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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Treatment of CLABSIs in Children

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.

SOURCE: Wolf J, et al. Central line-associated bloodstream infection in children: An update on treatment. *Pediatr Infect Dis J* 2013;32:905-910.

Wolf and colleagues reviewed the current management of central line-associated bloodstream infection (CLABSI) in children, primarily focusing on non-neonates with long-term tunneled central venous catheters. Current treatments have a high failure rate predominantly due to relapse and reinfection because of the difficulty in preventing and eradicating intraluminal biofilm.

Infection rates vary depending on device type and patient characteristics; infection rates of 11 per 1000 catheter days are reported in infants with intestinal deficiency. Coagulase-negative and coagulase-positive staphylococci, enterococcus, and gram negative enteric bacteria join Candida as likely microbial etiologies of the infections. After the initial weeks following catheter insertion, intraluminal colonization is the most important source of infection, and bacteria can "hide" in biofilms along the catheter walls. CLABSI accounts for prolonged hospitalizations (median of 12 days in 1 study[1]), additional costs, missed medication doses, removal/replacement of central venous catheters, some intravascular thrombosis and rarely, death.

CLABSI typically, but not always, presents with fever and chills. The cutaneous insertion site does not usually appear to be abnormal. When simultaneously obtained blood cultures show growth more than 2½ hours sooner when

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Infectious Disease [ALERT]

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

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drawn from the catheter than from a peripheral vein, the infection is assumed to be related to (and not just associated with) the catheter. Similarly, variations of three hours or more in the delay to positivity between samples taken from different lumens are strongly associated the more rapidly positive site being in causal relation to the bloodstream infection.

Catheter salvage is often desirable, especially when a complicated child has limited potential replacement sites for another catheter and when the costs and medical risks of catheter replacement are high. Of course, catheters that are not being used for essential treatment can be removed, whether infected or not.

Catheters associated with tunnel infections and thrombophlebitis carry higher risk of adverse outcomes and should be removed. CLABSI due to fungi and mycobacteria have approximately 70% recurrence rates when catheters are left in place; recurrence rates for *S. aureus* CLABSI are around 50%. Children with infections due to other microbes could be candidates for ongoing catheter salvage attempts if the infection clears within 72 hours. If the catheter is removed, it should not be replaced until blood cultures demonstrate clearance of the blood stream infection.

Initial antibiotic therapy of a child with CLABSI should usually include vancomycin and broad-spectrum Gram-negative coverage (such as gentamicin or piperacillin-tazobactam or cefepime). If multiresistant Gram-negative infection is considered to be likely, meropenem could be used. If the patient is clinically septic, coverage with a second agent of a different class that provides broad spectrum Gram-negative activity could be considered. Antibiotic doses can be administered by rotating injection sites between the different lumens of the potentially infected catheter. Treatment should continue for 10 to 14 days after the infection is cleared (or the catheter removed); however, post- line removal treatment for "just" 5 to 7 days might be adequate for infections with coagulase-negative staphylococci.

In addition, treatment failures might be avoided by adding catheter lock therapy to systemic antibiotic therapy. An antimicrobial agent can be instilled into a potentially infected lumen in a volume adequate to fill that lumen. This can provide hours (or even days) of contact between high levels of anti-microbials and bacteria in the intraluminal biofilm. Various antibiotics and ethanol have been tried for this purpose. Catheter lock therapy seems safe, but studies so far have been small and inadequately powered to conclusively prove superiority of catheter lock therapy over "just" conventional systemic therapy. (Initial studies with hydrochloric acid lock therapy raised concern for mechanical complications.) Nonetheless, antibiotic lock therapy is recommended for adults and children with CLABSI.

■ COMMENTARY

Children are reaping the benefits of powerful advances in medical technology. At the same time, however, they may serve as proverbial lightning rods taking the heat before others know of danger. Children help us learn of the impact of anesthesia on brains,[2] CT scans on developing cells,[3] and indwelling venous catheters on microbial stability.

Clearly, critically ill children, like adults, benefit from indwelling central venous catheters for the delivery of powerful nutrition, blood products, and medication. Complications, particularly infections, however, remind us of the necessity of using technology carefully. Even as we have learned how to have judicious antibiotic stewardship and stringent isolation procedures to decrease the risks of infectious illnesses, so we are learning to improve our use of central lines to avoid unnecessary infections.

Initial efforts to decrease CLABSI centered on "bundles" of specific actions at the time of catheter insertion. Another wave of improvement came with efforts to

"scrub the hub" for the proper amount of time with the proper anti-septic material to decrease the risk of introducing infections. Now, newer evidence suggests that we must not only be attentive to how we insert and use lines but also when we use lines (minimizing the number of episodes of accessing the lines) and what we leave in them between uses.[4]

Despite great gains in the prevention of CLABSI, infections still occur – mostly in medically compromised patients with long-term indwelling lines. It is for these children that effective treatment of CLABSI is needed, and it was this population that served as the basis of the review by Wolf and colleagues.

The pathophysiology of CLABSI illustrates the problems and treatment requirements. Infections often relate to intraluminal biofilms that are incompletely penetrated with intermittent exposure to antibiotics. And, the "simple" treatment of removing the infected catheter (and needing to operatively replace it with a new line in a different venous site) is often laden with expense and risk that make preservation of the infected line important.

For now, the guidelines reviewed by Wolf and colleagues can direct management of children with CLABSI. Future studies of agents active against the physical intraluminal biofilm and about various treatment regimens will hopefully lead to further improvements in CLABSI management.

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ABSTRACT & COMMENTARY

Norovirus in Children: Vaccine Quest Continues as ED Visits Top a 1/4 Million

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: Norovirus infection accounts for almost one million medical encounters for children less than 5 years of age in the United States each year.

SOURCE: Payne DC, et al. Norovirus and medically attended gastroenteritis in U.S. children. *N Engl J Med* 2013;368:1121-30.

The New Vaccine Surveillance Network conducted active prospective surveillance for laboratory-confirmed cases of norovirus infection in children less than 5 years of age who presented for medical care with gastroenteritis. The study was performed in 3 counties in 2009 and 2010. Sites of care included hospital inpatient services, emergency departments, and outpatient clinics.

Norovirus was detected in the stool of 278 (21%) of 1295 patients and 19 (4%) of 493 healthy controls. During the same time period, rotavirus was detected in 152 (12%) of the children with acute gastroenteritis. The rate of outpatient visits for children less than 5 years of age precipitated by norovirus infection was 367.7 per 10,000, while the rates of emergency department visitations and of hospitalizations were 146.7 per 10,000 and 8.6 per 10,000, respectively.

■ COMMENTARY

This study demonstrates that norovirus infection of children less than 5 years of age accounts for almost 1 million health care visits per year (627, 000 outpatient visits, 281,000 emergency department visits, and 14,000 hospitalizations). The cost of these encounters was estimated to exceed $273 million.

Prior to the introduction of rotavirus vaccination in the United States in 2006, almost all children were infected with rotavirus before their 5th birthday. Each year in the United States in the pre-vaccine period, rotavirus was responsible for more than 400,000 doctor visits; more than 200,000 emergency room visits; 55,000 to 70,000 hospitalizations; and 20 to 60 deaths in children younger than 5 years of age. The efficacy of vaccination against rotavirus disease has changed the playing field and allowed norovirus to emerge as the leading cause of acute gastroenteritis in all age groups in the United States.

At least 3 companies are developing potential norovirus vaccines, each based on the use of virus-like particles[1], non-replicating particles lacking a viral genome, an approach that worked with human papillomavirus. An important barrier to success has been the existence of great antigenic diversity with 3 genogroups affecting humans and multiple genotypes of the virus, together with its continued evolution, including antigenic drift. In addition, immunity after infection is relatively short-lived.

Reference

1. Atmar RL, et al. Norovirus vaccine against experimental human Norwalk Virus illness. *N Engl J Med* 2011; 365:2178-87. ■

ABSTRACT & COMMENTARY

Reducing Antimicrobial Toxicity: Time to Move from Mice to Men in a Clinical Trial

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.

SYNOPSIS: Clinically relevant doses of bactericidal antibiotics (quinolones, aminoglycosides and β-lactams) were shown to cause mitochondrial dysfunction and overproduction of reactive oxygen species in mammalian cells in vitro and in mice, leading to oxidative tissue damage. The antioxidant acetylcysteine prevented these effects.

SOURCE: Kalghatgi S, et al. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in mammalian cells. *Sci Transl Med* 2013; 5:192ra85.

It is quite an understatement to say that antibiotics have been tremendously valuable for treating bacterial infections. Indeed, untold millions of humans and animals have benefited since widespread antimicrobial use began in the 1940s. Yet, clinicians are acutely aware of the downsides of these miracle drugs including adverse side effects, some of which have serious consequences for the recipient (i.e., nephrotoxicity, ototoxicity, tendinopathy). These toxicities and others tend to happen more with long-term rather than short-term antibiotic therapy. Efforts to understand the mechanisms of antibiotic toxicity and their prevention are the subject of ongoing experimental investigation. An emerging theory of how bactericidal antibiotics work is through the induction of a common cellular death pathway in bacteria that leads to the production of lethal reactive oxygen species (ROS).[1]

One of the innocent bystanders that can be affected by ROS is the mitochondria within mammalian cells. This consequence is not surprising since according to the endosymbiotic theory, mitochondria likely originated from free-living, aerobic bacteria. Moreover, it is known that high concentrations of antibiotics (greater than what is used clinically) inhibit mammalian cell growth and metabolism, although the mechanistic pathways by which this occurs remain obscure. Kalghatgi and colleagues sought to elucidate the effects of clinically relevant concentrations of bactericidal antibiotics on

mammalian cells, both in vitro and in vivo.

First, the investigators exposed a number of human cell lines to three different classes of bactericidal antibiotics: ciprofloxacin (fluoroquinolone), ampicillin (β-lactam), and kanamycin (aminoglycoside). They also exposed the cells to tetracycline to compare the effects of a bacteriostatic agent. All three bactericidal antibiotics induced a dose- and time-dependent increase in intracellular ROS production that damaged cellular DNA and protein and induced mitochondrial dysfunction, but tetracycline did not. Further experiments determined the mitochondrial electron transport chain as the major source for intracellular ROS and that the bactericidal but not bacteriostatic antibiotics reduced the overall respiratory capacity of the cell.

Next, the investigators tested whether this widespread cellular damage could be alleviated through the use of an antioxidant. They used N-acetyl-L-cysteine (NAC), an FDA-approved antioxidant used in clinical practice and a known buffer for extraneous intracellular ROS. Mammalian cells pretreated with NAC had reduced bactericidal-induced ROS levels and restored mitochondrial membrane potential compared to untreated cells. One concern with this approach is the potential to reduce the bacterial killing efficacy of the antibiotic, since bactericidal-induced ROS formation is a key mechanism for causing bacterial cell death. To address this concern a urinary tract infection model was constructed using *Escherichia coli* transurethrally introduced into the bladder of mice. Mice given ciprofloxacin compared to ciprofloxacin plus NAC had similar levels of bactericidal killing, which suggests that NAC does not interfere with antibacterial activity of ciprofloxacin. Serum glutathione levels were tested in the mice at 2 weeks and 16 weeks as a proxy measurement for ROS production. At 2 weeks mice treated with NAC plus the bactericidal antibiotics had lower glutathione levels compared to mice that did not receive NAC. At 16 weeks only ciprofloxacin caused a significant increase in ROS. Additional experiments using human epithelial cells yielded similar findings whereby NAC reduced bactericidal antibiotic-induced oxidative damage.

■ COMMENTARY

Through a series of well-conduced experiments, Kalghatgi and colleagues have provided evidence to support a novel mechanism of how bactericidal antibiotics can generate deleterious side effects. The three major classes of bactericidal antibiotics-quinolones, aminoglycosides, and β-lactams-cause ROS production that results in damage to mammalian DNA, proteins, and lipids. These data suggest a basis for potential therapeutic strategies that could reduce the toxicities associated with bactericidal antibiotics. One example is the co-administration of an intracellular antioxidant like NAC, which the investigators found reduced ROS levels and oxidative damage while not impacting the bacterial killing capacity of the antibiotics. The results from this study might be especially applicable to certain patients with a genetic predisposition towards developing a mitochondrial dysfunction disease. This group would in theory have an increased risk for toxicities from bactericidal agents. It remains to be elucidated whether monitoring specific blood markers (e.g. glutathione) would be beneficial.

The study had several limitations. First, many of the experiments were conducted in mice and the literature abounds with examples in which experimental data derived from animal models are different after testing in human subjects. Second, the hypothesis that all antibiotics kill by producing ROS, while biologically plausible, is controversial and other studies do not support it.[2] Third, the author's suggestion for reducing the risk of ROS and oxidative damage by using bacteriostatic rather than bactericidal antibiotics, especially for prolonged courses, needs to be taken with caution. The prevailing belief among many infectious disease experts is that bactericidal antibiotics are often preferred to bacteriostatic agents largely because of differences in pharmacokinetic and pharmacodynamics properties. Moreover, there are many examples in clinical practice (i.e. infective endocarditis, bacteremia, sepsis) where rapid bacterial killing is the goal.

Overall this paper advances our understanding of the mechanisms of bacterial action in mammalian cells in several ways. Whether antioxidants are helpful in preventing toxicities from bactericidal antibiotics in humans remains to be elucidated and a clinical trial seems warranted.

References

1. Kohanski MA, et al. A common mechanism of cellular death induced by bactericidal antibiotics. *Cell* 2007; 130:797-810.
2. Keren I, et al. Killing by bactericidal antibiotics does not depend on reactive oxygen species. *Science* 2013; 339:1213-1216. ■

Cyclosporiasis Spreads to 20 States

By Stan Deresinski, MD, FACP, FIDSA

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

SOURCE: Centers for Disease Control and Prevention: Investigation of an outbreak of cyclosporiasis in the United States: ow.ly/nX03j

SYNOPSIS: An outbreak of cyclosporiasis in the U.S. traced to lettuce has infected hundreds of individuals.

The notification of the CDC of 2 laboratory-confirmed cases of cyclospora infections on June 28, 2013 was their first evidence of an outbreak that, as of August 20, 2013, had reached 593 cases in 20 states with at least 36 hospitalizations. *(See map below.)* Most of the illness onset dates have ranged from mid-June through mid-July. *(See chart, p. 139)* Texas accounted for 247 cases. Investigations performed in Iowa and Nebraska indicated that the source was a commercial salad mix.

■ COMMENTARY

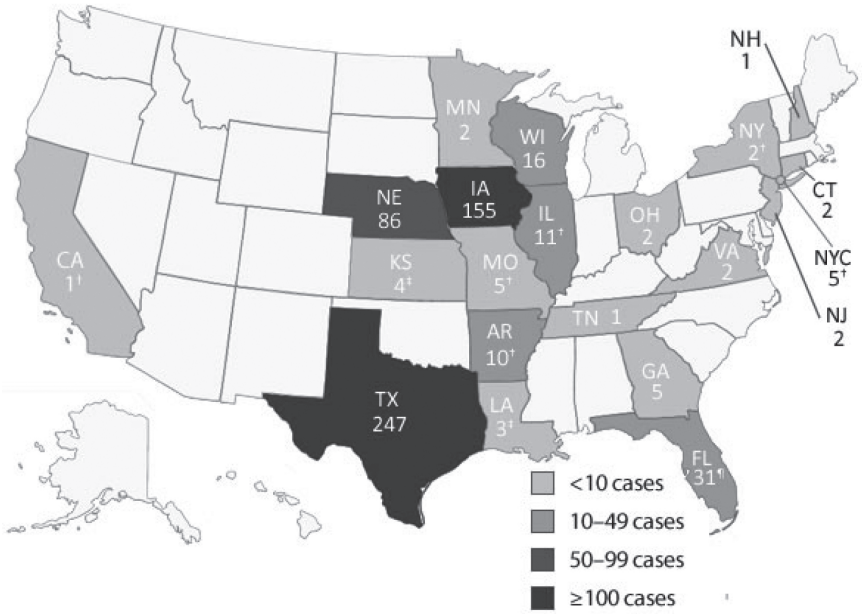
Cyclosporiasis is endemic in many countries in tropical and subtropical areas and many

Investigation of an Outbreak of Cyclosporiasis in the United States Map

Last updated August 20, 2013 9:15 AM EDT

Current Case Count Map

Cyclosporiasis cases notified to CDC, by state*



* Data are current as of 5pm EDT, 8/19/13. Data are preliminary and subject to change. A total of 593 cases of Cyclospora infection have been reported from 20 states and New York City. The number of cases identified in each area is as follows: Texas (247), Iowa (155), Nebraska (86), Florida (31)¶, Wisconsin (16), Illinois (11)†, Arkansas (10)†, Georgia (5), Missouri (5)†, New York City (5)†, Kansas (4)‡, Louisiana(3)‡, Connecticut (2), Minnesota (2), New Jersey (2), New York (2)†, Ohio (2), Virginia (2), California (1)†, New Hampshire (1), and Tennessee (1).

•† Includes one case that may have been acquired out of state.

•‡ Includes two cases that may have been out of state.

•¶ May include one travel-associated case.

SOURCE: Centers for Disease Control and Prevention

infections occur in travelers. Foodborne outbreaks in the U.S. have repeatedly been linked to imported produce, including raspberries, snow peas, and lettuce.[1,2]

Oocysts of this sporozoan parasite that are excreted in the feces are not themselves infective but require days or weeks for sporulation to the infective form that then may contaminate food or water. After they are ingested, the sporocysts, each containing 2 elongated sporozoites, exist within the gastrointestinal tract. The sporozoites then invade small intestine mucosal epithelial cells where they multiply and mature into oocysts. Cyclospora are resistant to disinfectants usually used in water and in food processing.

Cyclospora can be detected in stool specimens (preferably concentrated samples) by use of a modified acid fast stain. At least 3 specimens should be examined before accepting the testing as being negative. Alternatively, taking advantage of the fact that the oocysts naturally exhibit intense blue autofluorescence, the organism can be visualized by UV fluorescence microscopy. CDC can perform 18S rRNA amplification and sequencing on DNA extracted from stool for identification to the species level. To date, however, all human cases for whom speciation has been performed appear to have resulted from infection with *Cyclospora cayatanensis*.

In contrast to travelers and those infected in the U.S., infection of residents of endemic areas is often asymptomatic.[2] Symptomatic infection results in loss of appetite, nausea, abdominal cramping and flatulence, low-grade fever, and diarrhea. Treatment is with trimethoprim-sulfamethoxazole; there is no known effective alternative.

References

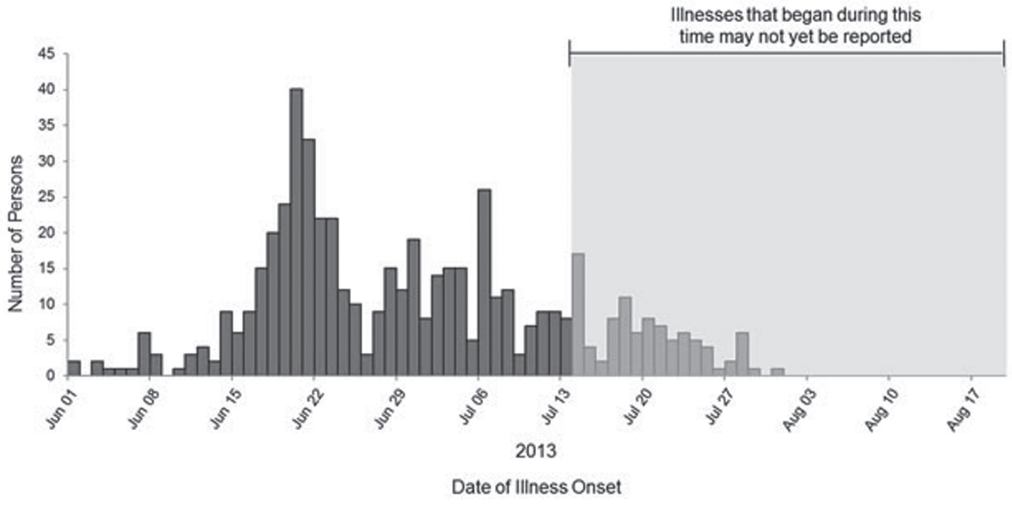
1. CDC. Surveillance for laboratory-confirmed sporadic cases of cyclosporiasis—United States, 1997-2008. *MMWR* 2011;60:1-11.
2. Ortega YR, et al. Update on Cyclospora cayetanensis, a food-borne and waterborne parasite. *Clin Microbiol Rev* 2010; 23:218-34. ■

Investigation of an Outbreak of Cyclosporiasis in the United States Epi Curve

Last Updated August 16, 2013 9:00 AM EDT

Current Epi Curve

Confirmed Cyclosporiasis Cases, United States, Since June 2013*



* N=542. Data are current as of 5pm EDT, 8/19/13. Data are preliminary and subject to change. Cases reported to CDC as of 5pm on 8/19/13 for which onset of illness dates were available. A case is defined as laboratory-confirmed Cyclospora infection in a person with onset of illness since June 1, 2013, and no known history of travel outside of the United States or Canada in the 14 days prior to onset of illness. Illnesses that occurred after July 13, 2013, might not yet be reported due to the time it takes between when a person becomes ill and when the illness is reported. It is not yet known whether all reported cases are part of the same outbreak.

SOURCE: Centers for Disease Control and Prevention

'Pulling Mussels from a Shell' Leads to Diarrhetic Shellfish Poisoning

"Of all the creatures living in the water, you may eat any that has fins and scales. But anything that does not have fins and scales you may not eat; for you it is unclean."
Deuteronomy 14:9. New International Version

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: Home-caught and cooked mussles in Canada and those served at restaurants in Washington state had elevated toxin levels that resulted in diarrhetic shellfish poisoning.

SOURCES: Lloyd JK, et al. Diarrhetic shellfish poisoning, Washington, USA, 2011. *Emerg Infect Dis* 2013;19:1314-6.

Taylor M, et al. Outbreak of diarrhetic shellfish poisoning associated with mussels, British Columbia, Canada. Mar Drugs 2013; 11;1669-76. (Abstract): http://ow.ly/nV7od

Public health authorities in Seattle and King County were notified in July 2011 of a cluster of cases of diarrheal illness occurring in 3 of 4 members of a family that had eaten mussels that they themselves had harvested and cooked. The 3 affected members, ages 2, 5, and 45 years, had eaten 8-15 mussels while the fourth, unaffected member, had only eaten 4. Symptoms began 4, 7, and 14 hours after their meal and included vomiting, diarrhea, body aches, fever and chills. The illness was self-limited with all 3 being well by 96 hours. Vomiting lasted for a mean duration of 3 hours while the mean duration of diarrhea was 52 hours.

Mussel samples collected from implicated public dock site were found to have excess toxin levels. Clams and oysters harvested from an adjacent commercial growing area were recalled (mussels were not commercially harvested). The park containing the public dock and the commercial site were closed until shellfish were cleared for harvesting based on reduced toxin levels.

Shortly after the Washington state outbreak, public health authorities in British Columbia were notified of the occurrence of gastrointestinal illness in individuals who had consumed cooked mussels at a number of restaurants. Investigation uncovered a total of 62 cases associated with 15 "food premises" where mussels had been eaten between July 28 and August 6. Symptoms, occurring after an incubation period of 5-15 hours and lasting 1-3 days most frequently included nausea, vomiting, diarrhea, and abdominal cramping pain.

The implicated mussels had been harvested at a single area in the Strait of Georgia between July 24-31 by a single enterprise that had taken steps to withdraw its product on August 3. Tested mussel samples contained elevated toxin levels.

■ COMMENTARY

Diarrhetic shellfish poisoning is one of a number of toxic events that may result from ingeston of these filter feeding marine molluscs. Diarrhetic shellfish poisoning is caused by the ingestion of excess amounts of okadaic acid group toxins as well as some related toxins.[1] Okadoic acid potently inhibits mammalian protein phosphorylase phosphatases that dephosphorylate serine and threonine and is believed to cause diarrhea by stimulating the phosphorylation involved in controlling sodium excretion by intestinal epithelial cells. Okadoic acid and other toxins are produced by dinoflagellate algae, particularly Dinophysis. As filter feeders, shellfish act as concentrators of these lipophilic and heat stable toxins, an event exacerbated by increased density of these dinoflagellates, as occurs with algal blooms. There has, unfortunately, been a global increase in the frequency of algal blooms with consequent okadoic acid production and increasing contamination of shellfish. The reasons for the increased frequency of algal blooms are likely to be multifactorial but likely include climate change.

Diarrhetic shellfish poisioning was first identified in the Netherlands 5 decades ago. Most outbreaks are reported from outside North America, although these have occurred in eastern Canada. Although toxin-containing dinoflagellates have long been known to exist in Pacific Coast waters, these are the first reported cases of diarrhetic shellfish poisoning acquired in this region.

The incubation period is brief. In general, symptoms (nausea, vomiting, diarrhea, chills, abdominal pain) begin 30 minutes to 12 hours after ingestion and last for as long as 3 days. A similar syndrome that has been called azaspiracid shellfish poiosoning is caused by a group of toxins that differ from those causing diarrhetic shellfish poisoning.[2] Treatment is supportive.

Reference

1. Trainer VL, et al. Diarrhetic shellfish toxins and other lipophilic toxins of human health concern in Washington state. *Mar Drugs* 2013; 11:1815-35.
2. James KI, et al. Shellfish toxicity: Human health implications of marine algal toxins. *Epidemiol Infect* 2010; 138:927-40. ■

ABSTRACT & COMMENTARY

For these Fishermen,a glass Haff empty

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: Three new cases of rhabdomyolysis after eating buffalo fish are reported.

SOURCE: The Mississippi State Department of Health Reports New Cases of Rare Disease: http://ow.ly/nX6gk

In early July 2013, three members of a Mississippi family became ill after eating buffalo fish that had been caught in the Yazoo River and that they had purchased and stored in a freezer prior to cooking. They recovered uneventfully.

■ COMMENTARY

Haff disease describes a syndrome of rhabdomyolysis within 24 hours of eating fish. It was first recognized in 1924 when individuals living along the shores of the Königsberg Haff (in German, a "haff" is a lagoon separated from the sea by a narrow sandbar) in East Prussia experienced an epidemic of rhabdomyolysis.[1] Mostly fishermen were affected. Seabirds and foxes died, as did village cats. All the affected humans had eaten fish.

Buffalo fish (genus Ictiobus) were caught by members of the Lewis and Clark expedition. It is a freshwater fish that may be mistaken for carp. The first case of Haff disease in the U.S. was recognized in 1984 in Texas and there have been only a total of approximately 33 identified to date. Many have been related to eating buffalo fish. Other fish, mostly bottom-feeding omnivores, that have been implicated in cases in Europe and China include burbot, eel, pike, crayfish, salmon, silver dollars, black-finned colossoma, freshwater pompano, and marine box fish.

Symptoms usually begin within 12 hours of eating the implicated fish. The include muscle weakness, chest and generalized pain, dry mouth, nausea and vomiting, confusion and, in some cases, dark urine. These symptoms are usually short-lived, but fatigue persists for months in some. Treatment is supportive with usual management, the key element of which is rapid fluid administration. Bicarbonate is often administered in an attempt to alkalinize the urine to prevent acute kidney injury, but its value is uncertain.

The etiologic toxin remains unknown, but since cooking does not prevent illness, it is not heat-labile. Cicutoxin produced by the water hemlock has been suggested as the cause, but this remains unproven.

References

1. Buchholz U, et al. Haff disease: from the Baltic Sea to the U.S. shore. *Emerg Infect Dis* 2000; 6:192-5. ■

NEWS BRIEF

FDA: Fluoroquinolones pose risk of Permanent Nerve Damage

The Food and Drug Administration is requiring drug labels and Medication Guides for all fluoroquinolone antibacterial drugs be updated to better describe the serious side effect of peripheral neuropathy.

"This serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent," the FDA stated in a safety alert issued Aug. 15, 2013.

The risk of peripheral neuropathy occurs only with fluoroquinolones that are taken by mouth or by injection. According to the FDA, approved fluoroquinolone drugs include levofloxacin (Levaquin), ciprofloxacin (Cipro), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and gemifloxacin (Factive). The topical formulations of fluoroquinolones, applied to the ears or eyes, are not known to be associated with this risk.

"Make sure your patients know to contact you if they develop symptoms of peripheral neuropathy," the FDA stated. "Make sure your patients receive the Medication Guide with every prescription. If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk"

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program. For more information go to: ow.ly/nZj4S ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Stool cytokine markers predict *C. diff* severity

El Feghaly RE, etc. Markers of intestinal inflammation, not bacterial burden, correlate with clinical outcomes in *Clostridium difficile* infection. *CID* 2013: 56:1713-21.

While certain factors, such as age, high white blood count, and comorbidities may be used in identifying patients at risk for more severe *C. difficile* enterocolitis, they are also used to justify the initial choice of antibacterial treatment. For example, current guidelines suggest that patients with mild to moderate disease receive metronidazole, but those patients with higher white blood counts (≥ 15,000 cells/ microL) receive, as initial therapy, orally administered vancomycin. But how valid are these predictors of disease severity?

These authors examined the correlation between 3 different disease severity scores (HINES VA, UPMCI, and CSI), fecal cytokine levels, quantitative fecal *C. difficile* burden, based on real-time PCR measurements of tcdB DNA, and clinical outcomes, including duration of diarrhea and length of hospital stay. Fecal CXCL-5 mRNA, IL-8 MRNA and quantitative IL-8 protein levels, and fecal lactoferrin concentrations were measured at baseline and then daily (when stools were available). CXCL-5 is a member of the CXC cytokine group, which is 22% homologous to IL-8, binds to the IL-8 receptor, recruits and activates neutrophils, and has been reportedly elevated in patients with inflammatory bowel disease.

A total of 131 patients were enrolled in the study; stools were available in 121. One patient had consistently negative tcdBDNA levels and was excluded from the analysis. Of the remaining 120 patients, 19 (16%) were initially started on oral vancomycin and the rest were treated with metronidazole. Of the latter group, 33 (33%) were switched to oral vancomycin at some point during the treatment course, presumably for lack of response. Diarrhea persisted for 5 or more days in slightly more than half of the patients (52%). Eleven patients (9%) were considered to have severe disease, based on the presence of toxic megacolon, colectomy, admission to ICU or death. Slightly more than half (52%) of the patients were considered immunosuppressed based on previous use of corticosteroids or other immunosuppressants within 90 days. There did not appear to be a difference in presentation between immunosuppressed and immune competent participants.

HINES VA and CSI scores, and leukocytosis (≥ 15,000 cells/mcl) were each significantly associated with disease severity. A more severe HINES VA score was also associated with higher levels of fecal IL-8 mRNA and lactoferrin protein concentrations. A higher UPMC1 score was also associated with higher IL-8 protein concentrations in stool.

Interestingly, fecal *C. difficile* bacterial burden at presentation did not appear to correlate with any of the severity scores, the frequency of stools, or pain

level. But CXCL-5 mRNA and IL-8 mRNA levels at study entry were statistically significantly associated with time to resolution of diarrhea (p = .009 and P = .03, respectively), and elevated levels correlated with diarrhea symptoms throughout the hospital course. As predicted, IL-8 protein levels decreased after starting therapy. Bacterial burden quickly decreased with initiation of therapy, but remained independent of diarrhea symptoms.

It appears that these biological markers are better correlates of disease severity and clinical outcomes (severity and duration of diarrhea) than *C. difficile* bacterial load. *C. difficile* toxins cause direct injury to the intestinal endothelium, resulting in a host inflammatory response with cytokine release. Fecal cytokines are therefore more likely reflecting the extent of tissue inflammation and damage – a better predictor of disease severity and outcome, and potential treatment failure.

Non-gonococcal urethritis – diminishing clinical response

Manhart LE, et al. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: A randomized controlled trial. *CID* 2013:56(7): 934-942.

Declining rates of response to standard treatment regimens for non-gonococcal urethritis (NGU) may prompt changes in accepted treatment strategies. Both single dose azithromycin 1 gram or doxycycline 100 mg twice daily x 7 days are currently accepted first line treatment regimens for patients with NGU, as defined by mucupurulent or purulent urethral discharge or a urethral swab with ≥ 5 white blood cells per HPF in the absence of gonorrhea; or a positive nucleic acid amplification test (NAAT) for *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), *Ureaplasma urealyticum biovar* 2(UU) or *Trichomanas vaginalis* (TV). Evidence suggests that rates of response to standard regimens may be declining, especially those infections due to *M. genitalium*. Previously, azithromycin was consistently more effective than doxycycline against *M. genitalium*. However, rates of microbiologic cure to azithromycin single dose treatment of M. genitalium in 3 recent U.S. studies ranged from a high of 77% in New Orleans to as low as 40% in Seattle.

These Seattle-based investigators examined the rates of response to standard therapy in a group of men ≥ 16 yrs of age, with NGU, defined as visible urethral discharge or ≥ 5 WBC per HPF in a randomized, double-blind clinical trial. Men were recruited between 2007 and 2011. Urine was tested using NAATs, which are highly sensitive methods for detecting specific pathogens. Clinical cure was assessed at 3 weeks (< 5 WBCs per HPC regardless of the presence of symptoms or absence of discharge) plus microbiologic cure (negative NAAT). Men with either *M. genitalium* or Ureaplasma spp. who failed to respond to their initial treatment received the alternate treatment, and were re-evaluated at 6 weeks of study.

A total of 606 men were randomized to either azithromycin 1 gram once vs placebo doxycycline (n – 304) vs azithromycin placebo plus doxycycline 100 mg bid x 7 days (n = 302). The mean age of participants was 33.7 yrs, slightly more than half had urethral discharge (53%), dysuria(51%) or other urethral complaints (26%). Fifteen of the men were HIV+ (2.5%). NAAT results were positive for CT (23%), UU (24%), and MG (13%).

In the intent to treat analyses, 80% of the men receiving azithromycin achieved clinical cure vs 76% for the doxycycline group (p = NS). Interestingly, clinical cure occurred less often in men returning for follow-up "early" within 3 weeks (67%) vs after 3-5 weeks (81%) (p = .004). While clinical cures for all causes were similar between the two treatment groups (83% for azithromycin and 82% for doxycycline), clinical cures in men with MG were significantly lower (63% for azithromycin and 48% for doxycycline). The intent-to-treat analyses for microbiologic cure rates were also similar for both treatment groups. No difference in response to treatment was observed for those few men who were HIV+.

These results suggest that current treatment regimens for NGU in men may not be adequate. Identification of the specific microbiologic cause is useful in guiding therapy – clinical testing should be expanded beyond the common protocol testing for CT and GC. Men with TV should be treated with metronidazole, in addition to azithromcyin. In addition, 30% of the men in this survey were diagnosed with MG, for which neither azithromycin nor doxycycline was effective in 37%-52% of individuals. Should they fail, current guidelines recommend switching to the other agent – which does not appear to be a very effective treatment strategy. Presently, the authors treat all treatment failures with moxifloxacin 400 mg po x 7 days. (Levofloxacin 500 mg per day for 7 days would be a reasonable alternative). And it may be appropriate to counsel men they should not expect rapid resolution of their clinical symptoms within a week or two of treatment. Based on this data, most men do not have symptomatic resolution for at least 3-5 weeks. ■

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 a recommended acceptable empiric antibiotic regimen for central line-associated bloodstream infections (CLABSI) in children?

A. Ceftriaxone and gentamicin.
B. Ceftriaxone and vancomycin.
C. Cefepime and gentamicin.
D. Cefepime and vancomycin.

2. Which of the following is correct?

A. Rotavirus infection is the leading cause of acute gastroenteritis infection in the U.S.
B Norovirus infection is the second leading cause of acute gastroenteritis infection in all age groups in the U.S.
C. Vaccination against norovirus infection has drastically reduced its incidence in the U.S.
D. Immunity against norovirus infection is relatively short-lived.

3. Which of the following is correct?

A. The major feature of Haff Disease is rhabdomyolysis.
B. Haff Disease is caused by okadaic acid ingestion.
C. Haff Disease is associated with ingestion of shellfish.
D. Haff disease can be prevented by cooking.

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]

Low-dose Steroids in Adult Septic Shock: Results of the Surviving Sepsis Campaign.

Hospital Outbreak of Middle East Respiratory Syndrome Coronavirus

U.S. Hospitalizations for Pneumonia after a Decade of Pneumococcal Vaccination

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.*

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Once-daily Tadalafil for ED: Efficacy and Safety

Source: Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

Psychological Disorders: How to Give Patients What They Want and What They Need

Source: McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

Reducing Stroke Risk After TIA or Minor Ischemic Stroke

Source: Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

Long-term Mortality Among Adults with Asthma

Source: Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

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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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Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Source: The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

New Hope for Hepatitis C Patients

Source: Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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.

ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■