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Internal Medicine

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ABSTRACT & COMMENTARY

CPAP is Great, But Don't Forget About the Weight

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speakers bureau for PotomaCME.

SOURCE: Chirinos JA, et al. CPAP, weight loss, or both for obstructive sleep apnea. *N Eng J Med* 2014;370:2265-2275.

SYNOPSIS: The combination of CPAP and weight loss improves blood pressure better than either treatment alone.

Because weight loss is beneficial for obese and overweight patients with obstructive sleep apnea (OSA), these investigators evaluated the effects of weight loss and continuous positive airway pressure (CPAP), singly and in combination, on clinical outcomes of OSA. To do this, they enrolled obese adults with moderate-to-severe OSA and a serum level of C-reactive protein (CRP) of at least 1.0 mg/L. Patients were randomized to either weight loss alone, CPAP alone, or CPAP and weight loss together. In the CPAP and CPAP plus weight loss groups, objective adherence to CPAP therapy was monitored. Participants in the weight loss and CPAP plus weight loss groups had individual weekly counseling sessions with specific caloric targets and initial dietary composition based on National Cholesterol Education Program (NCEP), with a more structured diet (including two to three liquid meal replacements/day after week 2), unsupervised exercise, and cognitive-behavioral treatment.

Assessments were performed at baseline, 8, and 24 weeks. Outcome measures included CRP, lipoproteins, insulin sensitivity, and blood pressure. The authors analyzed results both based on intention-to-treat and based on per protocol (achieving targets) outcomes. Per protocol targets were at least a 5% loss of baseline weight and CPAP adherence of at least 4 hours a night for 70% of nights. Because of the two ways of looking at the outcomes (what the patients actually did, in terms of weight loss and CPAP use, in contrast to what

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they were randomized to be doing), the results of this study are a bit complicated to sort out. In general, this discussion will focus on the per protocol analyses (those patients who actually met the targets of weight loss and/or CPAP use).

Of 181 patients initially enrolled, 136 completed the full 6 months of evaluation (a drop out rate of 1 in 4). For the patients who completed the study, the decline in body weight was similar in the weight loss and CPAP plus weight loss groups (about 15 pounds in each case). Those in the CPAP alone group did not lose weight. The average duration of CPAP use was 4 hours per night, with no significant differences between the CPAP and CPAP plus weight loss groups.

At the end of the study, CRP levels were significantly reduced in the weight loss and in the CPAP plus weight loss groups, but not in the CPAP alone group. Similarly, insulin sensitivity increased in the weight loss and CPAP plus weight loss groups, but not in the CPAP alone group. Similar findings were noted with changes in serum triglycerides and cholesterol levels, with greater reductions in patients assigned to weight loss (with or without CPAP) than in those the CPAP alone group. On the other hand, there was no significant change in HDL cholesterol levels in any of the study groups.

In the intention-to-treat analysis, systolic blood pressure was reduced in all three study groups with no significant between-group differences. In the per-protocol (targets met) population, the reduction in systolic blood pressure was greater in the combined-intervention group (14.1 mm Hg) than in the weight-loss group (6.8 mm Hg) or the CPAP group (3.0 mm Hg) and the reduction in mean arterial pressure was significantly greater in the CPAP plus weight loss group than in either the weight loss group or the CPAP group. In the per-protocol population, the reduction in pulse pressure was greater in the CPAP plus weight loss group and weight loss group than in the CPAP alone group.

In other words, in adults with obesity and OSA, CPAP combined with weight loss did not reduce CRP levels more than either intervention alone, but weight loss provided an additional improvement in insulin sensitivity and serum triglycerides when combined with CPAP. The combination of CPAP and weight loss caused significantly greater reduction in blood pressure than either treatment alone.

With regard to adverse events, nasal or upper airway symptoms were reported in an equal number of participants in each group (including the weight loss alone group!).

■ COMMENTARY

This interventional study goes a long way in helping to sort out the relative benefits of CPAP and weight loss on cardiovascular risk factors in patients with both sleep apnea and obesity (which tend to overlap). Perhaps the strongest message is that, at least in the short (6 month) run, weight loss appears to confer at least as much cardiovascular risk reduction as does CPAP. A couple of caveats are in order, though. The first is that the combination of CPAP and weight loss resulted in significantly greater reduction in blood pressure than either CPAP or weight loss alone. The second important footnote is that weight loss really did occur in patients randomized to a weight loss intervention in this study, probably because the weight loss intervention was intense, structured, and labor-intensive. In real life, this is much less likely to occur. Indeed, it's now pretty clear that CPAP does not facilitate weight loss, and probably even promotes weight gain.[1] Indeed, the patients randomized to CPAP alone in this study did not lose weight.

So, if we really want to optimize cardiovascular risk reduction in obese patients with sleep apnea, simply slapping on a CPAP mask is not enough. Specific, focused efforts at weight loss are essential. Not many of us have a mechanism to provide the kind of weight loss program that was used in this study. To quote the Methods section: "Dietary composition was aligned with recommendations from the National Cholesterol Education Program (NCEP). Self-selected foods within the framework of the NCEP diet were prescribed for the first 2 weeks. For weeks 3 to 19, a more structured diet was prescribed, including two to three liquid

meal replacements per day. Unsupervised exercise was initiated at week 4, starting with four 15-minute weekly sessions that increased progressively to four 50-minute weekly sessions by week … Cognitive-behavioral strategies, including self-monitoring, goal setting, stimulus control, problem solving … and relapse prevention, were used to facilitate and maintain weight loss." Not only is such a program difficult to organize, getting it paid for is virtually impossible. Further, my educated guess is that it was this intensive weight loss program, rather than any other aspect of this project, that resulted in the loss of about one-fourth of the research participants in this study.

So what's a clinician to do? This report strengthens the evidence that we are failing our obese patients if we don't address weight loss in some way. But maybe it doesn't have to be quite so complicated. Recent reports[2,3] indicate that commercial programs are at least as effective (and much more accessible) to real-world patients than intensive clinic-based programs. A specific referral for a commercial weight loss program is an option to consider. ■

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ABSTRACT & COMMENTARY

Neuraminidase Inhibitor Therapy of Influenza Virus Infections — Yes or No?

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski does research for the National Institutes of Health and is an advisory board member and consultant for Merck. This article originally appeared in the June 2014 issue of *Infectious Disease Alert*.

SYNOPSIS: A Cochrane review questions the value of osletamivir and zanamivir in the treatment of influenza virus infections – but the CDC and IDSA disagree.

SOURCE: Jefferson T, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014;4:CD008965.

Jefferson and colleagues examined data from all available results, including unpublished data, from randomized, placebo-controlled trials of therapy and prophylaxis of influenza virus infection with neuraminidase inhibitors in both children and adults to determine their safety and efficacy. Overall, 107 clinical trials were examined.

TREATMENT — ADULTS

Oseltamivir reduced the time to initial alleviation of symptoms in adults from a mean of 7 days to one of 6.3 days, a mean reduction of 16.8 hours (95% confidence interval [CI], 8.4-25.1 hours; $P < 0.0001$). Zanamivir reduced this measure from 6.6 to 6.0 days, a 0.60 day reduction (95% CI, 0.39-0.81 days; $P < 0.00001$). Neither oseltamivir nor zanamivir had a significant effect on hospitalizations or serious complications; this endpoint was not reported in zanamivir studies. Oseltamivir and zanamivir each significantly reduced "unverified" pneumonia, but not more stringently defined pneumonia in the few studies in which this was analyzed. Oseltamivir was associated with an increased risk of nausea and vomiting but decreased risks of diarrhea and cardiac events during treatment.

TREATMENT — CHILDREN

Oseltamivir reduced the time to initial alleviation of symptoms in previously healthy children by a mean of 29 hours (95% CI, 12-47 hours; $P = 0.001$), but the effect in children with asthma was non-significant. There was also no significant effect of oseltamivir on hospitalizations, serious influenza complications, or unverified pneumonia. Oseltamivir was associated with an increased risk of vomiting.

PROPHYLAXIS — ADULTS AND CHILDREN

Oseltamivir significantly reduced the risk of symptomatic influenza in individuals (risk difference [RD] 3.05%, 95% CI, 1.83-3.88) with a number needed to treat (NNT) of 33. The risk in households was also significantly reduced (RD 13.6%, 95% CI 9.52-15.47) with an NNT of 7. The results with zanamivir were similar.

The authors concluded that, overall, the benefit of neuraminidase therapy in these outpatient studies was small, and that there was no evidence of prevention of serious outcomes. There was, however, apparent benefit of prophylaxis in the prevention of symptomatic infection.

■ COMMENTARY

The CDC has carefully considered this analysis but, nonetheless, indicates that it does not alter their existing recommendations for influenza treatment that "emphasize initiation of antiviral treatment as soon as possible for patients who are severely ill and for those who are at greatest risk for complications from influenza. This includes hospitalized patients with suspected or confirmed influenza, those with severe or progressive illness, and outpatients who are at high risk of influenza complications (for example, young children, people aged 65 years and older, pregnant women, and persons with certain underlying chronic medical conditions). In addition, because other reviews of randomized clinical trials and observational studies have found consistent clinical benefit of early oseltamivir treatment in reducing the risk of lower respiratory tract complications such as those requiring antibiotics, persons with uncomplicated influenza who are not in a high risk group and who present within 48 hours of illness onset can be treated with antiviral medications based upon clinical judgment."[1]

The CDC points out that the studies analyzed by Jefferson and colleagues were not powered to detect the effects of therapy on severe outcomes such as hospitalization and death. Furthermore, patients at highest risk of severe outcome are often not included in randomized trials and, since a virological diagnosis was often not required, many included patients with influenza-like illness may not actually have had influenza virus infection. The trials included in the Cochrane analysis involved outpatients — there are no randomized trials in hospitalized patients — but there are a number of observational studies that have reported benefit from therapy. Thus, Muthuri and colleagues performed a meta-analysis of the effects of neuraminidase inhibitor therapy in hospitalized patients, examining 78 studies and more than 29,000 patients.[2] They found that administration of a neuraminidase inhibitor was associated with a significantly decreased risk of mortality (adjusted odds ratio [OR], 0.81; 95% CI, 0.70-0.93; P = 0.0024). Initiation of treatment within 2 days of symptom onset was associated with a reduction in mortality risk (adjusted OR, 0.48; 95% CI, 0.41-0.56; $P < 0.0001$) when compared to later initiation and, when compared to no treatment, a halving of the risk of mortality (adjusted OR, 0.50; 95% CI, 0.37-0.67; $P < 0.0001$). The benefit was greater in adults than in children.

The Infectious Diseases Society of America has issued a statement that concurs with the CDC recommendation confirming the benefit of neuraminidase inhibitors in both the prevention and treatment of influenza virus infection.[3] ■

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ABSTRACT & COMMENTARY

Current Utility of Exercise ECG Testing

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the June 2014 issue of *Clinical Cardiology Alert*.

SYNOPSIS: The authors concluded that these findings can be used to identify which patients would benefit from further testing after an initial exercise ECG test to diagnose coronary artery disease.

SOURCES: Christman MP, et al. Yield of downstream tests after exercise treadmill testing. *J Am Coll Cardiol* 2014;63:1264-1274. Sinusas AJ, Spatz ES. Reframing the interpretation and application of exercise electrocardiography. *J Am Coll Cardiol* 2014;63:1275-1277.

Most current guidelines recommend exercise electrocardiographic (ECG) testing for suspected coronary artery disease (CAD) in patients who can exercise and have a normal resting ECG. If the results are inconclusive, often another stress test with non-invasive imaging is done. These investigators sought

to analyze the results of this downstream testing and identify characteristics that would make such testing valuable or not. The patient sample was collected over 2 years and excluded patients with known CAD. The Bruce treadmill protocol was used and standard criteria for positive, negative, and inconclusive ECGs was used. They analyzed any subsequent testing done by the ordering physician for 6 months after the initial test. Also, the patients were followed for subsequent cardiac events (death, myocardial infarction, or revascularization). The study population included 3656 patients, of whom 90% (3270) had complete follow-up for a mean of 2.5 years. Negative tests were most common (68%), inconclusive next (28%), and positive least (4%). The most common reasons for an inconclusive test were suboptimal exercise (57%), rapid resolution of ECG changes (13%), and test cessation for typical angina (10%). Further testing was performed in 11% (9% noninvasive imagining, 2% invasive angiography). Subsequent noninvasive imaging included stress nuclear perfusion (81%), stress echo (12%), coronary CT angiography (5%), and cardiac MRI (2%). The combined outcome endpoint occurred in those with a negative initial test was 0.2%, inconclusive 1.3%, and positive 12%. Multivariate analysis showed that younger age, female sex, higher exercise performance, and rapid recovery of any ECG changes predicted negative further testing and event free survival. The development of typical angina during the initial test predicted positive downstream testing and a worse prognosis. The authors concluded that these findings can be used to identify which patients would benefit from further testing after an initial exercise ECG test to diagnose CAD.

■ COMMENTARY

The major limitation of this trial is that it is an observational study done at one center. However, since randomized trials are unlikely to be conducted on this topic, the data can help inform our decisions in this complex and controversial area. Treadmill exercise ECG testing is commonly used as the initial diagnostic test in patients with symptoms that could represent myocardial ischemia, with the caveat that they can exercise near maximally and have a normal resting ECG. Prior observational studies have shown that these requirements are only present in about one-third of patients referred for stress testing. Most undiagnosed patients either have abnormal ECGs, can't fully exercise, or have unstable angina. Even in this academic center series, more than half of the patients with an inconclusive test were not able to exercise fully. In my practice, anyone > 80 years of age or obese, I automatically eliminate exercise testing.

Interpreting this study is challenging because some of the downstream testing was obviously indicated, such as the patients with typical angina, but a normal ECG. In such patients, it is not inappropriate to do an imaging study or invasive angiography. In this study, 100% of those with obvious angina on stress testing had a significant coronary lesion that was stented. On the other side, a negative stress test would rarely indicate a need for further testing and in this study, the incidence of the combined endpoint was 0.2% in such patients. However, someone with angina symptoms and a negative stress test may have vasospasm or small vessel disease and further sophisticated imaging could be appropriate. There are nuanced areas in ischemic heart disease that may trump usual thinking.

Perhaps the most interesting data from this study are the subgroup with an inconclusive ECG exercise test because of rapid reversal of ST changes in recovery (< 60 seconds). There is considerable prior literature that suggests this may be characteristic of a false-positive test. In this study, such patients had an excellent prognosis. They had no positive downstream tests and no deaths or myocardial infarctions. Their data support the notion that this finding represents a false-positive test.

Another major limitation of this study is that we do not know the pre-test probability of disease. According to Bayes' Theorem, this markedly affects the outcome of testing. For example, not everyone in the study had further testing, so there may be a section bias toward the more likely to have CAD patients. This would make further testing seem more valuable.

My conclusion is that in the small group of patients who meet criteria for an exercise ECG test, it is still a reasonable test. If typical angina is provoked despite non-diagnostic ECG changes, further testing is indicated. Lacking angina, if there are ECG changes suggestive of ischemia that resolve in < 60 seconds of recovery, this is likely a false-positive test. ■

PHARMACOLOGY UPDATE

Dalbavancin Injection (Dalvance™)

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 relationships relevant to this field of study.

The FDA has approved a once-weekly antibiotic for the treatment of serious skin infections. Dalbavancin is the first antibiotic with the designation of a Qualified Infectious Disease Product (QIDP).[1] As part of this designation, the drug was given a priority and expedited review as well as an additional 5 years of marketing exclusivity. Dalbavancin is marketed by Durata Therapeutics as Dalvance.

INDICATIONS

Dalbavancin is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible gram-positive microorganisms.[2] These include *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiase*, and *Streptococcus anginosus* group.

DOSAGE

The recommended dose in adults is 1000 mg (by intravenous infusion over 30 minutes) followed by 500 mg 1 week later.[1] For patients with creatinine clearance < 30 mL/min (not receiving regularly scheduled hemodialysis), the dose is 750 mg and 375 mg. No dosage adjustment is needed for those on regularly scheduled dialysis. Dalbavancin is available as a 500 mg vial.

POTENTIAL ADVANTAGES

Dalbavancin has a very long elimination half-life (approximately 15 days), and thus is dosed once weekly. It is bactericidal in vitro against *S. aureus* and *S. pyogenes*.

POTENTIAL DISADVANTAGES

Serious hypersensitivity (anaphylactic and skin) reactions have been reported.[1] Rapid intravenous infusions can cause reactions that resemble "Red-Man Syndrome." A small percent of patients (0.8%) had elevations of ALT 3 × ULN.

COMMENTS

Dalbavancin is a lipoglycoprotein antibiotic synthesized from a precursor fermentation product of Actinomycetes *Nonomureaea* species. It has a broad range of activity against gram-positive microorganisms. The safety and efficacy of dalbavancin was evaluated in two Phase 3, randomized, double-blind, noninferiority, double-dummy trials of similar design (DISCOVER 1 and DISCOVER 2).[2,3] Subjects (n = 1312) were included if they had cellulitis, major abscess, or wound infection and at least 75 cm^2 of erythema (medium lesion area at baseline was 341 cm^2). They were randomized to dalbavancin (1 g IV followed by 500 mg 1 week later) or vancomycin (1 g or 15 mg/kg q 12 hour) with the option of switching to oral linezolide (600 mg q 12 hours) after 3 days, to complete 10-14 days of therapy. The dose of vancomycin and dalbavancin could be adjusted to ideal body weight for patients with renal insufficiency. The primary endpoint was measured at 48-72 hours of therapy. Treatment success was defined as cessation of spreading of erythema associated with the infection and a temperature of 37.6°C or less for three consecutive readings 6 hours apart. Noninferiority was achieved if the lower limit of the 95% confidence interval (CI) for the absolute difference between dalbavancin and vancomycin/linezolid was > -10%. Secondary endpoints were reduction in lesion area of 20% or more and clinical success at days 26-30. This study was based on the FDA guidance on the conduct of clinical trials for ABSSSI in 2010.[4] The primary endpoint for the pooled results was 79.7% for dalbavancin and 79.8% for vancomycin (95% CI; -0.1 (-4.5%, 4.2). The lower limits were -4.6% in one study and -7.4% in the second. There does not appear to be any significant difference between treatments based on infection type (e.g., cellulitis or major abscess), baseline pathogen, presence or absence of diabetes mellitus, or systemic inflammatory response syndrome.[3] Secondary endpoints were similar between treatments. Dalbavancin is generally well tolerated. Most common adverse events are nausea (5.5%), headache (4.7%), diarrhea (4.4%), vomiting (2.8%), and rash (2.7%).

CLINICAL IMPLICATIONS

Dalbavancin is the newest drug to be approved for ABSSSI based on the 2010 guidelines, using more objective endpoints. However, using lesion size as disease severity, cessation of lesion spread as success, and temperature as an

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By Louis Kuritzky, MD

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Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Another Win for Bariatric Surgery in Type 2 Diabetes

Source: Sjostrom L, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014;311:2297-2304.

Currently required FDA labeling for oral hypoglycemic agents includes the following wording: "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with _____ or any other antidiabetic drug." Since cardiovascular events are the No. 1 cause of death in type 2 diabetes, what does work?

The Swedish Obese Subjects study is a prospective trial that enrolled patients for bariatric surgery vs "usual care" between 1987-2001, and continues to follow their outcomes. Surgical interventions include nonadjustable banding (n = 61), vertical banded gastroplasty (n = 227), and gastric bypass (n = 55).

Remission of type 2 diabetes subsequent to surgery was impressive: At 2 years, 72% of surgical patients remained in remission, and at 15 years, still 30% of type 2 diabetes patients were in remission (compared with 16% and 7%, respectively, in the "usual care" group). Both microvascular complications (twice as frequent in the control group) and macrovascular endpoints (32% fewer in the surgical group), favored bariatric surgery patients.

The evidence accumulating on bariatric surgery has been consistently favorable, including perioperative 90-day mortality rates of < 1%. Benefits of bariatric surgery are prompt and enduring. ■

Weighing the Risk:Benefit Equation of Azithromycin for Pneumonia

Source: Mortensen EM, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. *JAMA* 2014;311:2199-2208.

Azithromycin is generally considered to be an antibiotic associated with a low risk of important adverse effects, reflecting its frequent use in diverse outpatient disorders such as sinusitis, otitis, and bronchitis. It has been recently recognized that azithromycin is uncommonly associated with QT prolongation, which could — at least in theory — lead to cardiac toxicity. Contradicting that belief are at least two large data sets that failed to identify any cardiovascular risk signal.

Mortensen et al performed a retrospective cohort study in older patients (≥ 65 years of age; mean age = 77.8 years) who had been hospitalized with pneumonia to compare outcomes in patients who had been treated with azithromycin (n = 31,863) vs other antibiotics (n = 31,863).

Ninety-day mortality was found to be lower in the group who had been treated with azithromycin than comparator antibiotics (odds ratio [OR] = 0.73). Even though there was a small relative increased risk of myocardial infarction (OR = 1.17; absolute event rate increase = 0.7%) in the azithromycin group, this was not sufficient to counteract the overall mortality advantage.

Because the population from which these data were drawn included only Veterans Administration patients, subjects were almost exclusively male (98.2%). Nonetheless, no differences in outcomes were discerned between genders (female study population, n = 1134). ■

Hemospermia: What's the Outcome?

Source: Zargooshi J, et al. Hemospermia: Long-term outcome in 165 patients. *Int J Impot Res* 2014;26:83-86.

The presence of blood in the semen is an unsettling experience for men and usually stimulates prompt consultation. Fortunately, this research article by Zargooshi et al provides very reassuring outcomes data.

From a general urology clinic in Iran, the investigators included all patients with hemospermia seen in their outpatient clinic over a 16-year span (n = 165). Mean age of the subjects was 38 years, but almost 20% of subjects were over age 50. Mean follow-up was 7 years. Study subjects underwent ultrasound of the testes and abdomen, and laboratory evaluation. In the absence of positive findings, subjects were empirically treated with a course of a fluoroquinolone plus a nonsteroidal anti-inflammatory drug (NSAID).

Pathology was discerned in only 3 of 165 patients: one case of tuberculosis, one case of bladder cancer, and one case of ejaculatory duct stones. The authors point out that during the 15-year span of the study, no patient developed life-threatening disease, and post-treatment recurrences were rare. According to this trial, if hemospermia resolves after a course of antibiotics and NSAIDs, further investigation is unlikely to disclose meaningful pathology. Full evaluation should be reserved for recurrences or other high-risk indicators. ■

endpoint have been a subject of debate.[5,6] The role of this drug in actual clinical practice remains to be determined as well as how results from clinical studies for ABSSSI are interpreted and translated to actual clinical practice and specific disease entities. Inclusion criteria in the clinical trial could include a wide and varying range of lesions.[7] Currently, the Infectious Diseases Society of America (IDSA) guidelines are by disease entity (e.g., nonprurulent cellulitis, purulent abscess, MSSA, MRSA SSTI, etc.).[8] The convenience of once-a-week administration is offset by the need for a 30-minute infusion for each dose and the wholesale cost of nearly $4500 for a full 2 week course. ■

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CME QUESTIONS

1. In a study of the effects of weight loss, CPAP, or the combination of both CPAP and weight loss:

a. patient retention and adherence was excellent.

b. there was robust improvement in high density lipoproteins with the combination of both CPAP and weight loss.

c. CPAP provided incremental improvement in insulin sensitivity when combined with weight loss.

d. weight loss combined with CPAP improved blood pressure more than either treatment alone.

2. Rapid resolution of ischemic ECG changes in recovery from treadmill exercise usually indicates:

a. mild myocardial ischemia.

b. false-positive test.

c. left ventricular aneurysm.

d. digitalis effect.

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.