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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Valganciclovir Improves Survival in Patients with Glioblastoma

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

SOURCE: Soderberg-Naucler C, et al. Survival in patients with glioblastoma receiving valganciclovir. *N Eng J Med* 2013;369:985-986.

Glioblastoma is one of the most aggressive solid tumors, with a median overall survival of 12 to 14 months and a two-year survival of 15% to 26% despite our best current therapies. Recently it has been suggested that cytomegalovirus (CMV) acts as a tumor promoter in breast cancer.[1] CMV is a very common infection in humans and has a seroprevalence rate of at least 50% in the U.S.[2] Investigators from Sweden sought to determine the prevalence of CMV in patients with glioblastoma and elucidate what effect valganciclovir might have on disease progression and survival.

Soderberg-Naucler and colleagues examined 250 cases of glioblastoma and all but one were CMV-positive. Of the 75 patients they further evaluated, the median survival rate was 33 months in those with low-grade CMV infection compared to 13 months in those with high-grade CMV infection (P=0.04). Using data from a

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double-blind clinical trial or a compassionate-use program at their institution, the investigators found two-year survival was 62% among 50 patients who received valganciclovir in addition to standard therapy compared to 18% of controls who did not receive valganciclovir (P<0.001).

The two groups were matched for disease stage, surgical-resection grade, and baseline treatment. Overall, the median survival was 25 months in the patients who received valganciclovir and 13.5 months in those who did not (P<0.001). Furthermore, in a subgroup analysis the median two-year survival of patients who received valganciclovir for at least 6 months was 70%, while those who received continuous valganciclovir after the first 6 months had a two-year survival of 90% (P<0.001). The median survival in this latter group was 56.4 months.

COMMENTARY

The results of this study and their possible clinical implications are profound given the dismal prognosis associated with glioblastoma. Indeed, such high survival rates have never been reported in previous studies. Although its high incidence in tumors has been appreciated for several years, many experts have dismissed CMV as a bystander and not a promoter of disease.

Enthusiasm for the findings of the present study must be somewhat mitigated by its limitations. First, it had a retrospective design, a small sample size, and was conducted at a single institution. Second, no information was provided about side-effects of the medication, specifics about the diagnosis of CMV, nor if those patients with increased survival had measurable improvement in their CMV viral indices. Third, there was no explanation why certain patients received a longer duration of therapy than others. Finally, while the authors suggested it was unlikely selection bias could have accounted for the high survival rates, this cannot be ascertained with a reasonable degree of certainty without a more detailed description of the study population.

While the results of this single study are impressive, they are preliminary and should be the impetus for additional multicenter, prospective trials. One important question still unanswered is which patients with glioblastoma and CMV should be treated? Should it be all of them or only those expected to survive at least 6 months to a year? Until more data are available, the routine use of valganciclovir for glioblastoma can not be recommended. The potential role of immunotherapy, such as a CMV vaccine, in the treatment of glioblastoma also requires further investigation.

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More Direct-Acting Antivirals for Treatment of Hepatitis C

By Dean L. Winslow, MD

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Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: In a phase 2b, randomized, open-label trial, faldepravir+deleobuvir+ribavirin resulted in 52-69% rate of sustained virologic response (SVR) at 12 weeks in patients with HCV genotype 1 infection.

SOURCE: Zerzem S, et al. Faldepravir and deleobuvir for HCV genotype 1 infection. *New Engl J Med* 2013;369:630-9.

Faldepravir (a HCV protease inhibitor) and deleobuvir (a nonnucleoside polymerase inhibitor) were studied in a phase 2b randomized, open-label trial. 362 patients, all with previously untreated HCV genotype 1 infection were randomly assigned to 5 groups: Faldepravir (FDV) 120 mg daily plus deleobuvir (DBV) 600 mg three times daily plus ribavirin (RBV) for 16, 28, or 40 weeks (TID 16W, TID 28W, TID 40W), FDV 120 mg daily plus DBV 600 mg twice daily plus RBV for 28 weeks (BID 28W), or FDV 120 mg daily plus DBV 600 mg three times daily without RBV for 28 weeks (TID 28W-NR). The primary endpoint was sustained virologic response 12 weeks after completion of treatment.

SVR was attained in 59% TID 16W group, 59% in the TID 28W group, 52% in the TID 40W group, 69% BID 28W group, and 39% in the TID 28W-NR group. The rate of SVR did not differ significantly by protease inhibitor (PI) dose or duration in the ribavirin-containing arms. However the SVR rate was significantly higher in the TID 28W dose than in the TID 28W-NR arm. Rates of SVR were higher in patients with genotype 1b infection (56-85%) than they were in patients with genotype 1a infection (11-47%) and also tended to be higher in patients with IL28B CC genotype. Rash, photosensitivity, nausea, vomiting and diarrhea were seen in all arms but serious adverse events were recorded in only 7% of patients. Anemia was more prominent in patients treated with RBV-containing regimens.

COMMENTARY

We will soon have quite a few options for direct-acting antiviral (DAA) treatment of HCV infection which do not require the use of interferon. Faldepravir (like boceprevir and telaprevir) is inhibitor of the HCV NS3/4a serine protease. Deleobuvir is a non-nucleoside inhibitor of the NS5b polymerase. These drugs are only a bit behind a number of other DAA's in the drug development pipeline. These other agents include sofosbuvir,[1] a nucleoside analogue NS5b polymerase inhibitor and ABT-333,[2] another NS3/4a protease inhibitor, both of which also demonstrated excellent activity in combination with RBV for treatment of HCV genotype 1 infections. However at this point it appears that RBV may still be necessary as part of these various combination therapy regimens.

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Naegleria fowleri Amoeba Rarely Acquired, Rarely Survived

By Stan Deresinski, MD, FACP, FIDSA

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In 2011, 2 men died of amebic meningoencephalitis in Louisiana. Each had used neti pots to irrigate their sinuses with tap water, which was suspected as the source of infection. Definitive proof was not forthcoming, although vigorous sinus irrigation with tap water had previously been associated with the development of this infection.[1] In August 2012, a 4-year-old child in Louisiana's St. Bernard Parish — who had been playing on a Slip'n Slide whose water flow came from a household faucet — died of the infection.[2] This time, the Centers for Disease Control and Prevention detected *Naegleria fowleri* — the cause of amebic meningoencephalitis — in multiple household water samples, including one collected from the outside faucet that had been used, a water heater, and a toilet tank. The organism was also detected in water samples from nearby hydrants and faucets directly connected to water lines.

N. fowleri is found naturally in freshwater lakes, rivers, and hot springs in the US, particularly in southern-tier states.[3,4] *(See map and table p. 5)*. It is a thermophilic amoeba with an optimal growth temperature of 115°F (46°C). It is global in distribution and is naturally found in warm freshwater environments such as lakes and rivers, naturally hot (geothermal) water such as hot springs, warm water discharge from industrial or power plants, geothermal well water, poorly maintained or minimally chlorinated swimming pools, water heaters, and soil, where it lives by feeding on bacteria and other microbes in the environment. It is not found in salt water.

Infection occurs when the organism enters the nares and migrates along the olfactory nerve through the cribiform plate and into the central nervous system. *N. fowleri* causes a purulent meningitis heralded by the abrupt onset of severe headache followed by vomiting with progression to coma and, most often, death. The diagnosis is made by visualization of the organism in cerebrospinal fluid or tissue samples, PCR, or growth in tissue or axenic culture at elevated temperature.

Recreational water users should assume that there is always a low level of risk whenever they enter warm freshwater lakes, rivers, and hot springs (for example, when swimming, diving, or waterskiing), particularly in the southern U.S. (although infection has occurred as far north as Minnesota) and particularly in warm months. The infection is rare, with only 32 infections reported in the US from 2001-2010. Of these, 30 had been infected by exposure to contaminated recreational water and 2 by water from a geothermal drinking water supply.

Only 1 of the first 128 U.S. patients have survived the infection, although another survivor has been reported in Mexico. Commonly used treatment regimens have included multiple agents, including amphotericin B, fluconazole, rifampin, and others. A drug used in the treatment of leishmaniasis, miltefosine, that has been used to treat infection with other free-living amoebae *(Balamuthia mandrillaris* and *Acanthamoeba spp.)*, was previously unavailable in the U.S., but it is now available from CDC. Milefosine can be obtained by contacting the CDC Emergency Operations Center at 770-488-7100 to consult with a CDC expert regarding the use of this drug.

While the risk is low, it is wise to consider preventive measures, such as those listed by CDC:

SWIMMING-RELATED RISK

• Hold your nose shut, use nose clips, or keep your head above water when taking part in

water-related activities in bodies of warm freshwater.

• Avoid putting your head under the water in hot springs and other untreated thermal waters.

• Avoid water-related activities in warm freshwater during periods of high water temperature and low water levels.

• Avoid digging in, or stirring up, the sediment while taking part in water-related activities in shallow, warm freshwater areas.

NON-SWIMMING-RELATED RISK

If you are making a solution for irrigating, flushing, or rinsing your sinuses (for example, by using a neti-pot, sinus rinse bottle or other irrigation device), use water that has been:

• previously boiled for 1 minute (at elevations above 6,500 feet, boil for 3 minutes) and left to cool

OR

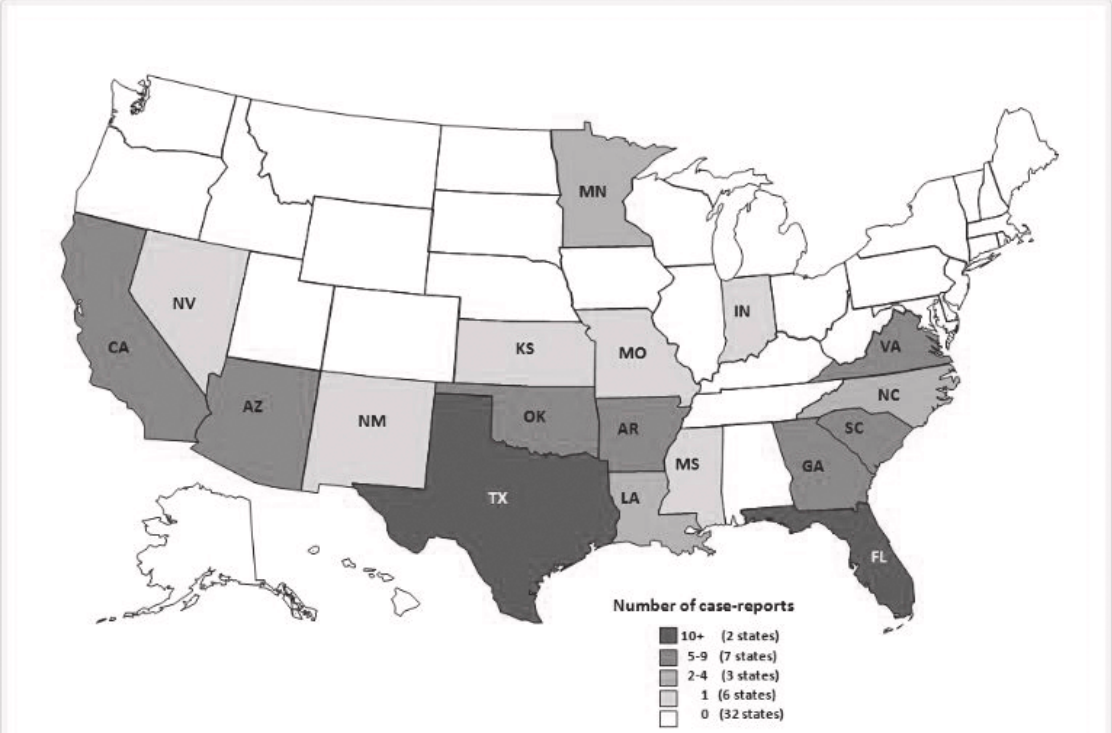
(Continued on p. 6.)

Number of Case-reports for Each State

State (Abbreviation)	# of Cases
Arizona (AZ)	7
Arkansas (AR)	5
California (CA)	7
Florida (FL)	33
Georgia (GA)	5
Indiana (IN)	1
Kansas (KS)	1
Louisiana (LA)	3
Minnesota (MN)	2
Mississippi (MS)	1
Missouri (MO)	1
Nevada (NV)	1
New Mexico (NM)	1
North Carolina (NC)	4
Oklahoma (OK)	6
South Carolina (SC)	7
Texas (TX)	31
Virginia (VA)	7

SOURCE: Centers for Disease Control and Prevention

Number of Case-reports of Primary Amebic Meningoencephalitis by State of Exposure: United States, 1962-2012



States where cases of *Naegleria fowleri* have occurred. N=128; state of exposure unknown for 4 cases. Map does not picture 1 case from the U.S. Virgin Islands.

SOURCE: Centers for Disease Control and Prevention

• filtered, using a filter with an absolute pore size of 1 micron or smaller

OR

• purchased with a label specifying that it contains distilled or sterile water

Rinse the irrigation device after each use with water that has been previously boiled, filtered, distilled, or sterilized and leave the device open to air dry completely.

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4. http://www.cdc.gov/parasites/naegleria/state-map.html ■

Infectious Disease Malpractice: The $1.2 Million Miscommunication

By Joseph Patterson, MD, Emergency Medicine Residency, Madigan Army Medical Center, Tacoma, WA; Cyril Fider, MD, Madigan Army Medical Center, Tacoma, WA; and Gregory Moore, MD, Emergency Medicine Residency Director,Madigan Army Medical Center, Tacoma, WA

The authors report no financial relationships in this field of study.

Infectious diseases account for a significant percentage of emergency department (ED) visits each year and are frequent sources of litigation. A plaintiff verdict or settlement is usually based on a delay in diagnosis and subsequent substandard treatment. It is important to recognize specific infectious entities early to avoid medical-legal exposure.

In Anonymous Woman v. Anonymous Physician and Anonymous Nurse, a 40-year-old female was referred from her primary care physician to the ED after presenting with five days of headache, fever, and body aches. An initial evaluation consisting of a lumbar puncture, urinalysis, and blood cultures was performed, and she was discharged with blood cultures pending after the other tests were negative. Two days later, the blood cultures grew group B streptococcus. A nurse was instructed to call the patient back, but was unsuccessful after two attempts at the home number on different days — no attempt was made to contact the primary care doctor who referred the patient. The physician stated that the nurse was instructed to call the patient back for treatment, while the nurse stated that the culture results were thought to be a contaminant and the call was meant to see how the patient was doing. The patient returned six days after the initial visit with worsening symptoms and was admitted for treatment of endocarditis. The patient was also found to have aortic regurgitation and valvular disease, expected to require a valve replacement. The defense claimed that the damage was pre-existing and not worsened by the delay in diagnosis and treatment, but a $1.2 million settlement was reached.[1]

Infective endocarditis is an inflammation of the lining of the heart or its valves with an infectious agent, usually bacteria. Diagnosis is challenging, and untreated disease is associated with significant complications and a mortality rate approaching 100%.[2] The above case illustrates two excellent points. The first concerns follow-up. The follow-up call was delegated to a nurse, and the physician and nurse gave conflicting statements on the purpose of the calls. Additionally, the primary care doctor was not contacted as another means of reaching the patient. In the end, the patient was never reached with the results and it would be difficult to say that every effort had been made to contact the patient.

There are a plethora of cases in which blood culture results were inadequately

communicated. These cases universally result in court settlements or payouts. It is imperative that the ED have a follow-up protocol that is 100% compliant. Interestingly, the defense argument was that the damage was already done, not that the delay was the patient's fault for not giving a reliable phone number or checking her messages.

The second point is that infective endocarditis bears special consideration as a diagnosis that is both difficult to make and dangerous to miss. Patients typically present with vague constitutional symptoms and fevers. The median age of onset is 67, although this can occur at much younger ages based on other co-morbidities or IV drug abuse,[3] and the median time from symptom onset to diagnosis is eight days.[4]

Diagnosis has been standardized with the Duke criteria, which are quoted at approximately 90% sensitivity. They consist of two major and six minor criteria. The major criteria are blood cultures (the presence of typical bacteria from two separate blood cultures or in persistently positive blood cultures) and evidence of echocardiographic involvement. The minor criteria are a predisposition to the disease, fever (> 38° C), vascular phenomena, immunologic phenomena, suggestive echocardiogram, and suggestive microbiologic findings.[5] In 2000, these criteria were modified to drop suggestive echocardiogram findings as a minor criterion and divide cases into one of three categories — definite infective endocarditis (two major criteria; one major and three minor; or five minor), possible (one major and one minor; or three minor), or rejected (due to a firm alternative diagnosis, resolution of the syndrome with four or less days of antibiotics, no pathologic evidence on autopsy or surgery, or not meeting the criteria above).[6]

While most of the criteria are self evident, one deserves additional discussion. Predisposition to the disease is anything that allows bacteria to accumulate on the endocardium and is generally due to an anatomic valvular defect, causing turbulent flow that injures the endothelium, a foreign object such as a mechanical valve, or injection drug use. A thorough history or review of records can provide one of the criteria, along with raising the clinician's index of suspicion. Along with the formal diagnostic criteria, lab findings of anemia, hematuria, and elevated ESR, CRP, or procalcitonin have been identified as being strongly associated with the disease but nonspecific.[2]

As noted above, patients are at risk of significant morbidity and mortality if the disease is not identified and treated with a prolonged course of antibiotics. Along with the ill effects of prolonged bacteremia, the disease process can result in direct damage to the heart or valves, with heart failure or arrhythmias as a result. Additionally, fragments of the bacteria and clot that cling to the heart valve can break off and embolize, causing infarction or abscess in any area of the body, including the lungs, the mesentery, the eyes, and the brain, with the most common CNS complication being a middle cerebral artery embolic stroke.[2,3] These devastating complications can be minimized or avoided with admission for IV antibiotics as well as early surgical removal of the bacterial vegetation in higher risk cases.

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ABSTRACT & COMMENTARY

Mortality Decline With the Use of a Sepsis Treatment Bundle

By Eric C. Walter, MD, MSc

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

SYNOPSIS: This large, multicenter, quality improvement project showed a dramatic reduction in mortality among patients with severe sepsis or septic shock after implementation of a sepsis treatment bundle.

SOURCE: Miller RR, et al. Multicenter implementation of a severe sepsis and septic shock treatment bundle. *Am J Respir Crit Care Med* 2013; 188:77-82.

Guidelines for the treatment of severe sepsis and septic shock over the last decade have focused on early recognition and rapid, aggressive resuscitative efforts. Implementation of these guidelines has consistently been shown to improve outcomes. However, the relative importance of different elements has been debated. As part of a multicenter quality improvement project, a sepsis treatment bundle was implemented for all patients admitted from the emergency department (ED) to the ICU in 11 hospitals within a single health care system (Intermountain Healthcare).

The sepsis treatment bundle was comprised of seven "resuscitative elements" and four "maintenance elements." The first three resuscitative elements — 1) measuring lactate, 2) blood cultures prior to antibiotic administration, and 3) administration of broad-spectrum antibiotics — had to be completed within 3 hours of ED arrival. The additional resuscitation elements were: 4) administration of fluids of 20-40 mL/kg for hypotension or lactate ≥ 4 mmol/L, 5) administration of vasopressors for hypotension despite appropriate fluid administration, 6) obtaining central venous pressure (CVP) and central venous oxygen saturation ($ScVO_2$) at regular intervals with a goal CVP ≥ 8 cm H_2O and $ScVO_2$ ≥ 70%, and 7) administration of inotropes and/or packed red cells (if hematocrit < 30%) if $ScVO_2$ was < 70% and CVP ≥ 8 cm H_2O. All had to be accomplished within 6 hours of ED admission. The four maintenance elements consisted of 1) mean glucose ≤ 180 mg/dL between 12-24 hours following admission, 2) administration of glucocorticoids for persistent hypotension despite adequate fluid resuscitation, or a high dose of a single vasopressor or requiring more than 1 vasopressor, 3) assessment of drotrecogin alfa eligibility (no longer part of the bundle), and 4) use of low tidal volume ventilation (6 mL/kg predicted body weight) if mechanically ventilated.

From 2004-2010, 4329 subjects were diagnosed with severe sepsis or septic shock. All-or-none total bundle compliance increased from 4.9% to 73.4% over the study period, showing that a sepsis treatment bundle could be effectively implemented. Over the same time period, in-hospital mortality declined from 21.2% to 8.7%. Interestingly, the decline in mortality did not appear to be due to 100% bundle adherence, as the a similar decline in mortality was seen in subjects for whom not all bundle elements were implemented (21.7% to 9.7%). Throughout the study, however, the number of bundle elements successfully achieved per patient steadily increased.

The first three resuscitative elements were applied to all subjects. Additional elements were only applied if subjects were

eligible (i.e., one could only be eligible for vasopressors, inotropes/red cell transfusion, glucocorticoids, or lung protective ventilation if one was hypotensive, had low $ScVO_2$, or was intubated). A 100% compliance with the first three elements was associated with ineligibility for inotropes/red cell transfusions, glucocorticoids, and lung protective ventilation. Another way of saying this is that in subjects for whom lactate was measured, blood cultures were drawn prior to antibiotics, and broad-spectrum antibiotics were provided within the first 3 hours of ED arrival were less likely to have persistent hypotension, low $ScVO_2$ or require mechanical ventilation. They were also less likely to die ($P < 0.0001$).

■ COMMENTARY

The authors should be commended on a tremendous amount of work put forth to implement this quality improvement project across 18 ICUs in 11 hospitals as well as to collate data from more than 4000 patients. The authors show that with an effective collaboration between the ED and ICU, a detailed sepsis treatment bundle can be effectively implemented. They also show that aggressive sepsis treatment should not be restricted to the first 6 hours; it should extend into comprehensive ICU care. The all-or-none measurement bar prevented providers from picking and choosing elements they felt were most beneficial. Supporters will argue that this demanding approach standardized care and led to the impressive decline in mortality. Detractors will argue the extensive bundle was "overkill" and not needed, as mortality declined equally among subjects in whom not all bundle elements were implemented. The truth probably lies somewhere in the middle. Like other pre-post studies evaluating practice changes, the outcome cannot be definitely attributed to the intervention. We may not definitely know what part or parts of the treatment bundle led to the mortality improvement, but clearly the implementation of this bundle achieved a very positive outcome.

The strong association between 100% compliance of the first three resuscitation bundle elements and subsequent severity of illness and death is intriguing. Simply asking physicians to consider sepsis and treat early is vital. Future studies will help delineate the added importance of invasive monitoring, vasopressors, inotropes, and transfusions. In the absence of such studies, these data argue that adherence to most, if not all, sepsis treatment guidelines should be the go-to approach. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Fit for a king, but not a parasite

Piers D, et al. The intestinal parasites of King Richard III. *The Lancet*, early online publication, September 4, 2013. Doi:10.1016.S0140-6736 (13)61757-2.

"History is a myth that men believe" – Napoleon Bonaparte

With a nose for solving a mystery, members of the Richard III Society in England, in conjunction with researchers at the University of Leicester, have discovered the remains of Richard III, King of England, under what is now a city parking lot, in the location of the ancient ruins of Greyfriars Priory, 20 miles outside of Leicester. The story was described in the *New York Times*, February 4th of this year. Richard III, who was killed at the Battle of Bosworth Field August 22, 1485 was immortalized as a demonic figure of epic proportions

by Shakespeare for having usurped the throne and murdered his two young nephews. The king's supporters theorize the case against him may have been a political smoke and mirrors maneuver by the Tudors, and hope the identification of his remains will prompt a more just reassessment of his reign, and suitable burial with honor as a king.

In a fun ID twist to the story, samples taken from the sacral area – where the intestines would have been – show evidence of roundworm eggs, consistent with Ascaris lumbricoides. Samples of earth from the sacral area were collected, microsifted, and analyzed, and the eggs were identified by light microscopy. They measured 55 to 70 micrometers in length. There was no evidence of other parasite eggs. Control samples taken from the skull and surrounding earth were also negative (the authors indicate that minimal environmental soil contamination with parasites was found, as expected).

Since several other species of intestinal parasites were common in England at the time, including fish, pork and beef tapeworms, whipworm, and the liver fluke, *Fasciola hepatica*, the authors argue King Richard must have eaten very well-cooked meat. Investigation of his remains also revealed the extent of his scoliosis, photos of which are available in the *Times*' article. ■

Popsicles with fungal antigen?

Guigue N, et al. False positive galactomannan test after ice-pop ingestion. *New Engl Jrl Med* 2013;369:1:97-98.

Positive galactomannan blood tests by enzyme immunoassay are taken as proof of Aspergillus antigenemia — and generally prompt specific antifungal therapy. However, a few published reports suggest there may occasionally be false-positive test results, possibly as the result of cross contamination or cross reaction with certain food substances. The actual basis for the false positive results has not been elucidated.

A 42-year–old bone marrow transplant candidate had multiple negative serial galactomannan blood tests for 30 days post-transplantation. On days 32 and 34 post- transplant, her tests became positive. Extensive work up with CT scans, cultures, and a PCR on blood for Aspergillus were all negative. She was presumptively started on voriconazole. She had been suffering from graft vs host disease, and not eating anything — except apparently 3-4 flavored popsicles a day (sans stick), which she started on day 29 post-transplantation.

Popsicles from the same batch were tested for galactomannan, and surprisingly came up positive! Within 7 days of not eating any more popsicles, her blood tests became negative. Sadly, she went on to die of her GVH disease, but developed no evidence of fungal infection.

High levels of galactomannan were observed in 37 samples of different flavored ice-pops from 3 brands. No evidence of Aspergillus was found by PCR or culture of any of the 37 different pops. Three of the cultures grew penicillium, possibly from cross-contamination from the paper wrapping. Broad based fungal DNA multiplex PCR of the pops were negative. The galactomannan tests actually exhibited a prozone effect, and were negative when the popsicles were straight tested, but positive on serial dilutions. The source of the galactomannan in the ice-pops is not known, but food additives or thickeners are suspected to possibly cross with the assay. ■

Should MSM receive meningococcal vaccine?

Simon MS, et al. Invasive meningococcal disease in men who have sex with men. *Ann Intern Med* 2013;159(4):300-301.

A question we've been asking ourselves in our HIV clinic is whether to administer meningococcal vaccine to which, if any, of our HIV+ patients in Santa Clara County, California. Since 2010, 22 cases of invasive meningococcal disease have been reported in men who have sex with men (MSM) by the New York City Public Health authorities. The estimated incidence of invasive meningococcal disease in MSM in 2012 in New York City was approximately 50-fold higher than that of the general population (0.3 cases per 1000,000) (age-adjusted). The mean age of these men was 34 years, and the fatality rate was 32%. Twelve (54%) were HIV +, and their mean CD4 count was 525 cells/mm3; 70% were virologically suppressed on their most recent blood work. Four additional cases in MSM have been reported by Los Angeles health authorities during the same time period. Many of these cases occurred after hanging out in crowded bars or large social gatherings. Previous outbreaks of meningococcal meningitis were reported in Toronto in 2001 and in Chicago in 2003, resulting in a total of 12 cases, with a case fatality rate of 42%. Molecular studies suggest these outbreaks were each caused by a common strain of bacterium.

In response, the NYC Department of Health and Mental Hygiene (NYC DOHMH) began in October 2012 aggressively promoting vaccination of all MSM, and even offering free vaccine, especially for those participating in Gay Pride events. The advisory also recommended offering vaccine to all MSM, regardless of HIV status, with close or intimate contact with men met either through an online website, digital application, or at a party or bar. Since then, it is estimated more than 11,000 men in New York have received vaccine, and since February 2013, no similar cases have been reported in NYC. Health departments in other major urban areas including San Francisco, Los Angeles, and Toronto, as well as the Commonwealth of Massachusetts, also began similarly recommending immunizing MSM if they plan to travel to NYC or plan to "socialize with New Yorkers" (or anyone who could potentially be from New York). (I'm not sure how this would really work — since some of my patients don't even know the names of their sexual contacts, let alone where they are from.) Concern remains that hard to reach groups of MSM, such as African Americans, and those who do not identify as gay, may not be easily reached by these advisories.

The question remains whether all MSM — especially those who are HIV+ - should be candidates for meningococcal vaccine. Although there is limited evidence regarding the risk of invasive infection in HIV+ individuals, it follows that HIV-positive individuals may be at increased risk for invasive meningococcal infection, similar to their increased risk for pneumococcal infection (another encapsulated organism). And it is known that the meningococcal quadravalent vaccine is immunogenic in HIV+ individuals, at least in HIV+ adolescents. Two doses seems to improve the immunogenicity of vaccine.

While the risk of invasive meningococcal disease in MSM seems low, and clearly episodic, it seems no less significant than the risk of someone traveling to the Hajj, or going off to college to live in a dorm — both current indications for vaccination. Vaccination is also recommended for microbiologists, where the attack rate has been estimated to be 13 cases per 100,000, less than that described above. While the ACIP has made no formal recommendations, it seems reasonable to at least offer vaccination to my HIV+ patients. I cannot predict when they may wake up one day and take off for New York, or decide to participate in a Gay Pride event, or a picnic on the back forty with friends. But isn't the point of vaccination prevention? ■

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 NOT a free-living amoebal cause of central nervous system infection?

A. *Entamoeba histolytica*
B. *Acanthamoeba castellani*
C. *Balamuthia mandrillaris*
D. *Naegleria fowleri*

2. Which of the following is correct regarding *Naegleria fowleri*?

A. It grows best at body temperate – 37°C

B. It has been detected in household water

C. It causes infection when it is ingested

D. Infection with it occurs most commonly in the Great Plains states

3. Which of the following is correct with regard to the report by Miller and colleagues management of sepsis using the sepsis bundle?

A. Implementation of full (all-or-none) compliance was associated with a decrease in mortality from 21.2% to 17%

B. Partial implementation of the bundle was associated with a reduction in mortality similar to that seen with compliance with all bundle elements.

C. There was no change in the frequency of bundle compliance over the period of the study.
D. A key element of the bundle is the measurement of serum procalcitonin

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]

Pregnancy Dose Tdap and Postpartum Cocooning to Prevent Infant Pertussis: A Decision Analysis

Multidrug-resistant Bacteroides fragilis — Seattle, Washington, 2013

Transfusion-Related West Nile Virus Infection

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 10 | Pages 19-20 | October 2013

Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

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preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■