INTERNAL MEDICINE ALERT

A twice-monthly update of developments in internal and family medicine

Providing Evidence-based Clinical Information for 30 Years

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, serves on the advisory board for Amylin, Boehringer Ingelheim, Novo Nordisk, and Symbiotix; he serves on the speakers bureau of Boehringer Ingelheim, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

The Short and Long of Measuring Blood Pressures in Your Office

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

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

Synopsis: *Compared with manual, automated blood pressure measurements significantly reduced the white coat response in otherwise healthy primary care patients with systolic hypertension while demonstrating a stronger correlation with awake ambulatory blood pressure readings.*

Source: Myers MG, et al. Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: Randomised parallel design controlled trial. *BMJ* 2011;342:d286.

HYPERTENSION IS THE MOST COMMON PRIMARY DIAGNOSIS IN THE UNITED States. While about 30 percent of Americans are still unaware of being hypertensive, even in those diagnosed, the control rates (SBP < 140 mmHg and DBP < 90 mmHg) remain dismal at a mere 34 percent.[1] Diagnosis of hypertension is critically dependent on accurate blood pressure (BP) measurement. Once diagnosed, in the majority of patients, controlling systolic hypertension has been considerably more difficult than controlling diastolic hypertension. Because adequate control of systolic BP is linked to a lower incidence of cardiovascular diseases such as myocardial infarction, heart failure, and stroke as well as renal diseases, it is vital to obtain accurate measurements during these individuals' outpatient office visits.[2] Blood pressure readings taken in the physicians' office are often higher than home or ambulatory values. The level of BP measurement by using the 24-hour ambulatory blood pressure monitoring (ABPM) method correlates better than office measurements with target organ injury.[3] Current guidelines recommend using ABPM for evaluation of white-coat hypertension as well as

VOLUME 33 • NUMBER 6 • MARCH 29, 2011 • PAGES 41-48

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

in certain other situations (to assess patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction).[1] These guidelines also recommend using the auscultatory method of BP measurement for patients in the office as well as using home measurement devices for self measurement for patients. Interestingly, while fully automated sphygmomanometers are widely used in inpatient and outpatient settings across the United States and data suggests that such a use reduces or eliminates many of the factors contributing to imprecise BP readings in routine clinical practice, current guidelines do not recognize this use.[4] Therefore, it is important to examine whether these automated office BP devices can improve on the quality and accuracy of the readings when compared with manual office devices as well as reduce the white coat response. The implications of such an evaluation may not only lead us to avoid unnecessary treatment in many individuals, but also may improve our understanding of the number of individuals whose BP may actually be under control when being treated.

In the study by Myers et al, a total of 555 study patients with systolic hypertension from 67 primary care practices in five cities across eastern Canada were enrolled. In this randomized controlled trial, practices were randomly allocated to either ongoing use of manual office blood pressure measurement (control group) or automated office blood pressure measurement (intervention group) using the BpTRU device. Using the 24-hour ABPM (with calculations for awake period) as the gold standard, office BP readings were compared before and after enrollment in the intervention and control groups. The basic difference in the two groups was that for the intervention group, a rest period was not needed before the first reading since the automated sphygmomanometer records BP by the oscillometric method and is designed to take an initial reading to verify that the cuff is properly positioned and five more readings are taken automatically at pre-specified intervals without the need for office staff being present. Main outcomes were measured by calculating the difference in systolic blood pressure between awake ambulatory blood pressure minus automated office blood pressure and awake ambulatory blood pressure minus manual office blood pressure.

The authors discovered that without changing their antihypertensive drug regimens, both the manual and automated groups showed a decrease in mean office BP between the most recently recorded pre-study routine office visit and the first visit to the physician after enrollment in the study. However, the decrease in BP for the intervention group was much greater. Results further demonstrated that the introduction of automated office BP measurements into routine primary care practice significantly reduced the white-coat response compared with the ongoing use of manual BP measurement. Additionally, the quality and accuracy of automated office readings were also considerably better when compared with manual office readings.

■ COMMENTARY

As a medical student, I was always taught that taking the time to manually recheck BP in a hypertensive patient was an incumbent part of good medical practice. Similarly, I have always emphasized this part of the physical examination to my students throughout the years. I will admit that it is difficult to give up this core tradition of practicing good primary care. However, once again, our personal biases and preferences must give way to evidence. Currently, this study adds to the mounting evidence suggesting that automated methods of BP measurement in primary care practices may not only be the way to obtain the most accurate measurements, but also be the way to avoid misdiagnosis and the resultant treatment which can often occur based solely on white-coat response. However, one must caution that the current study applies to compliant, otherwise healthy, primary care patients with systolic hypertension. Also, much of the benefit in ruling out white-coat hypertension in the current study's intervention group may be attributed to office staff leaving the patient room after the first reading was obtained since data have shown that such automated readings are similar to manual readings if the staff remains present in the room when the reading is taken.[5] To me, there are two and a half issues to be considered here. One is accuracy for which the automated device seems to be superior.

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin.
SENIOR MANAGING EDITOR: Neill L. Kimball.

GST Registration Number: R128870672.

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

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

Back Issues: $21.

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

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: neill.kimball@ahcmedia.com
World-Wide Web: www.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.

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 designates this educational activity for a maximum of *45 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Internal Medicine Alert has been reviewed and is acceptable for up to 24 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/07. Term of approval is for one year from this date. Each issue is approved for 1 Prescribed credit. Credit may be claimed for 1 year from the date of each issue. The AAFP invites comments on any activity that has been approved for AAFP CME credit. Please forward your comments on the quality of this activity to cmecomment@aafp.org.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

AHC Media

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

Second is the issue of providing the patient adequate rest and privacy in order to rule out a falsely elevated reading due to white-coat hypertension. Clearly, an automated device would more likely be able to achieve this goal. Lastly is the half issue of environmental concerns related to mercury content in manual blood pressure devices. I consider this half an issue since the risks of mercury spills from such devices in a medical setting has not yet been researched adequately. With the Joint National Committee on track to release its eighth report on prevention, detection, evaluation, and treatment of high blood pressure in spring 2012, it is critical that this body evaluates the developing data on automated BP measuring devices and provides relevant and timely guidance to physicians across the United States on this particular issue. ■

References

1. Chobanian AV, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA* 2003;289:2560-2572.
2. Neal B, et al. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomized trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;356:1955-64.
3. Prisant LM, et al. Clinical utility of ambulatory blood pressure monitoring in target organ complications and equipment choices. *J Clin Pharmacol* 1992;32:620-626.
4. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. *J Hypertens* 2009;27:280-286.
5. Vidt DG, et al. Taking blood pressure: Too important to trust to humans? *Cleve Clin J Med* 2010;77:683-688.

Diagnosing DVT in a Primary Care Setting

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

Chair, Department of Integrative Medicine, Ross University School of Medicine, Commonwealth of Dominica

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

Synopsis: *The Wells rule for identifying patients at high risk for DVT did not perform as well as one developed from an outpatient population.*

Source: van der Velde EF, et al. Comparing the diagnostic performance of 2 clinical decision rules to rule out deep vein thrombosis in primary care patients. *Ann Fam Med* 2011;9:31-36.

THE WELLS RULE[1] (WR) WAS DEVELOPED IN 1995 FROM a tertiary care referral patient population to rule out deep vein thrombosis (DVT) in patients at very low risk. This group of investigators from the Department of General Practice at the University of Amsterdam previously published their research that WR does not work well in an outpatient population[2] and subsequently proposed their own rule (the primary care rule — PCR) based on an outpatient population.[3] One of their concerns is that WR requires the physician to estimate the probability that there is an alternative diagnosis for the problem that is at least as likely as DVT. They reasoned that since the prevalence of DVT is low in primary care (incidence ~1%[4]), the physician might not have a different diagnosis. A comparison of the two rules is contained in Table 1. The cutoff scores for high risk are 2 for WR and 4 for PCR.

In this study, they compared the performance of WR and PCR using their original research population. The subjects were patients with suspected DVT who presented to more than 300 Dutch general practitioners. Inclusion criteria were: age > 18 years and at least one of the following symptoms: swelling, redness, or lower

Table 1. Comparison of WR and PCR

Variables	WR	PCR
Male sex	NA	1
Oral contraceptive use	NA	1
Active cancer (treatment ongoing or within previous 6 months or palliative)	1	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1	NA
Major surgery (last 3 months)	1	1
Absence of leg trauma	NA	1
Localized tenderness along the distribution of the deep venous system	1	NA
Dilated collateral veins (not varicose)	1	1
Entire leg swelling	1	NA
Calf swelling ≥ 3 cm larger than the asymptomatic leg	1	2
Pitting edema confined to the symptomatic leg	1	NA
Previously documented DVT	1	NA
Alternative diagnosis at least as likely as DVT	-2	NA
Positive d-dimer result	NA	6
Cutoff scores for considering DVT as absent	≤ 1	≤ 3

extremity pain. They excluded patients taking a low-molecular-weight heparin or vitamin K antagonist. The 1002 subjects averaged 58 years and were 37% male. Subjects scoring 4 and above were referred for compression ultrasound (CUS). All other patients were assumed to not have a DVT, and thus were not referred for CUS nor started on an anticoagulant. Patients followed up with their physicians after about 1 week, and 3 months after entering the study they received a questionnaire.

PCR relies on the results of the d-dimer test as part of its scoring scheme. WR does not use d-dimer results in its score; patients with a low score, followed by a negative d-dimer are considered to be at low risk and are not referred for CUS. For an "apples-to-apples" evaluation, these researchers compared the two scores with and without the d-dimer results. In the first analysis, patients who scored ≤ 1 on the WR were labeled low risk. Patients who scored ≥ 2 were labeled high risk. Similarly, according to PCR, patients who scored ≤ 3 were low risk, and ≥ 4 were high risk. The results of the d-dimer test were not considered. In the second scenario (addition of d-dimer), the low-risk WR patients had a score ≤ 1 AND a negative d-dimer. High-risk patients had a score ≥ 2 OR a positive d-dimer. Similarly, low-risk PCR patients had a score ≤ 3 AND a negative d-dimer, and high-risk patients had a score ≥ 4 OR a positive d-dimer, which by itself scores 6.

The outcomes of interest were test safety (percentage of low-risk patients who within 3 months had developed a thromboembolic event) and test efficiency (how many patients were labeled high risk and required CUS). A thromboembolic event was defined as pulmonary embolism or DVT. The better test would identify all patients who would either have or go on to have a thromboembolic event, while sending fewer patients for CUS.

One hundred thirty-six (14%) of the 1002 subjects had DVT. In both low-risk groups, 7 patients subsequently had a thromboembolic event at 3-month follow-up. Three subjects were lost to follow-up.

The performance of the two tests without d-dimer is summarized in Table 2. For safety, PCR had a better rate (0.08% vs. 1.1%). Regarding efficiency, WR identified 121 more patients than PCR as being high-risk and requiring CUS.

Table 2. Performance of tests without d-dimer

Test	High-risk	Low-risk
WR	373	629
PCR	152	850

The performance of the two tests with d-dimer is summarized in Table 3. In this situation, PCR and WR safety was nearly identical (1.4% vs. 1.6%). WR referred 48 more patients for CUS than PCR.

Table 3. Performance of tests with d-dimer

Test	High-risk	Low-risk
WR	555	447
PCR	507	495

The two tests did not always agree. When the d-dimer results were not considered, 22 patients identified as high risk by PCR scored as low risk by WR, and 243 high-risk WR patients were low risk by PCR. The 7 patients who were low risk by PCR and who subsequently had a thromboembolic event were not the same 7 in the WR group. The overlap was 4.

■ COMMENTARY

The technology for diagnosing DVT has progressed along two fronts, imaging and biochemical. Compression ultrasound, which demonstrates the presence of a noncompressible vein, confirms the diagnosis, but costs at least 10 times what a d-dimer does. As was demonstrated in this study, a negative d-dimer — no matter which rule was used — did not rule out thromboembolic events absolutely, and a positive one does not clinch the diagnosis. Point-of-care d-dimer tests are available, which, if negative, could save your patient a trip to an imaging center. Both rules performed well, but PCR appears to be more cost effective. ■

References

1. Scarvelis D, Wells PS. Diagnosis and treatment of deep-vein thrombosis. *CMAJ* 2006;175:1087-1092.
2. Oudega R, et al. The wells rule does not adequately rule out deep venous thrombosis in primary are patients. *Ann Intern Med* 2005;143:100-107.
3. Oudega R, et al. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost* 2005;94:200-205.
4. U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism-2008. Available at: http://www.surgeongeneral.gov/topics/deepvein/calltoaction/call-to-action-on-dvt-2008.pdf. Accessed March 7, 2011.

Make No Bones About Nitroglycerin

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

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

Synopsis: *In a two-year study, postmenopausal women randomized to nitroglycerin ointment group had significant increases in areal BMD at the lumbar spine, total hip, and femoral neck and decreased bone resorption.*

Source: Jamal SA, et al. Effect of nitroglycerin ointment on bone density and strength in postmenopausal women: A randomized trial. *JAMA* 2011;305:800-807.

Osteoporosis is both common and serious. It is estimated that by the year 2025, total expenditure resulting from osteoporosis will exceed $19 billion.[1] It is also clear that the patients that are most likely to benefit from therapy are those at the highest risk for osteoporosis-related fractures. The National Osteoporosis Foundation recommends treatment of postmenopausal women (and men ≥ 50 years) with a history of hip or vertebral fracture or with a diagnosis of osteoporosis based upon bone mineral density (BMD) measurement (T-score ≤ -2.5).[2] The guidelines also provide specific treatment recommendations for postmenopausal women with findings of osteopenia on BMD (T-score between -1 and -2.5). In addition to the non-pharmacologic therapy, several factors play a role when considering prescribing a pharmaceutical agent. Along with costs (alendronate and estrogen being generic), prescription coverage status, sex, age, menopausal status, tolerability, and patient/provider preferences are factors that can influence the choice of an agent. With the exception of teriparatide (which stimulates new bone formation), all current agents work primarily by increasing the BMD through inhibiting bone resorption.

An ideal drug for osteoporosis would be one that works to reverse osteoporosis, not just prevent it by inhibiting bone resorption as well as stimulating new bone formation. Other characteristics of an ideal agent may include a reasonable price, wide acceptability (lower serious adverse event profile), and ease of use. Some observational studies have suggested that women taking nitrates for angina may not only have higher BMD but also fewer fractures.[3] Studies have demonstrated that whereas menopause-associated decreased estrogen levels increase osteoclast activity and bone turnover, resulting in bone loss, nitric oxide (NO) has an estrogen-like beneficial effect in bone, but without estrogenic adverse effects.[4] However, there is a lack of data on well conducted studies examining the effect of nitrates on BMD as a therapeutic option for treatment of osteoporosis.

In this Canadian study, Jamal et al conducted a double-blind, placebo-controlled randomized trial of 243 postmenopausal women. Participants included in the study were women aged 50 years or older who were at least 1 year postmenopausal with BMD T scores between 0 and −2.0 at the lumbar spine and higher than −2.0 at the total hip. Patients were randomized to either the nitroglycerin ointment (15 mg/d) group or placebo group, each agent being applied to skin at bedtime for 24 months. Areal BMD was measured using dual-energy x-ray absorptiometry at the lumbar spine, femoral neck, and total hip at baseline, 12 months, and 24 months.

Researchers found that compared with placebo, women randomized to the nitroglycerin group had 6.7 percent significant increases in areal BMD at the lumbar spine at 2 years. Similarly, the increases at total hip and femoral neck BMD were 6.2 percent and 7 percent, respectively. The nitroglycerin group also had increased volumetric trabecular BMD in the distal radius and tibia. Nitroglycerin ointment therapy was also associated with increases in indices of bone strength. Finally, testing for markers revealed that nitroglycerin treatment was associated with significant increases in markers of bone formation while having significant reductions in markers of bone resorption. Although the incidence of serious adverse events was not different between the two groups, women in the nitroglycerin group did report a higher incidence of headaches.

■ COMMENTARY

This is a well-designed study that raises the issue of whether a commonly prescribed medication such as nitroglycerin may serve as an ideal anti-osteoporosis drug. The findings of increases in areal BMD at the spine and proximal femur associated with transdermal nitroglycerin therapy as well as evidence of increased bone formation and decreased bone resorption make a compelling case. Although not studied directly, the study team even suggested that nitroglycerin therapy may lead to a reduction in bone fractures (especially in long bones). This is certainly an inexpensive option for a drug that is easy to use via a variety of routes and already widely acceptable.

It is important to point out that another recent randomized study of transdermal nitroglycerin ointment did not find any substantial BMD changes at the lumbar spine, femoral neck, or total hip between postmenopausal women who received the dose of nitroglycerin in comparison with a placebo.[5] However, the patient adherence in that study was much lower, unlike the current study.

There is clearly more work to be done in this field prior to recommending nitroglycerin specifically for osteoporosis prevention, treatment, or both. This includes well designed studies to evaluate the effect of various nitroglycerin preparations in patients with osteoporosis since this study excluded such individuals. In particular, evaluating the effect of this agent on osteoporosis-related fractures is critical. Eventually, while some will have to discontinue nitroglycerin due to headaches, I believe the day is not far off when we may be able to recommend nitroglycerin as an

inexpensive agent against osteoporosis. Of course, I would also not be surprised if newer, more expensive NO donor agents with specific skeletal affinity and reduced incidence of headaches also made it to the market in the next few years. Until then, I think many of us should just feel better knowing that there is at least one medication on that list for our patients that is working to provide more benefits than we thought it was intended to. ■

References

1. Burge R, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res* 2007;22:465-475.
2. NOF's New Clinician's Guide to Prevention and Treatment of Osteoporosis. http://www.nof.org/professionals/clinical-guidelines. Accessed March 19, 2011.
3. Rejnmark L, et al. Decreased fracture risk in users of organic nitrates: a nationwide case-control study. *J Bone Miner Res* 2006;21:1811–1817.
4. Wimalawansa SJ. Nitroglycerin therapy is as efficacious as standard estrogen replacement therapy (premarin) in prevention of oophorectomy-induced bone loss: A human pilot clinical study. *J Bone Miner Res* 2000; 15:2240–2244.
5. Wimalawansa SJ, et al. Transdermal nitroglycerin therapy may not prevent early postmenopausal bone loss. *J Clin Endocrinol Metab* 2009;94:3356–3364.

Pharmacology Update

Ceftaroline Fosamil Injection (Teflaro™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

A BROAD-SPECTRUM, PARENTERAL, CEPHALOSPORIN WITH activity against both gram-positive and gram-negative bacteria has been approved by the FDA. Ceftaroline fosamil is the prodrug of ceftaroline and is marketed by Forest Pharmaceuticals as Teflaro™.

Indications

Ceftaroline is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSI) and community-acquired bacterial pneumonia (CABP) due to susceptible microorganisms.[1] For ABSSI, these organisms include *Staphylococcus aureus* (including methicillin-susceptible and resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiace*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. For CABP, *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *S. aureus* (including methicillin-susceptible isolates only), *Haemophilus influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E.coli*.

Dosage

The recommended dose for ABSSI is 600 mg every 12 hours, given by intravenous infusion over 1 hour, for 5–14 days. For CABP, the dose is 600 mg every 12 hours for 5–7 days.[1] The dose needs to be reduced with reduced creatinine clearance.

Ceftaroline is available as 400 mg and 600 mg single-use vials.

Potential Advantages

Ceftaroline is the first cephalosporin to show antibacterial activity against methicillin-resistant *S. aureus* (MRSA). There is minimal potential for drug-drug interactions involving the CYP450 isoenzyme system.

Potential Disadvantages

Ceftaroline is susceptible to beta-lactamases produced by gram-negative bacteria.[1]

Comments

Ceftaroline is a fifth-generation cephalosporin with antibacterial activity against gram-negative and gram-positive bacteria including MRSA. Its efficacy was shown in 4 Phase 3 studies, two in CABP (FOCUS I and II), and two in ABSSI (CANVAS I and CANVAS II).[1-5] For CABP, adult patients (n = 1231) with radiographically confirmed CAP requiring hospitalization and treatment with IV antimicrobial therapy were randomized to ceftaroline (600 mg every 12 hours) or ceftriaxone (1 g every 24 hours) for 5-7 days.[1,2] The primary objective was to determine noninferiority in clinical cure rates of ceftaroline and ceftriaxone in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITT) populations at the test-of-cure (TOC) visit (8-15 days after end of therapy). The CE population represents the subset that adhered to protocol and the MITT represents the population that received any amount of the drug. In both cases, ceftaroline met noninferiority margins well above the predetermined -10%. Overall the clinical cure rates were 84.3% for ceftaroline and 77.7% for ceftriaxone in the CE population and 82.6% and 76.6%, respectively, for the MITT population. Ceftaroline was noninferior to ceftriaxone (although the cure rates were numerally higher). For ABSSI, patients with

complicated skin and skin structure infections (n = 1378) were randomized to ceftaroline (600 mg every 12 hours) or vancomycin and aztreonam (1 g each every 12 hours) for 5–14 days.[1,4,5] The primary objective was similar to that for CABP. Overall cure rate for the CE population was 91.6% for ceftaroline and 92.7% for vancomycin/aztreonam. For the MITT, rates were 85.9% and 85.5%, respectively.[3] Ceftaroline was demonstrated to be noninferior to vancomycin/aztreonam. Cure rates were similar for MRSA and MSSA.[3] The FDA also analyzed these studies based on clinical response on day 3 for ABSSI (cessation of lesion spread and absence of fever) and day 4 for CABP (stable vital signs and improved symtoms). Response rates were similar between ceftaroline and comparator in these studies.[1] Ceftaroline is well tolerated with low frequencies of adverse events (e.g., diarrhea, nausea, constipation, rash, increased transaminases, phlebitis) 5% or less.[1]

Clinical Implications

Ceftaroline is the newest antimicrobial for the treatment of CABP and ASSBI. Ceftriaxone is a mainstay for CABP and ceftaroline was noninferior to ceftriaxone and was numerically better. For ASSBI, ceftaroline was noninferior to vancomycin/aztreonam. Ceftaoline looks promising, but its role in the treatment of these infections remains to be determined. ■

References

1. Teflaro Prescribing Information. Forest Laboratories, Inc. October 2010.
2. File TM, et al. Integrated analysis of FOCUS 1 and FOCUS 2: Randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis* 2010;51:1395-1405.
3. Corey GR, et al. Integrated analysis of CANVAS 1 and 2: Phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 2010;51:641-650.
4. Corey GR, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010;65 Suppl 4:iv41-51.
5. Wilcox MH, et al. CANVAS 2: The second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010;65 Suppl 4:iv53-65.

CME Questions

17. Which of the following provides the most accurate blood pressure measurement in an outpatient setting?
a. 24-hour ambulatory blood pressure monitoring
b. Manual blood pressure check in the office
c. Automated blood pressure check in the office
d. Intra-arterial blood pressure monitoring

18. Choose the correct statement regarding the Wells rule and the primary care rule and the diagnosis of deep vein thrombosis (DVT).
a. The primary care rule identifies fewer patients at high risk for DVT.
b. The Wells rule misses fewer patients who subsequently will have a DVT.
c. A positive d-dimer test is diagnostic for DVT.
d. A negative d-dimer test rules out DVT.

19. Which of the following has not been demonstrated as a beneficial effect of transdermal nitroglycerin in post menopausal women?
a. Decreased fractures
b. Increased bone mineral density
c. Increased bone strength
d. Increased bone formation
e. Decreased bone resorption

Answers: 17. a; 18. a; 19. a

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Aspirin and Risk of Death from Cancer

Source: Rothwell PM, et al. Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomized trials. *Lancet* 2011;377:31-41.

In animal models, aspirin (ASA) has favorable effects on the incidence and/or growth rate of some cancers (CA). Most clinical trials of ASA have been for primary or secondary prevention of cardiovascular disease. Rothwell et al analyzed data from three UK clinical trials that included CA mortality outcomes, although none of the trials was designed specifically to study the impact of ASA upon CA as a primary or secondary endpoint. Their data set of almost 24,000 adult men and women divided treatment groups by duration of follow-up: 0-5 years of treatment, and > 5 years of ASA treatment.

ASA was associated with an 18% relative risk reduction in deaths due to cancer; risk reduction was greatest in subjects treated for more than 5 years. Gastrointestinal (GI) cancer deaths were reduced most prominently, but other cancers (e.g., lung) also showed favorable impact from ASA treatment. Although bleeding induced by ASA typically is viewed as an adverse effect, it has been suggested that ASA treatment also makes GI tumors more likely to bleed, facilitating their discovery. There appears to be a "latent period" of at least 5 years before the effects of ASA impact esophageal, pancreatic, brain, and lung cancer.

When evaluating the risk-benefit of ASA for cardiovascular risk reduction, the favorable impact of ASA upon cancer mortality also should be considered. ■

Reducing Incontinence After Prostatectomy

Source: Goode PS, et al. Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: A randomized controlled trial. *JAMA* 2011;305:151-159.

When prostate cancer (PCA) was diagnosed primarily at the later stages of disease, post-surgical adverse effects such as incontinence or erectile dysfunction weighed less heavily on the risk-benefit scale, since without surgery outcomes were poor. In an era when most PCA is diagnosed at a stage of localized disease, much of which would be destined to never evolve to clinical relevance, balancing adverse surgical consequences, becomes more complex.

Incontinence occurs and persists in the majority of men after radical prostatectomy. Two-thirds of men have persistent incontinence 5 years postoperatively. Encouraging results have been seen in trials that incorporate behavioral and physical therapies promptly after surgery. Little insight is available about the success of intervention for persistent incontinence distant from surgery.

Goode et al enrolled 208 men who had undergone prostatectomy and continued to suffer incontinence 4-5 years later. Participants were randomized to behavioral therapy (pelvic floor exercises, bladder control methods, fluid management) plus biofeedback and/or pelvic floor electrical stimulation versus control.

The reduction in incontinence was significantly greater in treatment groups (55% reduction) than in the control group (24% reduction). Neither biofeedback nor pelvic floor electrical stimulation added effectiveness to behavioral therapy alone. Clinicians should be encouraged that even late employment of behavioral therapies can provide substantial incontinence improvement. ■

Real-life Efficacy of Herpes Zoster Vaccine

Source: Tseng HF, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA* 2011;305:160-166.

Herpes zoster vaccine (Zostavax) was licensed in the United States in 2006 subsequent to the publication of the Shingles Prevention Study, a large (n = 38,546) prospective trial that demonstrated a 51% reduction in zoster and a 67% reduction in postherpetic neuralgia in vaccines compared to controls. Clinicians may wonder whether the favorable results seen in a major clinical trial would be replicated in their private clinical settings. According to this report by Tseng et al, that may very well be the case.

Enrollees in the Southern California Kaiser Permanente health plan older than 60 years of age who had received zoster vaccine (n = 75,761) were compared with age-matched controls (n = 227,283) in this retrospective analysis. The Kaiser Permanente study population was comprised of healthy, immunocompetent, community-dwelling adults. The primary outcome of interest was incidence of zoster.

The rate of zoster in the vaccine recipients (6.4/1000 person-years) was significantly less than the rate in unvaccinated study subjects (13.0/1000 person-years). This 55% relative risk reduction is highly concordant with the reductions seen in the Shingles Prevention Study, confirming the generalizability of their results. ■

In Future Issues:

Coffee Consumption and Risk of Stroke in Women