AHC Media

Vol. 30, Issue 12, September 2011
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

Fidaxomicin: Cost Considerations for the Treatment of Clostridium difficile Infection

By Jessica C. Song, MA, PharmD, Paul Hsiao, PharmD, and Stephanie Tran, PharmD

Dr. Song is Assistant Professor, Pharmacy Practice, University of the Pacific, Stockton, CA; Pharmacy Clerkship and Coordinator, Santa Clara Valley Medical Center. Dr. Hsiao is a Pharmacist Specialist, Santa Clara Valley Medical Center. Dr. Tran is a PGY1 Pharmacy Resident, Santa Clara Valley Medical Center.

Drs. Song, Hsiao, and Tran report no financial relationship to this field of study.

INTRODUCTION

Clostridium difficile infection (CDI) is a serious medical condition associated with significant morbidity and mortality. Thirty-day mortality rates associated with CDI have been estimated to be anywhere from 6.0% to 32.5%, with higher mortality rates observed in older patients.[1,2] Rates of CDI have increased worldwide over the past decade, with an estimated 500,000 cases in U.S. hospitals and nursing homes per year.[3] Recent outbreaks of more aggressive CDI have been temporally associated with a hypervirulent strain of *Clostridium difficile*, known as North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis group B1, PCR ribotype 027 (NAP1/BI/027). This strain has been shown to exhibit greater spore-forming capabilities, heightened toxin production, and higher rates of failure with metronidazole treatment compared with other strains.[4]

New clinical practice guidelines for CDI were recently developed by the Society for Healthcare Epidemiology of America (SHEA)

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.

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.

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

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
paula.cousins@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada Add 7% GST and $30 shipping.
Elsewhere Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 25 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

AHC Media

and the Infectious Diseases Society of America (IDSA).[5] The working group recommended the use of oral metronidazole 500 mg three times a day for mild-to-moderate cases of CDI. Oral vancomycin 125 mg four times a day was recommended for severe cases of CDI. Complicated cases of CDI merited a higher dose of vancomycin (500 mg orally four times a day), either as monotherapy or in combination with intravenous (IV) metronidazole 500 mg every 8 hours. The same regimen that was used for the initial infection could be used for first recurrences, provided that disease severity is taken into account. Tapered and/or pulsed-dose vancomycin regimens should be considered for infections beyond the first recurrence.

At present, alternative treatment options for primary and recurrent infection in the United States are limited. Small case series and studies have featured the use of alternative agents such as rifaximin,[6,7] nitazoxanide,[8] and tigecycline[9] in patients with recurrent infections. Fidaxomicin, an 18-membered macrocyclic antibiotic with activity against Gram-positive anaerobes and aerobes, was recently granted FDA approval for the indication of CDI, making it the second FDA-approved agent (after vancomycin) for this indication.[10]

Given the economic downturn in recent years, institutions have been under greater scrutiny with regard to selection of antimicrobial agents for formulary inclusion. The purpose of this review is to discuss clinical and cost considerations of drugs used for the treatment of patients with primary and recurrent CDI.

AVERAGE WHOLESALE PRICING AND CLINICAL EFFICACY DATA

Metronidazole, the first-line agent for mild-to-moderate CDI, is available as a generic tablet, priced at $0.07 per tablet. A 10-day treatment course would cost $2.10. Because of its higher acquisition cost and the concern for selecting vancomycin-resistant bacteria in hospitals, oral vancomycin therapy is usually reserved for use in patients with severe or complicated cases of CDI. The costs of the 125 mg and 250 mg capsule formulations (Vancocin®) are $26.52 and $48.93, respectively. A 10-day treatment course would cost $1061 and $3914, respectively. At Santa Clara Valley Medical Center (San Jose, CA), prior to oral administration, vancomycin IV is diluted with 10 mL of normal saline. Since one 500 mg vial costs $2.21, the cost of a 10-day course of therapy for complicated CDI would approach $88 for hospitalized patients. With the addition of IV metronidazole (500 mg IV every 8 hours), the cost would increase by $34, assuming that the IV piggyback formulation is used for treatment.

To date, the safety and efficacy of fidaxomicin has mainly been established in patients with mild-to-moderate primary CDI.[11] Louie and associates conducted a prospective, multicenter, double-blind, randomized, parallel group trial that included 629 patients with CDI.[11] The rate of clinical cure in the modified intention-to-treat and per-protocol populations upon completion of treatment or at the time of discontinuing participation in the study was the primary efficacy outcome measure. Patients underwent randomization to receive oral vancomycin (125 mg four times a day) or fidaxomicin (200 mg twice daily by mouth) for 10 days. Approximately 83% of patients in the modified intention-to-treat and per-protocol populations did not have a previous CDI episode. The proportions of patients diagnosed with mild-to-moderate CDI ranged from 59% to 62% in the modified intention-to-treat and per-protocol populations. The proportions of patients displaying strain type NAP1/BI/027 ranged from 35.3% to 38.6% in the modified intention-to-treat and per-protocol populations. Clinical cure rates seen in fidaxomicin-treated patients were non-inferior to those who received vancomycin in both the modified intent-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin, respectively) and the per-protocol analysis (92.1% and 89.8%, respectively).

Of note, a secondary outcome measure, recurrence of CDI during the 28-day period following the end of the 10-day treatment course, was assessed in the study conducted by Louie and colleagues.[11] Fidaxomicin-treated patients were less likely to experience infection recurrence than vancomycin-treated patients in both the modified intention-to-treat population (15.4% vs. 25.3%; $P = 0.005$) and the per-protocol population (13.3% vs. 24.0%; $P = 0.004$). However, recurrence rates did not differ significantly between fidaxomicin-treated patients and vancomycin-treated patients with the NAP1/BI/027 strain.

A 10-day course of fidaxomicin (200 mg twice daily by mouth) costs $2,800, since one 200 mg tablet costs $140. The use of fidaxomicin in patients with two or more recurrences of CDI has not been established, and this drug has not been compared to other drug regimens such as oral/IV metronidazole or to tapered and/or pulsed-dose vancomycin.

Rifaximin, a non-systemic, rifamycin-derived antibiotic, exerts its in vitro bactericidal activity against *Clostridium difficile* through inhibiting bacterial RNA synthesis.[6] In addition to case reports of its success in the treatment of patients with recurrent CDI, four small studies (n = 6-25) of patients with CDI treated with rifaximin support its clinical use.[7] Tannous et al reported a case of a patient with recurrent CDI who had previously received: 1) two 14-day courses of metronidazole 500 mg three times daily by mouth; 2) a 2-week course of vancomycin 125 mg four times daily by mouth; and 3) tapered oral vancomycin: 125 mg four times daily for 1 week, 125 mg three times daily for 1 week, 125 mg once daily for 1 week, 125 mg every other day for 1 week, then 125 mg every third day for 1 week.[6] The patient received rifaximin 400 mg three times daily for 28 days and showed sustained response to therapy (no further episodes of diarrhea) within 6 months after completion of therapy. A single 200 mg tablet costs $9.13, so a 4-week course of rifaximin 1200 mg/day would cost $1,534.

Patrick-Basu and associates evaluated the efficacy of a 2-week course of rifaximin 400 mg three times daily in 25 patients with mild-to-moderate CDI unresponsive to metronidazole therapy.[7] Twenty-two of the 25 recruited patients completed the 2-week treatment. At the end of treatment, 16 of the 22 patients (73%) had stool samples negative for *Clostridium difficile*. This response to therapy was sustained for at least 56 days post-treatment. Other smaller studies (n = 6-8) showed response rates (defined as being symptom-free or achieving complete resolution of diarrhea) ranging from 67% to 88%, with follow-up times of 54-780 days.[7] Rifaximin dosing featured in the smaller studies included 400-800 mg daily for 14 days ($256-$511), and 400 mg three times daily for 14 days, followed by 200 mg three times daily for 14 days ($1,150).

Musher et al evaluated the efficacy of a 10-day course of nitazoxanide 500 mg twice daily by mouth in 35 patients with CDI recalcitrant to standard therapies (metronidazole or vancomycin).[8] Nitazoxanide, a nitrothiazolide, blocks anaerobic metabolism, and has been shown to inhibit *Clostridium difficile* (in vitro studies). Twenty-eight patients had previously received a minimum of 14 days of metronidazole 500 mg three times daily and 7 patients had at least two recurrences despite receiving appropriate therapy (two courses of metronidazole or vancomycin). Twenty-six of the 35 patients (74%) responded to nitazoxanide, but recurrences occurred in 7 of the 26 patients within a mean of 12.1 (range 7-24) days. Three of the 9 patients who initially failed nitazoxanide therapy and 1 patient with recurrent CDI responded to a second course of nitazoxanide. Since one nitazoxanide tablet costs $20.60, the cost of a 10-day treatment course is $412.

Tigecycline, an analog of minocycline, has demonstrated activity against *Clostridium difficile* in numerous in vitro studies.[9] Larson and associates recently reviewed 7 cases of patients with CDI who received this broad spectrum antibiotic as monotherapy or in combination with other drugs.[9] Six of the 7 patients received tigecycline after failing to respond to treatment with metronidazole, vancomycin, or to the combination of metronidazole and vancomycin. Three patients received tigecycline alone and the other patients received it in combination with other agents such as vancomycin, metronidazole, and/or IVIG. Treatment duration ranged from 14 to 24 days for patients who received tigecycline monotherapy. One patient with septic shock and acute respiratory distress syndrome received a 7-day course of tigecycline as primary therapy, followed by a 4-week course of oral vancomycin. Six of the 7 patients achieved treatment success with tigecycline that was sustained for at least 3 months. One patient discontinued tigecycline therapy because of worsening hepatic function and eventually died of multiple organ failure and refractory septic shock. A single 50 mg IV tigecycline vial costs $65.53, so a 2-week course of tigecyline 50 mg IV given twice a day would cost $1,835.

CONCLUSION

CDI has been a major cause of hospital infections for the past few decades, with increasing rates noted over the past decade. Moreover, CDI has become more problematic in recent years, given the emergence of hypervirulent strains that are well-adapted to health care settings. At present, vancomycin and fidaxomicin are FDA-approved for use in the treatment of patients with CDI. Metronidazole, because of its low cost, is the first-line therapeutic option for patients with mild-to-moderate CDI. However, recurrence rates associated with metronidazole and vancomycin treatment regimens, the current standards of care, have been increasing over the past decade. Some alternative therapeutic strategies have demonstrated encouraging results in the treatment of CDI, but these agents are considerably more expensive than metronidazole. Providers should consider the acquisition costs of treatment options and the potential for reducing the frequency of recurrences, along with the development of complicated disease when selecting appropriate agents for treating patients with CDI. ■

References

1. Karas JA, et al. A review of mortality due to Clostridium difficile infection. J Infect 2010;61:1-8.
2. McGowan AP, et al. Thirty-day mortality of Clostridium difficile infection in a UK National Health Service Foundation Trust between 2002 and 2008. J Hosp Infect 2011;77:11-15.
3. Rupnik M, et al. Clostridium difficile infection: New developments in epidemiology and pathogenesis. Nat Rev Microbiol 2009;7:526-536.
4. Warny M, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet 2005;366:1079-1084.
5. Cohen SH, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-455.
6. Tannous G, et al. Therapeutic success of rifaximin for Clostridium difficile infection refractory to metronidazole and vancomycin. Case Rep Gastroenterol 2010;4:404-409.
7. Patrick Basu P, et al. Rifaximin therapy for metronidazole-unresponsive Clostridium difficile infection: A prospective pilot trial. Ther Adv Gastroenterol 2010;3:221-225.
8. Musher DM, et al. Clostridium difficile colitis that fails conventional metronidazole therapy: response to nitazoxanide. J Antimicrob Chemother 2007;59:705-710.
9. Larson KC, et al. Tigecycline for the treatment of severe Clostridium difficile infection. Ann Pharmacother 2011;45:1005-1010.
10. PRNewswire. FDA Approves Optimer's DIFICID (fidaxomicin) Tablets for the Treatment of Patients with Clostridium difficile-Associated Diarrhea (CDAD). Available at: http://multivu.prnewswire.com/mnr/optimerpharma/50177/. Accessed Aug. 8, 2011.
11. Louie TJ, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011;364:422-431.

ABSTRACT & COMMENTARY

Bladder Cancer Associated with HPV Infection

By Joseph F. John, Jr., MD

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston

Dr. John reports no financial relationship to this field of study.

SYNOPSIS: A large new meta-analysis reveals an association between infection of bladder tissue with human papilloma virus (HPV) and evolving bladder cancer. Future trends may include screening of men for infection with bladder-associated genotypes.

SOURCES: Li N, et al. Human papillomavirus infection and bladder cancer risk: A meta-analysis. J Infect Dis 2011;204:217-223.

The association of HPV infection and bladder cancer has been a topic of discussion for the last decade, but has not surfaced because of important other outcomes of HPV infection. HPV is increasing in its prevalence globally and its chronic nature raises many issues in and around the genital tract. We already know of the oncogenic nature of this virus and its genetic plasticity, so an association with bladder cancer would not be so surprising.

An earlier meta-analysis was been published in 2007,[1] but several questions remained unanswered. Thus, this new meta-analysis from Beijing and Yale now includes 52 publications, making for a robust meta-analysis. Li et al found 2,855 cases of bladder cancer, most of which occurred in Europe. The prevalence of HPV averaged nearly 17%. HPV prevalence was higher when fresh HPV DNA was isolated from

the bladder tissue in question. There are high-risk types of HPV seen in bladder cancer and stratification in this analysis found that clades A9, A7, and A10 were the most common. The five most common types were HPV-16, 18, 33, 6, and 31. The meta-analysis of 17 of 19 controlled studies revealed an odds ratio of 2.84 (confidence interval, 1.39-5.80). PCR detection of HPV DNA seemed to be the most sensitive way to demonstrate the association with HPV infection and the cancer.

■ COMMENTARY

Genital HPV infection may be associated with bladder cancer. Physicians seeing patients with HPV infection should be alerted to this association. Further studies are needed to determine the approach to this risk factor for bladder cancer. Since bladder cancer affects more men than women, there may be strategies that can mirror the effective use of Pap smears in women to detect HPV infection and even cervical neoplasia.

The authors of this study acknowledge that most of their analyses rested on tissue diagnosis of HPV, whereas a PCR test for HPV DNA will be more sensitive. One issue is whether urine would be a good reflection of bladder wall involvement with HPV as a precursor of bladder cancer. Many other scenarios can be advanced. Still, the major message of this article is fascinating and has been hanging out there for some time. Now we have this meta-analysis, which shows the relationship of HPV to bladder cancer. The next steps will be very exciting and of great benefit to those patients at greatest risk. ■

Reference

1. de Sanjose S, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: A meta-analysis. Lancet Infect Dis 2007;7:453-459.

ABSTRACT & COMMENTARY

Prevention of HIV Infection in Serodiscordant Couples with Early Antiretroviral Therapy

By Dean L. Winslow, MD, FACP, FIDSA

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine

Dr. Winslow is a speaker for GSK and a consultant for Siemens Diagnostics.

SYNOPSIS: A total of 1,763 couples serodiscordant for HIV-1 infection were enrolled in this prospective trial. HIV-1-infected patients with CD4+ lymphocyte counts between 350 and 500 cells/mL were randomized to receive either immediate therapy or have antiretroviral therapy deferred until either onset of HIV-related symptoms or decline in CD4+ count. At the time of this analysis, 39 HIV-1 transmissions were observed and 28 were virologically linked to the infected partner. Of these, only 1 occurred in the early therapy group..

SOURCES: Cohen MS, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 July 18; Epub ahead of print.

A total of 1,763 HIV-1 serodiscordant couples in nine countries with the infected partner having CD4+ counts of 350-500/mL were randomized 1:1 to early (immediate) vs. delayed (CD4+ had declined to ≤ 250/mL or after development of an AIDS-related illness) antiretroviral therapy of the infected partner. Fifty-four percent of the subjects were from Africa; 50% of the infected partners were men; 97% of couples were heterosexual; and 94% were married.

As of February 2011, after a median follow-up of 1.7 years, a total of 39 HIV-1 transmissions were observed. Sequencing of the *pol* genes from linked cases showed that 28 were virologically linked to the infected partner. Of these linked transmissions, only 1 occurred in the early therapy group. Early antiretroviral therapy also resulted in fewer primary clinical endpoints (occurrence of pulmonary TB, severe bacterial infections, a WHO stage 4 event or death) in the HIV infected partners.

■ COMMENTARY

This is a very important study, which conclusively shows that early initiation of antiretroviral therapy reduces transmission of HIV-1 in

serodiscordant couples. Consistent with previous studies, high viral load at baseline predicted HIV-1 transmission. In the early treatment group, 89% of patients had plasma HIV RNA < 400 copies/mL after 3 months of treatment. The study has obvious direct relevance to HIV prevention efforts and, even in the absence of formal cost-benefit analyses, provides additional justification for universal implementation of early antiretroviral therapy in the developing world. ■

SPECIAL FEATURE

The Newest Technology Coming (Soon?) to a Lab Near You: MALDI-TOF MS and PCR ESI-MS

By Ellen Jo Baron, PhD, D(ABMM)
Professor of Pathology and Medicine, Stanford University;
Medical School Director, Clinical Microbiology Laboratory, Stanford University School of Medicine
Dr. Baron reports no financial relationship to this field of study.

It took polymerase chain reaction at least 30 years (by my reckoning) to evolve from its inception as a promising method for laboratory detection of infectious agents in patient samples to its widespread utilization in diagnostic clinical microbiology laboratories. The speed of adoption of some new technologies, in contrast, appears to be three times faster. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) is one of these.[1]

As a tool for use in clinical microbiology, the method was first exploited to create a database for identifying anaerobic bacteria back in 2002.[2] Today, there are at least three commercial instruments with two different formats available. The Shimadzu FLEXIMASS and Bruker MALDI Biotyper employ MALDI-TOF technology and the Abbott PLEX-ID uses an initial amplification of nucleic acids by PCR, followed by electrospray ionization mass spectrometry (PCR ESI-MS). The Bruker method is fast becoming the standard in European laboratories for organism identification from colonies grown on culture. A few laboratories in the United States have begun to use one of these systems for culture identification as well and, within the next few years, I believe that many of the larger laboratories in the United States will probably be moving from biochemical systems (which require 8 hours to overnight incubation for organism identification by growth characteristics in various biochemical solutions) to the more rapid method of MALDI-TOF MS.

The original investment, on the order of more than half a million dollars, is radically more expensive than buying, say, a Vitek2 (bioMerieux) or Phoenix (BD) or MicroScan (Siemens) instrument, but individual identifications from isolated colonies cost only pennies in reagents for MALDI-TOF, compared to around $3-$4 per organism on a Vitek2 or MicroScan. The PCR ESI-MS final results are quite a bit more expensive (requiring first PCR and more labor and reagents), but results are more complete, too. Of course, susceptibilities will still need to be performed for most organisms for which resistance-determining genetic sequences are not all known, probably on the lab's old Vitek2, Phoenix, or MicroScan. The huge cost and relatively large size of the mass spec instruments will initially limit early adoption, but in time the cost will drop and the instruments will become smaller.

The publication named above, by Schmidt and colleagues, focuses on another exciting use of these technologies: direct identification of bacteria from positive blood culture broths, bypassing at least a day of incubation in obtaining final organism names. This is not the first publication on the topic. In the United States, one laboratory currently uses this technology for routine identification of the organisms in positive blood cultures daily.[3] In the near future, a variant of the technology also may be employed to detect some resistance mechanisms.[4]

MALDI-TOF processing begins with a cell paste or concentrate of bacterial cells in suspension (such as a centrifuged sediment from a positive blood culture broth). The suspension undergoes a simple extraction in one or several steps involving heating and quick centrifugations, and the resulting cell

mass is treated with an organic solvent (the matrix) and deposited (or dropped) onto a grid on a plate (which can accommodate a number of extracts at one time), and allowed to dry down. For positive blood culture broths, this may take only 20 minutes of hands-on time. For colonies, a toothpick can be used to spread colony paste on the metal grid plate, and preparation time is less than 5 minutes. The plate is placed into the instrument, the chamber is placed under vacuum pressure, and a laser beam bombards the spots, causing protein molecules from bacterial cell walls and other structures to vaporize and ionize in that state to be dispersed and moved in the vacuum toward a detector. The ions move through the system based on mass and charge, and the ratio of mass to charge determines their speed (or time of flight) to reach the detector, a type of mass spectrometer. The results are displayed as peaks on a mass/charge scale. And the ions move through the system to the detector in nanoseconds! Once the grid has been placed on the instrument the whole process takes no more than 20 minutes, primarily for computer algorithms to run through their paces. And almost every organism species has a unique pattern. Building databases from known organisms is one challenge for the technology, but the current instrument manufacturers have been working on their databases for several years now and the accuracy for organism identification (from colonies) usually is excellent.[1,5]

The ESI-MS system first requires amplification of bacterial, viral, or fungal DNA using broad primers and then extraction of the DNA. The resulting suspensions (up to 96 per plate) are placed into the instrument, electrospray ionization (ESI) occurs to move ionized nucleic acid particles into the detector module, which also uses mass to charge ratio to develop patterns of recognition. Although in contrast to MALDI-TOF's current capabilities, the ESI-MS can identify mixtures of organisms including viruses and resistance determinants as well.[1,4] The key difference from a previously used method that relied on patterns developed by molecules traveling through a matrix via high pressure liquid chromatography (which, although I used it as recently as 1997, now seems positively ancient), known as cell wall fatty acid methyl ester analysis, is that the atmosphere and medium on which the organisms are grown does not influence the results.[6] Thus, any colony or any suspension of microbes, including direct specimens from infected sites, can be analyzed by MALDI-TOF if enough organism mass is present in the sample. This is not a limitation of ESI-MS, as the microbial DNA or RNA is first amplified before detection, which does slow down the process and delay final results for up to 6-8 hours.

The MALDI-TOF technology currently requires a minimum cell volume (about 10^6 organisms in a drop of liquid) to yield an answer, and there are still some technical problems to overcome, but these are bumps on the road. Schmidt and colleagues used blood cultures from two currently popular instruments and broth formulations to compare sample processing methods for testing with the Shimadzu instrument. Unfortunately, media from one of two of the blood culture systems seemed to interfere with performance, and at this time cannot be recommended. Both of the articles by Schmidt and colleagues and Stevenson et al found that the systems had difficulties differentiating viridans streptococci from *Streptococcus pneumoniae*.[3,5] Obviously this must be improved upon. Gram-negative rods seem to be better identified than Gram-positive organisms. The rate of correct identifications from positive blood culture broths from the manufacturer with the broth that worked better was around 72% overall, but this broke down to 87% for Gram-negative bacteria and only 60% for Gram-positive organisms. The Stevenson publication evaluated true positive blood cultures sequentially using the Bruker instrument. They found that 20% of the positive blood cultures had too few organisms to yield any result; however, among the remaining 170 cultures, 95% were correctly identified and those that failed were *S. mitis* incorrectly identified as *S. pneumoniae*.[3] In contrast, direct colony identifications were 97%-99% correct in at least two recent studies.[1,7]

In summary, utilization of one of these mass spectrometry methods for identification of all organisms detected in positive blood culture broths is still not ready for routine performance in every laboratory. However, for those laboratories able to pry loose the capital budget funds from their administrators, the use of MALDI-TOF for direct identification from isolated colonies is a real option. Results are available faster and more accurately than biochemical results are now, and I predict that the use of this technology will expand dramatically in the next few years. ■

References

1. Cherkaoui A, et al. Comparison of two matrix-assisted laser desorption ionization-time of flight mass spectrometry methods with conventional phenotypic identification for routine identification of bacteria to the species level. J Clin Microbiol 2010;48:1169-1175.
2. ShahHN,etal.Matrix-assistedlaserdesorption/ionisationtime of flight mass spectrometry and proteomics; a new era in anaerobic microbiology. Clin Infectious Diseases 2002;35: 58-64.

3. Stevenson LG, et. Rapid identification of bacteria in positive blood culture broths by matrix-assisted laser desorption ionization-time of flight mass spectrometry. J Clin Microbiol 2010;48:444-447.
4. Wolk DM, et al. Pathogen profiling: Rapid molecular characterization of Staphylococcus aureus by PCR/electrospray ionization-mass spectrometry and correlation with phenotype. J Clin Microbiol 2009;47:3129-3137.
5. Schmidt V, et al. Rapid identification of bacteria in positive blood culture by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Eur J Clin Microbiol Infect Dis 2011 June 23; Epub ahead of print.
6. Sasser M, et al. Identification of Bacillus anthracis from culture using gas chromatographic analysis of fatty acid methyl esters. J AOAC International 2005;88:178-181.
7. Kaleta EJ, et al. Comparative analysis of PCR-electrospray ionization/mass spectrometry (MS) and MALDI-TOF/MS for the Identification of bacteria and yeast from positive blood culture bottles. Clinical Chemistry 2011;57:1057-1067.

ABSTRACT & COMMENTARY

Interferon-γ Release Assays: Utility and Limitations

By Lin H. Chen, MD
Assistant Clinical Professor, Harvard Medical School;
Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, MA

Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex. This article originally appeared in the August 2011 issue of *Travel Medicine Advisor*. At that time it was peer reviewed by Philip R. Fischer, MD, DTM&H, Professor of Pediatrics, Department of Pediatric & Adolescent Medicine, Mayo Clinic, Rochester, MN. Dr. Fischer reports no financial relationship to this field of study.

SYNOPSIS: Interferon-γ release assays are recommended in the screening for latent tuberculosis infection, but issues with discordance and reproducibility, lack of prognostic value, and low efficacy in children require further refinement to achieve proper interpretation.

SOURCES: Herrera V, et al. Clinical application and limitations of interferon-gamma release assays for the diagnosis of latent tuberculosis infection. Clin Infect Dis 2011;52:1031-1037.

Herrera and colleagues reviewed the use of interferon-γ release assays (IGRAs) for the diagnosis of latent tuberculosis infection (LTBI). Interferon-γ is released by CD4 cells when infected with *Mycobacterium tuberculosis* (MTB), and IGRAs measure interferon-γ response in blood. The FDA approved the first IGRA, QuantiFERON-TB test (QFT), in 2001, followed by QuantiFERON-TB Gold test (QFT-G) in 2005. More recently, the FDA approved QuantiFERON-TB Gold-In-Tube test (QFT-GIT) in 2007 and T-Spot in 2008.

QFT-G uses an enzyme-linked immunosorbent assay [ELISA] to measure the interferon-γ released when whole blood is incubated with MTB antigens. The GIT simplified the procedure by collecting blood directly into pre-coated tubes for incubation. T-Spot uses an enzyme-linked immunospot assay to count the cells that produce interferon-γ on pre-coated plates. The two newer tests, QFT-GIT and T-Spot, use specific MTB antigens (early-secreted antigen 6 [ESAT6] and culture filtrate protein 10 [CFP10]) that are not present in other strains of mycobacteria or the BCG vaccine strain; therefore, these tests have increased specificity compared to the tuberculin skin test (TST).

In the United States, TB screening primarily targets persons that may have been infected recently and persons with health conditions that increase their susceptibility for reactivation of LTBI. The ideal timing of screening test is considered to be 8-10 weeks after the possible exposure, prior to which the test may be falsely negative.

Herrera et al note that the QFT-GIT, T-Spot, and TST vary in performance depending on the test population, study type, study definitions/parameters, and that there are very few direct comparisons. Nevertheless, the pooled sensitivity was 83%, 90%, and 89%, respectively, and pooled specificity was 99%, 88%, and 85%, respectively. The IGRAs are superior to TST in its specificity in BCG-vaccinated populations.
The limitations highlighted in this paper include:

- IGRAs are not sufficiently sensitive to detect a very recent TB exposure.
- IGRAs have shown discordance with TST.
- A negative IGRA result does not rule out the

diagnosis of LTBI.
- The quantitative results from IGRAs have not yet demonstrated prognostic value regarding progression to active TB.
- IGRAs cannot differentiate between active TB, LTBI, treated infection, or recent vs. remote infection.
- Reproducibility of IGRAs has been variable and serial tests have found conversions and reversions in the range of 12%-50%.
- Efficacy in children is low and a negative IGRA test does not exclude infection.

The authors recommend some practical approaches to interpreting IGRA and TST results. First of all, conversion from a negative to a positive result could mean a false-positive test in a low-risk person, and possibly could be associated with concurrent illness, laboratory determinants, and nonspecific boosting of interferon-γ. Reversion from a positive to a negative result may be influenced by similar factors. Treatment can lead to reversion, or more likely to a decline in the quantitative result. Because delays in incubation and sample processing can lower interferon-γ responses, quantitative results aid in predicting reversion or conversion when the interferon-γ result is near the test cutoff point.

Regarding discordant IGRA and TST results in a low-risk person, a negative IGRA is more reliable than a positive TST in BCG-vaccinated individuals. On the other hand, a negative TST and a positive IGRA in a high-risk individual should not preclude further evaluation for TB.

■ COMMENTARY

A total of 11,181 TB cases were reported in the United States in 2010, corresponding to a rate of 3.6 cases per 100,000 population.[1] TB cases in foreign-born individuals comprised 60.5% of all cases in those with known country of origin, at a case rate of 18.1 cases per 100,000 population, and has remained in the range of 7,000-8,000 cases per year since 1993.[1] Foreign-born persons younger than 18 years of age also have a disproportionately high TB case rate, at 11.4 per 100,000 population or almost 20 times higher than that of their U.S.-born counterparts.[2] The burden of disease among foreign-born individuals suggests that screening these populations for LTBI should be a highly effective strategy for TB control and prevention in the United States.[3]

Similar to foreign-born persons, previous studies have also established that travel destinations determine the TB exposure risk and long-term travelers have risks that resemble the local incidence.[4,5] Additionally, health care work overseas was associated with increased risk, and travelers who are visiting friends and relatives (VFR) also have an increased risk.[4,6] For example, travelers who participate in health care work overseas had a TST conversion rate of 7.9 per 1,000 person-months of travel, whereas non-health care workers had a rate of 2.8 per 1,000 person-months.[4] Travelers whose trips include such activities should be prioritized for screening.

Since the FDA approval of IGRAs, the CDC has published guidelines for using these tests to detect MTB infection.[1] All indications focus on their use for TB screening, as an alternative or a complement to TST. Their major advantages over the long-standing TST are: 1) the convenience of a single visit; 2) the omission of trained staff to read and interpret the reaction; and 3) the higher specificity in BCG-vaccinated persons. However, a blood sample is required to perform IGRAs, and Herrera et al have pointed out some significant limitations.

In the U.S. population, IGRAs are more specific, but less sensitive, than TST for predicting future disease. Horsburgh recently summarized the sensitivity of IGRAs for predicting progression to active TB within several years after exposure to be 80%-90% with specificity of 56%-83%, or a positive predictive value of 4%-8%, and negative predictive value of 99%-100%.[3] At the same time, a positive TST of 5 mm has a sensitivity of 90%-100% to predict progression to active TB and a specificity of 29%-39%, or a positive predictive value of 2.7%-3.1%, and a negative predictive value of 99%-100%.[3]

An additional issue noted by Herrera and other authors is the establishment of cutoff points. Whereas TST conversion is defined as an increased induration of 10 mm or more, cutoffs for IGRA conversions are not fully defined.[3] Interestingly, screening guidelines using IGRAs vary among countries.[3,7] However, most experts agree that IGRAs are valuable when screening BCG-vaccinated individuals, and also better when there is high prevalence of recent TB infection, including recently arrived foreign-born individuals and likely international travelers.[1,3]

IGRAs can be especially useful in screening BCG-vaccinated travelers, VFR travelers, long-term travelers, and health care travelers. Travel medicine practitioners should be aware of the limitations articulated by Herrera et al. Finally, we need more data to assess the efficacy of IGRAs in screening the specific population of travelers and to establish proper IGRA

continued on page 144

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

There's a Fly in My Soupy Tissue

Source: Mowlavi GH, et al. Fatal nosocomial myiasis caused by Luciliasericata (letter). J Hosp Infect 2011;78:338-339.

Unless you were bent on becoming a forensic entomologist as a kid, there is nothing worse than pulling back a bed sheet and finding ... maggots. Every so many years, I find an ICU patient, typically sedated and intubated, with fly larvae crawling out of some orifice or wound.

This brief report describes a 54-year-old woman with acute respiratory distress syndrome requiring prolonged intubation, status 22 days post-CABG. She was found to have maggots crawling out of her nose, around her endotracheal tube, and filling her sinuses. The larvae were reared, and identified as those of the green bottle fly, *Lucilia sericata*, which is a common type of blow fly that generally lays its eggs in devitalized tissue or open, foul-smelling wounds. In fact, the fly so reliably lays its eggs in cadaver tissue within hours of death, forensic investigators use the age of the maggots to determine time of death. The patient had inflamed nostrils, coated with petroleum jelly. In total, 75 larvae were removed from her nostrils, but continued to fill her maxillary, ethmoid, and sphenoid sinuses, and possibly her airways.

Unfortunately, the patient became increasingly unstable, precluding more aggressive efforts to remove the larvae. The authors believed the infestation contributed to her death.

Although an infrequent occurrence, flies are an important infection control issue for hospitals — and one of the reasons that windows and doors are kept shut at all times. Visitors can unknowingly carry insects on their clothing, packages, or flowers. Unconscious patients, especially those intubated and sedated in the ICU, cannot fend off flies. Many physicians do not realize that even one fly in the ICU requires attention. ■

Over-treatment of Urinary Tract Infections

Source: Rotjanapan P, et al. Potentially inappropriate treatment of urinary tract infections in two Rhode Island nursing homes. Arch Intern Med 2011;171:438-443.

I found this paper devastatingly in line with my everyday experience as an ID consultant. How many times have we been asked to consult on a frail older nursing home lady with "recurrent UTIs," who has received repeated courses of antibiotics. She is often asymptomatic or the urinalysis does not support a diagnosis of urinary tract infection by current criteria. She can barely stand, let alone provide a "clean catch." By the time I see her, she has developed a severe vaginal yeast infection from all the antibiotics, which is then causing "symptoms," but no one ever looks "down there."

These authors examined the use of antibacterials used for "urinary tract infection" in two nursing homes during a 6-month period in 2008. Once patients with Foley catheters, stones, and pyelonephritis were excluded, 132 patients with a total of 172 "episodes" of urine specimens being obtained were included in the analysis. The mean age of these case-patients was 83 years (range, 65-99 years); 78% were female. Nearly half (48%) of the specimens were obtained in persons with moderate-to-severe cognitive impairment; 7% were totally dependent.

Of the 172 cases, 26 (15%) met current criteria for a UTI, 100% of whom received antibacterials. A total of 146 (85%) cases did not meet current criteria for infection, many of which were asymptomatic bacteruria without pyuria.[1] Despite this, antibiotics were administered to 70 (41%) of these cases. Women were 2.4 times more likely to receive antibacterials than men. Empiric antibacterials were administered in 27 cases before the results of urine studies were available; two-thirds of this was fluoroquinolones.

Of the 96 cases that were treated with antibiotics, only 26% met criteria for appropriate antibacterial use. The mean duration of antibiotics was 7.8 days (range, 3-14 days). Based on current Infectious Disease Society of America guidelines, two-thirds of the cases received antibiotics for longer than justified. Nearly half (46%) of the antibiotic selected was either considered inappropriate or an incorrect dose based on patient age, weight, and renal function (12 patients with normal renal function received inadequate dosing, and 14 patients received trimethoprim-sulfamethoxazole

or nitrofurantoin, despite CrCl < 30 mL/min).

Sadly, 11 of the 96 case-patients who received antibacterials developed *Clostridium difficile* infection within 3 weeks of antibacterial use. Ironically, all 11 had received unnecessary antibiotics. None of the 76 patients who did not receive antibiotics experienced problems or consequences from a lack of treatment.

Careful interpretation of urine test results based on current criteria should guide the decision whether to treat. Empiric treatment for 3 days pending test results may be reasonable, keeping in mind that most patients with asymptomatic bacteruria do just fine without antibiotics. ■

Reference

1. McGeer A, et al. Definitions of infection for surveillance in long-term care facilities. Am J Infect Control 1991;19:1-7.

HIV Integrase Inhibitor Resistance: What Do We Know?

Source: Blanco JL, et al. HIV-1 integrase inhibitor resistance and its clinical implications. J Infect Dis 2011;203:1204-1214.

Since its introduction in 2007, raltegravir has proven useful in combination multi-drug regimens for salvage therapy in patients with multi-drug resistant virus, as well as simplification of treatment regimens in patients beginning treatment. Two new integrase inhibitors (INI), elvitegravir (EVG) and S/GSK1349572, may have similar value.

De novo resistance to raltegravir is rare (< 0.1% of HIV+ patients). This class of drugs is, however, limited by its "vulnerability" — meaning drug-resistant virus can develop fairly readily in some patients, generally within the first few months of drug use. Only one or two genetic mutations appear necessary to significantly reduce the agent's virologic efficacy, and there is likely significant (but not complete) cross-resistance to other members of its class. Similar to the non-nucleoside reverse transcriptase inhibitors, diminished INI susceptibility is caused by a primary mutation, coupled with one or more secondary mutations, which either further reduce susceptibility or affect viral fitness. Fortunately, most patients with low-level virological rebound while receiving raltegravir do not have evidence of INI resistance.

This article summarizes the viral mutations observed either in vitro or in patients receiving INIs. Although good clinical data are not yet available to provide phenotypic cut-offs or clinical validation of these suspected mutations, a number of mutations have been identified as likely significant for reduced susceptibility to INIs.

The two most common combinations of mutations observed in vitro or in patients receiving INIs include Q148HRK + G140SAC, and N1554 ± E92Q, which appear also to cause EVG cross-resistance. A third common resistance pathway appears to be Y143CR ± T97A, which does not appear to cause EVG cross-resistance. The S/GSK1349572 compound demonstrates 10- to 20-fold diminished efficacy to isolates with the former combination of mutations, but appears fully active against isolates with either of the latter combination mutations.

Although good clinical data correlating these findings are not yet available, patients with these three major mutations (Y143CR, Q148HRK, N155H) are not likely to respond to raltegravir. It is possible, however, that future INI products, including those in development, may remain active against some raltegravir-resistant isolates. ■

Childhood Polio in India

Source: Doshi SJ, et al. Poliomyelitis-related case-fatality ratio in India, 2002-2006. Clin Infect Dis 2011;53:13-19.

These authors assessed the case-fatality rate (CFR) of acute poliovirus infection in India from 2002 to 2006. Following an outbreak in 2002, the Acute Flacid Paralysis (AFP) Surveillance System amended its protocols for case definition, and an AFP Medical Officer was assigned to the Moradabad district in Utter Pradesh, which had been hardest hit by the infection. This allowed for enhanced surveillance and tracking of cases in this area of concern; all cases were reported within a week, and the mean time from notification to investigation decreased to < 1 day, and the time from onset of paralysis to investigation was 3.5 days.

During the 2002 outbreak, 1,600 WPV cases occurred, for which 1,584 had follow-up data. The overall CFR was 4.1%. During the 2006 outbreak, 676 cases of WPV infection occurred, for which 673 had follow-up data. The CFR was 6.7% (7.3% for WPV1 infection and 0% for WPV3 infection). Children < 5 years of age accounted for 98% of the deaths in 2002 and 100% of the deaths in 2006. Of these, 73% were in children < age 2 — yielding a significantly higher death rate (16%) in this age group than previously recognized. More than 70% of the fatal cases in children reportedly had received 3 or more doses of polio vaccine, which points to some serious flaws in the administration of the poliovirus vaccine to children, with obvious misrepresentation by parents and/or schools in the area. ■

continued from page 141

cutoff values and interpretation for this population. ■

References

1. Centers for Disease Control and Prevention. Trends in tuberculosis — United States, 2010. MMWR Morb Mortal Wkly Rep 2011;60:333-337.
2. Menzies HJ, et al. Epidemiology of tuberculosis among US- and foreign-born children and adolescents in the United States, 1994-2007. Am J Public Health 2010;100:1724-1729.
3. Horsburgh CR, Rubin EJ. Latent tuberculosis infection in the United States. N Engl J Med 2011;364:1441-1448.
4. Cobelens F, et al. Risk of infection with Mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity. Lancet 2000;356:461-465.
5. Jung P, Banks RH. Tuberculosis risk in US Peace Corps Volunteers, 1996 to 2005. J Travel Med 2008;15:87-94.
6. Leder K, et al. Illness in travelers visiting friends and relatives: A review of the GeoSentinel Surveillance Network. Clin Infect Dis 2006;43:1185-1193.
7. Apers L, et al. The use of interferon-gamma release assays for tuberculosis screening in international travelers. Curr Infect Dis Rep 2011;13:229-235; doi: 10.1007/s11908-011-0173-0.

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 estimated to have the lowest drug aquisition cost for a 10-day course of treatment of *Clostridium difficile* colitis?

a. Vancomycin
b. Nitazoxanide
c. Fidaxomicin
d. Metronidazole

2. Which virus is associated with bladder cancer?

a. EBV
b. HSV
c. HPV
d. HCV

3. Which of the following is *correct* regarding interferon-gamma release assays (IGRAs) for the detection of latent tuberculosis?

a. They are superior in sensitivity to the tuberculin skin test in patients who have received BCG vaccination.
b. They are capable of distinguishing latent from active tuberculosis.
c. A negative IGRA rules out the diagnosis of latent tuberculosis.
d. It can distinguish recent from remote infection.

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]

Azithromycin restores chloride efflux in cells of CF patients

Frequency of cytomegalovirus in stillbirths

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.*

ACEIs and ARBs Help Patients with Aortic Stenosis

In this issue: ACEI/ARB therapy for AS; safety alert issued for dronedarone; statins and cancer risk; nesiritide and heart failure; and FDA actions.

ACEI/ARB therapy for aortic stenosis

Drugs that block the renin-angiotensin system are not only safe, they are beneficial in patients with aortic stenosis (AS) according to a new study. This runs counter to current recommendations that suggest that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are relatively contraindicated in patients with AS. The study looked at more than 2000 patients with AS in Scotland, of which the majority had mild-to-moderate stenosis, while about one-quarter had severe AS. Of the total number, nearly 700 were on ACEI or ARB therapy. Over a mean follow-up of 4.2 years, just over half the patients died, of which 48% died from cardiovascular (CV) deaths. Those treated with ACEIs or ARBs had a significantly lower mortality rate (adjusted hazard ratio [HR] 0.76; confidence interval [CI] 0.67-0.92; $P < 0.0001$) and fewer CV events (adjusted HR 0.77; 95% CI: 0.65-0.92; $P < 0.0001$) compared to those not on ACEIs/ARBs. The authors conclude that ACEI/ARB therapy is associated with improved survival and lower risk of CV events in patients with AS. These findings were consistent in patients with nonsevere and severe AS. The rate of valve replacement also was lower in patients treated with ACEIs/ARBs (*J Am Coll Cardiol* 2011;58:570-576). This study was a retrospective observational study and prospective, randomized, controlled trials are warranted to confirm these findings. ■

Drug safety alert issued for dronedarone

The antiarrhythmic dronedarone (Multaq) is again coming under scrutiny from the FDA after review of the company-sponsored PALLAS study of more than 3000 patients, which showed that the drug is associated with an increased mortality rate in patients with atrial fibrillation (AF). Dronedarone currently is approved for treatment of paroxysmal AF and atrial flutter. The new study investigated its use in patients with permanent AF. The study was halted early when the mortality rate in the treatment group was found to be double the rate in the placebo group (32 deaths [2%] in the dronedarone arm vs 14 [0.9%] in the placebo arm). The rate of unplanned hospitalization and stroke also was double in the dronedarone group vs the placebo group. All findings were statistically significant. These findings led the FDA to issue a drug safety alert on July 21, 2011. This follows a January 2011 drug safety alert regarding rare but severe liver injury associated with use of dronedarone. Currently, the FDA is recommending that physicians should not prescribe dronedarone to patients with permanent AF while they further evaluate the data (FDA Drug Safety Communication at www.FDA.gov/drugs/drug safety). ■

Statins do not increase risk of cancer

A new retrospective cohort analysis suggests that statins are not associated with an increased risk of cancer. Researchers used the General

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.

Electric Centricity electronic medical record database of more than 11 million adult Americans to match nearly 46,000 patient pairs by propensity scores receiving and not receiving statin therapy. With an average time in the database of 8 years, the incidence of cancer in patients taking a statin was 11.37% compared with 11.11% in matched patients not taking a statin (HR 1.04; 95% CI: 0.99-1.09). The authors conclude that this analysis demonstrates no statistically significant increase in cancer risk associated with statins, although they do suggest that more research is needed (*J Am Coll Cardiol* 2011;58:530-537). Lingering fears about cancer risk associated with statins was strengthened by the SEAS trial published in 2008, which showed the combination drug simvastatin/ezetimibe (Vytorin) was associated with a two-fold increase in the rate of cancer in a small group of patients. The FDA has continued to study these data along with data from other studies, but this new analysis adds significant evidence of a lack of association between statins and cancer. ■

Nesiritide and heart failure

Nesiritide can no longer be recommended for use in congestive heart failure based on the findings of a new study. The drug is a recombinant B-type naturetic peptide (BNP) that was approved in 2001 for use in patients with acute heart failure. The approval was based on small studies showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea 3 hours after administration. However, subsequent data raised questions about the drug's safety, especially with regard to worsening renal function and even increased mortality. Based on the recommendations of an independent panel, the manufacturer performed a placebo-controlled randomized trial of more than 7000 patients hospitalized with acute heart failure to assess the drug's safety and efficacy. Patients with heart failure were randomized to receive nesiritide or placebo for 24-168 hours in addition to standard care. The drug was modestly effective at reducing symptoms of dyspnea at 6 and 24 hours. More significantly, however, the rate of rehospitalization for heart failure or death from any cause within 30 days was no different. Nesiritide was not associated with a worsening of renal function but was associated with worsening hypotension. The authors conclude that on the basis of these results, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure" (*N Engl J Med* 2011;365:32-43). ■

FDA actions

The highly anticipated oral factor Xa inhibitor rivaroxaban has been approved by the FDA to reduce the risk of deep venous thrombosis, blood clots, and pulmonary embolism in patients undergoing knee or hip replacement. The once-a-day medication should be taken for 12 days by patients undergoing knee replacement and 35 days for patients undergoing hip replacement. The approval was based on three studies (RECORD 1, 2, and 3) which showed that rivaroxaban is superior to subcutaneous enoxaparin in this role. Bleeding, the primary side effect of the drug, was no more common with rivaroxaban than enoxaparin. Rivaroxaban also has been looked at in phase III trials for stroke prevention in patients with nonvalvular atrial fibrillation, and treatment and secondary prevention of venous thromboembolism, although the FDA has yet to act on approval for these indications. Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals as Xarelto.

The FDA has approved ticagrelor, a new antiplatelet drug for patients with acute coronary syndrome, including unstable angina and myocardial infarction (MI). The approval was based on studies that coupled ticagrelor with low-dose aspirin. The approval recommends use with aspirin although it carries a warning that aspirin doses above 100 mg per day may decrease the effectiveness of the drug. Ticagrelor requires twice a day dosing in contrast to the other drugs in this class, clopidogrel and prasugrel, which can be dosed once daily. The approval was based on the PLATO trial, a head-to-head study with clopidogrel which showed that in combination with aspirin, ticagrelor resulted in the lower composite endpoint of cardiovascular death, stroke, or MI (9.8% vs 11.7% with clopidogrel, $P < 0.001$).

The FDA has approved six manufacturers for the 2011-2012 flu vaccine. The strains included this year are A/California7/09 (H1N10), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 — the exact same components as last year's vaccine. One of the manufacturers, Sanofi Pasteur, has received permission to market Fluzone Intradermal, the first flu vaccine administered via a novel intradermal microinjection that is touted as being more comfortable than intramuscular injections. The new intradermal system in approved for adults ages 18-64 years. ■