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INSIDE

Insurance Administrators, Take Note!

ABSTRACT & COMMENTARY

Synopsis: *Sleepiness, obesity, hypertension, witnessed apneas, and frequent snoring are prevalent in the general population; demand for diagnostic and treatment services for sleep apnea is likely to skyrocket.*

Source: Netzer NC, et al. *Chest*. 2003;124:1406-1414.

THIS STUDY WAS DONE TO DETERMINE THE PREVALENCE OF CLASSIC findings of sleep apnea in a geographically and socioeconomically diverse primary care population. For this study, 26 US sites and 14 European sites distributed Berlin Questionnaires to consecutive patients who were at least 15 years old when they visited a primary care physician for any reason. The patients completed the questionnaires in the physicians' office, and completed questionnaires were returned to the central analysis site (Cleveland, Ohio) for data entry and analysis. The Berlin Questionnaire has previously been shown to have a positive predictive value of 89% for a Respiratory Distress Index (RDI) of more than 5 events per hour of sleep, if at least 2 of the following are present:[1] frequent symptoms of snoring and/or witnessed apneas, frequent symptoms of sleepiness, or self-reported hypertension and/or a Body Mass Index (BMI) of > 30 kg/m^2. Care was taken to translate the questionnaire and to validate it in the European countries involved in this project. Frequency distributions and proportions were used to calculate prevalence rates. Most variables were dichotomized for analysis, and important confounders were controlled for—in calculating odds ratios and logistic regression.

There was an incredible 78% usable response rate (n = 6223), which was similar between the United States and Europe. The mean age of the respondents was 51.3 ± 17 years; obesity was more common in the United States than in Europe (27.9 vs 17.2%). The US population was also more likely to endorse "not rested after sleep" (36% vs 16%) and drowsy driving (17% vs 7%). Spaniards were the least sleepy of all Europeans, and Southerners were least sleepy of all Americans. Men were more likely than were women to report snoring, witnessed apneas, and drowsy driving. Women were more

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likely to complain of daytime sleepiness. Probability estimates of sleep apnea were 16.4% for the United States and 6.7% for Europe.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

If I were a health insurance administrator, these data and several studies like it[2-5] would make me rethink my policy about testing and treatment for sleep apnea. The fact is, sleep apnea is very prevalent and getting more so, since our population is getting older and fatter.[6,7] Further, we spend more on diagnosis than on treating this condition (a sleep study costs about 3 times what a Continuous Positive Airway Pressure [CPAP] machine does). CPAP is extraordinarily safe, cheap, and effective and has been shown to reverse most of the consequences of sleep apnea. A logical, safe, and cost-effective approach would be to reimburse treatment with autotitrating CPAP without testing for a month or two if a knowledgeable physician ordered it on the basis of a relevant history and physical examination. Documentation of follow-up and compliance, including sleepiness symptoms, nasal symptoms, hours of use, blood pressure, and weight would be required for purchase of the machine at that point. If the patient were not using or benefiting from the CPAP at follow-up, then he or she could take a trip to the sleep lab to find out if some other condition were present, to retitrate CPAP, and to work on issues related to CPAP compliance. Time, money, and lives would be saved.

In the meantime, primary care physicians need to know that the burden of our obesity epidemic includes a skyrocketing rate of sleep apnea.[7] Snoring, sleepiness, witnessed apneas and hypertension are fairly good predictors of the likelihood of sleep apnea in the obese patient. In particular, the likelihood of sleep-disordered breathing ought to be carefully considered in obese patients with hypertension, since CPAP has unequivocally been shown to lower blood pressure in hypertensive patients with sleep apnea, especially those with drug-resistant sleep apnea.[8-12] It is important to remember that in patients with heart failure, CPAP improves blood pressure and cardiac function even if the patients are not sleepy.[11]

It's time we got past the notion that the main treatable consequence of sleep apnea is sleepiness, and focused on preventing the excess cardiac mortality that results. Insurance company administrators, CPAP is actually cheaper than antihypertensive therapy and monitoring. Please listen! Our current system is cumbersome, overly expensive, and deadly. ■

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The Longer You Stay, the Longer You Stay

ABSTRACT & COMMENTARY

Synopsis: *Like patients hospitalized with acute myocardial infarction and total knee replacements, EM of hospitalized patients with CAP reduces overall hospital length of stay and institutional resources without increasing the risk of adverse outcomes.*

Source: Mundy LM, et al. *Chest*. 2003;124(3):883-889.

THIS PROSPECTIVE, RANDOMIZED TRIAL ASSESSED THE effect of early ambulation on length of stay and morbidity in patients admitted for community-acquired pneumonia (CAP). In this trial, 711 consecutive patients admitted with CAP were enrolled; 458 met the inclusion criteria of no prior hospitalization within 2 weeks, no ICU admission criteria and no large-volume aspiration pneumonia. Specific medical units were randomized to begin either usual care or an early mobilization (EM) protocol. The EM protocol consisted of the patient being out of bed in an upright posture for at least 20 minutes on the first day, with subsequent increases in upright posture and ambulation on subsequent days. The treatment and control groups were similar in all collected demographics, including PORT and SF-12 scores.[1,2]

Patients assigned to usual care had a mean length of stay of 6.9 days; those assigned to the early mobilization protocol had a 5.9-day mean length of stay (95% CI, 0.2-2.2; $P = 0.06$). As would be expected, patients with the lowest PORT risk scores (I and II) had the greatest likelihood of achieving early mobilization, though the treatment effect was marginal in these groups. The greatest effect was seen in the PORT III class, with a 2.6-day reduction in length of stay (95% CI, 0.2-5.0; $P = 0.05$). The estimated cost per admission was $10,159 for the intervention; $12,868 for the control. There was no statistical difference in mortality between the 2 groups.

COMMENT BY JEFF WIESE, MD

The results of this trial suggest that early mobilization beginning on the first day of hospitalization can reduce costs and length of stay in patients with CAP. One potential explanation is that early mobilization results in better aeration of lung tissue, thereby facilitating mobilization of pulmonary secretions and quicker resolution of the pneumonia. Another possible explanation is that enhanced nursing care resulted in greater compliance to the medical regimen and more vigilant observation for and response to complications. Physicians were blinded to the treatment and control assignments, making a Hawthorne effect unlikely.

The results of this study should be interpreted with caution, however. Aside from the PORT III class of patients, none of the end points were statistically significant. The confidence intervals for all end points were wide, suggesting that the study was underpowered with its subject enrollment. Subsequent studies will be required to confirm these results, although the effect size of the intervention is large, suggesting that larger trials will likely confirm the same.

The most interesting feature of the study is the effect in patients with PORT III classification, as these are typically the most ill of patients allowed to remain on the medical wards (ie, non-ICU care). The robust and statistically significant reduction in length of stay and cost suggest that even patients' physicians do not routinely deem capable of early mobilization benefit from such an intervention. In designing hospital care protocols, this subgroup may be a target of allocating additional physical therapy and nursing resources to reduce length of stay and hospital cost.

This trial was not large enough to assess for complications of pneumonia therapy, including DVT and compression ulcers. It is likely, however, that with a greater sample size, early mobilization would also show benefit in these outcomes.[3] ■

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Duration of Antiviral Immunity After Smallpox Vaccination

ABSTRACT & COMMENTARY

Synopsis: *More than 90% of individuals studied maintain measurable humoral or T-cell-mediated immunity against vaccinia virus for as long as 75 years after smallpox vaccination.*

Source: Hammarlund E, et al. *Nature Med*. 2003;9:1131-1137.

HAMMARLUND AND COLLEAGUES AT THE UNIVERSITY of Oregon examined a group of individuals who had received smallpox vaccination 1-75 years previously

in order to determine the duration and magnitude of immunity against vaccinia virus. The in vitro studies performed included the quantification of virus-specific CD4+ and CD8+ lymphocyte responses as well as of neutralizing antibody.

More than 90% of volunteers who had been vaccinated 1-75 years previously had evidence of substantial humoral and/or cellular immunity against vaccinia. While antiviral T-cell responses declined slowly over time with a half-life of 8-15 years, antibody responses remained stable for 1-75 years after vaccination.

COMMENT BY STAN DERESINSKI, MD, FACP

The duration of immunity after receipt of vaccinia has been a matter of some discussion. Often accepted is a duration of only 3-5 years, and this was the figure that was used in the structuring of the vaccination program recently held in abeyance by the United States. Mack, however, cites a number of epidemiological studies that suggest the period of protection is many years longer, with at least 90-95% protection against lethal infection for more than 20 years after vaccination.[1] This is consistent with the long-term immunity induced by other live attenuated virus vaccines.

The nationwide smallpox vaccination program was recently halted. The vaccine had been offered to the approximately 2.5 million health care professionals and technicians working in US hospitals. Based on previous estimates of risk, at least 7-8 vaccine-related deaths were expected.[2,3] The vaccine was offered regardless of prior vaccination—more than 90% of Americans older than 35 have been vaccinated against smallpox, mostly as infants. However, by the end of March 2003, only 25,645 public health and health care workers in the United States had been vaccinated. Many health care workers opted out of the program for a number of reasons, including the reports of the occurrence of myocarditis and cardiac deaths in a small number of vaccine recipients. For many health care workers who chose to not be vaccinated, it is likely that their calculus was something like the following: While the risk of an attack is unknowable, there have been no cases. There is some risk from vaccination. Postexposure vaccination, especially combined with vaccinia immune globulin, is quite effective in prevention of severe disease.

The program also proved costly in terms of dollars. In April, the Association of State and Territorial Health Officials estimated the average cost of a single vaccination to be $249, with the cost ranging from $79 in Tennessee to more than $1000 in Hawaii and Alaska. Randy Cohen in his column on ethics in the *New York Times Sunday Magazine* (Jan 19, 2003, page 18) pointed out another aspect of this issue. "Financing an expensive smallpox vaccination program necessarily means neglecting many pressing medical problems, both here and abroad. In our era of tight budgets, deciding how to allocate health care resources is a question with both moral and political implications." In other words, is it moral to spend large amounts of money on a problem, which we may never confront, or on ones, such as malaria and diarrheal illness that kill children every day? ■

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Do You Know the Difference Between Impaired Fasting Glucose and Impaired Glucose Tolerance?

ABSTRACT & COMMENTARY

Synopsis: *The new criterion for FPG will identify many more individuals who are at risk for developing diabetes.*

Source: The Expert Committee On Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2003;26:3160-3167.

THE CURRENT RECOMMENDATIONS FOR THE DIAGNOSIS of diabetes and for lesser degrees of impaired glucose regulation, ie, impaired fasting glucose and impaired glucose tolerance (IFG & IFT) were established by an International Expert Committee in 1997. The committee recommended several changes to the diagnostic criteria for diabetes and for lesser degrees of impaired glucose regulation. The following major changes addressed:

- The 1997 report recommended that the cut point for the diagnosis of diabetes be changed from a fasting blood glucose of 140 mg/dL or above, to a level of 126 mg/dL or above. This change was based on data that showed an increase in the prevalence and inci-

dence of diabetic retinopathy beginning at approximately 126 mg/dL, as well as to reduce the discrepancy that existed in the number of cases detected by the FPG cut point of 140 mg/dL and the 2-h value in the oral glucose tolerance test (OGTT) of 200 mg/dL or higher.

- The normal fasting glucose was defined as 110 mg/dL.
- The HbA1c was not recommended as a diagnostic tests, because of a lack of standardization measures in various laboratories
- The OGTT (FPG and 2-h post glucose value) "was recognized as a valid way to diagnose diabetes." The use of the test for this purpose was discouraged because of inconvenience, lack of reproducibility, and greater cost. The diagnostic category IGT "was retained to describe people whose FPG was < 126 mg/dL but whose 2-h PG after 75 g of glucose was 140-199 mg/dL."
- The range of FPG levels between 110-126 mg/dLwas named impaired fasting glucose (IFG).

Since 1997, many new data related to the diagnosis of diabetes have been published. Impaired glucose tolerance has been associated with cardiovascular disease (CVD) risk factors and CVD events, whereas IFG is much less strongly associated with CVD events and CVD mortality. In addition, clinical trials have shown that progression of IFG to diabetes could be delayed or prevented by lifestyle modification (diet and exercise), metformin, and acarbose.

In light of these and other new observations, a reconstructed International Expert Committee has made the following recommendations:

- The 2-hour criterion of 200 mg/dL identifies a larger population as having diabetes than the previous criterion of 140 mg/dL or higher. The committee lowered the FPG to 126 mg/dL to reduce this discrepancy. The committee recommended that this category not be changed.
- The data indicate that a larger number of individuals with IGT will eventually develop diabetes than the IFG. To make the 2 measurements more uniform, the committee recommended that the IFG level be reduced to 100 mg/dL rather than 110 mg/dL. The cut point for IGT remains at 140-199 mg/dL.

Although the HbA1c has become more standardized in the United States, many countries have not been able to standardize the assay. Also, the HbA1c may be affected by pregnancy, transfusions, uremia, and hemolytic anemia. The committee therefore recommended that the HbA1c be used as a monitor of therapy rather than for a definitive diagnosis of diabetes.

The FBG and the 2-h PG remain the tests of choice for the diagnosis of diabetes. The k2-h PG is a more sensitive assay in most populations but the FPG is more reproducible, less costly and more concise.

Table

Diagnostic Thresholds for Diabetes and Lesser Degrees of Impaired Glucose Regulation

Category	FPG	2-h PG
Normal	< 100mg/dL	< 140 mg/dL
IFG	100-125 mg/dL	—
IGT	—	140-199 mg/dL
Diabetes	≥ 126 mg/dL	≥ 200 mg/dL

Adapted from The Follow up Report on the Diagnosis of Diabetes. Diabetes Care. 2003;26:3161.

COMMENT BY RALPH R. HALL, MD, FACP

The extensive discussion of the pathophysiology and rationale for these recommendations, in this article, are well worth reading. The review needs little discussion except to note that the new criterion for FPG will identify many more individuals who are at risk for developing diabetes. This is the population we should work with to attempt to delay or prevent diabetes and CVD. ■

Pharmacology Update

Daptomycin Injection (Cubicin)

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

THE FDA HAS APPROVED THE FIRST OF A NEW CLASS OF antibiotics for the treatment of complicated skin and skin structure infections. Daptomycin is a cyclic lipopeptide that is active against Gram-positive bacteria. Daptomycin injection is manufactured by Abbott Laboratories and marketed by Cubist Pharmaceutical Inc as Cubicin.

Indications

Daptomycin is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of *Staphylococcus aureus* (including methicillin-resistant strain), *Streptococcus pyogenes*, *S agalactiae*, *S dysgalactiae* subsp equisimilis, and *Enterococcus faecalis* (vancomycin-susceptible strains only).[1]

Dosage

The dose of daptomycin is 4 mg/kg given by intra-

venous infusion for a 30-minute period once every 24 hours for 7-14 days. The dose should be reduced to 4 mg/kg every 48 hours if the patient's creatinine clearance is < 30 mL/min including patients on peritoneal or hemodialysis.[1]

Potential Advantages

Daptomycin has shown potent in vitro activity against *S aureus* and enterococci including resistant strains such as glycopeptide-resistant enterococci and methicillin-resistant *S aureus*.[1,2] In one in vitro study, daptomycin showed greater bactericidal activity than linezolid, quinupristin-dalfopristin, and vancomycin against methicillin-resistant *S aureus* and *Staphylococcus epidermidis*, vancomycin-resistant enterococci, and vancomycin-intermediate *S aureus*.[3] Cross-resistance to other classes of antimicrobials have not been identified. Daptomycin is dosed once daily.

Potential Disadvantages

Patients should be monitored for the development of muscle pain or weakness. In clinical studies about 3% of patients had elevated CK levels.[1] Most common side effects include gastrointestinal disorders (eg, constipation, nausea), injection site reactions, fever, headache, dizziness, and rash.[1] Daptomycin is not available in an oral dosage form. Daptomycin is not approved for pneumonia and appeared to be less effective than ceftriaxone for the treatment of pneumonia.[4]

Comments

Daptomycin is the first of a new class of antimicrobial agents, the cyclic lipopeptids, that are believed to act by causing depolarization of the bacterial membrane potentially leading to cell death.[1] It has been studied in 2, unpublished, randomized, multinational studies in adults with complicated skin and skin structure infections. In these studies, which were conducted primarily in non-US sites, 554 patients were treated with daptomycin and 558 patients were treated with a comparator. Comparators were vancomycin or a semi-synthetic penicillinase-resistant penicillin (eg, cloxacillin, nafcillin).[1] Overall, treatment success, whether assessed on an intent-to-treat (ITT) basis or in clinical evaluable (CE) population, were comparable. Success based on ITT and CE were 62.5% and 80.4% for the 2 studies, respectively, compared to 60.9% and 80.5% for the comparators. The majority of the pathogens isolated for each study arm were methicillin-susceptible *S aureus* (196 for daptomycin, 207 for comparators) followed by *S pyogens* (84-88) and *E facaelis* (37-53). More than 50% of the infections were wound infections or major abscess. Daptomycin appears to be well tolerated with side effects that are not dramatically different than the comparator except for CK elevations. The wholesale cost for daptomycin is about $11 for 4 mg. A 10-day cost for a 70 kg patient is about $7500.

Clinical Implications

Finding antimicrobial agents that are active against resistant Gram-positive pathogens is a continuing challenge. The most common of these pathogens are methicillin-resistant *S aureus* and vancomycin-resistant enterococci. Daptomycin has shown in vitro activity against these organisms but there are not enough clinical data to support an indication for vancomycin-resistant enterococci. Daptomycin may be an alternative to linezolid and quinupristin-dalfopristin for skin and skin structure infections. Currently, linezolid is approved for *S aureus* (methicillin-susceptible and resistant), *S pyogenes*, and *S agalactiae*, and quinupristin-dalfopristin is approved for methicillin-susceptible *S aureus* and *S pyogenes*. The ultimate role of daptomycin will be defined with broader clinical studies/experience. ■

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CME Questions

24. Which of the following is most likely true about the prevalence and risk factors for sleep apnea?

a. Europeans are more likely to have sleep apnea than are people from the United States.
b. Women are more likely to report drowsy driving than are men.
c. Europeans are more likely to endorse sleepiness than are people from the United States.
d. Women are more likely to report snoring and witnessed apneas than are men.
e. Women are more likely to report daytime sleepiness than are men.

25. Which of the following is true for a 55 year-old man admitted for community-acquired pneumonia?

a. He is unlikely to benefit from early mobilization regardless of his PORT score.
b. He is more likely to engage in early mobilization if his PORT score is III or above.

c. He is more likely to benefit from early mobilization if his PORT score is III as apposed to class I or II.
d. Early mobilization will accelerate his discharge from the hospital, but the costs incurred from EM will outweigh the cost-savings of the reduced length of stay.

26. Which of the following is *false*?

a. There are no interventions to delay the onset or the progression to diabetes in an individual with a FG of 109 mg/dL.
b. The IFG is much less strongly associated with CVD than IGT.
c. Both metformin and lifestyle changes may delay or prevent diabetes in an individual with a FBG of 112 mg/dL.
d. The HbA1c is best used to monitor diabetes rather for diagnosis.

Answers: 24 (e); 25 (c); 26 (a)

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By Louis Kuritzky, MD

St John's Wort and Drug Interactions

The cytochrome P450 system is responsible for the metabolism of the majority of currently prescribed medications. The 2 most common P450 pathways involved in drug metabolism are CYP 3A4 and 2D6, which together are responsible for metabolizing almost three quarters of currently available medications. Any agent that either blocks or enhances either of these enzyme pathways can potentially induce medication toxicity (through drug accumulation) or reduce drug efficacy (through more rapid metabolic disposal).

St. John's Wort (SJW) is a popular over-the-counter agent used for depression, the active ingredient of which is felt to be hypericum. Case reports have suggested that SJW might affect drugs as diverse as cyclosporine, indinavir, tricyclic antidepressants, simvastatin, and even oral contraceptives. For instance, it has been suggested that the enhanced activation of the CYP3A4 system by SJW might lead to increased metabolism of ethinyl estradiol in oral contraceptives, leading to unplanned pregnancy.

Markowitz and associates studied pharmacokinetics of substances metabolized by the 3A4 and 2D6 CYP systems when coadministered with SJW. A 2-fold increase in 3A4 activity was seen, but no effect upon 2D6 was found. Since many drugs are metabolized by the CYP 3A4 system, clinicians must recognize which patients are taking SJW to minimize adverse effects upon medication pharmacokinetics. ■

Markowitz JS, et al. JAMA. 2003;290: 1500-1504.

Serum Potassium and Stroke Risk Among Hypertensive Adults

Observational data indicate that persons who consume greater levels of dietary potassium have both lowered blood pressure and reduced risk of stroke. This protective effect of dietary potassium intake is seen in both hypertensive and normotensive persons, though it is more pronounced in men than women. In some hypertension trials, serum potassium levels have shown an inverse relationship with stroke, but of course many of these subjects received diuretic therapy with an anticipatable decline in serum potassium, and these findings have not been consistent among all populations.

Using data from the Group Health Cooperative observational study (a Washington state-based HMO), Smith and colleagues evaluated the relationship between hypokalemia and subsequent ischemic (n = 593) or hemorrhagic stroke (n = 125) in this population of hypertensive adults compared to controls (n = 2397). Potassium status was defined by traditional levels of hypokalemia (potassium < 3.5) measured in the year prior to stroke.

Hypokalemia was associated with substantial increases in risk of stroke, both for ischemic (odds ratio, 2.04) and hemorrhagic (odds ratio, 3.29) stroke. Since no gradient of stroke risk through the normal range of potassium was discerned, the likelihood that it is indeed the hypokalemia that is etiologically related to stroke risk is further strengthened. Use or non-use of diuretics did not affect the relationship between hypokalemia and stroke. The mechanism by which hypokalemia might aggravate stroke risk is uncertain. ■

Smith NL, et al. Am J Hypertens. 2003;16:806-813.

Skin Cancer Prevention and Detection Practices Among Siblings of Patients with Melanoma

More than one-half million Americans have invasive malignant melanoma (MEL), and the incidence of this disorder has risen an alarming 15-fold since World War II. Family members (first degree) of persons with MEL have as much as a 2-8-fold increased risk of developing MEL.

Recommendations by such agencies as the United States Preventive Services Task Force and the National Institute of Health include the suggestion that family members of patients with MEL should be provided skin cancer screening, risk education, and reduction of ultraviolet radiation exposure. When surveillance for MEL is carried out amongs family members, the stage at which MEL is discovered is earlier than that of the index case. Whether such recommendations are adequately used has not been studied.

Geller and associates contacted 585 siblings of 278 persons diagnosed with MEL within the previous 2 months. Although most of the siblings (62%) had examined their skin in the past year, only slightly more than half used sunscreen with at least SPF 15, and only 27% had received a skin cancer examination by a dermatologist. The message to family members of MEL victims about positive steps to maintain their own cutaneous health requires greater advocacy. ■

Geller AC, et al. J Am Acad Dermatol. 2003;49:631-638.

In Future Issues: Metabolic Markers and Insulin Resistance