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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Fidaxomicin More Effective than Vancomycin for *Clostridium difficile* Infection in Cancer Patients?

Superior cure rates, fewer C. diff *recurrences, but limitations warrant larger trial*

By Richard R. Watkins, MD, MS, FACP

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

SOURCE: Cornely OA, et al. Resolution of Clostridium difficile-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. *J Clin Oncol* 2013; 31:2493-2499.

The burden of *C. difficile* infection (CDI) among oncology patients is high, resulting in significant morbidity and mortality. These patients have multiple risk factors that predispose them to CDI including depressed immune function, prolonged hospitalizations, antibiotic treatments, and the adverse effects of chemotherapy on the gut microbiome. Moreover, patients who undergo stem-cell transplantation and develop graft-vs.-host disease are particularly susceptible to developing CDI. In an industry-sponsored study, Cornely et al present favorable data for fidaxomicin compared to vancomycin in the treatment of CDI in adult patients with cancer.

The study was a post-hoc analysis of data

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from two independent, double-blind, controlled trials that enrolled 1,105 patients with CDI and randomized them to receive either fidaxomicin or oral vancomycin. Of these, 183 had cancer (124 with solid tumors and the rest had either hematologic malignancy alone or hematologic malignancy and a solid tumor). The investigators assessed clinical cure which they defined as fewer than 3 unformed bowel movements in 24 hours for 2 consecutive days maintained until end of therapy and 2 days thereafter, and also examined recurrence of CDI, sustained response at 4 weeks after completing therapy, and all-cause mortality in both treatment arms.

Cure rates were similar with fidaxomicin and vancomycin in patients without cancer (88.5% vs. 88.7%, respectively P = .913). However, in those with cancer, fidaxomicin had a higher cure rate (85.1%) compared to vancomycin (74%) (OR = 2.0; 95% CI, 0.95 to 4.22; P = .065). Median time to resolution of diarrhea in cancer patients was 74 hours with fidaxomicin and 123 hours with vancomycin (P = .045). The likelihood of recurrence in cancer patients treated with vancomycin was double that of those treated with fidaxomicin. Furthermore, the relative odds of a sustained response at 28 days in patients with cancer were more than 2.5 times for the fidaxomicin group vs. vancomycin. The adverse event rate was not significantly different between the two treatment arms and was relatively high for both groups (85.3% for fidaxomicin and 83.5% for vancomycin), which is likely a consequence of the underlying malignancy. Finally, there was no significant difference in mortality between the two treatment arms.

COMMENTARY

The main finding from this study, that fidaxomicin is superior to vancomycin for CDI in patients with cancer, is interesting and important especially given the high prevalence of CDI in this population. Indeed, earlier resolution of diarrhea often allows for the resumption of chemotherapy, potentially improving the chances for remission of the underlying malignancy. However, there are several limitations to the study that deserve mention. First, the overall number of patients with cancer who were treated in the two study arms was relatively modest which increases the risk of sampling error. Second, as mentioned in a follow up letter to the editor, the cohort was heterogeneous in the immune competency of the subjects resulting from their chemotherapy, their intrinsic immunity due to the different underlying malignancies, different anticancer regimens, and different supportive therapies.[1] For example, patients with hematologic malignancies are more likely than those with solid tumors to receive antibiotic prophylaxis with a fluoroquinolone and a proton pump inhibitor to lessen the effects of oral steroids, and have prolonged neutropenia. Third, the study was a post-hoc subset analysis and not specifically designed to evaluate the efficacy of treatment in cancer patients. Fourth, a third treatment arm that included oral metronidazole would have been useful since this agent is still frequently used in cancer patients with mild

to moderate CDI. Finally, the study was industry sponsored and multiple authors had a direct financial interest in the manufacturer of fidaxomicin.

Cornely et al have provided us with good preliminary evidence for the effectiveness of fidaxomicin in treating cancer patients with CDI. However, I believe the limitations of the study (particularly the small sample size) mandate that additional larger, multicenter, randomized clinical trials be conducted before any major changes to clinical practice are implemented.

Reference

1. Green MR, et al. Is fidaxomicin the drug of choice for treating Clostridium difficile-associated diarrhea in patients with cancer? *J Clin Oncol* 2013; Oct 28. [Epub ahead of print] ■

Rapid Detection of TB and of Rifampin Resistance

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: The CDC recommends incorporating the Cepheid Xpert MTB/RIF assay in the management of patients with suspected pulmonary tuberculosis.

SOURCE: Centers for Disease Control and Prevention. Availability of an assay for detecting *Mycobacterium tuberculosis*, including rifampin-resistant strains, and considerations for its use – United States, 2013. *MMWR* 2013;62(41):821-824.

In 2009, CDC recommended that testing for Mycobacterium tuberculosis infection include nucleic acid amplification (NAA) testing. CDC indicated that NAA testing which should be performed on at least one (preferably the first) respiratory specimen from patients with suspected, but unproven, pulmonary tuberculosis. This was not to replace the need for culture, which should also be performed.

The Cepheid Xpert MTB/RIF assay for detection of Mycobacterium tuberculosis complex (MTBC) DNA and for mutations associated with rifampin resistance in unprocessed sputum and concentrated sputum specimens was approved by the U.S. FDA in August 2013. This NAA system utilizes a disposable cartridge together with the Cepheid instrument and is easy and simple to use. CDC has now outlined "interim practical considerations" for incorporation of the Xpert MTB/RIF assay into diagnostic algorithms for the diagnosis of pulmonary tuberculosis (*See Tables, p. xx; p. xx*).

The low prevalence of rifampin resistant MTBC in the U.S. results in the potential for low positive predictive values, even for very effective and accurate tests. For that reason, a positive result should be confirmed by sequencing of genetic regions associated with rifampin resistance, including rpoB, as well as of inhA and katG, which are associated with isoniazid resistance. If mutations associated with rifampin resistance are confirmed, rapid molecular testing of genes associated with resistance to other first and second line drugs should be performed. Phenotypic drug susceptibility testing should, of course, also be performed. Even though a negative result for rifampin resistance genes in the Xpert MTB/RIF assay has a very high negative predictive value to rule out resistance, phenotypic drug susceptibility testing is still necessary.

TABLE 1. Interpretation and proposed minimum laboratory report laboratoy for results from the Cepheid Xpert MTB/RIF assay* — United States 2013

GeneXpert Instrument System generated result using Xpert MTB/RIF assay	Interpretation of Xpert MTB/RIF assay result	Minimum laboratory report language†
MTB detected, RIF resistance detected	MTB target is detected within the sample. A mutation§ in the *rpoB* gene has been detected.	MTBC detected. A mutation in *rpoB* gene has been detected, indicating possible RMP resistance. Confirmatory testing should follow.¶
MTB detected, RIF resistance not detected	MTB target is detected within the sample. A mutation in the *rpoB* gene has not been detected.	MTBC detected. No *rpoB* gene mutations detected; probably RMP susceptible.
MTB detected, RIF resistance indeterminate	MTB target is detected within the sample. A mutation in the *rpoB* gene because of insufficient signal detection.	MTBC detected; presence of *rpoB* gene mutations cannot be accurately determined.
MTB not detected	MTB target is not detected within the sample.	MTBC not detected.

Abbreviations: To be consistent with the Xpert MTB/RIF assay package insert, MTB and MTBC = *Mycobacterium tuberculosis* complex; and RIF and RMP = rifampin.

* All samples tested by the Xpert MTB/RIF assay should have concomitant mycobacterial culture, regardless of the Xpert MTB/RIF assay results, to address lower sensitivity of the Xpert MTB/RIF for sputum samples that are negative on acid-fast bacilli microscopy, and to obtain isolates for drug susceptibility testing and genotyping.

† CDC suggested minimum language for the laboratory report. Laboratories are encouraged to enhance and customize this basic language in accordance with the capabilities or referral systems of their institution.

§ Might refer to more than one mutation.

¶ Because of the low positive predictive value of RMP resistance results in low prevalence populations, in the United States, confirmatory testing should include prompt DNA sequencing and subsequent phenotypic drug susceptibility testing of cultured isolates. DNA sequencing of direct patient samples (or if not available, isolates) with possible RMP resistance should include genetic loci associated with resistance to RMP (to include *rpoB*) as well as isoniazid (to include *inhA* and *katG*) to assess for multidrug-resistant tuberculosis; *rpoB* mutations detected by the Xpert MTB/RIF assay might be silent mutations that do not affect RMP susceptibility. DNA sequencing can distinguish silent mutations, which in this context refer to synonymous single nucleotide polymorphisms (also known as sSNPs).

COMMENTARY

NAA testing, because of its sensitivity and rapid turnaround time, may avoid delays in the diagnosis and treatment of tuberculosis, especially in patients with negative sputum smears. It may also help to avoid unnecessary isolation, treatment and contact investigation. As stated by CDC: "Three sputum specimens, each collected 8-24 hours apart, with one being an early morning specimen, should be collected to inform decisions regarding the discontinuation of precautions for patients with suspected TB in health-care settings. For patients with a diagnosis of TB, decisions regarding discontinuation of precautions should be based on microscopy (i.e., three consecutive negative smears) and other clinical criteria."

In a footnote to Table 1 in this article, CDC warns that "rpoB mutations detected by the Xpert MTB/RIF assay might be silent mutations that do not affect rifampin susceptibility" and indicate this is another reason for gene sequencing in order to distinguish silent (synonymous) single nucleotide polymorphisms. A recent study, however, found that the Xpert MTB/RIF assay could detect "occult" rifampin resistance – i.e., resistance not detected by phenotypic testing and that this finding may predict failure of antituberculosis therapy with rifampin containing regimens. [1,2]

References

1. Williamson DA, et al. Clinical failures associated with rpoB mutations in phenotypically occult multidrug-resistant *Mycobacterium tuberculosis. Int J Tuberc Lung Dis* 2012;16:216-20.
2. Ho J, et al. Phenotypically occult multidrug-resistant *Mycobacterium tuberculosis:* Dilemmas in diagnosis and treatment. *J Antimicrob Chemother* 2013; 68:2915-20.

■

TABLE 2. Analysis of results of SS and NAA testing for infection control in health-care settings involving patients with suspected tuberculosis (TB) — United States, 2013

Results of combinations of SS and NAA testing on a total of at least three specimens, each collected 8–24 hours apart, with one being an early morning specimen		Decisional analysis
SS results	**NAA test results**	
All SS tests are negative.	All NAA tests are negative for the detection of MTBC.	In combination with other requirements,* supports discontinuation of airborne infection isolation (AII) precautions.
At least one SS test is positive.	All NAA tests are negative for the detection of MTBC.	Consistent with presence of NTM; pulmonary or laryngeal TB is unlikely but cannot be excluded, pending culture results and other clinical determinants. Decision to discontinue AII precautions based on evaluation of all clinical information and potential risk for transmission.
At least one SS is positive.	At least one NAA test is positive for the detection of MTBC.	Consistent with pulmonary or laryngeal TB; supports continuation of AII precautions until recommended criteria are met.*
At least one SS is positive.	At least one Xpert MTB/RIF assay is positive for the detection of MTBC and rifampin (RMP) resistance.	Consistent with suspected pulmonary or laryngeal MDR TB; Xpert MTB/RIF assay rifampin resistance result should be confirmed by rapid DNA sequencing and be accompanied by first and second line growth-based DST; if RMP resistance is confirmed, some infection-control practitioners may choose AII precautions during the entire hospitalization or until culture conversion is documented.*
SS is not available.	At least one NAA test is positive for the detection of MTBC.	Consistent with pulmonary or laryngeal TB; SS needed to contribute to infection control decision making.
All SS are negative.	At least one NAA test is positive for the detection of MTBC.	Consistent with pulmonary TB but less contagious where three SS are negative; may support discontinuation of AII precautions if other criteria for discontinuing AII precautions are met (e.g., patient has received a sufficient duration of effective TB treatment) or patient is housed in setting where risk for transmission is low and treatment is started promptly.
All SS are negative.	At least one Xpert MTB/RIF assay is positive for the detection of MTBC and RMP resistance	Consistent with suspected pulmonary TB but less contagious where three SS are negative; the Xpert MTB/RIF assay rifampin resistance result should be confirmed by rapid DNA sequencing and be accompanied by first and second line growth-based DST; if confirmed as RMP resistant, some infection-control practitioners may choose AII precautions during the entire hospitalization, or until culture conversion is documented.*

Abbreviations: To be consistent with the Xpert MTB/RIF assay package insert, MTB and MTBC = *Mycobacterium tuberculosis* complex; and RIF and RMP = rifampin. SS = sputum-smear microscopic examination for acid-fast bacilli; NAA = nucleic acid amplification; MTBC = *Mycobacterium tuberculosis* complex; AII = airborne infection isolation; NTM = nontuberculous mycobacteria; MDR = multidrug-resistant (defined as resistance to at least isoniazid and RMP); DST = drug susceptibility testing.

* **Source:** CDC. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR 2005;54(No. RR-17).

ABSTRACT & COMMENTARY

A new Dimorphic Fungus causing Disseminated Infection in AIDS Patients in South Africa

By Dean L. Winslow, MD, FACP, FIDSA

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

Dr. Winslow is a consultant for Siemens Diagnostic.

SYNOPSIS: Between 2008 and 2011 surveillance at hospitals in Capetown revealed 24 cases of dimorphic fungal infection, 13 of which were shown to be caused by Emmonsia species. All 13 patients had advanced HIV infection.

SOURCE: Kenyon C, et al. A dimorphic fungus causing disseminated infection in South Africa. *New Engl J Med* 2013;369:1416-24.

Between July 2008 and July 2011 enhanced surveillance was conducted to identify the cause of systemic dimorphic fungal infections in patients presenting to Groote Schuur and affiliated hospitals in Capetown, South Africa. A total of 24 cases of dimorphic fungal infection were diagnosed during this time, of which 13 were subsequently shown to be due to Emmonsia species. All patients were HIV-infected and their median CD4+ lymphocyte count was 16 cells/uL. All 13 patients had evidence of disseminated fungal disease with fever, anemia and prominent skin lesions. The skin lesions included erythematous papules and plaques, to ulcers and crusted, boggy plaques. 5/11 patients had emmonsia isolated from blood cultures and 9/9 patients had the organism isolated from skin biopsies.

Three patients died soon after presentation. The remaining patients generally exhibited a favorable response to treatment with an initial 14 day course of amphotericin B deoxycholate 1 mg/kg/day followed by maintenance therapy with itraconazole. Patients were also started on ART if they were not already receiving ART at the time of diagnosis.

The isolated organism showed mycelial phase growth at 25 deg. C. and yeast phase growth at 37 deg. C. Phylogenetic analysis of 5 genes amplified by PCR revealed that this fungus belongs to the genus Emmonsia and is most closely related to E.pasteuriana.

COMMENTARY

The genus Emmonsia has included 3 species associated with human disease. *E.crescens* and *E.parva* are the agents which cause adiaspiromycosis (a pulmonary disease of small mammals and occasionally of humans). *E.pasteuriana* had previously been described in a single human case of an Italian patient with late stage AIDS.

The recognition of this "new" pathogen undoubtedly reflects the power of broad-range PCR to identify many pathogens. It is of note that many of these 13 patients subsequently shown to have systemic infection with Emmonsia were originally felt to have disseminated histoplasmosis. Since the institution of routine use of broad-range PCR to identify fungal pathogens, the diagnosis of histoplasmosis has declined and emmonsia infection has increased in proportion in patients in the Groote Schuur hospital system.

This is an important report for clinicians caring for patients in sub-Saharan Africa. So now we can add Emmonsia to the list of dimorphic fungi which can cause human disease. ■

ABSTRACT & COMMENTARY

Mayaro Virus Infection – another Alphavirus Causing Prolonged Joint Symptoms

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Mayaro virus, like other alphaviruses such as chikungunya, may cause incapacitating joint symptoms that persist for prolonged periods

SOURCE: Halsey ES, et al. Mayaro virus infection, Amazon Basin Region, Peru, 2010-2013. *Emerg Infect Dis* 2013;19:1839-42.

As part of a passive febrile surveillance study of individuals >5 years of age in 4 Peruvian cities within the Amazon Basin Region, Halsey and colleagues identified acute Mayaro infection in 16 of 2094 (0.8%). All were positive by cell culture (11) and/or RT-PCR (13) and all demonstrated IgM seroconversion by ELISA between their acute phase and their 20 day follow-up visit. No seroconversion for non-alphaviruses was identified, but this was seen with another alphavirus, Venezuelan equine encephalitis virus, apparently as the result of serological cross-reactivity.

All 16 subjects, by definition, were febrile. Additional symptoms commonly reported were malaise, headache, arthralgia, myalgia, and retro-orbital discomfort. Joint pain, most commonly involving joints of the hand, wrist, elbow, feet and knee, was a prominent part of the symptom complex and persisted in 54% of subjects for at least 12 months. The discomfort was often sufficient to interfere with activities of daily living.

COMMENTARY

Mayaro is an alphavirus, most of which are arthritogenic.[1] In addition to Mayaro virus, the other arthritogenic alphaviruses are Ross River, Barmah Forest, Sindbis, o'nyong-nyong, and chikungunya virus. Other alphaviruses, Venezuelan, Eastern Equine, and Western equine viruses, predominantly cause, as their names imply, encephalitis. All are arboviruses transmitted mostly by mosquitoes.

Chikungunya is a Swahili word for "that which bends up," describing the effects of the severe joint pains associated with this disease on the posture of the affected individual. This virus caused as many as 6.5 million cases during its recent (and continuing) explosion. Chikungunya is seen in Africa, and in and along the Indian Ocean littoral, as well as in Southeast Asia. The name of the highly related alphavirus, o'nyong-nyong, and also found in Africa, is derived from the Acholi word for "joint breaker." Ross River and Barmah Forest virus infections are acquired in northern Australia during the wet season (December to February); Ross River virus is also found in Papua New Guinea. Sindbis group viruses (Karelian, Ockelbo, Posogosta) are found in Eurasia, Africa, and Oceania, but human cases are largely limited to northern Europe.

Mayaro virus is enzootic in the northern regions of South America, mostly in humid forested areas and is believed to be maintained in small mammals. It has been identified in French Guinea, Suriname, Venezuela, Peru, Bolivia, and Brazil. Its primary vector is likely to be Haemogogus mosquitoes, although laboratory studies indicate that Aedes aegypti is also a competent vector.

While the incubation period of Mayaro virus infection is uncertain, that of other arthritogenic alphaviruses may range from 2 to 10 days. In addition to fever, 30%-50% of patients develop a rash and as many as 90% complain of joint pain. Headache and retro-ocular pain are also common.

Prolonged joint disability has also been reported after infection with sindbis virus as well as with chikungunya virus in which it has been reported to persist for >3 years. The study reviewed here found that half of patients with Mayaro virus infection have persisting joint complaints for at least one year and that these symptoms may be of sufficient severity to interfere with daily activities. Prolonged joint symptoms have also been reported in returning travelers who have acquired this infection.

Reference

1. Suhrbier A, et al. Arthritogenic alphaviruses--an overview. *Nat Rev Rheumatol* 2012;8:420-9. ■

ABSTRACT & COMMENTARY

Drug-resistant E. coli in Women with Acute Cystitis in Canada

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

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

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

SYNOPSIS: 330 family physicians assessed 752 women with suspected acute cystitis between 2009 and 2011 in Canada. Physicians documented clinical features and collected urine for cultures for 430 (57.2%) women. The proportion of TMP-SMX-resistant *Escherichia coli* was 16.0% nationally.

SOURCE: McIsaac WJ, et al. Antibiotic-resistant *Escherichia coli* in women with acute cystitis in Canada. *Can J Infect Dis Med Microbiol* 2013;24:143-149.

Canada is a bit like middle America. It is not that the entire landscape escapes metropolis. Yet Canada is a land of vast spaces and smaller towns and cities, like much of America still. So this article about 330 family practices across Canada provides information about a broad middle class. From 2009 through 2011 there were 14,576 family physicians eligible to enroll. Only 4.5% did so but these practices provided 430 cultures from women with a diagnosis of acute cystitis. When complete information on the women was analyzed, 91.4% of the women had acute cystitis; 31% had received antibiotics in the previous 3 months. In 61.2% of women, urine cultures were positive. *Escherichia coli* was by far the most common pathogen (79.1%). *Staphylococcus saprophyticus* and Enterococcus species caused 2.3% and 1.9% of cystitis respectively.

The prevalence of antibiotic resistance was the feature of the study. Nationwide, TMP-SMX resistance was 16% compared to only 10.9% back in 2002. Ciprofloxacin resistance jumped from 1.1% in 2002 to 5.5% in the current study. There were regional variations. For example in British Columbia there was a 17.7% resistance to ciprofloxacin compared to only 2.7% nationally. TMP-SMX resistance was higher in premenopausal women than older women. The percentage of resistance to ampicillin, TMP-SMX, or ciprofloxacin did not change statistically over the 3 years of the study. In the entire study only one isolate, an *E. coli*, produced an extended spectrum beta-lactamase.

COMMENTARY

Physicians will respond to thresholds, particularly with regard to the use of antimicrobials. When resistance rates hits a certain threshold—and these thresholds may not always be well established—physicians will alter their prescribing patterns. The question of how high a rate of antimicrobial resistance is necessary to alter prescribing preferences is not easy to answer. From my experience a threshold like 20% seems a maximum level that will change perceptions. What may be a minimal rate is a harder question to answer, but physicians become uneasy when 10% of a population has a certain trait.

In applying these biases to the current study, almost all primary care physicians would not use ampicillin as first line therapy of acute cystitis because the national resistant rate is >30%. Many would feel very safe using ciprofloxacin since the resistance in most locations is very low, although it climbs to 17% in British Columbia.

The toughest issue is whether TMP-SMX can be used comfortably in most locations as primary therapy. Nationwide the rate of TMP-SMZ resistance was 16%, but it was higher and a little lower in some locations and in some populations. In an accompanying editorial, Lindsay Nicole, MD, an international scholar in the field of urinary tract infections, felt – and I agree – that TMP-SMZ can be used as first line therapy in acute cystitis. She cautions that even with the relatively low rates of resistance

nationally in Canada, rates of resistance for the commonly used antimicrobials are rising for the most part. We should not generalize too much, as the response rate was only 4.5% of potential family physicians. More surveillance studies like these are needed with larger, perhaps more diverse, populations. For U.S. clinicians, the study is a window into simpler times in a more homogenous world. Gradually, however, the antimicrobial resistance world is changing even in Canada. We all must use our most innovative ideas to halt the snowball of antibiotic resistance and preserve the antimicrobial agents that remain. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Environmental reservoirs for human infection

Mystery blastomycosis in Wisconsin Hmong

Roy, M, et al. A larger community outbreak of Blastomycosis in Wisconsin with geographic and ethnic clustering. *Clin Infect Dis* 2013:57:655-662.

An increase in human Blastomycosis cases in Marathon County, Wisconsin from 2005 to 2010, many of which appeared to cluster within households and neighborhoods, prompted epidemiological investigation. Many of the cases occurred in children (not the usual victims), nor with the usual risk factors for exposure, such as outdoor activities. Cases of blastomycosis in Northern Minnesota and Wisconsin are often related to such outdoor activities as camping, hiking, hunting, spending time at a cabin, clearing brush, and gardening.

Cases were defined as a compatible clinical illness, with microbiologic confirmation (either by a positive culture or a clinical specimen with consistent fungal morphology). In all, 55 cases were identified, 70% of which were hospitalized, including two deaths; 20 (45%) of the cases occurred in Hmong residents. This represents a significant increase in the number of annual cases in this area since 2005 - an estimated 11% annual increase – with peaks in 2006 and 2010. Asians were disproportionately affected compared with non-Asians (the age-adjusted incidence in Asians increased 586% compared with a decrease of 9% in non-Asians).

Using spatial analysis to map cases, 5 distinct clusters involving 30 (55%) of the cases were identified within certain residences or neighborhoods. Compared with non-Asian cases, case-control analysis demonstrated that Asian cases were more likely to have underlying chronic illness, a household member with Blastomycosis infection, and exposure to an excavation or construction site – but they are much less likely to smoke, significantly less likely to participate in those kinds of outdoor activities generally associated with Blastomycosis infection, and they were less likely to travel within 90 days of onset of infection.

While no specific environmental foci could be identified, the authors believe the clustered cases must be related to one or more similar environmental sources, with suspected aerosolization to the neighborhoods or homes. They also speculate that Hmong – similar to Filipinos – may have a genetic predisposition to B. dermatitidis infection. ■

Saxophone lung: an off-note?

Similar to the Scottish bagpiper who developed severe fungal pneumonia from exposure to his uncleaned

pipes (both Rhodoturula and Fusarium were cultured from the bag on his pipes, which had not been cleaned for years, (*see IDA July 2013, p. 118)*, a recent case study presented at the annual meeting of the American College of Allergy, Asthma and Immunology described a man with persistent cough and wheezing. He was initially treated for allergic pulmonary broncho-aspergillosis (ABPA), but failed to improve with corticosteroids. It was discovered he played the clarinet in a Dixie band – but had not cleaned his clarinet in 30 years. Cultures from a reed grew Exophiala spp. and his symptoms resolved once his instrument was cleaned.

Increasingly it is being recognized that woodwind instruments can harbor bacteria and fungi if they are not cleaned properly on a regular basis. "Saxophone lung" is the result of an allergic reaction to repeated exposure to a mold colonizing an instrument. Case reports describe patients with persistent cough, wheezing, and/or shortness of breath — including saxophone, trombone and clarinet players. Similar to ABPA, it may respond to steroids, but removal of the source is ultimately curative. Another similar case in the literature was described as a 48-year-old man who presented with interstitial pneumonia.[1] CT scan showed patchy ground glass infiltrates, and bronchoalveolar lavage suggested a lymphocytic alveolitis consistent with a hypersensitivity pneumonitis. Open-lung biopsy showed a non-specific interstitial pneumonitis. The cause of the hypersensitivity was not discovered until it was revealed that he played the saxophone – at which point two different molds were cultured from his instrument (*Ulocladium botrytis* and *Phoma spp*.). Serologic studies showed precipitating antibodies to both molds.

So the next time you see a patient with persistent cough or wheezing, or possible ABPA – ask the key question – do they play a wind instrument?

Reference

1. Metzger F, et al. Hypersensitivity pneumonitis due to molds in a saxophone player. *Chest* 2010 138:724-6. ■

Aedes Aegypti in my backyard

San Mateo County Mosquito and Vector Control District, Press releases dated August 23 and October 22, 2013; http://smcmad.org/data.

Adult and larval Aedes Aegypti mosquitoes have been identified in my backyard (and across the creek from Stanford University) in Menlo Park, California according to press releases from the San Mateo County Mosquito and Vector Control District. Eggs of the mosquito were first identified at Holy Cross cemetery on August 23rd – right down the street from Peet's coffee, prompting an extensive canvassing of the neighborhood, and distribution of traps throughout the area. As of October 11, 246 samples from 1101 homes in Menlo Park yielded 4 adult mosquitos and 5 eggs. Alerts have been distributed to residents to eliminate standing water, drain untended pools or spas, flowerpots, etc.

Efficient biters – A. aegypti can easily transmit yellow fever, dengue, malaria, chikungunya - (which are not endemic to this area and we'd prefer to keep it that way)- as well as several arboviruses that may result in encephalitis – most of which is not endemic in this area (and we'd prefer to keep it that way). The mosquito is present in the Southeastern United States, but is seldom seen this far north in California. It was last found in Northern California near the San Francisco airport in 1979, but successfully eradicated. With a turn of good luck – temperatures dropped this week into the low 40's – enough to eliminate the problem - for now. ■

Camels as vector for MERS-CoV?

Perara RA, et al. Seroepidemiology for MERS coronavirus using microneutralisation and pseudoparticle virus neutralization assays reveal a high prevalence of antibody in dromedary camels in Egypt, June 2013. *Eurosurveill* 2013;18(36): ProMED-mail post, September 5, 2103. www.promedmail.org.

Epidemiological studies have attempted to pinpoint the source (or sources) of human infection from Middle East respiratory syndrome coronavirus (MERS-CoV). Preliminary observations suggest MERS-CoV may infect insectivorous bats, and a recent report described an Egyptian tomb bat containing fragments of DNA consistent with MERS-CoV, although there was not sufficient genetic material for complete comparison. Because an index human case of MERS-CoV infection reported exposure to camels – investigators turned their attention toward camels as a potential source.

Samples from 110 dromedary camels, 8 water buffalo, 25 cows, 5 sheep, and 13 goats, along with 815 human samples from Egypt were analyzed, and compared with control specimens obtained from archived specimens from Hong Kong, including 260 swine, 204 bird, and 528 human specimens. Specimens were tested using a novel pseudoparticle neutralization assay and a conventional microneutrolisation assay specific for MERS-CoV, distinct from other coronaviruses.

Remarkably, in two separate serological studies, 93.6% and 98.2% of the dromedary camels tested positive for MERS-CoV, some with extra-ordinary high titers. There was no evidence of cross-reactivity with SARS. Until the "camel virus" can be sequenced, it is not known whether the antibodies identified could be cross-reacting with a closely related virus, a chimeric virus, or the true MERS-CoV. Although camels serve as both a source for meat and milk in that area, serologic studies of Egyptian people fail to find much evidence of serologic reactivity, suggesting this viral infection is not common in people living in Egypt.

Because the camels were brought from Northern Africa, the Sudan and Oman for slaughter in Cairo – and had been present for some number of weeks before sampling, it is not known where the camels may have acquired infection. Other studies of camels from Oman and the Canary Islands have also found evidence of antibodies to MERS-CoV in camels, suggesting this virus may generally be present in the camel population in Northern Africa and the Middle East – and could serve as a potential reservoir for the occasional human infection.

Pilot whales with MRSA – blame the sand

Hower S, et al. Clonally related methicillin-resistant Staphylococcus aureus isolated from short-finned pilot whales *(Globicephala macro-rhynchus)*, human volunteers, and a Bayfront Cetacean Rehabilitation Facility. *Micro Ecol* 2013 (epub ahead of print).

MRSA has complicated the care of non-human mammals, such as prized pigs, deer, circus elephants, and horses in critical care with PICC lines. This brief report describes a group of 26 short-finned pilot whales that were accidently beached in a mass stranding in the Florida keys. They were bused to a rehabilitation center for care, during which routine cultures, obtained for clinical purposes, including those obtained from a dead whale necropsy, yielded both MSSA and MRSA.

In order to determine whether there was a reservoir of infection at the facility, surveillance cultures were obtained from whales, staff, volunteers, multiple sites at the facility, the seawater, and the sand from nearby beaches. Samples were obtained at baseline, two weeks later, and 2 months after the whales had departed the facility. MSSA and MRSA were found at the facility when whales and volunteers were present – and samples from the adjacent beach were positive all 3 times, including 2 months later. Molecular studies suggested the majority of the MRSA isolates were clonally related to USA300, although there were multiple other non-identical MSSA and MRSA identified from distinct sources. It appears that MSSA and MRSA may be present in the sandy beach environment – either from shedding from animals or humans – and which can serve as a reservoir for infection. ■

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 the post hoc subset analysis of patients with cancer from 2 randomized trials comparing fidaxomicin to vancomycin in the treatment of *Clostridium difficile* infection?

A. Fidaxomicin recipients had a higher rate of cure than did vancomycin recipients.

B. Recurrences occurred less frequently after treatment with vancomycin.

C. Adverse events occurred with significantly greater frequency in vancomycin recipients.

D. Mortality was significantly higher in the vancomycin recipients.

2. Which of the following is correct with regard to CDC recommendations in the diagnosis of pulmonary tuberculosis?

A. Nucleic acid amplification testing of sputum for detection of *Mycobacterium tuberculosis* DNA should only be performed if 3 consecutive sputum smears are negative.

B. If the Xpert MTB/RIF assay indicates the presence of rifampin resistance mutations in *M. tuberculosis*, phenotypic drug susceptibility testing is unnecessary.

C. Sputum specimens for testing must be collected at intervals of >24 hours.

D. Although a negative result for rifampin resistance mutations by the Xpert MTB/RIF assay has a very high negative predictive value in ruling out the presence of rifampin resistance, phenotypic drug susceptibility testing should still be performed.

3. Which of the following is NOT an arthritogenic alphavirus?

A. Mayaro virus.

B. Sinbis virus.

C. Westerh equine encephalitis virus.

D. Ross River virus.

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]

Nonmedical Vaccine Exemptions and Pertussis in California, 2010.

Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: A Prospective Cohort Study

High rate of Schistosomiasis in Travelers after a brief Exposure to the high-altitude Nyinambuga Crater Lake, Uganda

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 12 Pages 23-24 December 2013

Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldilocks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

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Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

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Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■