimination of separate informed consent[5] and this recommendation has basically now been adopted by the U.S. Preventive Services Task Force. It is also critical that clinicians be alert to the diagnosis of acute HIV infection. CDC now recommends that current practice be changed to reflect the results of the studies reviewed here.

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ABSTRACT & COMMENTARY

Preventing ICU Infections: An Effective Application of An Old Public Health Strategy

By Michael Young, MD

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Dr. Young reports no financial relationships relevant to this field of study.

SYNOPSIS: Despite better compliance with hand hygiene and screening, use of isolation, and other techniques, ICUs remain notorious breeding grounds for hospital-acquired infections. A universal decolonization strategy reduces the total number of ICU bloodborne infections.

SOURCE: Huang SS, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;368:2255-2265.

In the 1840s, the Hungarian physician Ignaz Semmelweis demonstrated that maternal mortality was reduced by 90% when physicians washed their hands with a chlorinated lime solution prior to doing pelvic exams on women in labor. The physician community at that time was harshly skeptical of Semmelweis's observations and recommendations. Women of the time were aware that something was lethal about having babies in the hospital. Some women in the 1840s preferred having their babies literally in the street vs the high-mortality obstetrical wards in teaching hospitals. A century and a half later, hand hygiene is widely accepted as a technique to reduce transmission of infections among hospitalized patients. Uniform compliance with recommended hygiene practices remains disappointing.

About 100 years after Semmelweis's discovery that hand hygiene really matters, ICUs came into existence. It made sense to clinicians to cluster the sickest patients in one area of the hospital to more conveniently apply new technologies such as mechanical ventilation, central venous lines, and the rapidly evolving skill sets of clinicians who focused on managing critically ill patients. Unfortunately, those life-preserving technologies and the ICU population of patients and their clinicians became reservoirs of methicillin-resistant *Staphylococcus aureus* (MRSA) as early as the 1960s. By 2005, it was estimated that hospitals see more than 18,000 deaths/year from MRSA — more deaths than those reported from AIDS and breast cancer combined. The ICU was no small contributor to the rising death toll from MRSA infections.

In the past two decades, a number of strategies have come into use to prevent the spread of MRSA and other infectious agents in the ICU. The effectiveness of some of these strategies, such as screening patients for MRSA, isolation, contact precautions, and decolonization, has been uncertain. The study by Huang and colleagues provides clinicians, nurses, and infection control specialists much needed guidance.

The authors conducted the study in 43 Hospital Corporation of America hospitals, including 74 ICUs. A 12-month baseline period was followed by an 18-month intervention period in which participating hospitals were randomized, using a stratified technique, to one of three infection control groups. In group 1, > 90% of ICU patients received screening and isolation if their nasal swab was positive for MRSA. Contact precautions were used among patients who screened positive for MRSA. In group 2 ("targeted decolonization"), MRSA screening and isolation occurred as in group 1. MRSA-positive patients underwent a 5-day decolonization process. In group 3 ("universal decolonization"), patients were not screened on admission to the ICU. All ICU patients in group 3 received twice-daily intra-nasal mupirocin for 4 days, plus daily baths with chlorhexidine-soaked cloths during the patients' entire ICU stay. Adherence to the infection control interventions in each of the three groups was encouraged by monthly educational teleconferences and use of on-site hospital personnel. Infections/pathogens were defined using Centers for Disease Control and Prevention (CDC) criteria. Compliance rates of 85% were cited.

There were nearly 100,000 patients enrolled in each of the three groups. Each group had largely similar baseline demographic characteristics. MRSA-positive isolates and the risk of developing a bloodborne pathogen were significantly reduced by universal decolonization. With universal decolonization, the number needed to treat to prevent one bloodstream infection was 54 ICU patients. The rate of blood-borne infections from MRSA was not reduced by either targeted or universal precautions.

■ COMMENTARY

Limitations of the study include lack of an explicit and detailed protocol for each of the three groups. In addition, it remains uncertain if routine use of chlorhexidine and mupirocin will lead to resistance.

Severity of illness on ICU admission was not reported. Most of the hospitals included in the study were community hospitals, so it remains unknown if similar results will be seen in large teaching hospitals. It is also unclear why a decrease in MRSA colonization rates, the primary outcome, was not associated with a decrease in MRSA bacteremia.

Study strengths are considerable. Implementing universal decolonization was undertaken with existing personnel without apparent increased costs. The sample size was substantial. Randomization ensured similar baseline characteristics. The size of the reduction in MRSA colonization and positive blood cultures was both statistically and clinically significant. Finally, use of universal decolonization techniques in ICUs is becoming a more common practice.

Should this study change standard infection control measures in our ICUs? I believe that the answer to this question is an emphatic yes. As this study demonstrates, isolation and contact precautions lack effectiveness at preventing infection, and they also reduce clinician bedside presence. Arguably, it is intensivist bedside presence that is at least partly responsible for the improved patient outcomes seen with the intensivist "high intensity" model. In addition, from the use of "bundles" in the ICU over the past 10 years, such as those used for ventilator-associated pneumonia, central line infection reduction, and early resuscitation for sepsis, we have learned that ICU outcomes dramatically improve when a practice becomes universal and applied to all rather than applied selectively or simply at physician discretion.

Will many or all ICUs make the change to universal decolonization soon? This seems less certain, but my forecast is largely positive for the following reasons. We recognize that changes in hospital infection control practices involve complicated organizational and cultural shifts. However, physicians and hospitals change practice patterns over a period of months rather than over years if certain forces align, including: a convincing level of medical evidence; minimal cost to implementing the intervention; the intervention makes "life" easier for the clinicians; and authoritative groups such as the Society of Critical Care Medicine, the American Thoracic Society, and the CDC endorse the change in practice. Finally, the "stick" used by regulatory bodies such as the Centers for Medicare & Medicaid Services can provide powerful incentives to accelerate change in practice.

In summary, this is the time for us to develop a new infection control bundle in the ICU that includes universal decolonization. If Semmelweis were alive today, he would surely agree with this approach. On the other hand, he might be distraught to learn that in 2013 we are still struggling to achieve better compliance with hand hygiene. ■

Halomonas: An Emerging Pathogen?

By Joseph F John, Jr., MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston, co-editor of Infectious Disease Alert.

Dr. John reports no financial relationships with this field of study.

SYNOPSIS: A 54-year old female with end stage renal disease presented with nausea, vomiting, hypertension and minimal fever. One of two blood cultures grew a gram-negative rod that was eventually identified as *Halomonas jonsoniae*. None of the local dialysis centers had reported such infections, however, the center under question in Santa Clara, CA reported heavy contamination with *H. johnsoniae* in 2009.

SOURCE: Stevens DA, et al. *Halomonas jonsoniae*: Review of a medically underappreciated genus of growing human importance. *Am J Med Sci* 2013;345:335-338.

A 54-year old female with end stage renal disease presented with nausea, vomiting, hypertension and minimal fever. One of two blood cultures grew a gram-negative rod that was eventually identified as *Halomonas jonsoniae*. In the current report there was no Halomonas isolated after scrupulous culturing of the dialysis unit. None of the local dialysis centers had reported such infections, however, the center under question in Santa Clara reported heavy contamination with *H. johnsoniae* in 2009.Two years had passed since two initial patients had bacteremia with Halomonas infection, thus there is no hint where patient exposure originated. The authors make the point that the organism is not considered in infectious disease texts as a pathogen, but with this publication and several others Halomonas has established an ability to cause infection. Although the analysis of environment

did not yield halomonas, a previous epidemiologic analysis revealed that the environment and the hands of nurses were contaminated with the organism. Halomonas species are salt lovers and isolation of this genus from the environment requires special media, which may limit its ability to grow in some commercial blood culture systems.

■ COMMENTARY

The microbial world continues to fascinate and infect us humans. Now we have another evolving genus, halomonas, which has many species. Stevens et al have done the medical community a great service with this assiduous epidemiologic analysis of halomonas contamination in dialysis units. Clearly there is a troublesome connection between the high tonicity of dialysate, its distribution through the dialysis unit and the ability of the gram-negative bacterium species to grow in high salt concentrations. It would be interesting to know how well human blood supports halomonas growth. From this patient and several others we know it can survive long enough to grow in blood. There have also been outbreaks in neonatal units, again suggesting challenged hosts and environments that may support contamination by halomonas.

Infectious disease specialists and clinical microbiologists have a new organism to watch. Halomonas combines the potential for environmental contamination with susceptibility in patients around high salt medicaments who have risk for opportunistic infections. New pathogens do not come along that often and the medical community stands in appreciation of those investigators who can uncover these "new" organisms. In the current article, all of the references date to after 2000, the first one emanating from the great German microbiologist, Alexander von Graevenitz, who discovered and catalogued many new gram-positive bacteria during his academic life in Zurich. On the Gram-negative front he was also one of the first to report a case of the genus under question, a Halomonas venusta infection following a fish bite (*J Clin Micro* 2000;38:3123-4). Dr. von Graevenitz headed a renowned basic and clinical lab at the University of Zurich until the last decade, maintaining a close affiliation with investigators and infectious diseases physicians in the United States and throughout the world. During his long career, von Graevenitz befriended a global cadre of infectious disease workers, including myself. His knowledge is encyclopedic and though now less active in the laboratory, he continues to have an influence on modern clinical and academic microbiologists. The current paper on halomonas species indicates the importance of investigating and speciating new bacterial entities. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

An old disease returns:

Syphilis in North America

Syphilis is making a resurgence in the U.S. and Canada, especially in urban areas, where the rates of newly diagnosed infection have soared, especially in men-who-have-sex-with-men (MSM). The problem has begun "spilling over" into the heterosexual community. This epidemic may be largely attributed to the availability of internet hook-ups and networking mobile smartphone apps, such as Grindr, the increased use of methamphetamines, as well as what is termed "prevention fatigue." San Francisco County has recorded spikes in all STDs for six straight years — and the number of early syphilis cases rose from 659 in 2010 to 682 in 2011 (the last year for which unofficial numbers are available). It is estimated that each new cases of syphilis results, on average, in exposure to 10 additional people.

Grindr is a gay social networking application launched in 2009 and available worldwide — it runs on the iPhone, blackberry and Android. The app allows users to meet other men within close proximity who are interested and available for whatever specified sexual activity using the phones mobile location services. We tried it in our Santa Clara county HIV clinic the other day and someone was available and interested in having sex not more than 75 feet away – they were in the same building!

Some public health officials are now recommending syphilis screening of high-risk individuals every 3-6 months. This might make good sense — in our HIV clinic, we routinely screen on an annual basis — but based on these figures, screening at shorter intervals makes sense. ■

Syphilis in Africa

Dionne-Odom J, et al. Syphilis treatment response among HIV-discordant couples in Zambia and Rwanda. *Clin Infect Dis* 2013: 1829-1837.

One of the toughest problems with managing syphilis is discerning the adequacy of therapy, and deciding when ≥ someone is "serofast" or failing to respond to therapy. Generally, I've believed, the longer someone has been RPR-positive, the longer they take to respond, and true failures of therapy are uncommon. In a recent prospective clinical trial involving 465 HIV-negative adults treated for early syphilis, 79% were considered responders and 21% were serofast at 6 months of treatment (response was a negative RPR or at least a ≥ 4-fold drop in RPR titer; and serofast was defined as a ≤ 2-fold decrease in titer or persistent titers).[1] There were no treatment failures. Serologic response was associated with younger age, fewer sexual partners, higher baseline antibody titers, and earlier syphilis stage.

Over the years, concern has been expressed that HIV-infection may increase the risk of treatment failure for early syphilis. These authors retrospectively examined the frequency of syphilis infection in HIV-discordant couples cohorts, and compared the frequency and predictors of response to therapy between those who were HIV-positive versus -negative. Two large HIV-discordant couples cohorts in Zambia and Rwanda formed the basis for this investigation. Originally, 6,688 individuals were enrolled in the project between 2002-2008, 6016 of whom had at least one follow-up visit. At one site, RPR testing was performed at baseline, at every 3 months of follow-up for 3 years, and then annually for 3 years, while at the other site, RPR testing was performed every 6 months for the first 3 years of the study, and annually thereafter.

The presence of an RPR ≥ 1:2 was considered a positive, and persons with a positive test were offered a single dose of 2.4 million units of benzathine PCN IM, although a few patients with positive RPR's at baseline were treated with 2 to 3 weekly doses of benzathine PCN (n= 68 people). Responses were defined as at least a 4-fold fall in RPR titer.

A total of 1,810 episodes of syphilis were treated in 1,321 individuals during the study period. A positive RPR was found at entry to the study in 18% of patients in Zambia and 9% of patients in Rwanda. At entry to the study, the prevalence of a positive RPR in women was higher than men (20% vs 15%), and the RPR prevalence in HIV-positive individuals was higher than in HIV-negative individuals (16% vs 10%). In total, 35% of RPR-positive participants had an RPR positive spouse, although RPR-positive men were more likely to have an RPR-positive wife (45%), than RPR-positive women, whose male partners were positive 27% of the time.

The difference in the responses seen between genders did not remain significant in multivariate analysis when adjusted for other factors.

The rates of serofast titers were 20% for those with newly diagnosed disease during study, and 33% of those diagnosed with syphilis on entry to study. This difference may, in part, reflect the differences in response to therapy for someone with early primary disease vs. latent disease but, additionally, individuals with more long-standing infection are at greater risk for persistent antibody production and a serofast titer, despite cure. The association between serologic response and a higher RPR titer (≥ 1:4) may also reflect whether a patient was newly diagnosed, or may have had a previously treated, low-grade, positive serofast titer. But it becomes difficult to know for certain whether a serofast titer represents residual disease burden or persistent antibody production. As is often the case, many of the individuals in this study with persistent positive RPR titers received repeated injections of penicillin. While undiagnosed neurologic infection could be an explanation for persistent serofast titers in some individuals, detection of neurosyphilis by lumbar puncture could not, unfortunately, readily be done in this study.

Reference

1. Sena AC, et al. Predictors of serological cure and serofast state after treatment in HIV negative persons with early syphilis. *Clin Infect Dis* 2011; 53(11): 1092-9. ■

United States HIV prevention stance

Moyer, V, et al. Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2013;159: 51-60; and accompanying editorial: Das M. Bringing the end in sight: Consensus regarding HV screening strategies. *Ann Intern Med* 2013;159:63-4.

When the U.S. Preventive Services Task Force (USPSTF) last issued guidelines for HIV screening in 2005, the committee expressed concern about the psychological ramifications and social stigmatization of testing HIV-positive, and cautiously focused their screening recommendations on persons at risk and pregnant women. Broad-based screening of the population was given non-committal consideration (a "C" rating).

In 2006, the CDC took a step towards universal screening by recommending what has been framed as an "opt-out" approach – persons aged 13 to 64 years could be offered HIV testing — with an

new emphasis on testing in sites where screening had previously been discouraged, such as emergency rooms, and screening of all pregnant women.

The USPSTF has finally taken the next step and, in the new 2013 U.S. HIV Screening Guidelines, recommends universal HIV screening for all adolescents and adults ages 15 to 65 years of age. Their recommendations were based on several important factors: An estimated 20% of the HIV-infected population in the U.S. (approximately 236,000 people) is unaware of their HIV infection. While 11% of existing infections are attributed to heterosexual sexual contact, 25-27% of newly diagnosed HIV infections are attributed only to heterosexual sex, including many young Hispanic and black women. In addition, nearly half of all STDs occur in adolescents — putting them at increased risk for HIV. Many younger people are at risk for HIV infection but do not necessarily enter into the health care system in an established way that provides them testing. If these individuals are going to be tested at all, it must occur when they present for the occasional sore throat, STD, trauma, or pregnancy.

In addition, the USPSTF recognized the significant benefit of HIV treatment on reducing the risk of progression to AIDS, opportunistic infection and death, although they spent several paragraphs attempting to discuss the optimal timing of antiretroviral therapy (early initiation of antiretroviral therapy has previously been vigorously debated and has now been accepted as standard of care). They also acknowledged that while HIV treatment is associated with some risk, including long-term side effects, numerous clinical trials demonstrate a clear benefit-risk ratio. And while the psychological impact of finding out you are positive is a negative — the chance of earlier treatment and longer-term survival seems like a better bet. The Task Force also acknowledged that both conventional and rapid HIV testing provide sensitive and specific test results, with a relatively low rate of false-positives. Even in a low-risk population, conventional HIV testing may result in 1 false positive test in 250,000 tests.

An important consideration in favor of universal screening is the concept of "community HIV viral load" — effectively, the burden of unrecognized/untreated HIV disease in a community is fueling the occurrence of new infections. Simply put, if we could find that 20% of people who are unaware of their HIV infection, and get them into treatment, they would be less likely to transmit infection to others.
The Task Force recommends continued emphasis on screening in higher risk areas such as STD clinics, homeless shelters, TB clinics, and adolescent health clinics that treat STDs. Persons younger than 15 or older than 65 years of age who engage in risky activities should also be tested.
All pregnant women should continue to be screened with every pregnancy, regardless of the appearance of no risk. Women with risk factors should have repeated screening in the third trimester. This affords the opportunity to confirm HIV infection and provide effective therapy during pregnancy, which is highly effective at reducing transmission to the infant.
All women should continue to be screened in subsequent pregnancies. Particular emphasis is given to peri-partum testing in women presented to labor and delivery who have not been previously tested – recognizing that the small risk of a false-positive test may result in unnecessary treatment and some limited risk.

The premise here — and I believe it's a good one — is anyone who has sex is at risk for HIV, and risk behaviors may not be recognized or acknowledged. Screening people for HIV, in addition to hepatitis C, should become the norm. Physicians should make an effort to screen all teenagers, young adults, and even older adults at least once — and I make a habit of HIV testing anyone who comes in with a new STD as well as all new ID consults in the hospital, even if the presenting problem is not clearly related to HIV (e.g., MRSA abscess).

A question not well answered by this document, however, is how often re-testing should occur. The Task Force suggested that a reasonable approach might be to screen individuals at "very high risk" every year, and those at "increased risk" every 3 to 5 years. I'm not sure I understand the distinction between these two groups, but presumably the task force is referring to MSM and injection drug users as high risk. Once again, clinicians who are treating these individuals may be changing practice ahead of the published guidelines — it is not unusual for MSM in our area who engage in unprotected sex with multiple partners to be screened every 3 to 6 months (Remember, sex is a great multiplier — it was estimated above that one new case of syphilis may result, on average, in 10 new cases.) Recent 2013 data examining the risk of HIV-infection in young, largely black women in 10 high risk urban areas within the U.S. identified an annual incidence of HIV-infection of 0.32% — comparable to adults living in sub-Saharan Africa. The only way we are going to stem this "tide" is by identifying people who are positive and getting them into care and on treatment. ■

CME INSTRUCTIONS

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

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

CME QUESTIONS

1. Which of the following is correct?

A. Statins are primarily metabolized via a glucuronidation pathway
B. Clarithromycin inhibits CYP3A4
C. Statins inhibit CYP3A4
D. Erythromycin significantly interacts with statins by effects on glucuronidation

2. Which of the following is a potential benefit of identification and treatment of patients with acute HIV infection?

A. Since viral loads are highest during acute infection, treatment may significantly reduce the likelihood of transmission
B. Treatment of acute infection is associated with improved CD4+ T cell recovery
C. Treatment of acute infection is associated with reduced neuronal inflammation
D. All of the above

3. In a study on preventing MRSA infections in ICU patients, what was determined to be the most effective strategy?

A. MRSA screening and isolation
B. Targeted decolonization
C. MRSA screening, isolation, and universal decolonization
D. Universal decolonization without MRSA screening

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]

Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus.

Increased Risk of Herpes Zoster in Children with Asthma: A Population-Based Case-Control Study.

Fungal infections associated with contaminated methylprednisolone injections

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

Volume 18, Number 8 Pages 15-16 August 2013

Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are *not* visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word,

yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Diabetes and Cognitive Function

Source: Spauwen PJJ, et al. *Diabetes Care* 2013;36:1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

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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.*

Prostate Medications and Cancer Risks — New Evidence

In this issue: Risk of high-grade prostate cancers; clopidogrel and stroke risk; antibiotics and statins; and FDA actions.

Prostate cancer risk and 5-ARIs

The 5-alpha reductase inhibitors (5-ARI) finasteride (Proscar) and dutasteride (Avodart) are used to treat lower urinary tract symptoms in men. They are known to reduce prostate-specific antigen (PSA) levels and there was hope that they may also reduce the incidence of prostate cancer. But in two large trials, PCPT (finasteride) and REDUCE (dustasteride), despite a nearly 25% reduction in the overall rate of prostate cancer, the risk for high-grade prostate cancers was increased (Gleason score 8-10). Debate has raged for the last several years about the significance of these findings and whether the increase was real or spurious due to detection bias. A new study from Sweden attempts to clarify this issue. Using the National Prostate Cancer Register along with prescription data, nearly 27,000 cases of prostate cancer were identified along with some 134,000 matched controls. More than 7800 men were exposed to a 5-ARI, including 1500 with prostate cancer and 6300 controls. As noted in previous studies, the risk of prostate cancer decreased with increasing duration of use of a 5-ARI. With 3 years of treatment, the risk of prostate cancer was 28% lower in the treatment group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59-0.89; $P < 0.001$ for trend). The reduction was seen primarily for Gleason score 2-6 and score 7 tumors ($P < 0.001$ for trend for both). However, as opposed to previous studies, the risk for higher grade tumors was not significantly increased, although the risk was not decreased either. By 3 years, the OR was 1.23 (95% CI, 0.90-1.68; $P = 0.46$ for trend), but did not reach statistical significance. The ORs for shorter exposures were 0.96 for 0-1 year exposure, 1.07 for 1-2 years, and 0.96 for 2-3 years. The authors conclude that men treated with a 5-ARI for lower urinary tract symptoms had a lower risk of prostate cancer with Gleason scores 2-7 and no evidence of increased risk of Gleason score 8-10 of cancers up to 4 years of treatment (*BMJ* 2013;346:f3406). The FDA issued a safety warning in 2011 regarding finasteride and dutasteride and the risk of high-grade prostate cancers and it is unlikely that this study alone will reverse that, but it is reassuring for the millions of men who take these drugs for lower urinary tract symptoms. ■

Clopidogrel could reduce stroke risk

Adding clopidogrel to aspirin in patients with minor stroke or a transient ischemic attack (TIA) may help reduce the risk of stroke within the next 90 days, according to a new study from China. In a randomized, double-blind, placebo-controlled trial, nearly 5200 patients were seen within 24 hours after onset of minor ischemic stroke or high-risk TIA and randomized to a combination of clopidogrel with aspirin or aspirin alone. The combination group was given clopidogrel at an initial dose of 300 mg followed by 75 mg per day for 90 days along with aspirin 75 mg per day for the first 21 days, while the aspirin alone group got placebo plus aspirin 75 mg for 90 days. The primary outcome was stroke (isch-

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.

emic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Stroke occurred in 8.2% of the clopidogrel-aspirin group as compared to 11.7% in the aspirin alone group (hazard ratio 0.68; 95% CI, 0.57-0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients in the clopidogrel-aspirin group and eight in the aspirin alone group. The rate of hemorrhagic stroke was the same (0.3%) in both groups. The authors conclude that among patients with TIA or minor stroke who are seen within the first 24 hours of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the next 90 days. The combination does not increase the risk of hemorrhagic stroke or hemorrhage (*N Engl J Med* published online June 26, 2013). An accompanying editorial states that this trial "proves the concept that dual platelet therapy can be more effective than single platelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis...," and also shows that dual platelet therapy can be given without excess harm in patients with acute focal brain ischemia. There is slight concern that the results may not apply to non-Chinese patients with different forms of underlying arterial disease (*N Engl J Med* published online June 26, 2013). ■

Antibiotic coprescription and statins

Use caution if you prescribe clarithromycin or erythromycin to patients on statins. Both drugs (but not azithromycin) inhibit cytochrome P450 isoenzyme 3A4, which can increase blood concentrations of statins, especially atorvastatin, simvastatin, and lovastatin. Researchers from Canada looked at the records of continuous statin users who were prescribed clarithromycin (n = 72,591) or erythromycin (n = 3267) with azithromycin use as a comparator (n = 68,478). The risk of hospitalization for rhabdomyolysis within 30 days was the main outcome. Although the absolute risk was low, concomitant use of clarithromycin/erythromycin with atorvastatin, simvastatin, or lovastatin was associated with a higher rate of hospitalization with rhabdomyolysis, especially in those with acute kidney injury. There was also an increase in all-cause mortality when the drugs were combined (absolute risk for rhabdomyolysis 0.02%, with acute kidney disease 1.26%, all-cause mortality 0.25%, relative risks 2.17, 1.78, and 1.56, respectively). These data suggest that coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 (atorvastatin, simvastatin, and lovastatin) increases the risk of statin toxicity (*Ann Intern Med* 2013;158:869-876). ■

FDA actions

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and has the same active ingredient in the antidepressant Paxil. It is the first non-hormone based drug approved for this indication. The safety and efficacy of the drug was established in two randomized, double-blind, placebo-controlled trials of 1175 postmenopausal women with moderate-to-severe hot flashes that showed paroxetine was more effective in relieving symptoms than placebo. This new form of paroxetine contains 7.5 mg of the drug and is dosed once daily at bedtime. Paroxetine for depression and other psychiatric indications is dosed at 10-40 mg. All forms of paroxetine carry a boxed warning about increased risk of suicide. There is also concern about reduced effectiveness of tamoxifen if both medications are taken together. Paroxetine 7.5 mg for hot flashes is marketed by Noven Therapeutics as Brisdelle.

The FDA has approved a new formulation of selegiline — a once-daily, orally dissolving tablet — for the treatment of Parkinson's disease (PD) in patients who are losing responsiveness to levodopa/carbidopa. Most PD patients start treatment with levodopa/carbidopa, but for many, the effectiveness wanes with increasing "off" periods during which time symptoms worsen. In clinical trials, the new combination of selegiline reduced "off" periods by an average of 2.2 hours per day compared to 0.6 hours for placebo. The dissolvable tablet uses a new system that delivers more drug at a lower dose. The drug company claims this results in fewer side effects. Selegiline, a monoamine oxidase (MAO) inhibitor, has been available as a generic and also as the branded drugs Eldepryl and Zelapar. Like other MAO inhibitors, it can cause severe, even fatal, reactions if given in combination with certain other drugs including meperidine, tramadol, SSRIs, TCA antidepressants, and the over-the-counter medication dextromethorphan. The new orally dissolving selegiline is marketed by Valeant Pharmaceuticals as Zelapar.

The FDA has approved the TNF blocker golimumab for the treatment of ulcerative colitis. The drug was previously approved to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The approval for ulcerative colitis was based on two studies of more than 800 patients, one group had failed other treatments and the other group were responders who were evaluated for maintenance. In both groups, golimumab was superior to placebo. Golimumab is marketed by Janssen Biotech as Simponi. ■