AHC Media

Vol. 33, Issue 2, November 2013
www.ahcmedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

C. diff Transmission: It's Complicated

Surprisingly, most CDI cases are not transmitted by symptomatic patients

By Richard R. Watkins, MD, MS, FACP

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

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

SOURCE: Eyre DW, et al. Diverse Sources of *C. difficile* Infection Identified on Whole-Genome Sequencing. *N Eng J Med* 2013;369:1195-1205.

The prevailing theory of *Clostridium difficile* transmission is that most cases occur after recent exposure to symptomatic patients in health care settings. Infected patients are known to shed large numbers of *C. difficile* spores and current infection control recommendations focus on preventing spore transmission from the environment through contact precautions and decontamination of surfaces and equipment. However, the rate of *C. difficile* infection (CDI) continues to increase, bringing into question the effectiveness of these methods.

A new study by Eyre and colleagues provides evidence that the widely accepted paradigm of horizontal *C. difficile* transmission may not be valid. Over a period of 3.6 years the investigators performed whole genome sequencing on more than 1,200 clinical isolates of C. difficile from the Oxford University Hospitals. Any two cases were considered to be linked if they met two conditions: no more than two single-

Financial Disclosure: *Infectious Disease Alert*'s editor, Stan Deresinski, MD, FACP, FIDSA, does research for the National Institutes of Health, and is an advisory board member and consultant for Merck; Updates author, Carol A. Kemper, MD, FACP, does research for Abbott Laboratories and Merck. Peer reviewer Timothy Jenkins, MD, and executive editor Gary Evans report no financial relationships to this field of study.

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Infectious Disease Alert,
ISSN 0739-7348, is published monthly by AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry NE, Suite 2850
Atlanta, GA 30326.
www.ahcmedia.com
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 550669, Atlanta, GA 30355.

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

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nucleotide variants (SNVs), and the patients had direct or indirect contact while one was symptomatic or contact occurred within a 12-week incubation period.

The analysis determined only 35% of the isolates were genetically linked to a prior case, while 45% had more than 10 SNVs and therefore were not related. Patients with genetically linked isolates tended to be older than those with genetically distinct isolates (median age 81 years vs. 76 years, respectively; P <0.001). Moreover, 38% of the linked cases had ward contact with the previous genetically related case while 9% shared the same time in the hospital but were never on the same ward. Interestingly, no hospital-based contact could be established for 46% of the patients, implying diverse sources of acquisition. For instance, some of the patients were in the same medical practice (10%) or lived in the same postal-code district (11%) as previous cases, but no pairs of patients with 2 or fewer SNVs attended the same outpatient clinic on the same day. Among the 45% of cases that represented transmission from sources other than symptomatic cases, it is reasonable to conclude their CDI was acquired from either asymptomatic individuals or some other environmental reservoir i.e. food, animals, or surfaces.

There are a few limitations to the study that require mention. First, the toxin testing used by Eyre and colleagues has been largely supplanted by more sensitive assays (e.g. polymerase chain reaction or nucleic acid tests) which probably led to an underestimation of *C. difficile* incidence in the local regions. Second, the institutions that participated in the study housed patients in four-bed bays, an arrangement that is unusual in the U.S. Since the majority of patients in U.S. hospitals are in private rooms that afford less opportunity for patient-to-patient contact, the rate of *C. difficile* transmission is likely to be different between the two countries. Third, the study was conducted during a period when infection control precautions to limit the spread of *C. difficile* were widely practiced, which likely reduced the impact of symptomatic patients. Finally, it is possible that *C. difficile* has other still-unidentified reservoirs in the environment or hospitals that are important for transmission. In the study, the authors did not perform whole genome sequencing on any strains from extended-care facilities, which are known to be sources for outbreaks of *C. difficile*.

COMMENTARY

This study is significant because it provides evidence that in a majority of cases, CDI is not transmitted by symptomatic patients. Instead, asymptomatic individuals or other sources are likely to be the main perpetrators. This finding compels us to re-examine infection control protocols whose goal is to limit the transmission of multidrug resistant pathogens like *C. difficile*. This is not to say we should abandon basic control methods since the infrequent transmission from symptomatic patients in the study hospitals may attest to their effectiveness. Rather, future studies that elucidate novel routes of transmission can identify currently unknown sources of CDI. For example, should all patients who are admitted to the hospital be screened for *C. difficile?* If

so, what should happen to asymptomatic carriers especially since isolation in general is unpopular with patients, their families, and health care workers?

Another take away point from this study is that perhaps more emphasis should be placed on minimizing disruptions to the gut microbiome and its restoration (i.e. through probiotics) should be a priority. Although physicians and the public already have more than enough reasons to limit the use of unnecessary antibiotics, the threat of acquiring CDI is a valid concern and should be taken into consideration whenever these agents are prescribed. As Eyre and colleagues note, the rate of fluoroquinolone and cephalosporin usage in the UK fell between 2006 and 2009, and during this period active restriction of these agents in one Scottish hospital resulted in a relative reduction of 77% in the incidence of CDI. Thus, reducing the susceptibility of patients to CDI may be more effective than lowering transmission rates. Finally, this study demonstrated the usefulness of whole genome sequencing in determining the transmission of one major disease and this method holds great promise for uncovering the mechanisms of transmission for other serious pathogens. ■

ABSTRACT & COMMENTARY

Pertussis Vaccination during Pregnancy could Substantially Reduce Infant Deaths

By Philip R Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

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

SYNOPSIS: A mathematical model of three Tdap vaccination strategies supported the authors' conclusion that pregnancy vaccination is an economically efficient method to substantially reduce infant pertussis morbidity and mortality.

SOURCE: Terranella A, et al. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. *Pediatrics* 2013;131:e1748-1756.

From 2001 to 2010, there were 27,995 reported cases of pertussis during the first year of life in the United States; 189 of these babies died. Children during the first two months of life account for most of these cases and deaths. When a source is identifiable, it is usually one of the parents. Various vaccine strategies have been proposed, including prenatal maternal vaccination and post-partum cocooning (providing vaccine to adults in close contact with the baby after birth). These strategies had been found to be cost-effective in Europe. Liang and colleagues sought to determine cost-effectiveness of pertussis vaccination in preventing infant pertussis in the United States.

A mathematical model was used based on the approximately four million babies born in the United States in 2009. The authors analyzed three vaccination strategies: 1) a pregnancy dose of Tdap vaccine, 2) a post-partum dose of Tdap, and 3) limited "cocoon" doses of Tdap to the parents and a grandparent.

Vaccine effectiveness was assumed to be 85% for the first six months post-vaccine. Transplacentally transferred maternal antibody was assumed to be 60% protective for two months in the infants.

Modeling suggested that without new intervention there would be 2041 infant pertussis cases per year with 1463 hospitalizations and 22 deaths. Post-partum maternal vaccination would avert 20% of infant cases, and third trimester maternal vaccination would prevent 33% of cases. Post-partum parental and grandparental vaccination would prevent 32% of cases. Intra-pregnancy vaccination was similarly predicted to prevent more hospitalizations and deaths and to save more quality-associated life years.

With these models, vaccination during

pregnancy led to medical care cost savings of 37%, post-partum vaccination yielded 19% savings, and cocooned vaccinations prompted 32% savings.

The authors acknowledge that there are still questions of the safety of vaccination during pregnancy, the risk of blunting responses to subsequent infant pertussis vaccination, and implementation systems to reach pregnant women. While awaiting further studies, the authors claim that "pregnancy vaccination offers an economically efficient method to substantially reduce infant pertussis morbidity and mortality."

COMMENTARY

Despite widespread use of infant and adolescent pertussis vaccinations, babies are still dying of pertussis in the United States. The Centers for Disease Control and Prevention carefully considered various vaccination schemes, and this recent paper from Liang and colleagues explains some of those considerations. **Based in part on these data, the CDC Advisory Committee on Immunization Practice (ACIP) recommended in February 2013 that all women receive Tdap during pregnancy, regardless of their previous vaccination history.**[1] This vaccine should be given between 27 and 36 weeks of gestation. In addition, all adolescents and adults who anticipate being in close contact with an infant should receive Tdap if they have not previously been vaccinated with Tdap.

Is Tdap safe enough during pregnancy? Byington and colleagues reviewed 162,448 pregnancies in a large health system in the western United States.[2] Neither the 138 women who received Tdap vaccine during pregnancy (many during the first trimester as part of wound care) nor their babies had an increased incidence of adverse outcomes. Intra-partum use of Tdap seems safe.

National authorities making vaccine recommendations must balance the desire to prevent all disease and a desire to be wise with the use of limited health care resources. Societal pressure similarly pushes toward full protection with no risk. Wisdom is needed to balance these varied demands, and ACIP demonstrated wisdom with their recommendations earlier this year.

Some people might claim that ACIP simply wants to make people use all available vaccines. In their recent recommendations, as supported by the data in Liang's paper, the committee showed reasonable restraint in not obligating repeat Tdap for all contacts of infants. And, the new recommendations for intra-partum vaccination would clearly prevent illness, save lives, and reduce medical care costs.

The data are clear, and the time is now. All pregnant women should be vaccinated with Tdap between the 27th and 36th weeks of gestation, regardless of previous vaccination history.

References

1. Sawyer M, et al. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) in Pregnant Women — Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR* 2013;62:131-135.
2. Shakib JH, et al. Tetanus, Diphtheria, Acellular Pertussis Vaccine during Pregnancy: Pregnancy and Infant Health Outcomes. *J Pediatr* 2013;in press. ■

ABSTRACT & COMMENTARY

Multistate Outbreak of Listeriosis associated with cantaloupe

By Dean L. Winslow, MD

Clinical Professor of Medicine and Pediatrics Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Associate Editor of Infectious Disease Alert

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: A total of 147 outbreak-related cases of listeriosis were identified in 28 states. Epidemiologic study confirmed that whole cantaloupe produced by a single Colorado farm was the outbreak source.

SOURCE: McCollum JT, et al. Multistate outbreak of listeriosis associated with cantaloupe. *New Eng Jrl Med* 2013;369:944-53.

During 2011 the Centers for Disease Control and Prevention and Colorado Department of Public Health and Environment (CDPHE) investigated a nation-wide listeriosis outbreak. Multistate epidemiologic, trace-back, and environmental investigations were conducted, and outbreak-related cases (as shown by pulse-field gel electrophoresis) were compared to previously-reported sporadic cases of listeriosis identified by the Listeria Initiative (an enhanced surveillance system that routinely collects detailed information about U.S. cases of listeriosis).

147 outbreak-related cases were identified in 28 states. 86% of patients were 60 years of age or older (median age 77). Seven infections occurred in pregnant women (4) and newborns (3) and one related miscarriage was reported. 88% of patients had one or more potentially immunosuppressing conditions. 99% of patients were hospitalized and 22% died. 84% of patients had positive blood cultures and 5% of patients had positive CSF cultures.

Patients with outbreak-related illness were more likely than sporadic listeriosis cases to have eaten cantaloupe (odds ratio 8.5). Cantaloupe and environmental samples collected during the investigation yielded isolates matching the five outbreak-related subtypes. Unsanitary conditions identified at the processing facility operated by a farm in Colorado likely resulted in contamination of the cantaloupes with L. monocytogenes.

COMMENTARY

Listeria monocytogenes is an interesting organism, unusual in that it can continue to grow in cold conditions (in contrast to most bacteria which grow optimally at warm temperatures). Listeria is a facultative intracellular bacterium and generally causes disease in elderly individuals, pregnant women, neonates, and individuals with defects in cellular immunity. Because it is so unusual even a few cases should prompt an investigation into the source of infection.

Many outbreaks of Listeria have occurred over the years and have been related to ingestion of things like cabbage stored over the winter in cellars, in Mexican-style cheese (queso fresco), other unpasteurized dairy products, hot dogs, ham and cold cuts. Contamination generally is felt to occur during harvesting or processing of food and then storage at refrigerator temperatures actually results in amplification of the original inoculum of Listeria.

In this particular outbreak, the investigation revealed that the implicated farm had recently switched from a cantaloupe cleaning process that used recirculating, chlorinated, chilled-water wash to one where they used non-recirculated municipal water without chlorination and a series of brush and felt rollers to mechanically clean and dry the cantaloupe. ■

ABSTRACT & COMMENTARY

Is a Newly Discovered Bacterium Causing Cord Colitis Syndrome?

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: It has been hypothesized that the cord colitis syndrome, a complication of umbilical-cord hematopoietic stem-cell transplantation, is infectious in origin. The authors assembled a novel bacterial draft genome from the direct sequencing of tissue specimens from patients with cord colitis. Association of these sequences with cord colitis suggests a newly discovered bacterium, which was provisionally named *Bradyrhizobium enterica.*

SOURCE: Bhatt AS, Freeman SS, Herrera AF, et al. Sequence-based discovery of Bradyrhizobium enterica in cord colitis syndrome. *New Engl J Med* 2013;369:5617-28.

We have come into an age of discovering non-culturable pathogens and commensals. Many microbial surprises await. The latest surprise comes from a study of a new entity called cord colitis, a term coined in 2011 via the *New England Journal of Medicine*. Cord colitis is a diarrheal illness in patients undergoing hematopoietic stem-cell transplantation (HSCT) with umbilical cord cells. The role of the cord cells and the actual cause of the enterocolitis remained unknown. The symptoms of the illness have responded in previous patients to antibacterial agents (ciprofloxacin and metronidazole) so there was a suspicion that the illness was infectious in origin. An army of investigators at Harvard hospitals and Memorial Sloan-Kettering Cancer Center in New York embarked on a molecular journey to discover if there was an infectious component to the disease.

Complex DNA extraction and amplification was performed on 16 of 23 colonic biopsy specimens from 11 patients with cord colitis. Most of the patients had a lymphoma or leukemia, ablation therapy antibiotic therapy and enterocolitis. Initial DNA sequence analysis suggested that the DNA was from a plant bacterium known as Bradyrhizopium, and the new species was named B. enterica. The new genome was pieced together from biopsy specimens using computer software, then compared to a known species, *B. japonicum*. The size of the genome compared to other bradyrhisopium species with about 7112 potentially expressed proteins. On a phylogenetic tree, *B. enterica* linked closely to *B. japonicum*.

In the extracted DNA there was present sequence from other known bacteria but in much less abundance. For example after 600,000 reads for *B. enterica*, the next most common bacterial DNA were in base pairs fewer by a log 2 and included *Delftia acidovorans*, *Stenotrophermonas maltophilia*, other deftia species, *Proprionobacterium acnes*, *Ralstonia pickettii*, and several Pseudomonas species. In qualitative analysis searching for *B. enterica* DNA in control colonic specimens, none was found. In a patient with cord colitis, *B. enterica* DNA was found not only in colonic specimens but also in gastric and duodenal biopsy specimens. In one patient, the *B. enterica* DNA intensity decreased by 84% after antimicrobial therapy.

COMMENTARY

Before this study, bradyrhizopia had not been reported as human pathogens. Indeed, they are nitrogen-fixing species, endosymbionts such as *B. japonicum*, used in commercial agriculture. The suspected pathogen *B. enterica* actually has lost its nitrogen-fixing genes and replaced them with ones that are potentially related to pathogenic potential, filamentous hemagglutins used for binding in some pathogens like Bordetella pertussis that causes whooping cough. This new bacterium and perhaps other bacteria from the ecosphere may be evolving into potential human pathogens using mobile genetic elements to survive in human hosts while sacrificing genes vital for survival in the ecosphere.

An excellent accompanying editorial, **Eric Pamer**, MD, notes that some immune reconstitution is needed for *B. enterica* to colonize human epithelium cells. He further suggests that a combination of epithelial damage, changes in gut microbiome, and altered immune function may be factors. Thus, the quandary arises whether B. enterica is a causal pathogen or a subsequent commensal (colonizer). Certainly its preponderance suggests the former but we have been fooled before by new organisms appearing to be pathogenic. Let us see the impact of more microbial molecular data in this unusual disease of modern man.

Reference

1. Pamer, EG. Cuffed and Exposed — Perp-Walking Bradyrhizobium. Editorial. *N Engl J Med* 2013; 369:572-574 ■

CDC Recalls Employees to Fight Drug-Resistant Salmonella Outbreak

By Stan Deresinski, MD, FACP, FIDSA

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

As a result of the shutdown of the federal government, approximately 9000 of the 14,000 CDC employees were placed on furlough. On October 8th, however, 30 of the furloughed employees were recalled to assist in the response to an epidemic of *Salmonella Heidelberg* infections.

A total of 317 individuals infected with the outbreak strains of Salmonella heidelberg have been reported as of October 11, 2013.[1] While cases have occurred in 20 states and Puerto Rico, most of the ill persons (73%) have been reported from California. Among 310 persons for whom information was available, illness onset dates range from March 1, 2013 to September 26, 2013. Those affected range in age from less than 1 year to 93 years, with a median age of 20 years; 51% were male. Hospitalization was felt necessary for 79 of 189 (42%) individuals for whom the information was available. Bloodstream infection was detected in 13% — a proportion more than twice as great as normally seen in Salmonella infections. There have been no deaths to date.

Based on pulsed field gel electrophoresis, 7 strains of *S. heidelberg* have been identified as being involved in the outbreak. Resistance to commonly used antibiotics was frequent and multidrug resistance was seen in some. The epidemic strains were traced back, using classical and molecular epidemiology, to ingestion of chicken processed by Foster Farms.

Salmonella and chicken go together. A recent analysis of raw chicken purchased from retail outlets in central Pennsylvania found Salmonella in 84 of 378 (22%) samples.[2] Furthermore, 26 of the Salmonella isolates were resistant to 3 or more antibiotics, and with frequently reduced susceptibility to ceftriaxone. The high incidence of hospitalization, however, distinguishes this outbreak from most others and suggests the possibility that the strains involved have enhanced virulence.

Reference

1. Centers for Disease Control and Prevention. Multistate Outbreak of Multidrug-Resistant Salmonella Heidelberg Infections Linked to Foster Farms Brand Chicken: http://www.cdc.gov/salmonella/heidelberg-10-13/index.html
2. M'ikanatha NM, Sandt CH, Localio AR, et al. Multidrug-resistant Salmonella isolates from retail chicken meat compared with human clinical isolates. *Foodborne Pathog Dis* 2010;7:929-34. ■

Tigecycline Graduates to a Black Box

By Stan Deresinski, MD, FACP, FIDSA

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

In the U.S., tigecycline has received indications for use in the treatment of complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CABP) caused by susceptible strains of designated bacteria. Several years ago, however, analysis of 13 randomized trials found evidence of numerically excess mortality in those assigned tigecycline in 12. This finding was obviously of concern and a bolded statement was added to product prescribing information. At the time, the explanation was unclear and it was felt that further analysis was warranted.

Further analysis of the trials has led to alterations of the product label that include:

"Addition of a boxed warning to highlight the increased all-cause mortality risk in adults that has been observed in a meta-analysis of all Phase 3 and 4 clinical trials and stating that TYGACIL should be reserved for use in situations when alternative treatments are not suitable. The previous TYGACIL label included a bolded warning … which provided data from this analysis, which showed an increase in all-cause mortality in TYGACIL-treated adult patients compared to controls with a risk difference of 0.6% (95% CI 0.1, 1.2).

"Addition of information to the Warnings and Precautions section (5.1) that an increase in all-cause mortality was also seen in a meta-analysis limited to the approved indications with a risk difference of 0.6% (95% CI 0.0, 1.2).

"Addition of Limitations of Use to the Indications and Usage section. Based on data from clinical trials, TYGACIL is not indicated for treatment of diabetic foot infection or hospital-acquired or ventilator-associated pneumonia.

"TYGACIL should be reserved for use in situations when alternative treatments are not suitable."

This change was based on evidence of an increase in all-cause mortality observed in a meta-analysis of the 13 Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. In these trials, death occurred in 150/3788 (4.0%) of patients receiving tigecycline and 110/3646 (3.0%) of patients receiving comparator antibiotics. Using a random effects model by trial weight in a pooled analysis of all 13 trials, the adjusted difference in risk of all-cause mortality was 0.6% (95% CI, 0.1 to 1.2), with tigecycline having the higher mortality risk.

Further analysis of mortality observed in all the trials, including post-marketing trials, that were conducted for the 3 approved indications, found an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) for comparator agents, respectively. When stratified by trial weight, the adjusted risk difference was 0.6% (95% CI, 0.0 to 1.2).

The cause of this mortality difference has not been unequivocally established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities. The most dramatic difference in the individual trials was in a randomized, double-blind Phase 3 study comparing tigecycline to imipenem/cilastatin in the treatment of 945 patients with hospital-acquired pneumonia (HAP), including patients with ventilator-associated pneumonia and it is suspected that dosing was inadequate for this infection.

As a consequence of these findings, tigecycline administration should be reserved for use in situations when alternative treatments are not available.

Reference

1. FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning: http://www.fda.gov/Drugs/DrugSafety/ucm369580.htm
TYGACIL Full Prescribing Information: www.tygacil.com ■

Cholera, Diarrhea and Dysentery Update, Mexico

By Stan Deresinski, MD, FACP, FIDSA

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

On October 4, 2013, the Mexican government reported that 79 cases of cholera, a disease that had been absent from the country for more than a decade, had been identified in the country. Two of the cases had occurred in the State of Hidalgo, while

the remaining 2 were from the neighboring Federal District of Mexico City. They also reported that the outbreak strain, which is a toxigenic *Vibrio cholerae* O:1 Ogawa, was the same as that currently present in Haiti, the Dominican Republic, and China. The strain differs from the one that circulated in Mexico during the last sustained period of autochthonous transmission during 1991-2001. CDC has issued a Level 1 Watch (Practice Usual Precautions) and provided instructions by which travelers to Mexico can protect themselves.[1]

Reference

1. Centers for Disease Control and Prevention. Cholera in Mexico: http://wwwnc.cdc.gov/travel/notices/watch/cholera-in-mexico ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Fluconazole during pregnancy, does lower dose lower risk?

Molgaard-Nielsen D et al. Use of oral fluconazole during pregnancy and the risk of birth defects. *New Engl J Med* 2013;369:830-839.

I keenly remember a young Asian woman, 4 months pregnant with her first child, admitted to hospital in the 1990's with severe pulmonary coccidioidomycosis. Her husband, a local dentist, had conscientiously taken her on a pre-baby vacation to Phoenix, Arizona for a golf trip a few weeks earlier. At the time, it was just recognized that fluconazole was associated with teratogenicity — although there was not as much information available then as there is now. She developed severe hypotension with an initial attempt at treatment with Amphotericin. Fearing the consequences of azole therapy, I held my breath, and attempted a single rechallenge 2 days later with Ampho. She nearly died from hypotension. With little else to offer — high dose fluconazole was administered. Her infection resolved, and baby was fine.

Studies have since provided more information on the teratogenicity of fluconazole in pregnancy. Fifteen birth defects have been linked to fluconazole therapy during pregnancy, including craniofacial defects, middle-ear defects, cleft palate, cleft lip, limb defects, limb-reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, pulmonary-artery hypoplasia, VSD, and hypoplastic left heart. Most of the risk has, however, been associated with higher doses (400 – 800 mg daily) for sustained periods of time during the first trimester. In contrast, itraconazole during pregnancy does not appear to confer a significant increased risk of fetal defects, and ketoconazole is not known to be teratogenic. Less is known about the use of lower dose fluconazole for limited durations in the first trimester.

These investigators examined the risk of birth defects identified in the Danish National Registry, cross-checking them against prescriptions for azoles. Only those prescriptions filled within 4 weeks of pregnancy onset were examined. Most of the use was single dose fluconazole 150 mg or 300 mg — presumably given for yeast vaginitis prior to recognition of pregnancy in these women.

A total of 976,300 live births were included in the study, 7,352 of which were exposed to fluconazole; 687 were exposed to itraconazole (44 of whom also received fluconazole); and 72 were exposed to ketoconazole (3 also received fluconazole).

Compared with unexposed pregnancies, there was no statistically significant increase in the overall prevalence of birth defects in pregnancies exposed to fluconazole (prevalence 2.6%, prevalence odds ratio 1.06). Analysis of the risks associated with each of the 15 recognized birth defects above failed to show any increased risk with one exception: 7 cases of

Tetralogy of Fallot occurred in fluconazole — exposed cases (prevalence 0.03%, prevalence odds ratio 3.16) compared with 287 cases in unexposed pregnancies. There was no observed increase in craniosynostosis, cleft palate, or other craniofacial defects, more frequently associated with fluconazole administration during pregnancy. There was also no evidence of increased birth defects in patients receiving either itraconazole or ketoconazole. And there was no observed risk associated with fluconazole exposure in the second or third trimester.

A potential limitation of this study was the absence of data related to fetal death or spontaneous miscarriage due to birth defects. Pregnancies terminated specifically for birth defects were examined, and no unusual activity was observed in women receiving fluconazole, with the possible exception of births terminated for hypoplastic left ventricle. ■

ID consultants lower mortality and cost of hospital stay

Schmitt S, et al. Infectious Disease specialty intervention is associated with decreased mortality and lower healthcare costs. *Clin Infect Dis*, 2013 Sep 25. [Epub ahead of print]

The most heavily curbsided specialty may also be one of the more valuable, especially in an era of cost-consciousness, and focus on quality markers such as shorter stays and fewer 30-day readmissions. The impact of ID consultation on important markers, such as length of ICU stay, length of hospital stay, mortality, and frequency of 30-day readmission was assessed for patients admitted to an acute care hospital (ACH) with at least one of 11 specific infections between January 2008 and November 2009. These common infections were selected based on the ability to query fee-for-service Medicare claims based on DRG code (bacteremia, *C difficile* infection, central line-associated bloodstream infection, bacterial endocarditis, HIV, meningitis, osteomyelitis, prosthetic joint infections, septic arthritis, septic shock, and vascular device infections).

A total of 101,991 ACH stays with ID consultation and 170,366 without ID involvement (59.8%) were examined. Patients with ID consultation generally had more than one infection, and were more likely to be male, they were younger, more likely to be admitted to ICU, and were more likely admitted to a teaching hospital compared to those without ID intervention. A matched cohort of more than 120,000 cases was created, and those patients with ID consultation also appeared more likely to have orthopedic infection, were more likely to have had surgery, and were less likely to have respiratory infections compared with the non-ID intervention cohort. Prior to adjusting for any risk factors, patients with ID intervention generally appeared more ill, had longer lengths of hospital stay, more days in ICU, but a lower index stay mortality.

After adjustment for risk factors, cases with ID involvement had statistically significantly lower rates of index stay (odds ratio, .89), lower rates of 30-day mortality (OR, .86), and lower rates of 30-day readmissions (OR, .96). In addition, stays with ID involvement within the first 2 days of hospitalization were associated with a significantly lower 30 day mortality (OR, .87) and readmission rate (OR, 0.92). Furthermore, those cases were associated with a 3.8% reduction in overall hospital stay, 5.1% fewer ICU days, and significantly lower cost of hospital charges, Medicare payments to ACH, and Medicare payments to all providers. These differences were small (on the order of 2.9% to 6.2%) but highly statistically significant.

In a multivariate analysis using case controls, involvement of an ID specialist in the care of patients admitted to ACH resulted in improved outcomes and a lower cost of care, especially when the ID consultant was involved early in the hospitalization. ■

Antiphospholipid Syndrome masquerading as infection

Erkan DE, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. *Annals of Rheum Dis* 2013.

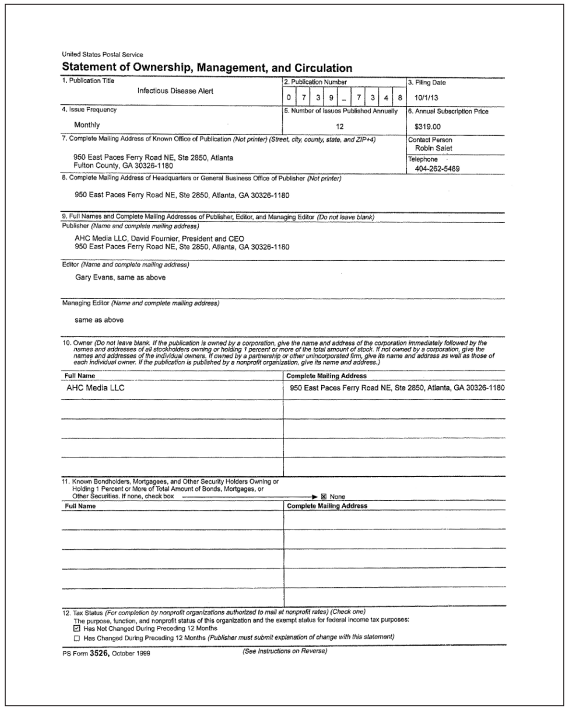
A previously healthy young man was admitted to an ICU with apparent sepsis,

with multiple brain and lung abscesses. He received broad-spectrum empiric antimicrobials, including amphotericin for a week in ICU, and failed to improve. Despite vigorous attempts to identify an etiology, including bronchoalveolar lavage, lumbar puncture, lung needle biopsy, bone marrow biopsy, and finally a lung biopsy, as well as numerous cultures and serological studies — no specific infection or agent could be identified. The lung biopsy strangely showed "cold" microabscesses with an absence of neutrophils, and fibrin deposition with vascular structures; and he began to develop evidence of thrombus in several vessels. Catastrophic antiphospholipid syndrome (CAPS) was put forward as a diagnosis — and the patient improved with high dose steroids and plasmapheresis although remains critically ill with a guarded prognosis.

CAPS is a poorly understood but overwhelming illness consisting of microangiopathy, multiple organ thrombosis, and tissue death. Mortality occurs in about 50% of patients. While some cases are preceded by infection or trauma, which seems to act as a trigger, the cause is not understood but likely related to a systemic inflammatory response syndrome with overwhelming cytokine cascade in the setting of positive anti-phospholipid antibodies. There may be an underlying history of lupus or other connective tissue disease. Patients develop peripheral thrombosis in both veins and arteries, and involvement of all major organ systems may occur.

The Catastrophic Antiphospholipid Syndrome Registry Group Project has been created to obtain more information about this disease. A total of 130 cases of CAPS in the registry were examined to determine the long-term outcome of survivors of this devastating condition. Sixty-three (46%) of the patients died with the initial event. Sufficient information was available for 58 of the 73 survivors. Of these, 38 (66%) had no further APS-related events during an average follow-up of 67 months. Recurrent APS events occurred in 15 cases, resulting in 4 deaths. In addition 5 patients died of other causes, including 3 patients who died from multi-organ system failure, and one each from myelofibrosis and pneumonia. Therefore, of the patients who survived their initial CAPS episode, 9 (16%) died within an average of ~5 years.

Even in patients who survive an initial CAPS event, who presumably have the benefit of a recognized diagnosis and better attempt at treatment, the risk of future events is high (26% of survivors developed recurrent APS events), with a significant risk of mortality within a few years. ■



United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Infectious Disease Alert	0 7 3 9 _ 7 3 4 8	10/1/13
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*: 960 East Paces Ferry Road NE, Ste 2850, Atlanta, Fulton County, GA 30326-1180 — Contact Person: Robin Sailet; Telephone: 404-252-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*: 960 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*: AHC Media LLC, David Fournier, President and CEO, 960 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180

Editor *(Name and complete mailing address)*: Gary Evans, same as above

Managing Editor *(Name and complete mailing address)*: same as above

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11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☒ None

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12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
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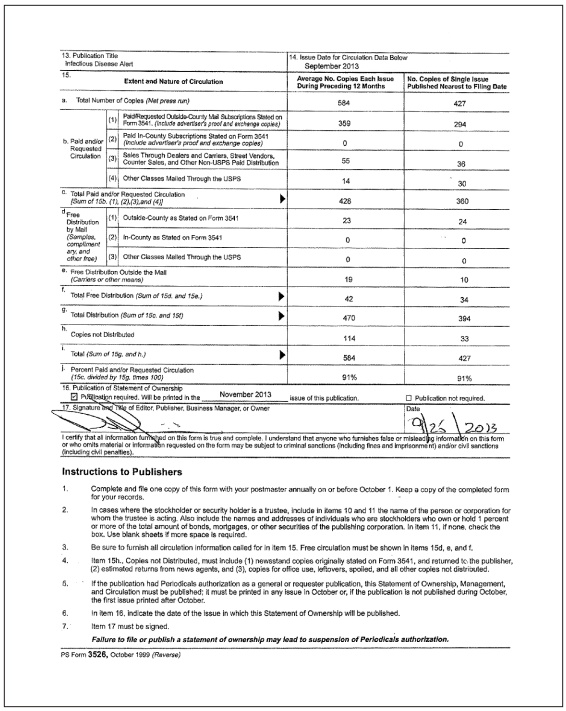

13. Publication Title: Infectious Disease Alert	14. Issue Date for Circulation Data Below: September 2013	
15. Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies *(Net press run)*	584	427
b. Paid and/or Requested Circulation (1) Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	359	294
(2) Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	55	38
(4) Other Classes Mailed Through the USPS	14	30
c. Total Paid and/or Requested Circulation *(Sum of 15b. (1), (2),(3),and (4))*	428	360
d. Free Distribution by Mail *(Samples, complimentary, and other free)* (1) Outside-County as Stated on Form 3541	23	24
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f. Total Free Distribution *(Sum of 15d. and 15e.)*	42	34
g. Total Distribution *(Sum of 15c. and 15f)*	470	394
h. Copies not Distributed	114	33
i. Total *(Sum of 15g. and h.)*	584	427
j. Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*	91%	91%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2013 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date: 9/25/2013

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CME QUESTIONS

1. Which of the following is correct with regard to the study of *Clostridium difficile* transmission in Oxford University Hospitals?

A. All isolates were genetically linked

B. Only approximately 5% of isolates were genetically linked.

C. Approximately one-third of isolates were genetically linked.

D. All patients with C. *difficile* infection were epidemiologically and genetically linked to other cases.

2. Which of the following is correct with regard to pertussis in the U.S.?

A. Most deaths from pertussis occur in immune compromised teenagers.

B. Most cases occur in infancy.

C. Vaccination against pertussis is contraindicated during pregnancy.

D. There is no reason for vaccination of adults.

3. Which of the following is correct with regard to the recent outbreak of *Salmonella heidelberg* infections in the U.S.?

A. It was localized to just 3 states.

B. It was associated with a higher incidence of bacteremia than usually seen with Salmonella infections.

C. Only 3% of patients required hospitalization.

D. The source was found to be fresh yogurt.

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]

Universal Glove and Gown Use and Acquisition of Antibiotic-Resistant Bacteria in the ICU: A Randomized Trial

Short Course Antibiotic Treatment for Community-Acquired Alveolar Pneumonia in Ambulatory Children: A Double Blind, Randomized, Placebo Controlled Trial

Preventing Infections in the ICU: One Size Does Not Fit All

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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 11 PAGES 21-22 NOVEMBER 2013

Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media, LLC.

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

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

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Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

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.

20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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