AHC Media

Vol. 31, Issue 11, August 2012
www.ahcmedia.com

Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

SPECIAL FEATURE

Cefepime: FDA Drug Safety Communication on Non-Convulsive Status Epilepticus Risk

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

The U.S. Food and Drug Administration (FDA) recently issued an alert on the potential risk of non-convulsive status epilepticus associated with the use of cefepime, a broad spectrum fourth generation cephalosporin.[1] The FDA Adverse Event Reporting System database yielded 59 cases of non-convulsive status epilepticus that occurred during cefepime administration from 1996 through February 2012. Approximately two thirds of the cases involved females and over half of the cases involved older patients (>65 years). Of note, with the exception of 1 patient (renal function unknown), all patients had varying degrees of renal impairment. In 56 of 59 patients, prescribers failed to comply with dose adjustments for renal function as recommended in the cefepime label.

Cefepime provides broad-spectrum coverage for numerous infections, including skin, soft tissue, lower respiratory tract, complicated intraabdominal, urinary tract infections, and for suspected febrile neutropenia.[2] This agent, along with ceftazidime, a third-generation cephalosporin, are distinguished by providing bactericidal activity against a wide array of organisms, including *Pseudomonas aeruginosa*.[2,3]

Cefepime is primarily cleared from the body by renal excretion, with 85% of the drug recovered

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

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Infectious Disease [ALERT]

Infectious Disease Alert,
ISSN 0739-7348, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Infectious Disease Alert*, P.O. Box 105109, Atlanta, GA 30348.

SUBSCRIBER INFORMATION
1-800-688-2421
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Subscription Prices

United States:
1 year with *free AMA PRA Category 1 Credits™*: $319
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unchanged in the urine.[2] The half-life of cefepime in adults with normal renal function approaches 2 hours. In patients with renal dysfunction, the increase in elimination half-life and the reduction in total body clearance are proportional to the decline in renal function. Cefepime is dialyzable; 68% of a dose may be removed during a 3-hour hemodialysis session.[2] Because of its pharmacokinetic properties, adjustment in cefepime dosage is imperative for patients with renal insufficiency. Table 1 summarizes manufacturer recommended dosing of cefepime in patients with normal and impaired renal function.[2] It should be noted that, at least for patients with normal renal functions, their recommended dose may be inadequate for treatment of infection due to organisms such a *P. aeruginosa*.

Penicillins, cefepime, third generation cephalosporins (ceftazidime, cefotaxime, ceftriaxone), carbapenems, and quinolones have been reported to be associated with non-convulsive status epilepticus.[3] Predisposing factors for antibiotic-induced seizures include history of seizures, renal impairment, meningitis or central nervous system infections which lead to opening of blood brain barrier, extremes of age, low serum albumin resulting in higher free drug concentration, and co-administration of other seizure-provoking medications.[3]

The mechanism of non-convulsive status epilepticus provocation is not sufficiently established, but the most likely explanation arises from competitive inhibition of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), resulting in decreased suppression of epileptogenic discharges.3 Furthermore, renally impaired patients may accumulate toxic organic agents, which will competitively inhibit active transport of antibiotics from cerebrospinal fluid to blood.

The purpose of this article is to review published reports of cefepime-associated non-convulsive status epilepticus, and to provide dosing recommendations in order to minimize the risk of cefepime-treated patients experiencing non-convulsive status epilepticus.

PUBLISHED REPORTS OF CEFEPIME-ASSOCIATED NON-CONVULSIVE STATUS EPILEPTICUS

To date, at least 26 cases of cefepime-associated non-convulsive status epilepticus have been published.[5-19] Table 2 provides summaries of the 26 cases (*see page 124*). Similar to the FDA Adverse Event Reporting System database, approximately 60% of the cases involved females and half of the cases involved patients between the ages of 65 years to 86 years.

With the exception of 1 patient, all patients had impaired renal function (18 cases of chronic renal failure; 7 cases of acute renal failure). The dosage of cefepime exceeded manufacturer recommendations in 19 of the 26 cases. Of note, despite the absence of other risk factors for seizure, 4 of the 7 patients who received appropriate dose adjustment of cefepime still experienced non-convulsive status epilepticus, which raises the question of optimal dosing of cefepime in renally impaired patients.

In nearly half of the cases, confounding factors that may have predisposed patients to experiencing non-convulsive status epilepticus included possible alcohol withdrawal, use of other seizure-provoking drugs, and history of seizures. The mean time to onset of non-convulsive status epilepticus approached 6 days (range, 1-15 days). Twenty-four patients recovered following cessation of cefepime therapy and administration of anticonvulsant agents, but 2 deaths occurred, with 1 fatality attributed to status epilepticus and multiorgan failure.

CEFTAZIDIME-ASSOCIATED NON-

CONVULSIVE STATUS EPILEPTICUS

To date, there are far fewer published cases of ceftazidime-associated non-convulsive status epilepticus, compared with cefepime. Eight cases have been published from 1994 to 2012, showing onset times to non-convulsive status epilepticus of 3 to 8 days after starting ceftazidime therapy.[4,8,14,15,20] All except 1 patient had renal impairment, and in the reports which provided dosing regimens, all patients received excessively high doses of ceftazidime. Three of the 8 patients had other risk factors for seizure, including receipt of ciprofloxacin and/or prior history of stroke.

CONCLUSION

Based on published reports and the warning from the FDA, the following guidelines should be considered by healthcare professionals:

- Refer to the FDA-approved package insert for reducing doses of cefepime in renally impaired patients.
- Providers should carefully consider the risks and benefits of using cefepime in patients with renal impairment and other risk factors predisposing them to seizure.
- Patients receiving cefepime should be monitored for changes in renal function and the appropriateness of dosage should be assessed periodically during treatment.
- Patients receiving cefepime should be monitored for signs and symptoms of non-convulsive status epilepticus, such as confusion, loss of attention, disorientation, abnormal behavior, agitation, hallucinations, mutism, myoclonic jerks, or coma. An electroencephalogram should be considered in older patients with unexplained mental status changes.
- Since cefepime-induced non-convulsive status epilepticus is able to be reversed, prompt treatment cessation can prevent further morbidity and mortality. ■

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Table 1. Manufacturer's FDA-Approved Recommended Adult Dosing Regimens for Cefepime Based on Renal Function

Manufacturer's Recommended Dosing Schedule Based on Indication				
Creatinine Clearance (mL/min)	UTI[a]	UTI[a], Pneumonia[b]	Pneumonia[b], UTI[c], Intra-abdominal[d], SSSI[e]	Febrile Neutropenia[f]
> 60	500 mg IV Q 12 h	1 g IV Q 12h	2 g IV Q 12h	2 g IV Q 8h
30-60	500 mg IV Q 24h	1 g IV Q 24h	2 g IV Q 24h	2 g IV Q 12h
11-29	500 mg IV Q 24h	500 mg IV Q 24h	1 g IV Q 24h	2 g IV Q 24h
<11	250 mg IV Q 24h	250 mg IV Q 24h	500 mg IV Q 24h	1 g IV Q 24h
CAPD	500 mg IV Q 48h	1 g IV Q 48h	2 g IV Q 48h	2 g IV Q 48h
Hemodialysis (post-dialysis on dialysis day)	1 g on day 1, then 500 mg IV Q 24h	1 g on day 1, then 500 mg IV Q 24h	1 g on day 1, then 500 mg IV Q 24h	1 g IV Q 24h

UTI = urinary tract infection; SSSI = skin and skin structure infection; CAPD = continuous ambulatory peritoneal dialysis
[a]For mild-to-moderate uncomplicated or complicated UTIs, including pyelonephritis
[b]For moderate-to-severe pneumonia
[c]For severe uncomplicated or complicated UTIs, including pyelonephritis
[d]For complicated intra-abdominal infections when used concurrently with metronidazole
[e]For moderate-to-severe uncomplicated skin and skin structure infections
[f]Empiric treatment for febrile neutropenia

Table 2. Summary of Published Cases of Cefepime-Associated Non-Convulsive Status Epilepticus

Patient [Reference]	Age in Years, Gender	Indication	Dosing Regimen	Renal Function	Confounding Factors
1 [5]	54, M	Febrile neutropenia	1 g IV Q 24h	CrCl – 12-27 mL/min	None
2 [5]	60, F	Febrile neutropenia	1 g IV Q 24h	CrCl – 13-15 mL/min	None
3 [6]	79, F	Urinary tract infection	2 g IV Q 12h	CrCl – 45 mL/min	None
4 [7]	76, F	Gangrenous pyoderma	2 g IV Q 8h	SCr – 3 mg/dL	Chronic alcoholism
5 [7]	38, F	Febrile neutropenia	2 g IV Q 8h	SCr – 3.2 mg/dL	None
6 [7]	43, M	Abdominal sepsis	2 g IV Q 12h	SCr – 1.7 mg/dL	Chronic alcoholism
7 [8]	74, F	Pneumonia	4 g IV/day	SCr – 10.1 mg/dL	Prior ceftriaxone use
8 [9]	15, M	Pneumonia	12.5 mg/kg/day	Peritoneal dialysis	None
9 [10]	66, F	Febrile neutropenia	2 g IV Q 8h	CrCl – 30 mL/min	None
10 [11]	65, M	Febrile neutropenia	2 g IV Q 8h	SCr – 2.8 mg/dL	Prior cloxacillin use
11 [12]	82, M	Pneumonia	1 g IV Q 24h	Hemodialysis	None
12 [13]	65, M	Gram-negative bacteremia	2 g/day	SCr – 12 mg/dL	None
13 [13]	73, F	Knee prosthesis infection	2 g/day	SCr – 17.7 mg/dL	None
14 [14]	69, F	Pneumonia	2 g/day	Peritoneal dialysis	None
15 [15]	79, M	Pneumonia	1 g/day	SCr – 4.5 mg/dL	Erythropoietin use
16 [15]	67, F	Pneumonia	2 g IV Q 6h	SCr – 3.5 mg/dL	None
17 [15]	64, F	Pneumonia	1 g/day	SCr – 5 mg/dL	Cyclosporine use
18 [15]	54, M	Immunocompromised	2 g/day	SCr- 3.2 mg/dL	Ciprofloxacin use
19 [15]	86, M	Osteomyelitis	2 g IV Q 12h	SCr – 5.1 mg/dL	Ganciclovir use
20 [15]	79, F	Pneumonia	2 g IV Q 12h	SCr – 5.2 mg/dL	None
21 [16]	NR, NR	Unable to translate	Not reported	Not reported	Unable to translate
22 [16]	NR, NR	Unable to translate	Not reported	Not reported	Unable to translate
23 [17]	44, M	Pneumonia	2 g/day	Hemodialysis	Ciprofloxacin, Tacrolimus use
24 [17]	28, F	Urinary tract infection	1 g IV Q 12h	SCr – 1.8 mg/dL	Prior seizures, ceftazidime
25 [18]	15, F	Gram-negative bacteremia	1 g IV Q 12h	Hemodialysis	None
26 [19]	70, F	Febrile neutropenia	2 g IV Q 24h	CrCl – 14-17 mL/min	Prior seizure

NR = Not reported

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Early Surgery for Infective Endocarditis Decreases Risk of Embolization, Mortality

By Richard R. Watkins, MD, MS, FACP

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

SYNOPSIS: In this randomized study, patients with left-sided infective endocarditis and large vegetations who underwent valve replacement surgery within 48 hours of randomization had lower rates of embolic events and death from any cause after 6 months compared to those who underwent surgery later.

SOURCE: Kang D-Y, et al. Early Surgery versus Conventional Treatment for Infective Endocarditis. N Engl J Med 2012;366:2466-2473.

Infective endocarditis (IE) continues to be a serious illness with high morbidity and mortality despite modern therapies. Current guidelines from the American Heart Association state that the benefit from surgical intervention is greatest in the early phases of IE, when embolic rates are highest and other predictors of a complicated course are present.[1] Kang and colleagues conducted a prospective, randomized, controlled trial in patients 18 years of age and older with left-sided, native-valve IE and a high risk of embolization. Eligible patients received a diagnosis of IE by the modified Duke criteria, had severe mitral or aortic valve disease and a vegetation ≥ 10 mm in diameter. All patients underwent transesophageal echocardiography and computed tomography of the brain and abdomen to evaluate for embolism. They were assigned in a 1:1 ratio to the early-surgery group (valve replacement within 48 hours after randomization) or the conventional treatment group (surgery performed only if complications developed during medical therapy or if symptoms persisted after completion of antibiotic therapy). Between September 2006 and March 2011, 37 patients were assigned to early surgery and 39 to conventional therapy. The primary end point was in-hospital death or clinical embolic events within 6 weeks of randomization. Secondary end points at 6 months of follow-up were death from any cause, embolic events, recurrence of IE, and hospitalization due to congestive heart failure (CHF).

The investigators found that the most common pathogens were viridans streptococci (30% of patients), other streptococci (in 30%), and *Staphylococcus aureus* (in 11%). There were no significant differences in antibiotic therapy between the two groups. The median time

from randomization to surgery in the early-surgery group was 24 hours (range 7 to 45 hours). The primary end point of in-hospital death or embolic events within the first 6 weeks occurred in one patient (3%) in the early-surgery group, compared to 9 (23%) in the conventional-treatment group (hazard ratio, 0.10; 95% confidence interval 0.01 to 0.82; P=0.03). At 6 weeks after randomization, the rate of embolization in the early-surgery group was 0% compared to 21% in the conventional-treatment group (P=0.005). Among the 11 patients in the conventional-treatment group who were discharged without having surgery, 1 (3%) died suddenly, 7 (18%) had symptoms related to severe valve disease or recurrence of IE, and 3 (8%) had no symptoms or embolic events. At 6 months the rate of death from any cause, embolic events, recurrence of IE, or repeat hospitalization due to the development of CHF was 3% in the early-surgery group, compared to 28% in the conventional-treatment group (hazard ratio, 0.08; 95% confidence interval, 0.01 to 0.65; P=0.02). There was no significant difference between the groups in all-cause mortality at 6 months (3% and 5%, P=0.59).

There were several limitations to the study. One was the overall number of patients in the two groups was small. This was likely a consequence of the exclusion criteria chosen by the authors: patients with strokes, IE involving prosthetic valves, or aortic abscess. Another limitation was the low incidence of *S. aureus* IE, which was lower than previously reported.[2] The rate of death within 30 days after surgery was low and the patients had a low operative risk. This implies that the results of the study may not be applicable to low-volume medical centers or to patients with a high operative risk. The study was conducted at two medical centers and the researchers did not analyze outcomes according to each participating center because of large differences in numbers of patients enrolled at each site. Follow-up imaging studies to detect subclinical embolic events were not done.

■ COMMENTARY

The decision about when a patient should undergo surgical intervention for IE is often challenging. The current IE guidelines strongly recommend urgent surgery for patients with CHF due to valvular regurgitation.[1] However, in patients with large vegetations and valve dysfunction but not CHF the guidance is less clear. The study by Kang and colleagues has provided valuable new data on this clinical conundrum. Their findings are very convincing to support the argument in favor of early surgery for patients with large vegetations and valvular dysfunction without overt CHF. As pointed out in an accompanying editorial, the benefits of timely intervention outweighed the additional risk of surgery in patients with active infection.[3] Adequate debridement during surgery and optimal antibiotic selection based on culture data is also paramount to achieve successful outcomes.

It was surprising that *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), was not a more common etiology of IE in the study. MRSA is highly pathogenic due to a multitude of virulence factors and is a frequent cause of embolic disease.[4] It is unclear if the outcomes would have been different if more patients had S. aureus IE. Additional research to investigate this issue, especially in areas where MRSA is highly prevalent, is warranted.

The authors reported the time from randomization to surgery but not from diagnosis to surgery. Presumably these times were similar in most cases but this was not explicitly stated in the study. Moreover, the interval from onset of symptoms to surgery was not mentioned.

Despite its limitations, this study provides compelling evidence to support surgery in the first 48 hours for patients with left-sided IE, large vegetations and evidence of valvular dysfunction. IE is a perilous condition with a high risk of embolic events. The study by Kang and colleagues is important and will hopefully lead to improved clinical outcomes for patients. Future studies to replicate these data, especially with larger numbers of participants and high risk patients, are necessary to further elucidate the optimal timing of surgery in IE. ■

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Antiretroviral Regimens to Prevent Intrapartum HIV Infection

ABSTRACT & COMMENTARY

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

SYNOPSIS: For infants whose mothers did not receive antiretroviral therapy during pregnancy, postpartum prophylaxis with a two- or three-drug antiretroviral regimen is superior to zidovudine alone for prevention of intrapartum HIV transmission. The three-drug regimen was associated with a significantly increased rate of neutropenia.

SOURCE: Nielsen-Saines K, et al. Three postpartum antiretrovirals regimens to prevent intrapartum HIV infection. N Engl J Med 2012;366:2368-70.

A total of 1745 infants from 17 sites in Brazil (70.1%), South Africa (27.4%), Argentina (1.6%) and the United States (0.8%) born to women with a peripartum diagnosis of HIV type I infection were randomized within 48 hours of birth to receive one of three six-week postpartum antiretroviral regimens. The mothers had not received antiretroviral therapy during pregnancy, and all infants were formula fed.

Ten infants did not receive study drugs, and 51 mothers were HIV-negative on than 40 confirmatory tests. There were a total of 1684 infants enrolled, including 566 infants receiving zidovudine alone for six weeks, 562 infants receiving zidovudine for six weeks plus three doses of nevirapine during the first eight days of life (first dose within 48 hours of birth, second dose 48 hours after the first dose, and third dose 96 hours after the second dose), and 556 infants receiving zidovudine for six weeks plus nelfinavir and lamivudine for two weeks. Fixed dosing was used based on weight categories (birth weight <=2.0 kg, or >2.0 kg).

The overall transmission rate at three months of life was 8.3% (140 infants), with an increased transmission rate in the zidovudine-alone group (P=0.03) compared to the other two groups. The overall rate of in utero transmission of HIV was 5.7%, ranging from 5.1% to 6.8% across the three groups. The rate in the zidovudine-alone group did not differ significantly from the other two groups (P=0.24 for both comparisons). Intrapartum transmission occurred in 24 infants in the zidovudine alone group (4.8%; 95% CI, 3.2-7.1%), compared to 11 infants in the two-drug group (2.2%; 95% CI, 1.2-3.9%) and 12 infants in the three-drug group (2.4%; 95% CI, 1.4-4.3%). Multivariate analysis showed that zidovudine monotherapy, higher maternal viral load, and maternal use of illegal substances were significantly associated with HIV transmission.

Complete blood count and hepatic aminotransferase levels were measured at birth, 4-7 days, 10-14 days, 4-6 weeks, and 3 months of age. The rate of neutropenia was significantly increased in the three-drug group (P<0.001). Elevated aminotransferase levels were uncommon and occurred in only 2.5% of all infants, which did not differ significantly among the groups.

Mutations conferring resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) were present in 12 infants: three in the zidovudine-alone group, six in the two-drug group, and three in the three-drug group (P=0.15 for multiple comparisons). Mutations conferring resistance to nucleoside analogue reverse-transcriptase inhibitors (NRTIs) were found in two infants in the three-drug group and one infant in the two-drug group, and mutations conferring resistance to protease inhibitors were present in two infants in the three-drug group. No significant differences in

the distribution of resistance mutations were found among the groups.

■ COMMENTARY

The standard antiretroviral regimen for infants whose mothers had not received antenatal therapy has been a six-week course of zidovudine alone, based on the Pediatrics AIDS Clinical Trials Group Protocol 076 study that was published in 1994. In this study, the intrapartum HIV transmission rate in the zidovudine-alone group was similar to other studies, and transmission rates were reduced by half in the two- and three-drug groups compared to zidovudine alone.

This study demonstrates that the administration of additional antiretroviral drugs to zidovudine significantly reduces the risk of intrapartum transmission of HIV. The availability, ease of administration, and low cost of the zidovudine-nevirapine regimen, and the significantly higher rate of neutropenia with the three-drug regimen, all favor the zidovudine-nevirapine regimen. Combination zidovudine-nevirapine therapy rather than zidovudine alone should be used for HIV prophylaxis of infants of mothers who have not received antenatal antiretroviral therapy. ■

ABSTRACT & COMMENTARY

In-Home HIV Test Empowers Patients

By Dean L. Winslow, MD, FACP, FIDSA

Chairman, Department of Medicine, Santa Clara Valley, Medical Center; Clinical Professor, Stanford University School of Medicine, is Associate Editor for Infectious Disease Alert

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: The OraQuick in-home HIV-1/2 antibody test was granted market clearance by FDA on 15 May 2012. Data presented included a <0.1% false positive rate and 91.7% sensitivity to correctly detect HIV infection compared to conventional ELISA performed on blood.SOURCE: http://ow.ly/ckHuF

On 15 May the FDA Center for Biologics Evaluation and Research/Office of Blood Research and Review (CBER/OBRR) granted market clearance to the OraQuick in-home HIV-1/2 antibody test based on the recommendation of the Blood Products Advisory Committee. The in-home assay is a rapid, CLIA-waived immunoassay using synthetic peptides as antigens formatted in a test strip format to be used on saliva. The in-home assay is similar to the OraQuick assay previously approved by FDA for rapid HIV testing of venous or fingerstick whole blood or plasma. Data submitted to the FDA included a study of 4999 individuals of unknown HIV status. Results obtained with OraQuick were compared to "gold standard" testing with a laboratory-based ELISA performed on serum or plasma.

Bottom line results from this performance trial showed that 4902/4903 HIV-negative patients were correctly identified (i.e. 1 false positive was seen). 88/96 (91.7%) of ELISA-positive patients were correctly identified (i.e. 8 false negatives were seen). 56/5055 (1.1%) failed to obtain a test result.

■ COMMENTARY

The FDA market clearance of this in-home, rapid assay to detect HIV-1/2 antibodies demonstrated fairly robust performance and seemed easy to use by most patients. The assay as performed by untrained personnel on saliva does appear to be somewhat less sensitive than the comparator laboratory-based serum or plasma HIV antibody assay. The product package insert is careful to point out the limitations of the test in laymen's terms and emphasizes that individuals should wait at least 3 months after a suspected exposure event to test themselves with OraQuick.

The impact of confidential in-home testing may or may not be significant in interrupting transmission of HIV on a large scale in the US or Western Europe. However, it is hard for me to imagine a scenario (other than acute HIV infection where the test may be negative yet the patient highly contagious) where harm could be done. I am a firm believer in empowering patients to take responsibility for their health and for transmission of sexually-transmitted infections to others. This is a step in the right direction and will be a useful development even if only a few new cases of HIV are prevented each year in North America and Western Europe. Hopefully the OraQuick test will be priced low enough in the developing world where its impact could potentially be very large. ■

Travel Infections: In FoodNet data *Campylobacter* tops the list

By Lin H. Chen, MD

Assistant Clinical Professor, Harvard Medical School and Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA

Dr. Chen has reviewed research grants from the Centers for Disease Control and Prevention and Xcellerex.

SYNOPSIS: Travel was associated with 13% of the enteric infections reported to FoodNet, and the most commonly identified pathogens were Campylobacter, nontyphoidal Salmonella, and Shigella species. Precautions to avoid consuming contaminated food and water remains highly relevant in advising travelers.

SOURCE: Kendall ME, et al. Travel-associated enteric infections diagnosed after return to the United States, Foodborne Diseases Active Surveillance Network (FoodNet), 2004-2009. Clin Infect Dis 2012;54(S5):S480-7.

FoodNet is an active surveillance program that collects data on 9 laboratory-confirmed pathogens from 10 sites in the United States: 7 states (Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, and Tennessee) and certain counties in California, Colorado, and New York. Kendall et al analyzed infections reported in this network from 2004-2009 that were considered to be travel-associated and compared them to infections in non-travelers; they also estimated risks according to travel destination. The authors defined travel associations based on the intervals between return date and illness onset: <30 days for *Listeria*, *Salmonella* (typhoid and paratyphoid), <15 days for *Cryptosporidium* and *Cyclospora*, and <7 days for all other enteric pathogens.

Approximately 13% (8270/64,039) of reported enteric infections that also contained travel information were considered travel-associated. Travel-associated cases had a mean age of 33.1 years, older than nontravelers (mean age 25.5 years), especially within the group aged 18-44 years. Travel-associated cases were more likely to be Asian, less likely to be black., and less likely to be hospitalized. Five deaths were reported for travel-associated cases, attributed to Listeria (n=1), Vibrio vulnificus (n=1), and nontyphoidal Salmonella (n=3).

The most frequently identified pathogens in travelers was Campylobacter (42%), followed by nontyphoidal Salmonella (32%) and Shigella infections(13%). These organisms were also the most common and top 3 for nontravelers, although nontyphoidal *Salmonella* was more common in nontravelers (47% of infections), and Campylobacter was less common (27% of infections). All 3 cases of cholera were travel-associated, as well as high proportions of typhoidal and paratyphoidal Salmonella (68% and 50%, respectively). *Shigella dysenteriae*, *S. boydii*, and *S. flexneri* were also often travel-associated (56%, 44%, and 24%, respectively), whereas non-cholera *Vibrio, Yersinia*, Shiga toxin-producing *Escherichia coli* (STEC), and *Listeria* occurred more commonly in nontravelers.

The most common countries for travel-associated infections were Mexico, India, Peru, Dominican Republic, and Jamaica, and account for half of the travel-associated cases. Furthermore, race and ethnicity correlated

with travel destinations. For example, 85% of Asian travelers reported travel to Asia, 95% of Hispanic travelers reported travel to Latin America and the Caribbean [LAC], and 58% of black travelers reported travel to Africa.

The authors estimated risk for each pathogen based on travel region. Africa had the highest risk for travel-associated infection (76 cases/100,000 travelers), followed by Asia (23 cases/100,000 travelers), and LAC (20 cases/100,000 travelers). Within LAC, South America had the highest rate of *Campylobacter* (26.4 cases/100,000 travelers). The Caribbean had the highest rate of nontyphoidal *Salmonella* (8.6 cases/100,000 travelers), and Central America had the highest rates of *Shigella*, *Cryptosporidium*, and STEC. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

The emerging NDM problem

NDM-1 Carrying Enterobateriaceae – USA: (Rhode Island) ex Viet Nam. A ProMED-mail post, June 21, 2012; http://www.promedmail.org.

This ProMED-mail alert describes the case of a young Rhode Island resident who traveled to Cambodia and Viet Nam, where she was hospitalized with spinal cord compression in December 2011. She returned to the United States in January 2012, with a chronic indwelling Foley catheter. She was initially found to have a urinary tract infection with an ESBL-containing E coli organism. Subsequent urine specimens obtained in February and March 2012 grew two strains of carbapenemase-producing Klebsiella pneumoniae, which was weakly positive on Hodge testing. The isolate was sent to the CDC, and was found to contain NDM producing carbapenemase, stricter isolation precautions were implemented, and no further cases were identified. The isolate was resistant to 24 different antimicrobials, and sensitive only to tigecycline (MIC = 2 micrograms/mL), colistin, and polymixin B. This case represents the 13th case of NDM identified in the United States.

It has been barely two years since the MMWR described the emergence of a novel resistance mechanism, called New Dehli metallo-beta lactamase (NDM-1), which was identified in 3 *Enterobacteriaceae* isolates in the U.S. between January and June 2010. These isolates, including an *E. Coli, Klebsiella pneumoniae*, and *Enterobacter cloacae*, all carried a plasmid-producing enzyme called "blaNDM-1", which confers resistance to all beta-lactams and carbapenems, with the exception of aztreonam. However many of these types of bacteria, including the 3 isolates above, harbor plasmids that encode for multiple resistance factors and are frequently broadly resistant to virtually all antibacterials. These plasmids are also easily transmitted to other *Enterobacteteriaceae* or other gram negatives. They can colonize the gastrointestinal tract for months and can spread through the environment through contaminated water sources or through surfaces. Nosocomial transmission is therefore of critical concern.

While initial reports suggested that many persons colonized or infected with these NDM isolates had recently received medical care in India or Pakistan, this is no longer an exclusive risk factor or identifier for these cases. NDM-containing isolates have been reported from every continent, with the exception of South America. In addition to the 13 isolates discovered in the United States, 29 cases have been identified in the United Kingdom, at least 17 of which were previously cared for or hospitalized in India or Pakistan. However, of the 77 cases identified in Europe up to 13 (17%) may have occurred as the result of nosocomial transmission.

It's only a matter of time before these isolates become more frequent, unless vigorous efforts are made to identify and isolate cases. The accompanying editorial argues for an increase in point prevalence studies in U.S. hospitals, including more vigorous screening of all ICU admissions or high risk cases using nucleic acid amplification methods. If NDM is identified, than surveillance should be extended to other persons in that unit (or skilled nursing facility). Only a rigorous active surveillance and infection control plan can limit the inevitable spread of these organisms. ■

When Pneumonia occurs with Flu: Think Influenza

Jain S, et al. Influenza-associated pneumonia among hospitalized patients with 2009 pandemic Influenza A (H1N1) virus – United States, 2009. *Clin Infect Dis* 2010;54: 1221-1228.

Cases of pandemic H1N1 requiring hospitalization were examined by reviewing two national case series from spring and fall 2009. During this period, a total of 451 patients with laboratory-confirmed H1N1 were hospitalized, 195 (43%) of whom were diagnosed with pneumonia based on chest radiographs. Not unexpectedly, those patients with pneumonia had higher rates of admission to ICU (52% vs 16%), were more likely to be diagnosed with ARDS (26% vs 2%), sepsis (18% vs 3%), and mortality (17% vs 2%), than those without pneumonia. More than half of those with pneumonia had bilateral infiltrates (67%); the others had multilobar infiltrates (7%), or unilobar involvement (31%). Bacterial infection, mostly bacteremia, was confirmed in 13 patients (7%) with pneumonia and 2 (< 1%) of those without.

What was not necessarily expected was the finding that patients with influenza-associated pneumonia were less likely to receive antivirals within 48 hours of admission compared with those admitted with influenza without pneumonia (28% vs 50%, p < .0001). Eventually during the hospitalization, a similar proportion of patients with or without influenza-associated pneumonia did receive antiviral therapy (78% vs 79%); 91% of this was oseltamivir.

The key to this paradox may be that the very presence of pneumonia or infiltrates on chest radiographs was more likely to prompt a diagnosis of bacterial infection and administration of antibacterials, rather than trigger a suspected diagnosis of influenza. "Sepsis" (which was based on clinical judgment) was diagnosed in 18% of these pneumonia cases, compared with only 2% of non-pneumonia cases, suggesting either bias in the suspicion of bacterial infection – or even more possibly, a more severe systemic inflammatory response from H1N1 infection in those with pneumonia.

During influenza season, Influenza (H1N1) should be included in the differential of patients admitted with severe illness and pneumonia, or "sepsis" and pneumonia, and presumptive antiviral treatment started as soon as possible, at least until additional information and the results of tests are available. ■

Voriconazole Safe in Renal Patients: To a limited degree

Neofytos D, et al. Administration of Voriconazole in patients with renal dysfunction. *Clin Infect Dis* 2012; 54:913-921.

Parenteral versions of voriconazole contain a cyclo-dextrin base, which acts as a solubilizing agent, that reportedly is inadequately renally cleared (by glomerular filtration) in patients with renal dysfunction. Animal studies have found that the administration of this cyclodextrin base to mice and rats can result in renal toxicity, and dose-related renal tubule vacuolization and obstruction in rats. Limited data in humans does not support this finding; adverse renal reactions to voriconazole are infrequent, and one report indicates that hemodialysis may result in clearance of the product.

These authors examined adults (greater than or equal to 18 years of age) with renal dysfunction (creatinine clearance < 50 mL/min) treated with voriconazole for a minimum of 3 days. Patients requiring hemodialysis or CVVH were excluded. The authors focused their investigation on 42 (25%) patients with CrCl < 50 mL/min receiving parenteral voriconazole; 77 (46%) patients with CrCl > 50 mL/min receiving parenteral voriconazole; and 47 (28%) patients with CrCl < 50 mL/min receiving orally administered voriconazole. Renal function was assessed at days 3 and 7 of treatment, and at the end of treatment, whenever that occurred. Changes in renal function were determined using pre-defined criteria (RIFLE).

The median duration of voriconazole treatment for each of the three groups, respectively, was 10 days (3 to 25 days), 10 days (3 to 59 days), and 9 days (2 to 86 days). Two-thirds (65.7%) of the patients received a loading dose at 6 mg/kg twice daily for one day. Thereafter, 47 patients received a standard dose of 200 mg twice daily; 35 (21%) received 2-3 mg/kg twice daily; 72 (43%) received 4 mg/kg twice daily, and 12 (7%) received 5-6 mg/kg twice daily. Voriconazole plasma levels were assessed in 27 patients. Eight patients had voriconazole levels > 5 micrograms/mL.

Changes in baseline renal function occurred in 19 (11.4%), 14 (8.4%), and 28 (16.9%) of patients at day 3, day 7, and end of treatment, respectively. In univariate analysis, voriconazole plasma levels > 5 micrograms/mL were associated with worsening renal function at the end of treatment.

However, in multivariate analysis, significant predictors of renal dysfunction included the administration of immunosuppressant agents/chemotherapy, the co-administration of penicillin antibacterials, hematologic malignancy, and the administration of fluconazole within 30 days of voriconazole use. In contrast, the administration of voriconazole was actually associated with a protective renal affect (OR 0.19; P = .01). Liver impairment was the only predictor of renal dysfunction at day 7 of treatment. Some of this may reflect the overall disease severity of the patient. However, there was no good evidence that voriconazole had a significant adverse impact on renal function in any of these groups of patients, with the possible exception of those with plasma levels > 5 micrograms/mL.

The authors advocate for the cautious use of voriconazole, in either oral or parenteral formulation, for those patients with renal impairment where it is deemed medically necessary. ■

CME INSTRUCTIONS

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

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

CME QUESTIONS

1. Which of the following is correct with regard to cefepime?

A. Dose reduction is required in the presence of significant renal insufficiency.
B. Cefepime is the only beta-lactam antibiotic that may be associated with non-convulsive status epilepticus when given in higher than appropriate dose.
C. The number of reports of non-convulsive status epilepticus associated with ceftazidime use exceeds that reported with cefepime use.
D. Myoclonic jerking is not a manifestation of non-convulsive status epilepticus .

2. Which of the following is correct with regard to the OraQuick test for diagnosis of HIV infection?

A. A blood specimen is required for its use.
B. It reliably detects antibodies to HIV within days after infection.
C. The false positive rate is less than 0.1%.
D. False negatives are less common than false positives.

3. Based on recent evidence concerning prevention of intrapartum HIV infection of infants by their infected mothers, which of the following is the optimal approach?

A. Post-partum administration of zidovudine (AZT) alone for 6 weeks to the infant.
B. Post-partum administration of zidovudine (AZT) for 6 weeks plus a total of 3 doses of nevirapine to the infant.
C. Post-partum administration of zidovudine (AZT) for 6 weeks plus nelfinavir and lamivudine for 2 weeks.
D. Post-partum administration of IVIG to the infant.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest 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]

Trends in Candida Central Line-Associated Bloodstream Infections Among NICUs,

Why Do Pertussis Vaccines Fail?

MRSA epidemic linked to a quickly spreading colonization and virulence determinant.

PHARMACOLOGY WATCH

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

FDA Approves First New Anti-Obesity Drug in Years

In this issue: Lorcaserin for weight loss; statins and fatigue; treatment-resistant gonorrhea; hydrocodone classification changes; USPSTF recommendations; and FDA actions.

Magic bullet for weight management?

The FDA has approved lorcaserin, the first new weight loss medication in more than a decade. The drug is approved for chronic weight management in adults with a body mass index of 30 or greater, or 27 or greater in those with weight-related conditions such as high blood pressure, type 2 diabetes, or hypercholesterolemia. Lorcaserin works by activating the serotonin 2C receptor in the brain, which promotes satiety. Approval was based on the results of three randomized, placebo-controlled trials of nearly 8000 obese and overweight patients with and without type 2 diabetes. All participants received lifestyle modification and reduced-calorie diets as well as exercise counseling. Lorcaserin was associated with an average weight loss of 3-3.7% compared to placebo over 1 year. Those with type 2 diabetes experienced favorable changes in glycemic control. There is no evidence of valvulopathy associated with the drug; although serotonin syndrome is a concern, especially when the locaserin is taken with an SSRI or some migraine drugs. The most common side effects include headache, dizziness, fatigue, nausea, dry mouth, and constipation as well as hypoglycemia in diabetic patients. Lorcaserin will be marketed by Arena Pharmaceuticals as Belviq. ■

Do statins cause fatigue?

Statins may be associated with fatigue and exertional intolerance, according to a small study from UC San Diego. Researchers randomized just over 1000 patients (692 men and 324 women) to simvastatin 20 mg (lipophilic statin), pravastatin 40 mg (hydrophilic statin), or placebo for 6 months. The outcomes were self-ratings of change in baseline in "energy" and "fatigue with exertion." Statin users were more likely to report worsening energy and fatigue compared to placebo ($P = 0.002$) Fatigue and exertional intolerance was worse with simvastatin compared to pravastatin (simvastatin, $P = 0.03$; pravastatin, $P = 0.01$). Women were more severely affected than men. The authors acknowledge that these findings are based on small numbers and findings are provisional. However, they also state that "this is the first randomized evidence of affirming unfavorable statin effects on energy and exertional fatigue." They further suggest that these effects "germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected morbidity/mortality benefit." (*Arch Intern Med* published online June 11, 2012. doi: 10.1001/archinternmed.2012.2171). The study also raises the potential issue of increased adverse effects of lipophilic statins such as simvastatin. The various risks and benefits of lipophilicity have been debated for years. It is clear that highly lipophilic statins, such as the now removed cerivastatin (Baycol), may have more muscle toxicity, and may have more CNS adverse effects as well. Of currently marketed statins, simvastatin is the most lipophilic, while pravastatin and rosuvastatin are the least. ■

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.

Call to action for resistant gonorrhea

The World Health Organization (WHO) is calling for urgent action to prevent the spread of "untreatable gonorrhea" around the world. The concern is based on reports from several countries, including Japan, United Kingdom, Australia, France, Sweden, and Norway, of gonorrhea that is resistant to cephalosporin antibiotics — the last remaining treatment option. According to WHO, more than 100 million people are infected with gonorrhea annually, and the world is faced with "dwindling treatment options." WHO is calling for greater vigilance on the correct use of antibiotics and more research into alternative treatment regimens for gonococcal infections. The agency also calls for increased monitoring and reporting of resistant strains as well as better prevention, diagnosis, and control of gonococcal infections. Single-dose treatment to assure adherence is also important as is the treatment of partners. WHO also stresses education and prevention, with special attention to high-risk groups such as sex workers and men who have sex with men. Cephalosporin-resistant gonorrhea has not been reported in the United States yet, but surveillance systems are in place. According to a recent CDC editorial in the *New England Journal of Medicine,* "It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense..." (*N Engl J Med* 2012; 366:485-487). ■

Changes on horizon for hydrocodone drugs

Could Vicodin soon be a Schedule II drug? The answer may be yes depending on congressional action this summer. The U.S. Senate recently passed The FDA Safety and Innovation Act (S 3187) with an amendment to classify all hydrocodone-containing products from Schedule III to Schedule II. The House of Representative's version of the bill did not contain similar language, and the proposal is under consideration for the final bill to be sent to the President for signature later this summer. Meanwhile, lawmakers in New York are moving forward with legislation that would make all hydrocodone-containing drugs Schedule II. If enacted, these laws would categorize hydrocodone containing drugs, such as Vicodin and Norco, in the same group with morphine, oxycodone, and methadone. Schedule II drugs cannot be phoned in, and patients are required to receive a new prescription for each refill. The proposed tightened regulations are in response to the explosion of prescription opioid abuse nationwide. Meanwhile, pharmacy groups, such as the American Pharmacists Association, are opposed to the legislation and are actively lobbying against it, arguing that it is unnecessarily restrictive to patients who legitimately need access to these drugs. ■

Vitamin D and calcium supplements

The U.S. Preventive Services Task Force (USPSTF) has now recommended that vitamin D and calcium supplements above the usual recommended daily allowances are of no benefit to help prevent bone fractures in healthy older women, and may actually cause harm. In a draft recommendation statement issued in early June, the USPSTF concluded that there is insufficient evidence to recommend vitamin D for prevention of cancer or combined vitamin D and calcium for the prevention of fractures in postmenopausal women or men. They further recommend against daily supplementation of more than 400 IU of vitamin D and 1000 mg of calcium carbonate. Older adults who are at risk for falls may continue to take vitamin D (www.uspreventiveserviestaskforce.org/draftrec3.htm). The draft recommendation was issued just after a study was published showing calcium plus vitamin D supplements appear to be associated with lower mortality in older individuals. In a large meta-analysis, patients receiving both calcium and vitamin D had a 9% reduction in mortality (hazard ratio, 0.91; 95% confidence interval, 0.84-0.98), although vitamin D alone did not affect mortality (*J Clin Endocrinol Metab* published online May 17, 2012, doi: 10.1210/jc.2011-3328). ■

FDA actions

The FDA has issued opinions on two oral novel anticoagulants. The agency turned down Janssen's application for approval of rivaroxaban (Xarelto) for the treatment of acute coronary syndrome, at least for now. The FDA did not release the reasons for the decision, but speculation is they want more information from the ATLAS-ACS trial. Rivaroxaban was approved last year for prevention of venous thromboembolism after hip or knee replacement surgery, and also for stroke prevention in patients with non-valvular atrial fibrillation (AF). The FDA also delayed the approval of apixaban (which would represent the third novel oral anticoagulant along with dabigatran and rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular AF. It had been widely speculated that the drug would be approved this spring, especially given that the FDA had granted a priority review for apixaban last November. The delay is similarly due to the need for additional information from the ARISTOTLE trial. Once approved apixaban will be marketed by Bristol-Myers Squibb as Eliquis. ■