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Dr. John E. Remmers: A new testing device for sleep apnea patients "removes a major barrier to oral appliance therapy."

New test could cause OSA's treatment success rate to rise

BY KATIE WAGNER LENNON

Frontline Medical News

A novel device has shown a high rate of accuracy in predicting which patients with obstructive sleep apnea (OSA) will improve with oral appliance therapy, according to a study.

"At the present time CPAP is our go-to standard medical therapy [for treating OSA]. While it is a wonderful therapy, it has a very serious drawback, which is poor compliance, and that undercuts its long-term effectiveness in reducing the incidence of cardiovascular disease," said John E. Remmers, MD, the principal investigator, in an interview.

Referring to the Sleep Apnea Cardiovascular Endpoints (SAVE) trial's finding that continuous positive airway pressure (CPAP) did not reduce long-term cardiovascular incidents, he claimed that "these incidents are not being reduced by CPAP, because people don't use it" (N Engl J Med. 2016 Sept 8;375[10]:919-31).

"We seem to be making no progress in reducing the prevalence of untreated, undiagnosed sleep apnea because we are using overnight studies in the lab and we are using a treatment that people don't like and don't want to use," added Dr. Remmers, who is chief medical officer of Zephyr Sleep Technologies.

In Dr. Remmers' new two-part study, 202

TEST HAD A SPECIFICITY OF 93% // *continued on page 6*

Pediatric version of SOFA effective

pSOFA outperformed other organ dysfunction scores

BY BIANCA NOGRADY

Frontline Medical News

An age-adjusted version of the Sequential Organ Failure Assessment score for sepsis has been found to be at least as good, if not better than, other pediatric organ dysfunction scores at predicting in-hospital mortality.

Writing in the Aug. 7 online edition of JAMA Pediatrics, researchers reported the outcome of a retrospective observational cohort study in 6,303 critically ill patients aged 21 years or younger, which was used to adapt and validate a pediatric version of the Sequential Organ Failure Assessment (SOFA) score.

"One of the major limitations of the SOFA score is that it was developed for adult patients and contains measures that vary significantly with age, which makes it unsuitable for children," wrote Travis J. Matics, DO, and L. Nelson Sanchez-Pinto, MD, of the department of pediatrics at the University of Chicago.

Several pediatric organ dysfunction scores

pSOFA COMPARABLE TO OTHER SCORES // *continued on page 4*

INSIDE HIGHLIGHT



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exist, but their range, scale, and coverage are different from those of the SOFA score, which makes them difficult to use concurrently (JAMA Pediatr. 2017 Aug 7. doi: 10.1001/jamapediatrics.2017.2352).

“Fundamentally, having different definitions of sepsis for patients

above or below the pediatric-adult threshold has no known physiologic justification and should therefore be avoided,” the authors wrote.

In this study, they modified the age-dependent cardiovascular and renal variables of the adult SOFA score by using validated cut-offs

from the updated Pediatric Logistic Organ Dysfunction (PELOD-2) scoring system. They also expanded the respiratory subscore to incorporate the $SpO_2:FiO_2$ ratio as an alternative surrogate of lung injury.

The neurologic subscore, based on the Glasgow Coma Scale, was

changed to a pediatric version of the scale. The coagulation and hepatic criteria remained the same as the adult version of the score.

Validating the pediatric version of the SOFA score (pSOFA) score in 8,711 hospital encounters, researchers found that nonsurvivors had a signifi-

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cantly higher median maximum pSOFA score, compared with survivors (13 vs. 2, P less than .001). The area under the curve (AUC) for discriminating in-hospital mortality was 0.94 (95% confidence interval, 0.92-0.95) and remained stable across sex, age groups, and admission types.

The maximum pSOFA score was as good as the PELOD and

The clinical utility on the day of admission of pSOFA and of the Pediatric Risk of Mortality III score was similar, while the pSOFA outperformed other organ dysfunction scores in this setting.

PELOD-2 scales at discriminating in-hospital mortality and better than the Pediatric Multiple Organ Dysfunction Score. It also showed “excellent” discrimination of in-hos-

pital mortality among the 48.4% of patients who had a confirmed or suspected infection in the pediatric intensive care unit (AUC, 0.92; 95% CI, 0.91-0.94), Dr. Matics and Dr.

Sanchez-Pinto reported.

Researchers also looked at the clinical utility of pSOFA on the day of admission, compared with the Pediatric Risk of Mortality (PRISM) III score, and found the two were similar, while the pSOFA outperformed other organ dysfunction scores in this setting.

Overall, 14.1% of the pediatric intensive care population met the sepsis criteria according to the adapted definitions and pSOFA scores, and this group had a mortality of 12.1%. Four percent of the population met the criteria for septic shock, with a mortality of 32.3%.

The SOFA score incorporates respiratory, coagulation, renal, hepatic, cardiovascular, and neurologic variables. The authors, however, argued that it does not account for

The pSOFA showed “excellent” discrimination of in-hospital mortality among the 48.4% of patients who had a confirmed or suspected infection in the pediatric intensive care unit, Dr. Matics and Dr. Sanchez-Pinto reported.

age-related variability, in particular in renal criteria and the detrimental effects of kidney dysfunction in younger patients.

“In addition, the respiratory subscore criteria – based on the ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) – have not been modified in previous adaptations of the SOFA score even though the decreased use of arterial blood gases in children is a known limitation,” they wrote.

“Having a harmonized definition of sepsis across age groups while recognizing the importance of the age-based variation of its measures can have many benefits, including better design of clinical trials, improved accuracy of reported outcomes, and better translation of the research and clinical strategies in the management of sepsis,” Dr. Matics and Dr. Sanchez-Pinto said.

They acknowledged, however, that their findings were limited because they were generated using retrospective data and needed to be validated in a large multicenter sample of critically ill children. They also pointed out that they did not evaluate the performance of pSOFA as a longitudinal biomarker and suggested that such studies would improve understanding of pSOFA’s clinical utility.

No conflicts of interest were reported.

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adults – primarily overweight, middle-aged men, diagnosed with moderate sleep apnea – were divided into two groups. The first included 149 people who were given a two-night, in-home, feedback controlled mandibular positioner (FCMP) test, using equipment manufactured by Zephyr Sleep Technologies. In this test, a custom-fit oral appliance is simulated using a temporary set of trays and impression material. The trays are connected to a small motor controlled by a little computer that sits on the stomach and moves the mandible when the patient has a problem breathing.

All patients received a custom oral appliance designed using data acquired from the test. The patients then wore the custom oral appliances while connected to a validated monitor as an outcomes study.

Finally, the researchers fed all of the data they collected from this first group of patients into a machine learning model. Then the second set of patients participated in the testing. Outcomes data on the appliance's performance in each individual in the first group were used to create a classification system to predict therapeutic outcomes for the 53 patients in the second group. The patients in the second group then received their custom oral appliances, connected to the same type of monitor used by the first group.

Therapeutic success or failure was defined as having mean oxygen desaturation index values of less than or greater than 10 events/hour, respectively. The investigators determined that the test had an 85% sensitivity level with 93% specificity, a positive predictive value of 97%, and a negative predictive value of 72%. Of those who were predicted to respond to therapy, the mandibular protrusive position was efficacious in 86% of patients.

The high rate of accuracy for predicting who will derive the most

benefit from the appliance, along with the demonstrated preference for oral appliances compared to continuous positive airway pressure devices among patients, increases the clinical utility of the appliance, and expands options for clinical management of sleep apnea, according to the study authors (Clin Sleep Med. 2017;13[7]:871-80).

“Our test allows the physician to prescribe the therapy knowing it will get rid of sleep apnea, and it tells the dentist how far the mandible needs to be pulled out by the custom fit device,” Dr. Remmers explained.

Dentists will also benefit from the test, because it allows them to make an appliance that will not need to be adjusted and will have a higher success rate than the current 60% success rate that oral appliances have at treating sleep apnea, he noted.

“This opens up a new alternative clinical avenue at a critical time, when we have just learned over the past few years that there are serious questions about the effectiveness of CPAP in the long term,” Dr. Remmers added. “[With oral appliance therapy] you have an opportunity for higher compliance, because people prefer the less obtrusive oral appliance therapy over CPAP, and they use it more than CPAP. ... Because our product says you don't treat everybody, you only undertake oral appliance therapy for those who we know in advance will have a favorable outcome, it removes a major barrier to oral appliance therapy that has been the barrier for many years.”

Dr. Remmers noted that his test was not nearly as good at identifying people who would be failures as it was at identifying people who would be successes and that he is carrying out another trial with a similar device.

Some participants reported sore gums when using the device, but there were no long-lasting adverse events reported.

The mandibular positioner home test has not been approved or cleared for use by the Food and Drug Administration, but is currently being sold in Canada, according to Dr. Remmers.

Zephyr Sleep Technologies and Alberta Innovates Technology Futures sponsored the study. It is registered on clinicaltrials.gov as NCT03011762. All of the investigators, other than Nikola Vranjes, are employed or associated with Zephyr Sleep Technologies.

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Politics and Pulmonary Medicine

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VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, PhD, FCCP, comments: This is an interesting study on promising technological advances in the area of mandibular advancement devices for sleep disordered breathing.



PICU admission not needed for high-flow nasal cannula

BY M. ALEXANDER OTTO

Frontline Medical News

NASHVILLE, TENN. – Young children with acute bronchiolitis do not need to be admitted to the pediatric ICU for high-flow nasal cannula treatment of up to 6 L/min and 50% oxygen; it is safe to administer it on the floor, according to a review of 6,804 acute bronchiolitis cases in children younger than 2 years treated at the University of Texas Southwestern Medical Center, Dallas.

Use of high-flow nasal cannulas (HFNC) has increased dramatically in recent years at UT Southwestern and elsewhere. It soothes children and can rapidly improve breathing without the nasal edema and nose bleeds common with cooler, drier, 100% oxygen. At Southwestern, HFNC use on the pediatric wards increased from 5% of acute bronchiolitis cases in the September 2010 to April 2011 season to 60% in the 2015-2016 season. Use for bronchiolitis in the PICU increased from 82% to 98% over the same period.

The increase correlated with a drop in intubation for acute bronchiolitis

from 14% of children in 2010-2011 to just 2% in 2015-2016. The only HFNC adverse events were minor air leaks in two children.

As HFNC became more common, however, the Dallas team found that length of stay for acute bronchiolitis increased from 1.8 days in 2011-2012 to 2.4 days in 2015-2016, perhaps because the use of HFNC gives providers the impression that children are sicker than they actually are.

To counter the problem, lead investigator Vineeta Mittal, MD, associate professor of pediatrics, and her colleagues created an HFNC weaning protocol that gradually steps down treatment based on blood oxygen saturation levels and breathing effort, leading ultimately to a room-air challenge. It helped; the mean length of stay as of November 2016 was 1.7 days.

There's been pushback in some places about giving HFNC on the floor: Intensivists sometimes consider it a form of ventilation that should be administered in the PICU. At levels up to 6 L/min and 50% oxygen, though, HFNC is "safe to give on the floor, because there's no



"We are managing 80% of cases on the floor" with the help of HFNC.

Dr. Vineeta Mittal

Frontline Medical News

pneumothorax risk," Dr. Mittal explained. HFNC "is not a ventilator; it's an effective form of noninvasive respiratory support in children with moderate to severe respiratory distress from bronchiolitis."

At Southwestern, "we are managing 80% of cases on the floor" with the help of HFNC, Dr. Mittal said at Pediatric Hospital Medicine.

At least for now, children at Southwestern go to the PICU if they need higher flow rates, but Dr. Mittal said it's not clear if that's necessary. "We said [6 L/min] is safe," but maybe "we could even use 8 L/min or even 12 L/min" – the maximum delivered in the PICU over the study period – "be-

cause we know it's safe," she said. In addition, keeping kids on the floor also saves money, she noted at the meeting, which was sponsored by the Society of Hospital Medicine, the American Academy of Pediatrics, and the Academic Pediatric Association.

Dr. Mittal is concerned HFNC might be overused. "We have gotten so used to this machine that the moment we see distress, we put the kid on high flow," rather than observing them for a bit to see if they recover on their own. More data are needed to determine when HFNC should be initiated, and when to pull the plug on HFNC and intubate, she said.

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CAP with empyema successfully treated with oral antibiotics

BY BRUCE JANCIN

Frontline Medical News

MADRID – Outpatient oral antibiotics were more successful than outpatient parenteral antibiotic therapy at treating children with community-acquired pneumonia (CAP) complicated by empyema, in a study presented at the annual meeting of the European Society for Paediatric Infectious Diseases.

Thirty-five percent of the patients were culture positive, a typically low rate that makes treatment of this disease particularly challenging, Lauren Kushner, a medical student at the University of California, Irvine, and one of the study's authors, said at the meeting.

The treatment success rates, which were defined as improvement with no change in treatment, were 93% for the patients taking oral antibiotics and 58% in the patients on outpatient parenteral antibiotic therapy.

This retrospective observational study included 149 patients under age 18 years hospitalized for community-acquired pneumonia complicated by empyema, at Children's Hospital of Orange County, Calif. Only 12 of the patients were treated with parenteral antibiotic therapy and none of the study participants had comorbid chronic medical conditions. As in other studies, *Strepto-*

coccus pneumoniae was the most commonly identified pathogen.

Laboratory markers of inflammation are useful in guiding oral antibiotic therapy for children with CAP complicated by empyema, reported Ms. Kushner.

"A rapid drop in C-reactive protein [CRP] in combination with a decrease in white blood cell count can be used acutely in the hospitalization phase to tell you the patient is improving on the selected antibiotic and also to help dictate when the patient might be able to go home, whereas improvement in the erythrocyte sedimentation rate [ESR] does not happen until much later in the course of treatment but can be used to tell you when a patient has been adequately treated," said Ms. Kushner.

One hundred thirty-seven patients were discharged on oral antibiotic therapy, as is strongly recommended in Infectious Diseases Society of America guidelines for postdischarge treatment of complicated pneumonia, even though there are no randomized clinical trials demonstrating it to be superior or even noninferior to outpatient parenteral antibiotics. An aminopenicillin was the most frequently prescribed type of oral antibiotic, while ceftriaxone was the top choice for outpatient parenteral therapy.

The average total duration of antibiotic therapy, inpatient plus outpatient, was similar in the two groups: 30.4 days in the oral antibiotic group and 33.2 days in children on outpatient IV therapy.

The transition to oral therapy occurred a median of 6 days after admission. At that point, CRP levels had dropped sharply by a mean of 204 mg/L from a baseline of more than 250 mg/L at admission. In the same time frame, mean WBC dropped by 6,400 cells/mcL from close to 20,000/mcL at admission. Thus, sharp declines in these two inflammatory markers while a patient is still in the hospital provide reassurance that antibiotic therapy is on the right track. Their rate of decline slowed considerably after the switch to oral therapy: for example, mean CRP decreased by only another 44 mg/L from switch to discharge, and by a further 19 mg/L from discharge to end of treatment.

In contrast, the mean ESR remained elevated at a level approaching 100 mm/hour with little fluctuation from admission through discharge. Weekly monitoring of ESR post discharge showed that this inflammatory marker improved only late in the course of oral therapy. A drop to less than 30 mm/hour indicates the infection has resolved, Ms. Kushner said.

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E-cigarettes: A health threat or cessation tool?

BY BRUCE JANCIN

Frontline Medical News

DENVER – Can e-cigarettes help smokers quit?

“So far, the evidence regarding e-cigarettes’ effectiveness for smoking cessation is equivocal at best,” Alison Breland, PhD, said at the annual meeting of the Teratology Society.

But Dr. Breland noted that there is significant controversy around this topic. “I can tell you that, at the conferences I go to, where there are lots of people studying nicotine and tobacco, scientists are fighting with each other over this question,” said Dr. Breland, a psychologist and project director at the Center for the Study of Tobacco Products at Virginia Commonwealth University in Richmond.

Several small, randomized, controlled trials suggest electronic cigarettes have efficacy comparable to the nicotine patch. But the bulk of the literature indicates otherwise. Dr. Breland found persuasive a systematic review and meta-analysis of 38 studies: Its investigators at the University of California, San Francisco, concluded that the odds of quitting smoking were 28% lower in smokers using e-cigarettes, compared with those not using the devices (*Lancet Respir Med.* 2016 Feb;4[2]:116-28).

That being said, she noted that this meta-analysis has generated unusually harsh printed comments from its critics.

“We could argue about the methodology of the studies all day. If you think all the studies are garbage

then you won’t believe the odds ratio, either. But I think right now the evidence shows that e-cigarettes don’t seem to help people quit,” she said. “That may change in the future with testing of different kinds of devices.”

To be useful for smoking cessation, she explained, a device would need to consistently deliver enough nicotine to enable the smoker to fend off withdrawal symptoms but not so much that the wish to quit evaporates. It’s a matter of finding the sweet spot in what is technically termed device nicotine flux.

There is a great deal of misconception about e-cigarettes, Dr. Breland said, some of it promoted through misleading product advertising. She sought to set the record straight.



DR. BRELAND

How e-cigarettes work

What are e-cigarettes? They are basically nicotine delivery devices. They use electricity to power a heating element that aerosolizes a liquid containing varying concentrations of nicotine; solvents, such as propylene glycol and vegetable glycerins; and flavorants. As a class, e-cigarettes are rapidly evolving. A vast array of devices are marketed with wide differences in design, materials, construction, amount of nicotine delivered, and electrical power – which, along with puff duration, is a key factor in how much nicotine gets into a user’s blood.

“Most of the devices have a battery, but it’s important to know that some of them can be plugged directly into a USB port on a computer,” Dr. Breland said.

E-cigarettes don’t generate a vapor, as is widely believed. It’s an aerosol, and it contains toxic byproducts. On the plus side, unlike combustible cigarettes, e-cigarettes don’t deliver carbon monoxide.

A vast array of flavorant mixtures

are sold, including some that are clearly designed to be attractive to children, with names like “blue cotton candy” and “Apple Jacks.”

User demographics

Who is using e-cigarettes? Primarily adolescents and young adults in prime reproductive age. National surveys indicate e-cigarettes are now the most widely used tobacco product among U.S. high school students, well ahead of combustible cigarettes.

Of particular concern, data from the Centers for Disease Control and Prevention’s National Health Interview Survey indicate that, among 18- to 24-year-olds who use e-cigarettes, about 40% also currently use conventional cigarettes, about 20% are former cigarette smokers, and about 40% are never smokers – that is, have never smoked combustible cigarettes (*MMWR Morb Mortal Wkly Rep.* 2016;65:1177. doi: 10.15585/mmwr.mm6542a7).

“We don’t know what’s going to happen to these never smokers who are currently using e-cigarettes. Are they starting on a lifetime of nicotine dependence via e-cigarettes, or perhaps even worse, are they going to transition to combustible cigarettes? There’s more and more evidence showing that’s happening,” Dr. Breland said.

The CDC survey also showed that 59% of adult users of e-cigarettes are what Dr. Breland called “dualies,” individuals who also smoke conventional cigarettes.

“That really diminishes any potential benefit of e-cigarettes,” she said.

Impact on pregnancy

What is known about the impact of e-cigarettes on pregnancy and birth outcomes? Almost nothing at this point. E-cigarettes deliver nicotine to the bloodstream, and nicotine is

“We could argue about the methodology of the studies all day. If you think all the studies are garbage then you won’t believe the odds ratio, either. But I think right now the evidence shows that e-cigarettes don’t seem to help people quit.”

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known to cause unwelcome, long-term changes in fetal brain development and in that of adolescents as well. The other aerosolized toxicants have not been well studied. A few small surveys conducted in obstetric practices indicate some pregnant women perceive e-cigarettes as posing only minor health risks and safer than combustible cigarettes. And some pregnant women are using e-cigarettes.

Dr. Breland is an investigator in an ongoing, multicenter, longitudinal study enrolling pregnant smokers during their first trimester and following them through childbirth. So far, the investigators have enrolled 93 conventional cigarette users and 24 dualies but have managed to enroll only three exclusive e-cigarette users.

“I think it’s notable that we’re not finding exclusive e-cigarette users. It’s early in the study, but so far the dual users are smoking the same number of cigarettes per day as cigarette-only users, and they have the same expired carbon monoxide levels. It makes me feel concerned in particular about dual use in pregnancy,” she said.

Dr. Breland’s research is supported by the National Institute on Drug Abuse and the Food and Drug Administration.

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Monotherapy effective for antibiotic-resistant infections

BY MICHELE G. SULLIVAN

Frontline Medical News

VIENNA – A single, well-targeted antibiotic may be enough to effectively combat serious bloodstream infections in patients who have a low baseline mortality risk.

Among these patients, overall

mortality was similar among those receiving a single antibiotic and those getting multiple antibiotics (35% vs. 41%). Patients with a high baseline mortality risk, however, did experience a significant 44% survival benefit when treated with a combination regimen, Jesus Rodríguez-Baño, MD, said at the Europe-

an Society of Clinical Microbiology and Infectious Diseases annual congress.

The finding is important when considering the ever-increasing imperative of antibiotic stewardship, Dr. Rodríguez-Baño said in an interview.

“In areas where these pathogens are common, particularly in in-

tensive care units, where they can become epidemic and infect many patients, the overuse of combination therapy will be fueling the problem,” said Dr. Rodríguez-Baño, head of infectious diseases and clinical microbiology at the University Hospital Virgen Macarena, Seville, Spain.

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“This is a way to avoid the overuse of some broad-spectrum antibiotics. Selecting the patients who should not receive combination therapy may significantly reduce the total consumption” on a unit.

The retrospective study, dubbed INCREMENT, was conducted at 37 hospitals in 10 countries. It enrolled patients with bloodstream infections caused by extended-spectrum beta-lactamase- or carbapenemase-producing *Enterobacteriaceae*. Dr. Rodríguez-Baño reported results for 437 patients whose infections were caused by the carbapenemase-producing strain.

It was simultaneously published in *Lancet Infectious Diseases* (2017. doi: 10.1016/S1473-3099[17]30228-1).

These patients were a mean of 66 years old; most (60%) were male. The primary infective agent was *Klebsiella pneumoniae* (86%); most infections were nosocomial. The origin of infections varied, but most (80%) arose from places other than the urinary or biliary tract. Sources were vascular catheters, pneumonia, intraabdominal, and skin and soft tissue. About half of the patients were in severe sepsis or septic shock when treated.

The group was first divided into those who received appropriate or inappropriate therapy (78% vs. 22%). Appropriate therapy was considered to be the early administration of a drug that could effectively target the infective organism. Next, those who got appropriate therapy were parsed by whether they received mono- or combination therapy (61% vs. 39%). Finally, these patients were stratified by a specially designed mortality risk score, the INCREMENT Carbapenemase-Producing *Enterobacteriaceae* (CPE) Mortality Score (Mayo Clinic Proceedings. doi: 10.1016/j.mayocp.2016.06.024):

- Severe sepsis or shock at presentation (5 points)
- Pitt score of 6 or more (4 points)
- Charlson comorbidity index of 2 or more (3 points)
- Source of bloodstream infection other than urinary or biliary tract (3 points)
- Inappropriate empirical therapy and inappropriate early targeted therapy (2 points)

Patients were considered low risk if they had a score of 0-7, and high if they had a score of 8 or more.

The risk assessment tool is quick, easy to figure, and extremely important, Dr. Rodríguez-Baño noted. “This is a very easy-to-use tool that can help us make many patient management decisions. All of the

information is already available in the patient’s chart, so it doesn’t require any additional assessments. It’s a very good way to individualize treatment.”

In the initial analysis, all-cause mortality at 30 days was 22% lower among patients who received appropriate early therapy than those who did not (38.5% vs. 60.6%). This translated to a 55% decrease in the risk of death (hazard ratio, 0.45 in the fully adjusted model).

The investigators next turned their attention toward the group that received appropriate therapy. All-cause 30-day mortality was 41% in those who got monotherapy and 34.8% among those who got combination therapy. Finally, this group was stratified according to the



“This is a very easy-to-use tool that can help us make many patient management decisions.”

DR. RODRÍGUEZ-BAÑO

INCREMENT-CPE mortality risk score.

In the low-risk category, combination therapy did not confer a survival advantage over monotherapy. Death occurred in 20% of those getting monotherapy and 24% receiving combination treatment – not a significant difference (HR, 1.21).

Combination therapy did, however, confer a significant survival benefit in the high-risk group. Death occurred in 62% of those receiving monotherapy and 48% of those receiving combination therapy – a 44% risk reduction (HR, 0.56).

As long as they were appropriately targeted against the infective organism, all drugs used in the high-mortality risk group were similarly effective at reducing the risk of death. Compared to colistin monotherapy, a combination that included tigecycline reduced the risk of death by 55% (HR, 0.45); combination with aminoglycosides by 58% (HR, 0.42); and combination with carbapenems by 44% (HR, 0.56).

A secondary analysis of this group determined each day delay after day 2 significantly increased the risk of death, Dr. Rodríguez-Baño said.

INCREMENT was funded in large part by the Spanish Network for Research in Infectious Diseases. Dr. Rodríguez-Baño has been a scientific adviser for Merck, AstraZeneca, and InfectoPharm.

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Short, simple antibiotic courses effective in latent TB

BY JENNIE SMITH

Frontline Medical News

Latent tuberculosis infection can be safely and effectively treated with 3- and 4-month medication regimens, including those using once-weekly dosing, according to results from a new meta-analysis.

The findings, published online July 31 in *Annals of Internal Medicine*, bolster evidence that shorter antibiotic regimens using rifamycins alone or in combination with other drugs are a viable alternative to the longer courses (*Ann Intern Med.* 2017;167:248-55).

While the new study looked at efficacy and toxicity across treatment strategies only and found no significant differences between shorter rifamycin-based regimens and isoniazid-based regimens lasting 6 months or longer, short courses are considered likely to see better patient adherence, previous research in latent TB has indicated (*BMC Infect Dis.* 2016;16:257).

For their research, Dominik Zenner, MD, an epidemiologist with Public Health England in London,

and his colleagues updated a meta-analysis they published in 2014. The team added 8 new randomized studies to the 53 that had been included in the earlier paper (*Ann Intern Med.* 2014 Sep;161:419-28).

Using pairwise comparisons and a Bayesian network analysis, they found comparable efficacy among isoniazid regimens of 6 months or more; rifampicin-isoniazid regimens of 3 or 4 months, rifampicin-only regimens, and rifampicin-pyrazinamide regimens, compared with placebo (*P* less than .05 for all).

Importantly, a rifampentine-based regimen in which patients took a weekly dose for 12 weeks was as effective as the others.

“We think that you can get away with shorter regimens,” Dr. Zenner said in an interview. Although 3- to 4-month courses are already recommended in some countries, including the United Kingdom, for most patients with latent TB, “clinicians in some settings have been quite slow to adopt them,” he said.

The U.S. Centers for Disease Control and Prevention currently

recommend multiple treatment strategies for latent TB, depending on patient characteristics. These include 6 or 9 months of isoniazid; 3 months of once-weekly isoniazid and rifampentine; or 4 months of daily rifampin.

In the meta-analysis, rifamycin-only regimens performed as well as did those regimens that also used isoniazid, the study showed, suggesting that, for most patients who can safely be treated with rifamycins, “there is no added gain of using isoniazid,” Dr. Zenner said.

Longer isoniazid-alone regimens are nonetheless effective and appropriate for some, including people who might have potential drug interactions, such as HIV patients taking antiretroviral medications, he noted.

About 2 billion people worldwide are estimated to have latent TB, and most will not go on to develop active TB. However, because latent TB acts as the reservoir for active TB, screening of high-risk groups and close contacts of TB patients and treating latent infections is a public health priority.

But many of these asymptomatic

patients will get lost between a positive screen result and successful treatment completion, Dr. Zenner said.

“We have huge drop-offs in the cascade of treatment, and treatment completion is one of the worries,” he said. “Whether it makes a huge difference in compliance to take only 12 doses is not sufficiently studied, but it does make a lot of sense. By reducing the pill burden, as we call it, we think that we will see quite good adherence rates – but that’s a subject of further detailed study.”

The investigators described the lack of availability of hepatotoxicity outcomes for all studies as a limitation, and said some of the included trials had a potential for bias. They did not see statistically significant differences in treatment efficacy between regimens in HIV-positive and HIV-negative patients, but noted in their analysis that “efficacy may have been weaker in HIV-positive populations.”

The U.K. National Institute for Health Research provided funding for the study. One coauthor reported nonfinancial support from Sanofi and financial support from Otsuka.

Prophylaxis prevents PCP in rheumatic disease patients

BY SARA FREEMAN

Frontline Medical News

MADRID – The benefits of primary prophylaxis for pneumocystis pneumonia (PCP) outweighed the risks of treatment in patients taking prolonged, high-dose corticosteroids for various rheumatic diseases in a study presented at the European Congress of Rheumatology.

In a single-center, retrospective cohort study of 1,522 corticosteroid treatment episodes in 1,092 patients with a variety of rheumatic conditions given over a 12-year follow-up period, the estimated incidence of PCP was 2.37 per 100 person-years.

Significantly fewer cases of PCP occurred at 1 year, however, in the 262 patients who were cotreated with the antibiotic combination of trimethoprim and sulfamethoxazole (TMP-SMX), than in the 1,260 patients who received no such antibiotic prophylaxis in addition to their steroid therapy.

The adjusted hazard ratio for no PCP at 1 year of follow-up in the prophylaxis group, versus the no prophylaxis group, was 0.096 (*P* = .022).

The TMP-SMX combination significantly reduced the mortality associated with PCP, with an adjusted HR of 0.09, versus no prophylaxis (*P* = .023).

“Pneumocystis pneumonia is a major opportunistic infection in immunocompromised patients associated with high morbidity and mortality,” explained the presenting study investigator Jun Won Park, MD, of Seoul National University Hospital, South Korea.

Dr. Park added that corticosteroid therapy was an important risk factor for PCP but that the risk-benefit ratio had not been evaluated sufficiently in patients with rheumatic diseases and that there was “different opinion among rheumatologists regarding [the value of] PCP prophylaxis.”

The current study aimed to see if primary antibiotic prophylaxis could prevent PCP in patients with rheumatic diseases, which included patients with systemic lupus erythematosus (SLE), dermatomyositis, rheumatoid arthritis, and Behçet’s disease.

For inclusion, patients had to have been treated with prednisolone at a dose of 30 mg/day or more (or its equivalent) for at least 4 weeks and observed for 1 year. Patients with a prior history of PCP or conditions associated with this opportunistic infection, such as HIV, cancer, or solid organ or hematopoietic stem cell transplantation, were excluded. PCP prophylaxis was given at the discretion of the treating physician, and the mean duration of TMP-SMX was 230 days.

In the prophylaxis group, 34 adverse drug reactions occurred. Two of these reactions were serious – one case of pancytopenia and one case of Steven’s Johnson syndrome – but both resolved

after the antibiotic treatment was discontinued.

A sensitivity analysis was performed, giving consistent results, and a risk-benefit analysis showed that the number needed to treat to prevent one case of PCP was 52, considering all rheumatic disease studied, while the number needed to cause one serious adverse drug reaction was 131.

Taken together, these results suggest a role for TMP-SMX as primary prophylaxis for PCP in patients with rheumatic diseases who need prolonged treatment with high-dose corticosteroids, Dr. Park said.



DR. PARK

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments:

As is standard in many conditions requiring long-term immunosuppression with corticosteroids of a certain dose, prophylaxis for PCP is advocated assuming no contraindication. Additionally, further consideration for starting prophylaxis is warranted if additional immunomodulating agents are concurrently being used (as is often the case in rheumatic diseases) – even if the corticosteroid dosing is deemed “not high.”



Metastasectomy prolongs soft-tissue sarcoma survival

BY RICHARD MARK KIRKNER

Frontline Medical News

The rate of soft-tissue sarcoma has nearly doubled over the past two decades, and up to 50% of patients with tissue sarcoma develop lung metastasis. A single-center study of 539 patients who had treatment for soft-tissue sarcoma has revealed disease and treatment characteristics that may aid patient selection and help predict overall and disease-free survival after diagnosis and treatment.

“Histologic subtype and size of the primary tumor were significantly associated with overall survival,” said lead author Neel P. Chudgar, MD, and his coauthors in the July issue of the *Journal of Thoracic and Cardiovascular Surgery* (2017;154:319-30).

“Patients who underwent pulmonary metastasectomy [PM] for pleomorphic sarcoma/malignant fibrous histiocytoma had the shortest median overall survival (23.6 months), whereas those who underwent PM for leiomyosarcoma had a median overall survival of 42 months,” he said.

The study subjects had pulmonary metastasectomies at Memorial Sloan Kettering Cancer Center, New York, during September 1991–June 2014. The median overall survival was 33.2 months, and median disease-free survival was 6.8 months for the entire cohort.

Among the disease characteristics associated with a lower hazard ratio of death shown by multivariable analyses were leiomyosarcoma histologic subtype (HR, 0.57), primary tumor size of 10 cm or less (HR, 1.00 vs. HR, 1.37 for those greater than 10 cm), increasing time from primary tumor resection to development of metastases (HR, 0.4 at less than 24 months vs. 1.0 at less than 6 months), solitary lung metastasis (HR, 1.0 vs. 1.8 for one year or more), and minimally invasive resection (HR, 0.71), all of which were statistically significant differences. Disease-free interval of more than 1 year and one pulmonary metastasis were significantly associated with lower hazard of disease recurrence.

Of patients, 70% had pulmonary metastasectomy as their primary treatment. The remainder had induction chemotherapy. In addition, 71% had open procedures over the 23-year study period, but minimally invasive operations became more common with time, increasing more than four-fold from the first half of the study period, vs. the last. They accounted

for more than half of all procedures in the last 5 years of the study.

With regard to tumor type, fibrosarcoma was associated with longest median overall survival (65.2

months). Dr. Chudgar and his colleagues noted that 43% of these patients had low-grade primary tumors. Patients with low-grade tumors of all types had a median overall survival

of 71.8 months, vs. 30.8 months for those with high-grade tumors.

“Our results indicate that therapeutic-intent pulmonary metastasectomy

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for soft-tissue sarcoma can be associated with prolonged survival,” Dr. Chudgar and his coauthors said. “The median survivals in our study are comparable with those in previous studies.” However, their analysis went beyond previous studies because they identified positive prognostic factors.

Dr. Chudgar and his coauthors acknowledge that various studies have drawn conflicting conclusions about the validity of histologic subtype as a prognostic factor, but their study differs from previous studies because it is a single-center cohort, “which increases the power to potentially identify significant differences, and we focused on soft-tissue

sarcoma exclusively to enhance the homogeneity of the study population.”

Nonetheless, the researchers noted some limitations of their study, namely their collective analysis of the various soft-tissue sarcoma subtypes and the lack of a control group. Soft-tissue sarcoma, because of its heterogeneous nature, chal-

lenges the adoption of precision medicine for this cancer type, but, until clinicians better understand the underlying mechanism of metastasis in these tumor types, Dr. Chudgar and his coauthors said, pulmonary metastasectomy “remains the best available treatment for soft tissue sarcoma pulmonary metastases.”

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VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: Pulmonary metastasectomy (PM) is a well-established component in the management of sarcoma. Although better survival has been reported with fewer metastases and longer intervals between diagnosis and the appearance of

metastases, data have been conflicting regarding outcomes based on histologic subtypes. Prior studies have revealed no significant difference in survival between patients with high-grade vs. low-grade tumors, histological type, and unilateral vs. bilateral lung metastasis (Thorac Cardiovasc Surg. 2016;64:1460). This large single-institution study reports

prolonged survival following PM and identifies clinical features that confer better prognosis including histologic subtype, disease-free interval, number of pulmonary metastases, and minimally invasive resection. This information will help in identifying patients best suited for undergoing pulmonary metastasectomy for soft-tissue sarcoma.



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Immune signature shows good prognostic performance

BY SUSAN LONDON

Frontline Medical News

A new tumor immune-related gene signature may help take the guesswork out of prognostication in patients with early-stage non-small cell lung cancer (NSCLC), according to a retrospective cohort study.

“Various components of the immune system have been shown to be a determining factor during cancer initiation and progression,” note the investigators, who were led by Bailiang Li, PhD, of Stanford (Calif.) University. “Recent immunotherapies targeting specific immune checkpoints such as programmed death 1 or programmed death ligand 1 have demonstrated a remarkable, durable response in NSCLC. Certain histopathologic patterns, such as intratumoral infiltration by cytotoxic lymphocytes, have also been associated with better prognoses in several cancer types, including NSCLC.”

For the study, the investigators developed and validated an immune-related gene signature using frozen tumors from 2,414 patients with stage I or II nonsquamous NSCLC from 19 public cohorts who underwent resection with negative margins and did not receive any neoadjuvant or adjuvant therapy.

The new signature contained 25 gene pairs consisting of 40 unique immune-related genes, Dr. Li and associates report (JAMA Oncol. 2017 Jul 6. doi: 10.1001/jamaoncol.2017.1609).

Processes such as chemotaxis were enriched among the included genes.

The signature significantly stratified patients into groups that have high and low risks of death during follow-up, both across and within subsets with stage I, IA, IB, or II dis-

Continued on following page

Invasive mediastinal staging rates run the gamut

BY BRUCE JANCIN

Frontline Medical News

COLORADO SPRINGS – Significant variability exists between hospitals in Washington state in their rates of invasive mediastinal staging for lung cancer, Farhood Farjah, MD, reported at the annual meeting of the Western Thoracic Surgical Association.

“We found evidence of a fivefold variation in hospital-level rates of invasive mediastinal staging not explained by chance or case mix,” according to Dr. Farjah of the University of Washington, Seattle.

Prior studies from across the country have documented widespread underutilization of invasive mediastinal staging in situations where the staging is recommended in major guidelines such as those published by the National Comprehensive Cancer Network.

“This has led to substantial concerns about quality of thoracic surgical care in the community at large,” he noted.

The Washington study is the first to show hospital-by-hospital variation in rates of invasive mediastinal staging.

Invasive mediastinal staging for lung cancer is considered important because imaging is known to have a substantial false-negative rate, and staging results have a profound impact on treatment recommendations, which can range from surgery alone to additional chemoradiation therapy.

Yet the meaning of the hospital-level huge variability in practice observed in the Washington study remains unclear.

“Our understanding of the underutilization of invasive mediastinal staging is further complicated by the fact that patterns of invasive mediastinal staging are highly variable across hospitals staffed by at least one board-certified thoracic surgeon with a noncardiac practice,” Dr. Farjah explained. “This variability could be a marker of poor-quality care. However, because the guidelines are not supported by level 1 evidence, it’s equally plausible that this variability might represent uncertainty or even disagreement with the practice guidelines – and specifically about the appropriate indication for invasive staging.”

He presented a retrospective cohort study of 406 patients whose non-small cell lung cancer was resected during July 2011–December 2013 at one of five Washington hospitals, each with at least one board-certified thoracic surgeon with a noncardiac practice on staff. The four participating commu-

nity hospitals and one academic medical center were involved in a National Cancer Institute–funded, physician-led quality improvement initiative.

Overall, 66% of the 406 patients underwent any form of invasive mediastinal staging: 85% by mediastinoscopy only; 12% by mediastinoscopy plus endobronchial ultrasound-guided nodal aspiration (EBUS); 3% by EBUS only; and the remaining handful by mediastinoscopy, EBUS, and esophageal ultrasound-guided nodal aspiration. The invasive staging was performed at the time of resection in 64% of cases. A median of three nodal stations were sampled.

After statistical adjustment for random variation and between-hospital differences in clinical stage, rates of invasive staging were all over the map. While an overall mean of 66% of the lung cancer patients underwent invasive mediastinal staging, the rates at the five hospitals were 94%, 84%, 31%, 80%, and 17%.

Dr. Farjah and his coinvestigators are now conducting provider



Dr. Farhood Farjah

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ease. Relative to counterparts falling into the signature-defined low-risk group, those falling into the signature-defined high-risk group had roughly twice the risk of death after adjustment for clinical and pathologic characteristics, with a hazard ratio range of 1.72 (P less than .001) to 2.36 (P less than .001).

Accuracy of the immune signature exceeded that of two commercialized gene signatures for estimating survival in similar validation cohorts (mean concordance index, 0.64 vs. 0.53 and 0.61).

Moreover, the combination of the immune signature with clinical factors outperformed the signature alone (mean C-index, 0.70 vs. 0.63) and another commercialized clinical-molecular combination signature (mean C-index, 0.68 vs. 0.65).

“The proposed immune-related gene pair–based signature is a promising prognostic biomarker in nonsquamous NSCLC, including early-stage disease,” concluded the investigators. “Prospective studies are needed to further validate its analytical accuracy for estimating prognoses and to test its clinical utility in individualized management of nonsquamous NSCLC.”

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP,

comments: As lung cancer screening implementation increases, it is expected that the prevalence of early-stage non-small cell lung cancer (NSCLC) will increase.

While surgical resection confers a good 5-year survival in early-stage NSCLC, the patients most likely to achieve long-term benefit are those with small tumors, T1a lesions.

Currently, adjuvant therapy is reserved for patients with tumors greater than 4 cm or those with N1 disease. Having reliable biomarkers to identify patients at a high risk for recurrence after surgical resection is a significant clinical advantage in order to guide adjuvant therapy. The clinical-immune signature described in this study is an exciting and promising biomarker for estimating overall survival in NSCLC.

interviews and focus groups in an effort to understand what drove the participating surgeons' wide variability in performing invasive mediastinal staging.

Discussant Jane Yanagawa, MD, of the University of California, Los Angeles, commented, "I think this is a really interesting study because, historically, lower rates of mediastinoscopy are assumed to be a reflection of low-quality care – and you suggest that might not be the case, that it might be more complicated than that."

Dr. Yanagawa sketched one fairly common scenario that might

represent a surgeon's reasonable avoidance of guideline-recommended invasive mediastinal staging: a patient who by all preoperative imaging appears to have stage IA lung cancer and wishes to avoid the morbidity, time, and cost of needle biopsy, instead choosing to go straight to the operating room for a diagnosis by wedge resection, followed by a

completion lobectomy based upon the frozen section results. Could such a pathway account for the variability seen in the Washington study?

"I think it could have," Dr. Farjah replied. "I would say that's probably one driver of variability."

As for the generalizability of the findings of a five-hospital study

carried out in a single state, Dr. Farjah said he thinks the results are applicable to any academic or community hospital with at least one board-certified thoracic surgeon with a noncardiac practice.

He reported having no financial conflicts of interest regarding the study.

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VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP,

comments: Staging of lung cancer is essential to select the best treatment strategy for a given patient. However, despite multiple guideline recommendations for mediastinal staging, a significant number of stage IIIA NSCLC do not receive guideline-adherent mediastinal staging. This study highlights the marked variability in mediastinal staging that persists across clinical centers. Lower rates of mediastinal staging have been blamed on lack of board-certified thoracic surgeons with training in mediastinoscopy, but in this study, each center involved had at least one board-certified thoracic surgeon. Striking is that only a small percentage (15%) of patients in this study underwent staging with bronchoscopic ultrasound-guided needle aspiration. Given the high sensitivity and low invasiveness, ultrasound-guided staging modalities should be considered before surgical techniques for hilar and mediastinal staging. The "gold standard" of mediastinoscopy for invasive staging is challenged by ultrasound-guided techniques, which guidelines recommend to be the initial invasive test in most instances for which lymph node staging is required. This study underscores the importance of continual education and training of pulmonologists and thoracic surgeons in ultrasound-guided techniques in order to improve mediastinal staging application and accuracy.

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Tips and tricks for appealing an audit

BY ALICIA GALLEGOS

Frontline Medical News

CHICAGO - The question is not if a physician will face a Medicare or Medicaid billing

audit, but when, according to Abby Pendleton, a New York-based health law attorney. That's why it pays to know how to handle an audit before one probe disrupts your practice. At a recent American Bar Association meet-

ing, Ms. Pendleton and H. Rusty Comley, a Jackson, Mississippi-based health law attorney, offered answers to top audit questions and provided guidance on how physicians can successfully appeal an audit.



MS. PENDLETON

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MR. COMLEY

When should you appeal?

There are a number of factors to consider when deciding whether to appeal audit findings. For starters, consider the cost of the payback amount and the basis of the findings.

If the amount of money is nominal, the audit involves a one-time mistake and the decision is not really disputable, a doctor may just want to pay the audit request, Mr.

Comley said in an interview.

“In other words, the provider would spend more money and time to appeal the audit than to pay the audit, and the issue or mistake is not likely repeated in past or future claims,” it might make sense to just pay, he said.

On the other hand, if the findings are arguable, the monetary amount is significant, and/or the audit could affect more

than just one billing, the doctor may want to consider appealing. Paying a small monetary amount could become problematic when the audit issue or “mistake” may have been repeated or will be repeated, Mr. Comley cautioned, adding that paying without dispute could create a precedent for future audits.

If the basis of the findings stem from

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an interpretation of a local coverage decision that the physician disagrees with, he or she may also want to appeal, Ms. Pendleton added.

“If you don’t fight it, there’s an argument that, ‘Well, guess what? You had that issue going back 6 years for all these other claims, and now we

get into the [Medicare] 60-day overpayment identification [rule],” she said at the meeting. “If a physician is [not] aware of payments they’re not entitled to, even if they think they were right on the front end, but they later become aware, they have 60 days to refund it or it’s a false claim. Those are considerations that really need to be looked at.”

What should you expect from an appeal?

Expect to go through more than one appeals process step to succeed. There are five stages to the appeals process (see box, pg. 23).

“At the redetermination stage, I don’t see a whole lot of movement in terms of great success at that first stage,” Ms. Pendleton said. “So, don’t

think, ‘If we get to that first level of appeal, we’re expecting to win.’ If you look at the statistics, it’s not really that realistic.”

Although a provider has 120 days to file an appeal, it’s smarter to file within the first 30 days, Ms. Pendleton advised. If an appeal is filed within 30 days, the government cannot recoup its demand from

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a doctor's current Medicare payments.

Expect a lengthy time frame for a final outcome. Under federal law, once an appeal gets to the administrative law judge (ALJ) stage (the third stage), the appellant should receive a hearing decision within 90 days. However, because of heavy case backlogs, physicians typically

don't get a hearing for 3 years, Ms. Pendleton said.

"The problem is, your MAC [Medicare administrative contractor] can start taking your money after the [second] stage," she said. "If it's a huge dollar amount, you're probably going to have to enter into a payment plan [with the government]. You will eventually get your

money back, if you win, 3-4 years later."

Note that physicians generally experience a higher degree of success at the ALJ stage, so it may be worth continuing the appeal through this stage, she noted.

Overall, more than one-third of audit findings are reversed in providers' favor during the appeals

process. Of 170,482 Medicare appeal decisions in 2015, 37% were made in favor of the health provider, an increase from 23% in 2014, according to 2015 Medicare data and 2014 reports.

The cost to appeal varies significantly between Medicaid and Medicare and depends largely on

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the complexity of the audit, Mr. Comley said. A Medicaid audit appeal, through an ALJ hearing and written appeal to a court, may cost between \$20,000 and \$60,000 depending on the circumstances, he said. By contrast, a Medicare appeal resolved in the first stage of appeal may cost only a few thou-

sand dollars for a relatively simple audit.

“Of course, the costs will rise at each level of the Medicare appeal process, especially in the third stage involving the ALJ telephonic hearing, but, in most cases, the Medicare appeal costs will still be below a similar Medicaid appeal,” he said.

What strategies can help you win?

Consider reaching out to your congressional representative or senators, Mr. Comley advised. Particularly if the issue involves a medical treatment decision or a medically necessary determination, it may be helpful to copy “your favorite Congressman or

senator’s office” on correspondence with the MAC. Clearly state your argument against the findings and how/why the medical decision was made. Legislators will often get involved and could help your appeal, Mr. Comley said.

Further, don’t review just the claims that auditors denied. Also evaluate the claims they have approved in the past, he added.

“In almost every case I’ve been involved in, they’ll approve claims that, on the other hand, they deny,” Mr. Comley said. “Under most legal standards, that’s a good way to win – it’s called arbitrary and capricious.”

Find the best experts to back your case, Ms. Pendleton advised. Consider including expert opinions in written responses to the government that support the services provided and/or have medical experts ready to testify during hearings. If the government based

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: The most effective way to handle an audit is not to be involved in one. This requires an appropriate knowledge of coding and billing tempered with a strong dose of honesty. While CMS rules for coding and billing can occasionally be confusing, they are not intended to “trick” physicians into making errors. Rather, either through lack of understanding, poor documentation, or dishonesty (upcoding), mistakes can be made. Unfortunately, the physician is considered guilty until proven otherwise. The 37% success rate of appeals argues that this is true more often than not. As noted in the article, a CMS audit can be a very anxiety-provoking, time-consuming, and expensive process that one should avoid at all costs. The key to doing this and improving the physician success rate if one is audited is through education of the providers and advocating to amend poorly written CMS policy. Dishonesty will have to correct itself.



its findings on statistics or cited statistics in its review, involve a statistical expert who can argue against the government's conclusion.

If the case is significant enough, consider skipping steps in the appeals process to get the case before a federal court sooner. Appellants can escalate their appeal through the process at nearly every stage if the government fails to respond within a timely manner. At the second stage, for example, if the qualified independent contractor does not issue a decision within 60 days, an appellant generally has the right to escalate the case to an administrative law judge. If the ALJ does not issue a decision within 90 days, the appeal can generally be escalated to the Appeals Council level, and, if the council does not issue a decision within 90 days, appellants can seek judicial review.

It may be worth it to have your day in court sooner, Ms. Pendleton said.

"It might be an option for providers if you have a large audit with a lot at stake," she said. "Escalate it through. Get it to federal court and argue it."

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The 5 steps of the Medicare appeals process

There are five stages of the Medicare audit appeals process. They include what follows:

1. Redetermination by the Fiscal Intermediary. A redetermination is an examination of a claim by a Medicare administrative contractor (MAC) separate from the personnel who made the initial claim determination. The appellant has 120 days from the date of initial claim determination receipt to file an appeal.
2. Reconsideration by a Qualified Independent Contractor (QIC). A QIC is an independent contractor who didn't take part in the level 1 decision. The QIC will review the request for a reconsideration and make a decision. An appellant must file a request for reconsideration within 180 days of Medicare redetermination notice or remittance advice receipt.
3. Administrative Law Judge (ALJ) hearing. Appellants present their case to an ALJ who will review the facts of the appeal and listen to testimony before making a decision. An ALJ hearing is usually held by phone or video conference. Appellants can ask the ALJ to make a decision without a hearing. The ALJ may also issue a decision without holding a hearing if evidence in the record supports a decision that's fully in the appellant's favor.
4. Medicare Appeals Council review. If you disagree with the ALJ decision or wish to escalate the appeal because the ALJ ruling time frame has passed, a request for a Medicare Appeals Council review can be made. A request for a Medicare Appeals Council review must be made within 60 days of receipt of the ALJ's decision or after the ALJ ruling time frame expires.
5. Judicial review in U.S. District Court. A party may file an action in federal district court within 60 calendar days after the date receiving notice of the Medicare Appeals Council's decision or after a council notice that it is not able to reach a decision. To get a judicial review in federal district court, the case amount must meet a minimum dollar amount (\$1,560 in 2017).

Each state has its own Medicaid appeals process. Contact your state's Medicaid office to find out how to appeal a Medicaid audit finding.

Source: The Centers for Medicare & Medicaid Services

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Physicians express mixed views on FDA tobacco plan

BY ALICIA GALLEGOS

Frontline Medical News

Physicians associations are expressing mixed opinions about the Food and Drug Administration's new plan for regulating tobacco products, such as flavored cigars, hookah tobacco, and e-cigarettes.

As part of the new plan, announced July 28, the FDA will relax previous application deadlines set for makers of newer tobacco products. The agency will also seek more public input on the role of flavors in tobacco products before moving forward with specific regulations.

The American Thoracic Society (ATS) expressed disappointment with the FDA's new plan, calling it a move that centers on delayed action. The agency already has more than enough information to proceed with regulation of flavored nicotine products, the ATS said in a statement.

"The delay outlined in [FDA Commissioner Scott Gottlieb's] vision will cost the American public continued death and disease as a result of tobacco use," Enid Neptune, MD, vice chair of the ATS Tobacco Action Committee said in the statement. "In short, Dr. Gottlieb's announcement of the FDA's new vision for regulating tobacco products is long on delay and short on action. The health of the American public, and particularly today's youth, will suffer as a result of the FDA's failure to act."

The American College of Chest Physicians, meanwhile, expressed its

support of the actions outlined.

"We welcome opportunities and actions that reduce tobacco use, addiction, and tobacco-related disease and death," said Gerard Silvestri, MD, president for the college, in a statement. "We support the actions proposed by the FDA, which are likely to improve public health and reduce the burden of disease on patients and our country."

As part of the FDA's revised plan, the agency intends to begin a public dialogue about lowering nicotine levels in combustible cigarettes to nonaddictive levels through "achievable product standards." The agency also plans to issue an advance notice of proposed rule making to seek input on the potential public health benefits and possible adverse effects of lowering nicotine in cigarettes.

Under revised time lines, applications for newly regulated combustible products, such as cigars, pipe tobacco, and hookah tobacco, must be submitted by makers to the FDA by Aug. 8, 2021, and applications for noncombustible products, such as e-cigarettes, must be submitted by Aug. 8, 2022. Manufacturers can continue to market their products while the agency reviews their product applications. The time frames push back previous deadlines that were established in a May 2016 final rule by the FDA. In the prior rule, manufacturers of all new tobacco products had 12-24 months to prepare and send applications for marketing authorization to the FDA and a 12-month continued compliance

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: While I always try to be open to others' opinions and encourage dialogue in situations where compromise is most appropriate, I must side with the "less than happy" group regarding this ruling. There is certainly enough scientific evidence to take a stand against tobacco products of any kind because of their lack of health benefits. Despite the potential benefit of aiding tobacco cessation efforts, adding flavoring to e-cigarettes does not enhance this benefit but certainly can enhance the taste and thereby nicotine addiction. It is past time for the FDA to step up to the plate and discourage business entities from developing products and services that are of little use to the health of the nation.

period after those dates in which to obtain FDA authorization.

The agency also plans to seek new public input on a range of related topics, including approaches to regulating kid-appealing flavors in e-cigarettes and cigars; the role that flavors in tobacco products, such as menthol, play in attracting youth; and the patterns of use and resulting public health impacts from premium cigars. Additionally, the agency will examine actions to increase access and use of FDA-approved medicinal nicotine products and work with sponsors to consider what steps can be taken under the safety and efficacy standard for products intended to help smokers quit, according to the FDA plan.

"This comprehensive plan and sweeping approach to tobacco and nicotine allows the FDA to apply the powerful tools given by Congress to achieve the most significant public health impact," Mitch Zeller, director of the FDA's Center for Tobacco

Products said in a statement. "Public input on these complex issues will help ensure the agency has the proper science-based policies in place to meaningfully reduce the harms caused by tobacco use."

However, the ATS said that many of the issues raised in the FDA's revised plan have already been discussed at length in the scientific literature and with the public.

"Scientific literature documenting the role cigars play in tobacco-related disease is extensive," and the FDA has already received public and industry input regarding exempting cigars, noted Harold J. Farber, MD, chair of the ATS Tobacco Action Committee. Additionally, multiple reports have been issued on the role of flavoring agents, showing that flavoring agents increase tobacco initiation and make tobacco cessation harder, noted Dr. Neptune.

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Fewer than half of office visits involve primary care

BY RICHARD FRANKI

Frontline Medical News

Visits to primary care generalists, which made up two-thirds of the visits to physician offices in 1980, now represent less than half of all visits, according to the results of a survey by the National Center for Health Statistics (NCHS).

Primary care physicians' share of office visits fell from 66.2% in 1980 to 49.1% in 2013, the NCHS reported in "Health, United States, 2016." The corresponding increase among specialty care physicians gave them a total of 50.9% of all office visits in 2013, up from 33.8% in 1980.

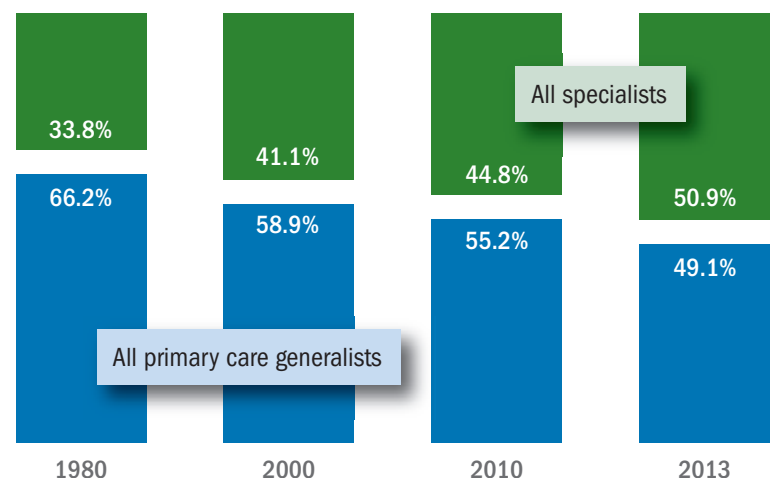
Age may be playing a part in this

shift. The generalists mostly held their own among patients younger than 18 years, who made 77.8% of all their office visits to primary care physicians in 1980, compared with 73.8% in 2013. The shift away from primary care, however, increased along with patient age: from 65.3% of visits in 1980 to 53.7% in 2013 for those aged 18-44 years; 60.2% to 42.1% for 45-64-year-olds, and 61.6% to 38.3% for those aged 65 years and over, the NCHS said.

The NCHS estimates are based on data collected by the National Ambulatory Medical Care Survey, which excluded Alaska and Hawaii in 1980.

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Distribution of visits to physician offices



Note: Based on data from the National Ambulatory Medical Care Survey.

Source: National Center for Health Statistics

Mild OSA: Does it affect cardiovascular health and should it be treated?

BY SOWJANYA DUTHULURU, MD; USMAN NAZIR, MD; AND DAMIEN R. STEVENS, MD, FCCP

The definition of mild obstructive sleep apnea (OSA) has varied over the years depending upon several factors, but based upon all definitions, it is highly prevalent. Depending upon presence of symptoms and gender, the prevalence may be as high 28% in men and 26% in women. (Young et al. *N Engl J Med.* 1993;328:1230). Typically, a combination of symptoms and frequency of respiratory events is required to make the diagnosis. Based upon the International Classification of Sleep Disorders-3rd edition (ICSD-3), the threshold apnea hypopnea index (AHI) for diagnosis depends upon the presence or absence of symptoms. If an individual has no symptoms, an AHI of 15 events per hour or more is required to make a diagnosis of OSA. However, there are several concerns about whether or not an individual may be “symptomatic.” This is most relevant when driving privileges may be at risk, such as with a commercial drivers’ licensing. If a person knows that their response to a list of questions could lead to further testing, additional costs, and/or treatment, then symptoms could be unreported or underestimated. Notwithstanding, specific symptoms that are typically noted include some sign of sleepiness or non-restorative sleep and apneic episodes. The presence of snoring, gasping, choking, or breathing interruptions, either witnessed or noted by the individuals themselves, are included in the criteria. The Epworth Sleepiness Scale is the most common measure of sleepiness, which includes the likelihood of falling asleep in eight different scenarios. However, there is only a weak correlation between the scale and severity of OSA with sensitivity as low as 0.36 reported in some studies, especially if only mild OSA is present. The presence of other comorbid disease can be used as criteria, including hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, and type 2 diabetes mellitus. If no signs, symptoms, or comorbid diseases are present, then an AHI greater than 15 events per hour or more is required to make the diagnosis of OSA (Chowdrui et al. *Am J Respir Crit Care Med.* 2016;193:e37).

There is still debate regarding

the association of mild OSA and cardiovascular disease and whether treatment may prevent or reduce cardiovascular outcomes. The four

main clinical outcomes typically reported are hypertension, cardiovascular events, cardiovascular and all-cause mortality, and ar-

rhythmias. Regarding mild OSA and hypertension, 5 prospective and 18 cross-sectional studies have

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Dr. Duthuluru is Assistant Professor, Dr. Nazir is Assistant Professor, and Dr. Stevens is Associate Professor at the University of Kansas Medical Center.



Continued from previous page

been reported with the two main studies being the Wisconsin Sleep Cohort study and the Sleep Heart Health Study. The Wisconsin Sleep Cohort study found mild OSA was associated with an increased risk of hypertension (Peppard et al. *N Engl J Med.* 2000;342:1378). However, the Sleep Heart Health study

followed individuals without hypertension, including 629 with mild OSA, for 5.2 years and assessed risk of incident hypertension. Stratified analyses found no evidence for an elevated risk of hypertension in subgroups defined by age, sex, BMI, or degree of sleepiness (O'Connor et al. *Am J Respir Crit Care Med.* 2009;179:1159). Therefore, it ap-

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pears current data are contradictory when it comes to mild OSA and subsequent risk of hypertension when stratified by age, sex, and BMI. Only retrospective analyses have been used to assess the risk of cardiovascular events. A large clinical cohort of patients referred for sleep studies showed no association of mild OSA with different com-

posite outcomes. Kendzerska and colleagues evaluated a composite outcome (myocardial infarction, stroke, CHF, revascularization procedures, or death from any cause) during a median follow-up of 68 months. No association of mild OSA with the composite cardiovascular endpoint was identified compared with those without

OSA (Kendzerska et al. *PLoS Med.* 2014;11[2]:e1001599). Only one population-based study (MrOS Sleep Study) looked at the association between mild OSA and nocturnal arrhythmias in elderly men. The study did not find an increased risk for atrial fibrillation or complex ventricular ectopy in patients with mild OSA vs no OSA

(Mehra et al. *Arch Intern Med.* 2009; 169:1147). Several cohort studies have reported mild OSA is not associated with increased cardiovascular mortality. In the 18-year follow-up of the Wisconsin Cohort Study, it was found that mild OSA was not associated with cardiovascular mortality (HR, 1.8; 95% CI, 0.7–4.9).

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All-cause mortality was also not significantly increased in the mild OSA group compared with the no-OSA group in the Wisconsin cohort after 8 years of follow-up (adjusted HR, 1.6; 95% CI, 0.8–2.8). In summary, compared with subjects without OSA, available evidence from population-based longitudinal studies

indicates that mild OSA is not associated with increased cardiovascular or all-cause mortality.

Does treatment of mild OSA vs no treatment change cardiovascular or mortality outcomes? This is still debated with no definitive answer. There have been several studies that have examined different therapies for OSA to reduce cardiovascular

events. Typical events include coronary artery disease, hypertension, heart failure, stroke, arrhythmias, and cardiovascular disease-related mortality. However, most studies have examined cohorts with moderate to severe OSA with limited evaluation in the mild OSA category. The effect of treatment of mild OSA on hypertension has been evaluated.

A single clinical trial randomized patients with mild OSA to either a very low calorie diet with supervised lifestyle modifications vs control arm and followed patients for 1 year (Tuomilehto et al. *Am J Respir Crit Care Med.* 2009;179:320). Participants in the intervention arm lost more weight than the control group. Hypertension was a secondary

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outcome measured from the study. There was no significant change in systolic and diastolic blood pressure after successful weight loss with diet and lifestyle modifications. Follow-up at 2 and 5 years did not show significant changes in systolic and diastolic blood pressure. Patients in the treatment group lost more weight than the control group

(10.7kg vs 2.4kg, respectively) and had greater resolution of sleep apnea (63% vs 35%, respectively). An observational study evaluated the effects of CPAP specifically in patients with mild OSA. There was no significant difference in the risk of developing hypertension among those patients ineligible for CPAP therapy, active on therapy, or those

who declined therapy (Marin et al. *JAMA*. 2012; 307:2169). In contrast, a retrospective longitudinal cohort with normal blood pressure at baseline (mild OSA without preexisting cardiovascular disease, diabetes, or hyperlipidemia) did show decrease in mean arterial blood pressure of 2 mm Hg in the treatment group (Jaimcharyatam et al. *Sleep Med*.

2010;11:837). The MOSAIC trial was a multicenter randomized trial that evaluated the effects of CPAP on cardiac function in minimally symptomatic patients with OSA. The use of CPAP reduced the oxygen desaturation index (ODI) and Epworth Sleepiness Scale values. However, 6 months of therapy did

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not change functional or structural parameters measured by echocardiogram or cardiac magnetic resonance scanning in patients with mild to moderate OSA (Craig et al. *J Clin Sleep Med.* 2015;11[9]:967). A single retrospective study reported the effects of CPAP in patients with mild OSA and all-cause mortality.

The study compared treatment with patients using CPAP more than 4 hours vs a combined group of non-adherent and those who refused therapy (Hudgel et al. *J Clin Sleep Med.* 2012;8:9). There was no significant difference in all-cause mortality in the two groups. However, this study did not analyze the impact of therapy on cardiovascular-specific

mortality. To date, there have been no studies that have evaluated the impact of treatment of mild OSA on cardiovascular events, arrhythmias, or stroke. In addition, there have been no randomized studies assessing treatment of mild OSA on fatal and nonfatal cardiovascular events. There is inadequate evidence regarding the effect of mild OSA on

elevated blood pressure, neurologic cognition, quality of life, and cardiovascular consequences. Future research is needed to investigate the impact of mild OSA on these outcomes.

In summary, mild OSA is a very prevalent disease but the association with hypertension remains unclear and the literature to date suggests no association with other cardiovascular outcomes. In addition, no clear prevention of cardiovascular outcomes with treatment has been proven in the setting of mild OSA.

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APAP improves aerophagia symptoms

BY JENNIE SMITH

Frontline Medical News

Switching continuous positive airway pressure–treated patients to autotitrating positive airway pressure (APAP) systems resulted in reduced severity of patient-reported aerophagia symptoms, according to results from a double-blind, randomized study.

Aerophagia, the swallowing of air leading to gastrointestinal distress, is a frequently reported adverse effect among people treated for obstructive sleep apnea with continuous positive airway pressure (CPAP).

The APAP-treated group saw significantly reduced median therapeutic pressure levels compared with the CPAP-treated patients (9.8 vs. 14.0 cm H₂O, *P* less than .001) and slight but statistically significant reductions in self-reported symptoms of bloating, flatulence, and belching. No significant difference was seen in compliance with therapy between the two treatment groups in this study, published in the August 2017 issue of *Journal of Clinical Sleep Medicine* (2017;13[7]:881-8).

For their research, Teresa Shirlaw and her colleagues in the sleep clinic at Princess Alexandra Hospital in Woolloongabba, Queensland, Australia, analyzed results from 56 adult patients with sleep apnea who had been recently treated with CPAP and reported bloating, flatulence, or belching following therapy.

Patients were randomized 1:1 to in-clinic nighttime CPAP or APAP for 2 weeks and blinded to treatment assignment, while investigators recorded therapy usage hours, pressure, leak, and residual apnea-hypopnea index across the study period. Most of the subjects

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Sleep apnea is often a comorbidity of nocturia

BY DOUGLAS S. PAAUW, MD

A 65-year-old man comes to a clinic concerned about frequent nocturia. He is getting up four times a night to urinate, and he has been urinating about every 5 hours during the day. He has been seen twice for this problem and was diagnosed with benign prostatic hyperplasia and started on tamsulosin.

He found a slight improvement when he started on 0.4 mg qhs, reducing his nocturia episodes from four to three. His dose was increased to 0.8 mg qhs, with no improvement in nocturia.

Exam today: BP, 140/94; pulse, 70. Rectal exam: Prostate is twice normal size without nodules.

Labs: Na, 140; K, 4.0; glucose, 80; Ca, 9.6.

He is frustrated because he feels tired and sleepy from having to get up so often to urinate every night.

What is the best treatment/advice at this point?

- A. Check hemoglobin A_{1c}.
- B. Start finasteride.
- C. Switch tamsulosin to terazosin.
- D. Evaluate for sleep apnea.

At this point, I think an evaluation for sleep apnea is the next appropriate step. It is unlikely that he has diabetes with high enough blood sugars to cause polyuria, with a random glucose of 80. His daytime sleepiness is a clue to a possible sleep disorder, and his nocturia is a symptom that is often overlooked or not appreciated in patients with sleep apnea.

Umpei Yamamoto, MD, of Kyushu (Japan) University Hospital and colleagues studied the prevalence of sleep disordered breathing among patients who presented to a urology clinic with nocturia and in those who visited a sleep apnea clinic with symptoms of excessive daytime sleep-

iness.¹ Sleep disordered breathing was found in 91% of the patients from the sleep apnea clinic and 70% of the patients from the urology clinic. The frequency of nocturia was reduced with continuous positive airway pressure (CPAP) in both groups in the patients who had not responded to conventional therapy or nocturia.

The symptom of nocturia as a symptom of sleep apnea might be even more common in women.² Ozen K. Basoglu, MD, and Mehmet Sezai Tasbakan, MD, of Ege University, Izmir, Turkey, described clinical similarities and differences based on gender in a large group of patients with sleep apnea. Both men and women with sleep apnea had similar rates of excessive daytime sleepiness, snoring, and impaired concentration. Women had more frequent nocturia.

Nocturia especially should be considered a possible clue for the presence of sleep apnea in younger patients who have fewer other reasons to have nocturia. Takahiro Maeda, MD, of Keio University, Tokyo, and colleagues found that men younger than 50 years had more nocturnal urinations the worse their apnea-hypopnea index was.³ Overall in the study, 85% of the patients had a reduction in nighttime urination after CPAP therapy.

Treatment of sleep apnea has been shown in several studies to improve the nocturia that occurs in patients with sleep apnea. Hyoung Keun Park, MD, of Konkuk University, Seoul, South Korea, and colleagues studied whether surgical intervention with uvulopalatopharyngoplasty (UPPP) reduced nocturia in patients with sleep apnea.⁴ In the study, there was a 73% success rate in treatment for sleep apnea with the UPPP surgery, and, among those who had



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successful surgeries, nocturia episodes decreased from 1.9 preoperatively to 0.7 postoperatively (P less than .001).

Minoru Miyazato, MD, PhD, of University of the Ryukyus, Okinawa, Japan, and colleagues looked at the effect of CPAP treatment on nighttime urine production in patients with obstructive sleep apnea.⁵ In this small study of 40 patients, mean nighttime voiding episodes decreased from 2.1 to 1.2 (P less than .01).

I think that this information helps us increase our recognition of sleep apnea and also counsel patients on the benefits of treatment.

Sleep apnea should be considered in the differential diagnosis of patients with nocturia, and treatment of sleep apnea may decrease nocturia.

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($n = 39$) used full face masks, while others used nasal-only systems.

The researchers considered differences in PAP therapy usage of at least 30 minutes per night to be statistically significant. The APAP group used the assigned therapy a mean 7 hours per night, vs. 6.8 for the CPAP group. Daytime sleepiness outcomes were also similar for the two treatment groups.

Ms. Shirlaw and her colleagues described the compliance findings as “somewhat surprising,” noting that an earlier meta-analysis had shown slight improvements in compliance associated with APAP (Syst Rev. 2012;1[1]:20). In clinical practice, patients complaining of aerophagia associated with CPAP are frequently switched to APAP based on the belief that doing so “will lead to improved therapy acceptance and ... improved compliance,” they wrote.

“Aerophagia is one of the common side effects of CPAP that has

not been adequately studied” and the experience of any side effect of CPAP treatment may impair adherence, noted Pedro Rodrigues Genta, MD; Gustavo Freitas Grad, MD; and Sara Herculano, University of São Paulo School of Medicine, São Paulo, Brazil, in an editorial (J Clin Sleep Med. 2017;13[7]:881-8).

“Auto-CPAP may improve aerophagia symptoms by reducing mean overnight CPAP level. ... Although auto-CPAP failed to improve adherence to therapy as compared to CPAP, aerophagia symptoms were significantly improved. These results provide clear evidence to switch treatment of patients experiencing aerophagia from fixed CPAP to auto-CPAP,” wrote the editorial’s authors, who reported having no conflicts of interest.

The investigators noted that they “could not demonstrate any difference in APAP pressure requirements (median and 95th centile pressures), leak, residual [Apnea-Hypopnea Index], or compliance between subjects

using a full face mask and subjects using a nasal mask.” They also found that “the use of a full face mask was associated with greater aerophagia symptoms in comparison with a nasal mask during the CPAP trial arm but not the APAP trial arm.”

The researchers described the self-reporting of aerophagia symptoms as one of the study’s limitations. They surmised that the lack of difference seen for compliance measures might be explained in part

by the 30-minute usage increments in the study design (compared with 10-minute increments used in some other studies), and the fact that the cohort had relatively high compliance with CPAP at baseline (5.5 hours/night), suggesting a motivated patient population at entry.

The study received some funding from the government of Queensland, and the researchers disclosed no conflicts of interest related to their findings.

VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, PhD, FCCP, comments: This is an interesting study, as currently we have very few therapeutic modalities available for patients with obstructive sleep apnea and positive airway pressure-induced or exacerbated aerophagia. The interesting findings of auto-adjusting continuous positive airway pressure being superior to fixed positive airway pressure therapy may be related to the large differences between the pressures seen in the two groups (larger than in prior studies). Nevertheless, this may be of help to clinicians. What does one do when a patient on autoPAP therapy has significant aerophagia? Well, this is for another article and another editorial ...



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CARDIOTHORACIC SURGERY

Low-dose aspirin bests dual-antiplatelet therapy in TAVR

BY BRUCE JANCIN

Frontline Medical News

PARIS – Single-antiplatelet therapy with low-dose aspirin following transcatheter aortic valve replacement (TAVR) reduced the occurrence of major adverse events, compared with guideline-recommended dual-antiplatelet therapy (DAPT), in the randomized ARTE trial.

The TAVR guideline recommendation for DAPT with low-dose aspirin plus clopidogrel is not based on evidence. It relies on expert opinion.



DR. RODÉS-CABAU

Josep Rodés-Cabau, MD, noted in presenting the ARTE results at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

Although a confirmatory randomized trial would be welcome, “in the meantime, the results of the ARTE trial may help us to guide clinical practice beyond empirical recommendations,” he said. “At the Quebec Heart and Lung Institute, we’ve stopped using DAPT completely for our TAVR patients unless they have a specific indication for it, such as a recently implanted coronary stent.”

ARTE (Aspirin Versus Aspirin + Clopidogrel Following TAVR) is the first sizable randomized trial to address the safety and efficacy of aspirin alone versus DAPT in the setting of TAVR,

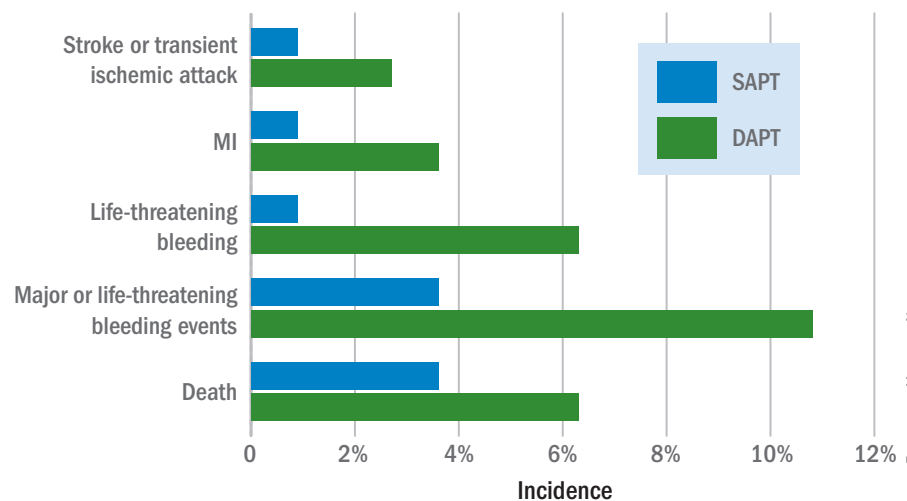
VIEW ON THE NEWS

Frank J. Podbielski, MD, FCCP, comments: As TAVR becomes more widely employed for older patients with aortic valve disease, optimal anticoagulation strategies become critical. The ARTE trial elegantly demonstrates that sometimes “less” is actually “more.” The general enthusiasm for widespread use of anticoagulants in the elderly coupled with their increasing potency has resulted in significant life-threatening bleeding complications – as is borne out in the data from this trial. While the trial did not reach its accrual goal and was concluded prematurely, these preliminary data are encouraging for patients requiring anticoagulation therapy who are at increased risk for bleeding due to age and other medical comorbidities.

ARTE was a multicenter, prospective, international open-label study of 222 TAVR patients who were randomized to 3 months of single-antiplatelet therapy (SAPT) with aspirin at 80-100 mg/day or to DAPT with aspirin at 80-100 mg/day plus clopidogrel at 75 mg/day after a single 300-mg loading dose. Participants had a mean Society of Thoracic Surgery Predicted Risk of Mortality score of 6.3%. The vast majority of participants received the balloon-ex-

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Outcomes: Single- vs. double-antiplatelet therapy in TAVR patients



Note: Based on data from a multicenter, prospective, open-label study of 222 patients.

Source: Dr. Rodés-Cabau

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pandable Edwards Lifesciences Sapien XT valve. The remainder got the Sapien 3 valve.

The primary outcome was the 3-month composite of death, MI, major or life-threatening bleeding, or stroke or transient ischemic attack. It occurred in 15.3% of the DAPT group and 7.2% on SAPT, a difference that didn't reach statistical significance ($P = .065$) because of small patient numbers.

ARTE was halted prematurely. The original plan was to recruit 300 TAVR patients for 12 months of follow-up. However, the investigators wound up capping the trial at 220 patients and 3 months of follow-up because of slow enrollment and withdrawal of financial support by the study sponsors. As a result, while all of the components of the composite endpoint showed strong, consistent benefit favoring SAPT, only the difference in major or life-threatening bleeding achieved statistical significance (see graphic).

All subjects were on a proton pump inhibitor. The type, timing, and severity of bleeding events differed between the two study arms. All 4 bleeding events in the SAPT group were vascular in nature, while 5 of the 12 in the DAPT group were gastrointestinal. All the bleeding events in the SAPT group occurred within 72 hours after TAVR, whereas 5 of 12 in the DAPT recipients occurred later. Only one patient on SAPT experienced life-threatening bleeding, compared with seven DAPT patients who did.

One prior study “showed no differences, and an Italian one showed a tendency toward more bleeding with DAPT. So, I think there has been no sign to date that adding clopidogrel protects this group of patients from anything,” noted Dr. Rodés-Cabau of Laval University in Quebec City. “

Discussant Luis Nombela-Franco, MD, an interventional cardiologist at San Carlos Hospital in Madrid, pronounced the ARTE trial guideline changing despite its limitations.

“With the expansion of TAVR to moderate- and, very soon, to low-risk patients, the results of this study are encouraging for the treating physicians and confirm the value of evidence-based medicine over expert opinion or empirical therapy,” noted Hossein Almassi, MD, FCCP.

ARTE was supported by grants from Edwards Lifesciences and the Quebec Heart and Lung Institute.

Simultaneous with Dr. Rodés-Cabau's presentation in Paris, the ARTE trial was published online (JACC Cardiovasc Interv. 2017 May 11. pii: S1936-8798[17]30812-9).

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Five-year outcomes favor on-pump CABG

BY DOUG BRUNK

Frontline Medical News

Compared with adults who underwent off-pump coronary-artery bypass grafting surgery, those who underwent on-pump CABG

had significantly lower rates of mortality and major adverse cardiovascular events at 5 years, results from a large randomized trial demonstrated.

“Given the results, it appears that innovative surgical approach-

es – such as the more technically demanding off-pump procedure – may not always provide superior clinical outcomes,” researchers led by A. Laurie Shroyer, PhD, wrote (N Engl J Med. 2017 Aug

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High TAVR rates linked to fewer readmissions

BY ELI ZIMMERMAN

Frontline Medical News

WASHINGTON – Hospitals with a higher volume of transcatheter aortic valve replacements (TAVRs) have significantly lower 30-day readmission rates, according to an observational study.

In a study of 129 hospitals, those that performed more than 100 TAVR procedures had a 24% and 25% lower readmission rate compared with hospitals that performed 50-100 TAVRs (P less than .001) and hospitals that performed fewer than 50 TAVRs (P = .007) respectively (JAMA Cardiol. 2017 May 11. doi: 10.1001/jamacardio.2017.1630).

This finding could have serious financial and medical implications for hospitals that are deciding whether or not to focus on this minimally invasive procedure, according to Sahil Khera, MD, MPH, chief resident and cardiology fellow at New York Medical College, Valhalla, and his colleagues.

“Lower readmission rates at

high-volume hospitals substantially reduce health care expenditure,” said Dr. Khera and colleagues. “As new TAVR programs open across the country, these data will guide policymakers to identify targets for optimizing and standardizing TAVR outcomes across hospitals.”

To study the correlation between TAVR procedures and readmission rates, the investigators gathered records on hospitals that performed at least five TAVRs in 2014, which were then categorized into high-, medium-, or low-volume categories, and cross-referenced with the 2014 Nationwide Readmissions Database.

Of the 16,252 TAVR procedures conducted in 2014, 663 (4%), 3,067 (19%), and 12,522 (77%) were performed at low-, medium-, and high-volume hospitals, respectively, according to the investigators.

Patients undergoing these procedures were on average 81 years of age, with an average of four Elixhauser comorbidities, most commonly dyslipidemia (64%), hypertension (80%), heart failure (75%), and known cor-

onary artery disease (69%), with a majority having undergone an endovascular procedure (83%).

However, the researchers found the population of TAVR patients of high-volume hospitals were slightly younger, had fewer women, were more likely to be in a higher-income household, and were less likely to undergo a transapical procedure than in low-volume hospitals, which Dr. Khera and fellow researchers believe may have some impact on their findings.

“Low-volume hospitals were more likely to operate on patients with a higher number of comorbidities compared with high-volume hospitals and were more likely to use the TA approach,” according to investigators, “Transapical TAVR is associated with poorer short- and intermediate-term mortality, increased use of skilled nursing care facilities, longer hospital stays, and readmissions when compared with transfemoral TAVR.”

Overall, there were 2,667 readmissions reported, among which high-volume hospitals reported a

30-day readmission rate of 15.6%, while low- and medium-volume hospitals reported similarly higher rates of 19.5% and 19%.

When looking into the causes for these readmissions, the investigators found that 1,619 (61%) were due to noncardiac causes, which appeared in all three hospitals, despite a larger proportion present in low-volume hospitals as opposed to medium- and high-volume hospitals (65.6% vs. 60.1% and 60.6%, respectively). Infection, respiratory, endocrine/metabolic, renal, and trauma problems were more common in low-volume hospitals, while gastrointestinal and transient ischemic attack/stroke issues were more common in medium- and high-volume hospitals.

One investigator received personal fees from Edwards Lifesciences and Medtronic; another received grants and personal fees from various pharmaceutical companies, educational institutions, and publications; and a third consulted for Medtronic.

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Continued from previous page

17;377:623-32). “Additional long-term follow-up, evaluating these same outcomes rigorously at 10 years after CABG, appears to be warranted.”

Dr. Shroyer, of the Northport (N.Y.) VA Medical Center, and her associates conducted a 5-year follow-up study of patients who had participated in the original Randomized On/Off Bypass (ROOBY) trial, which compared the effectiveness of the two surgical approaches (N Engl J Med. 2009 Nov 5;361:1827-37). During February 2002 – June 2007, 2,203 patients at 18 medical centers were randomly assigned to either on-pump or off-pump CABG, with 1-year assessments completed by May 2008. The primary outcomes were the rates mortality and major adverse cardiovascular events at 5 years, while the secondary 5-year outcomes included death from cardiac causes, repeat revascularization, and nonfatal myocardial infarction.

The mean age of patients was 63 years, nearly all were male, 46% were between the ages of 55 and 64, and about 21% had chronic obstructive pulmonary disease. The researchers found that at 5 years the rate of death was 15.2% in the off-pump group, compared with 11.9% in the on-pump group, which trans-

lated into a relative risk of 1.28 (P = .02). In addition, the rate of major cardiovascular events at 5 years was 31% in the off-pump group, compared with 27.1% in the on-pump group, which translated into a relative risk of 1.14 (P = .046). None of the secondary outcomes at 5 years met the prespecified threshold of a P value of .01 or less for statistical significance, when the off-pump and on-pump groups were compared. This included the rates of nonfatal myocardial infarction (12.1% vs. 9.6%, respectively; P = .05); death from cardiac causes (6.3% vs. 5.3%; P = .29); repeat vascularization (13.1% vs. 11.9%; P = .39); and repeat CABG (1.4% vs. 0.5%; P = .02).

“In combination with findings from other randomized trials and a 2012 Cochrane systematic review [Cochrane Database Syst Rev. 2012;14:CD007224], the 5-year outcomes in our study support the conclusion that off-pump CABG does not offer any substantial advantages over on-pump CABG except possibly in unusual situations

such as, for example, in patients with an extensively calcified (porcelain) aorta, in whom the off-pump technique may result in less manipulation of the aorta, potentially decreasing the risk of aortic emboli or stroke,” the researchers wrote. “In light of the low rates of use of off-pump CABG in the United States, the findings in our trial may provide more of a real-world experience than those in the CORONARY and GOPCABE trials, which required surgeons with a very high volume of experience with off-pump procedures, as compared with the ROOBY trial and with most other surgeons who are based in the United States.”

G. Hossein Almassi, MD, FCCP, one of the study’s other authors, noted that ROOBY was the world’s first large prospective randomized trial comparing off-pump to conventional CABG.

“The off-pump CABG was associated with a 28% higher risk of mortality at 5 years and more major adverse cardiovascular events. The long-term outcomes of this study along with data from other randomized trials suggest that off-pump not only does not provide an advantage over the conventional on-pump but it may actually lead to worse long-term outcomes,” Dr. Almassi said.

The study was supported by a grant from the Department of Veterans Affairs. Dr. Shroyer reported having received grants from the VA Cooperative Studies Program during the conduct of the study. Dr. Almassi is on the Editorial Advisory Board of this publication.

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DR. ALMASSI

VIEW ON THE NEWS

Frank J. Podbielski, MD, FCCP,

comments: The authors of this study conducted within the VA system demonstrated that the rate of death and the rate of major cardiovascular events are lower in patients undergoing on-



pump vs. off-pump CABG. Not examined in this study were neurocognitive differences between the two groups. The potential neurological benefit of off-pump CABG needs to be weighed against its increased technical complexity.

VIEW ON THE NEWS

Dangers of using readmissions as a measurement

Considering the idea of using readmissions in comparison to rate of TAVR procedures is interesting, but the number of confounds are too great to give any kind of accurate representation of medical practice. While the authors of this study do address its limitations, including a learning curve as it relates to the risk of inpatient mortality, the number of adjustments that must be made to account for the additional confounding factors are simply too insurmountable to give an accurate estimate of statistical and clinical importance.

For example, researchers found TAVR readmissions were associated with certain baseline comorbidities, access sites, and complications. However, association does not mean causation and so the categorization of cardiac-related vs. noncardiac-related readmissions must be approached with some caution.

If one were to try to use readmission rates after TAVR to argue for reimbursement of the procedure, one would need to determine a well-established, validated reimbursement rate for TAVR readmissions, which has not been done.

Also, the advancing nature of this procedure, combined with a constant focus from hospitals to reduce readmission rates means any baseline for readmissions used would most likely be out of date.

It would be unlikely for investigators to factor in the cause of reduced readmission rates, which could be a factor of increased technology, more experienced physicians, lower-risk patients, or any combination thereof. Holding TAVR sites accountable for quality of care is of course important, but using readmission rates to determine something like funding is not appropriate when the measurement being used is so complex.

Perhaps a better approach would be to widen access for low-volume hospitals to resources that would improve the TAVR processes and encourage using financial incentives.

Evaluations by physical therapists or a similar procedure should be put into place before discharge to assess a patient's risk of readmission.

Overall, this is a multifaceted issue that would be better helped by promoting TAVR best

practices and encouraging hospitals to compare themselves against each other to reduce unnecessary readmissions.

John D. Carroll, MD, is professor of medicine and director of the Cardiac and Vascular Center at the University

of Colorado, Denver, and a member of the Steering Committee of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. He made his remarks in an editorial in JAMA Cardiology (doi: 10.1001/jamacardio.2017.1650).

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Bailout stenting doubles adverse CV events risk

BY BRUCE JANCIN

Frontline Medical News

PARIS – Bailout stenting during percutaneous coronary intervention for coronary bifurcations doubled the risk of major adverse cardiovascular events in the world’s largest registry of patients with these often-challenging lesions treated using bio-

absorbable stents, Marco Zimarino, MD, reported at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

Indeed, resort to bailout stenting stood out as the major potentially modifiable risk factor for adverse outcomes among the 4,306 participants in the P2BiTO registry, an in-

ternational collaboration supported by members of the EuroBifurcation Club. Most of the other independent risk factors identified in a multivariate regression analysis of the P2BiTO database were beyond operator control, including diabetes, advanced age, and presentation with an acute coronary syndrome, according to Dr. Zimarino of the University of Chieti (Italy).



DR. ZIMARINO

“The message is that the relevant player in determining adverse outcomes is bailout stenting, meaning any stent deployed beyond the planned strategy of either single or double stenting,” he said.

Bailout stenting is largely avoidable through meticulous procedural planning, the interventional cardiologist added.

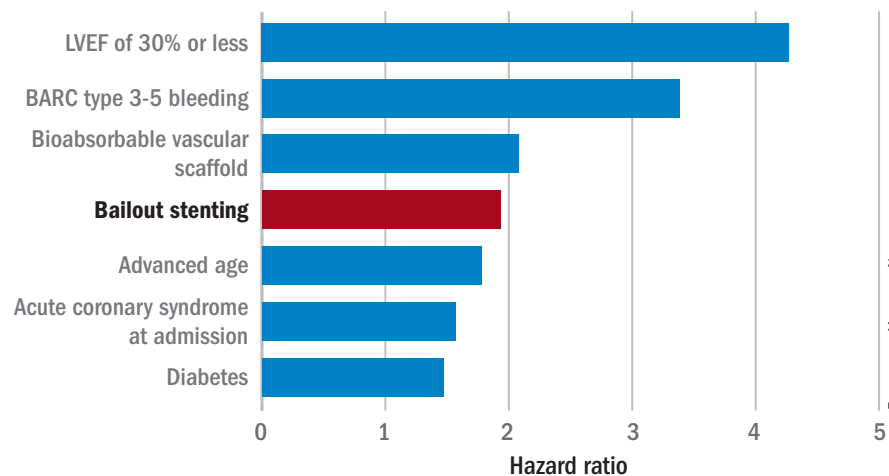
“Careful planning is always mandatory because bailout stenting is associated with an unacceptably

higher risk of both in-hospital and 1-year adverse outcomes,” Dr. Zimarino emphasized. “It’s much better to leave a degraded side branch instead of using bailout stenting to get an excellent angiographic outcome that’s a predictor of a worse clinical outcome.”

Conventional wisdom holds that single stenting of either the main artery or a side branch in a patient with coronary bifurcation is safer than double stenting of both. However, that wasn’t really borne out in the P2BiTO registry provided the operator’s plan was for double stenting. The difference in 1-year major adverse cardiovascular events (MACE) between patients treated

Continued on following page

Risk factors for MACE in patients treated for coronary bifurcations



Note: Based on data from 4,306 participants in the P2BiTO registry. LVEF = left ventricular ejection fraction; BARC = Bleeding Academic Research Consortium.

Source: Dr. Zimarino

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The findings of this study suggest that a careful preplanning and adherence to the planned procedure is in the best interest of the patient.

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Sinus of Valsalva preserved in aortic valve replacement

BY MARK S. LESNEY

Frontline Medical News

The sinus of Valsalva segment can be preserved during aortic valve replacement irrespective of the type of valve pathology, according to a recent study by Rita Karianna Milewski, MD, and her colleagues at the Hospital of the University of Pennsylvania, Philadelphia.

Severe aortic root dilation coupled to aortic valve disease requires root replacement in patients with a tricuspid or bicuspid aortic valve. Commonly, an aortic valve replacement and supracoronary ascending aorta replacement (AVRSCAAR) procedure has been used for patients who have a mild to moderately dilated sinus segment. One advantage of the procedure is that it retains the sinus of Valsalva (SOV) and preserves the intact coronary ostia.

However, the long-term behavior and risk of aortic events for the retained SOV in both BAV and TAV patients remains unclear, according to Dr. Milewski and her colleagues.

Previous researchers have suggested that patients with BAV and TAV have different rates of complications of the remaining aorta and dilation of the proximal aorta and retained sinus segment. In addition, it has been suggested that the cause of aortic dilation is different in patients with aortic stenosis (AS) and aortic insufficiency (AI) and is based on TAV and BAV morphology, histology, and hemodynamic flow patterns.

However, in the August issue of the *Journal of Thoracic and Cardiovascular Surgery*, Dr. Milewski and her colleagues reported on their study showing that, in patients with nonaneurysmal SOV undergoing AVRSCAAR, the sinus of Valsalva segment can be preserved regardless of the type of valvular pathology (aortic stenosis vs. aortic insufficiency) or valvular morphology (BAV vs. TAV).

The researchers retrospectively reviewed a prospectively maintained institutional database to stratify all patients by BAV or TAV valvular pathology with concomitant ascending aortic aneurysm who underwent an elective AVRSCAAR from 2002 to 2015 (*J Thorac Cardiovasc Surg.* 2017;154:421-32).

The distribution of the 428 patients meeting inclusion criteria by subgroups was: BAV group (254 patients: BAV-AS = 178; BAV-AI = 76); TAV group (174 patients: TAV-AS = 61;

TAV-AI = 113). Preoperative sinus of Valsalva dimensions were divided into three subgroups (less than 40 mm, 40-45 mm, and greater than 45 mm).

The mean patient age for patients with BAV and TAV was 59 years and 72 years (P less than .001), respectively (with 78% with BAV being men and 57% with TAV being men). There was a significantly higher subpopulation of AS in the BAV cohort vs. TAV-AS (70% vs. 35%; P less than .001).

With regard to SOV sizing, there was no significant difference in mean preoperative aortic root diameters between BAV and TAV cohorts for the AS or AI subpopulations.

In-hospital/30-day mortality was significantly higher in patients with TAV (5.2%) than in patients with BAV (1.6%, $P = .033$). In addition, the incidence of transient ischemic attack/stroke was significantly higher in the TAV group (3.4%) vs. the BAV group (0.8%, $P = .04$).

Valvular morphology and pathology at baseline, preoperative SOV diameter, postoperative time course, and interaction effect of preoperative SOV diameters and postoperative time course were used as covariates to assess outcomes. Within-subject and within-stratified subgroup comparison failed to show main effects across the follow-up times on postoperative SOV size patterns ($P = .935$), implying that the SOV trends were stable and sustained (discharge to greater than or equal to 10 years) irrespective of valvular morphology and pathology (BAV-AI, BAV-AS, TAV-AI, and TAV-AS).

Preoperative SOV dimensions significantly affected the retained postoperative sinus dimensions (P less than .001), according to Dr. Milewski and her colleagues.

The data indicated that an initial and pronounced postoperative decrease in SOV dimensions occurs with AVRSCAAR independently of aortic valve morphology, aortic valve pathology, and age, they added.

The 10-year freedom from aortic reoperation rates were 97% and 95% in the BAV and TAV subgroups, respectively. The BAV group had significantly improved reoperation-free survival, compared with the TAV group (P less than .001), while the type of valvular pathology within each group did not show a significant survival difference.

“Irrespective of the aortic valve morphology or valve pathology, in patients with mild to

moderate aortic root dilatation (less than 45 mm), preservation of the SOV segment in the context of an AVRSCAAR procedure is justified. Continued further follow-up will be important to understand the long-term outcomes of sinus preservation, especially in the younger population with BAVs,” the researchers concluded.

The authors reported having no financial conflicts to disclose.

VIEW ON THE NEWS

It's not cancer

With regard to the question, “Is it necessary to replace the sinuses of Valsalva in the setting of bicuspid aortic valve aortopathy?”, the researchers “leverage their enormous institutional experience to find an answer. The results suggest that this answer is ‘no.’ At least not in all cases,” Thoralf M. Sundt, MD, wrote in his invited commentary on the paper (*J Thorac Cardiovasc Surg.* 2017;154:419-20).

“The findings of this study argue for us to take a step back and ask how much really needs be done,” he added. And although “it is hard to ask a surgeon to do less rather than more; however, the balance of judgment has to be between the operative risk of the more aggressive approach and the natural history of the disease. In other words, what does it ‘cost’ to be aggressive, and what do we gain?” he asked.

“Bicuspid aortic valve aortopathy, it would appear, is not cancer after all. Regardless of theoretic arguments that are based on embryology and the migration of neural crest cells, it does not appear to require resection to ‘clean margins,’ even if we believe that the operative risk ‘in our hands’ is low,” concluded Dr. Sundt.

Thoralf M. Sundt, MD, is at Harvard Medical School, Boston. He reported having no disclosures.



using a single- or double-stenting strategy wasn't statistically significant, provided bailout stenting wasn't utilized. If bailout stenting was employed, though, the risk of MACE was 2.2-fold greater than if the cardiologist stuck with the plan.

Ninety-eight percent of patients in the P2BiTO registry received drug-eluting stents. The other 2% got the Absorb bioabsorbable vas-

cular scaffold. The percutaneous coronary intervention access site, treatment strategy, choice of stent, and duration of dual-antiplatelet therapy were left up to the operator's discretion.

The 1-year MACE rate was 10%, including a 5.1% incidence of all-cause mortality, 3.2% cardiovascular mortality, 1.7% stroke, 3.4% acute MI excluding periprocedural MI, 2.5% stent thrombosis, and 1.7%

Bleeding Academic Research Consortium type 3-5 bleeding. Bailout stenting was utilized in 8.8% of patients who experienced MACE and 4% of those who didn't.

The risk of MACE was reduced by 39% in patients on dual-antiplatelet therapy for 6-12 months, compared with less than 6 months.

Discussant Graham Cassel, MD, director of the heart transplant unit at Milpark Hospital in Johannes-

burg, commented, “The message comes through very clearly that, if you plan your procedure well, the chance of bailout is far less – and if you do have to bail out, the results are uniformly bad. If you can avoid putting in two or three stents, that's beneficial.”

Dr. Zimarino reported having no financial conflicts of interest regarding his presentation.

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Continued from previous page

Ventricular assist devices linked to sepsis

BY DAMIAN MCNAMARA

Frontline Medical News

NEW ORLEANS – Back in 2008, there was only one case.

Since then, however, the number of patients with ventricular assist devices who developed sepsis while being treated in the cardiac unit at Queen Elizabeth Hospital in Birmingham, England, appeared to be noticeably growing. So, investigators launched a study to confirm their suspicions and to learn more about the underlying causes.

“Bloodstream infection is a serious infection, so I thought, ‘Let’s see what’s happening,’” explained Ira Das, MD, a consultant microbiologist at Queen Elizabeth Hospital.

A total of 129 ventricular assist devices (VADs) were implanted in 118 patients between January 2008 and December 2016 at this institution. The researchers found 23 patients with a VAD (19.5%) had developed a microbiology-confirmed bloodstream infection. The 25 cases of sepsis in this group included two patients who each experienced episodes associated with different microorganisms.

Coagulase-negative staphylococci were the most common cause, present in 32% of the 25 cases. Sepsis was caused by *Enterococcus faecium* in 12%, *Candida parapsilosis* in 8%, and *Staphylococcus aureus* in 2%. Another 4% were either *Enterococcus faecalis*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *C. guilliermondii*, or *C. orthopsilosis*. The remaining 16% of bloodstream infections were polymicrobial.

Less certain was the source of these infections.

“In the majority of cases, we didn’t know where it was coming from,” Dr. Das said at the annual meeting

of the American Society for Microbiology. In 6 of the 25 cases, VAD was confirmed to be the focus of infection, either through imaging or because a failing component of the explanted device was examined later. An intravascular catheter was the source in another 5 patients, and in 14 cases, the source remained a mystery.

“Some of these infections just might have been hard to see,” Dr. Das said. “If the infection is inside the device, it’s not always easy to visualize.”

The study supports earlier findings from a review article that points to a significant infection risk associated with the implantation of VADs (Expert Rev Med Devices. 2011 Sep;8[5]:627-34). That article’s authors noted, “Despite recent improvements in outcomes, device-related infections remain a significant complication of LVAD [left ventricular assist device] therapy.”

In a previous study of people with end-stage heart failure, other investigators noted that, “despite the substantial survival benefit, the morbidity and mortality associated with the use of the left ventricular assist device were considerable. In particular, infection and mechanical failure of the device were major factors in the 2-year survival rate of only 23%” (N Engl J Med. 2001 Nov 15;345[20]:1435-43).

Similarly, in the current study, mortality was higher among those with sepsis and a VAD. Mortality was 39% – including eight patients who died with a VAD in situ and one following cardiac transplantation. However, Dr. Das cautioned, “It’s a small number, and there are other factors that could have contributed. They all go on anticoagulants so they have bleeding tendencies, and many of the patients are in the ICU with



“Some of these infections just might have been hard to see.”

Dr. Ira Das

multiorgan failure.”

Infection prevention remains paramount to minimize mortality and other adverse events associated with a patient’s having a VAD. “We have to make sure that infection control procedures and our treatments are up to the optimal standard,” Dr. Das said. “It’s not easy to remove the device.”

Of the 129 VADs implanted, 68 were long-term LVADs, 11 were short-term LVADs, 15 were right ventricular devices, and 35 were biventricular devices.

The study is ongoing. The data presented at the meeting were collected up until December 2016.

“Since then, I’ve seen two more cases, and – very interestingly – one was *Haemophilus influenzae*,” Dr. Das said. “The patient was on the device, he was at home, and he came in with bacteremia.” Again, the source of infection proved elusive. “With *H. influenzae*, you would think it was coming from his chest, but the chest x-ray was normal.”

The second case, a patient with a coagulase-negative staphylococci bloodstream infection, was scheduled for a PET scan at the time of Dr. Das’s presentation to try to identify the source of infection.

Dr. Das reported no relevant disclosures.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: The young, recently graduated clinic nurse came to see me before I went in to see my patient. “I can’t register a pulse or blood pressure”, she said, assuming that her failure to do so indicated a lack of clinical acumen on her part. “You won’t”, I told her. I took her with me into the exam room and watched her listen with her stethoscope in amazement to the mechanical hum of the LVAD device over the patient’s chest.

Modern technology saves our patients’ lives, but there is always another side to the coin. Reports that LVAD devices are associated with a high incidence of bloodstream infections is important for future clinical practice. The fact that the causes and risk factors for these infections are unknown make this phenomena one of high interest.



New drug choices emerging to battle antibiotic resistance

BY DOUG BRUNK

Frontline Medical News

SAN FRANCISCO – When the Infectious Diseases Society of America released the “Bad Bugs, No Drugs” report in 2004, its authors warned that effective antibiotics may not be available to treat seriously ill patients in the near future.

It also proposed legislative, regulatory, and funding solutions with a goal of developing and

licensing 10 new antibiotics by the year 2020.

One such advancement was the Generating Antibiotics Incentives Now Act, which was signed into law in 2012 and created a designation for new antibiotics that are used to treat serious and/or life-threatening diseases due to certain pathogens. It also extends the patent life of these antibiotics and allows for fast-track Food and Drug Administration approval.

“The reason for antibiotic resistance over time

has largely been ... the direct result of our antibiotic use both in humans and in animals,” Kim S. Erlich, MD, said at the UCSF Annual Advances in Internal Medicine meeting. “Many of these organisms have spread globally and are now part of normal flora, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE). It costs more across the board to take care of these patients, and they

Continued on following page

MRSA bacteremia outcomes improved

BY DAMIAN MCNAMARA

Frontline Medical News

NEW ORLEANS – Compared with vancomycin monotherapy, vancomycin combined with cefepime improved some outcomes for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections, a retrospective study of 109 patients revealed.

A lower likelihood of microbiological failure and fewer bloodstream infections persisting 7 days or more were the notable differences

between treatment groups.

“The center where I work, where the patients come from, the Detroit Medical Center – their ‘go-to therapy’ for empiric treatment is vancomycin plus cefepime, because they want to cover the gram positives and the gram negatives,” said Safana M. Atwan, a fourth-year pharmacy student at Wayne State University, Detroit. In vitro studies have also shown that “cefepime and vancomycin have a synergistic relationship.”

All patients had at least 72 hours of vancomycin therapy to treat

Continued from previous page

have higher mortality and higher morbidity.”

According to Dr. Erlich, chief of staff and medical director of infection control and antibiotic stewardship at Mills Peninsula Medical Center, Burlingame, Calif., increasingly common antibiotic-resistant pathogens besides MRSA and VRE include penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum beta-lactamase-producing gram-negative rods, carbapenem-resistant *Enterobacteriaceae* (CRE), multi-drug-resistant *Mycobacterium tuberculosis*, *Salmonella enterica* serotype Typhimurium DT 104, and drug-resistant *Candida* species.

Since 2010, several new antibiotics have been introduced to the market, including three second-generation lipoglycopeptide antibiotics with gram-positive coverage that are approved primarily for skin and soft-tissue infections: dalbavancin (Dalvance), telavancin (Vibativ), and oritavancin (Orbactiv).

Compared with vancomycin, these new agents have more convenient dosing and a longer half-life, “but they’re also more expensive,” said Dr. Erlich. Dalbavancin can be dosed once a week intravenously, telavancin can be dosed once daily intravenously, and oritavancin requires just one dose.

Another new agent is tedizolid phosphate (Sivextro), a second-generation oxazolidinone that is in the same drug class as linezolid (Zyvox). Tedizolid phosphate has gram-positive coverage including MRSA, but

it is not approved for VRE. “It’s FDA approved for skin and soft-tissue infections (SSTI) but can be used for other locations as well,” Dr. Erlich said. “It features once-daily dosing IV or PO.”

Ceftaroline fosamil (Teflaro), ceftolozane/tazobactam (Zerbaxa), and ceftazidime/avibactam (Avycaz) are broad-spectrum cephalosporins with or without beta-lactamase inhibitors resulting in extended gram-negative coverage. FDA-approved indications include complicated urinary tract infections, complicated abdominal infections, SSTI, and pneumonia.

The primary advantage of these drugs, compared with other agents, is for multidrug-resistant gram-negative bacteria such as extended-spectrum beta-lactamase producers and CRE. “We’re not using a lot of these drugs in clinical practice, but they are available for patients with multidrug-resistant gram-negative rods who have no other options,” Dr. Erlich said.

Practical ways that clinicians can prevent antibiotic resistance include prescribing antibiotics only when necessary. “Be aware of local resistance patterns, avoid antibiotics for probable viral infections, use narrow-spectrum choices when possible, use shorter durations when appropriate, and consult published guidelines for optimal empiric antibiotic therapy,” Dr. Erlich advised.

In addition, “advocate infection control measures to keep patients from developing infections, including proper wound care, hand washing, respiratory etiquette, vaccinations, and social isolation for symptomatic individuals,” he noted.

Dr. Erlich reported having no relevant financial disclosures.

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MRSA bacteremia confirmed by blood culture. During 2008-2015, 38 adults received vancomycin monotherapy and 71 received vancomycin plus 24 hours or more of cefepime.

Compared with monotherapy, the combination treatment was associated with a nonsignificant reduction in the primary composite treatment failure outcome of 30-day all-cause mortality, in bacteremia duration of 7 days or more, and in 60-day bloodstream-infection recurrence: 55% for monotherapy versus 42% for combination therapy ($P = .195$). The difference was primarily associated with decreased duration of sepsis and fewer MRSA bloodstream infections persisting 7 days or more in the combination cohort.

Rates of bacteremia duration of 7 days or more were 42% in monotherapy patients and 20% in combination patients ($P = .013$). Differences in 60-day bloodstream-infection recurrence were nonsignificant, 8% versus 4%, respectively ($P = .42$).

Thirty-day mortality, however, was lower among monotherapy patients than combination patients – 13% vs. 25% – although the difference was nonsignificant ($P = .21$).

“[It] seems like they will have a lower duration of bacteremia, which is always great,” Ms. Atwan said. “You want to decrease length of stay in the hospital,” which will cut down on costs and on patients’ risks of getting more infections.

Although the primary outcome was a composite endpoint, “when we looked at them separately, we found the patients in the combination group had more mortality,” Ms. Atwan said at the annual meeting of the American Society for Microbiology. “That surprised me initially. But those patients are sicker and more likely to get dual coverage.”

The investigators confirmed the association between the severity of MRSA bacteremia and combination therapy by looking at Acute Physiology and Chronic Health Evaluation (APACHE II) scores. The median APACHE score was 23 in the combination group, compared with 13.5 in the monotherapy group ($P = .0003$). Higher APACHE scores were associated with greater odds of meeting the composite failure endpoint (adjusted odds ratio, 1.08) and of developing endocarditis (aOR, 3.6) in multivariate analyses.



DR. ERLICH

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Lithoplasty tames heavily calcified coronary lesions

BY BRUCE JANCIN

Frontline Medical News

PARIS – A novel therapeutic ultrasound-based technology known as lithoplasty is turning heads in interventional cardiology and vascular medicine because it addresses the bane of interventionalists' existence: complex, heavily calcified coronary and peripheral artery lesions.

“Calcification is something we deal with every day in interventional cardiology. It makes the procedures more expensive, longer, and in fact several recent studies have shown that the complication rate for calcified lesions is higher than for any other lesion subtype. Calcification is the next big thing that we’re trying to take on in interventional cardiology,” Todd J. Brinton, MD, observed at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

As an example of the problems calcified lesions create, he cited an analysis of 6,855 acute coronary syndrome patients in whom percutaneous coronary intervention was performed in the ACUTY and HORIZONS-AMI trials. The 1-year rate of major adverse cardiovascular events (MACE) was 12.9% in those with no or mild coronary calcification, 15.3% with moderate calcification, and 19.9% with severe calcification. Moreover, the 1-year cardiac death rate of 4% in patients with severe calcification was more than twice that in those with no or minimal calcification (*J Am Coll Cardiol.* 2014 May 13;63[18]:1845-54).

At EuroPCR, he presented the results of DISRUPT CAD, a seven-center study in which 60 patients with heavily calcified coronary lesions underwent lithoplasty in order to facilitate stent placement. The study met all of its safety and performance endpoints. As a result, the week prior to EuroPCR the European regulatory agency granted marketing approval for Shockwave Medical’s coronary lithoplasty system; the indication is for coronary vessel preparation prior to stenting. A large phase III U.S. trial aimed at gaining Food and Drug Administration approval is planned.

Moreover, on the basis of the earlier favorable DISRUPT PAD trial, lithoplasty has already been approved for treatment of peripheral artery disease (PAD) in Europe since late 2015 and by the FDA since September 2016. Now

underway is DISRUPT PAD III, a large postmarketing randomized trial comparing lithoplasty with conventional balloon angioplasty in patients with heavily calcified PAD,

added Dr. Brinton, an interventional cardiologist at Stanford (Calif.) University and cofounder of Shockwave Medical.

Lithoplasty is a potentially trans-

formative technology which he described as “lithotripsy inside a balloon.” Lithotripsy has an established 30-year track record for the safe treatment of kidney stones.

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However, lithotripsy utilizes focused ultrasound, while lithoplasty relies upon circumferential unfocused therapeutic ultrasound delivered by miniaturized emitters placed inside a 12-mm intravascular balloon. The balloon is crossed to the target lesion, inflated to a modest pressure of 4 atmospheres, then the operator delivers lithoplasty pulses lasting

over 1 microsec in duration at a rate of 1/sec for 10 seconds in order to fracture the thick intramedial calcium plaque, allowing the lesion to open up and thereby normalize vessel compliance.

“Once you’ve cracked the calcium you can easily dilate the lesion. It’s the calcium that’s restricting the ability to dilate. The real fundamen-

tal need here is to maximize acute gain to get really good stent apposition. We’re trying to get expansion,” the cardiologist explained.

That was readily achieved in the DISRUPT CAD study. The 60 participants had reference vessel diameters of 2.5-4.0 mm, with an average target lesion length of 20 mm. The calcification was heavy, covering on

average 270 degrees of the vessel circumference as measured by optical coherence tomography, with an average calcium thickness of 0.97 mm and a calcified segment length of 22.3 mm.

The mean stent expansion was 112%. The minimum luminal diameter improved from 0.9 mm pre-

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treatment to 2.6 mm post treatment, for an acute gain of 1.7 mm. The amount of acute gain was similar across the full range of vessel diameters.

The mean diameter stenosis went from 68% pretreatment to 13% post-treatment.

The primary safety endpoint was

the 30-day rate of MACE, defined as cardiac death, MI, or target vessel revascularization. The rate was 5%, consisting of 3 patients with mild non-Q-wave MI defined by creatine kinase-MB elevations more than three times the upper limit of normal. The 6-month MACE rate was 8.5%, which included the three non-Q-wave MIs plus two cardiac

deaths not related to the procedure or technology.

Final angiographic results adjudicated in a central core laboratory showed no perforations, abrupt closures, slow or no reflow events, or residual dissections. These are complications commonly seen with debulking devices such as rotational or orbital atherectomy, Dr. Brinton noted.

The primary performance endpoint in DISRUPT CAD was clinical success, defined as a residual stenosis of less than 50% post percutaneous coronary intervention with no in-hospital MACE. This was achieved in 57 of 60 patients, or 95%. The device was successfully delivered to the target lesion with subsequent performance of litho-

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plasty in 59 of 60 patients. An even more flexible and deliverable device will be released in the coming year, according to the cardiologist.

“I’d say the take-home is that the disease has changed,” Dr. Brinton commented. “It’s not the same disease that we had when Gruentzig did his first balloon angioplasty. These lesions are more calcified,

more complex, yet for the most part we use the same balloon we’ve been using for the last 40 years. So lithoplasty is really an attempt to modernize the therapy in a new patient subset we now take care of who are much more complicated than the patients we originally took care of.”

“The reality is, we’re having difficulty taking care of these patients.

For myself as an interventionalist, it’s not uncommon to look around the table and see a massive amount of tools when we’re doing these complex cases. Lithoplasty is intended to bring the simplicity. I would say it’s not necessarily to make the best operators better, it’s to bring all operators up to the ability to take on these complex lesions that are now

usually reserved for high-volume centers that can do debulking,” he added.

Session cochair David R. Holmes Jr., MD, of the Mayo Clinic in Rochester, Minn., pronounced lithoplasty “tremendously exciting.” He and the other panelists focused on questions of safety and potential collateral damage: Where does the calcified debris go? What are the effects of the unfocused sonic pressure waves on noncalcified plaque? How hot does the vessel get?

Dr. Brinton replied that thick calcium plaque is located mostly in the medial vessel wall and stays there after fracturing. That’s why distal embolization wasn’t an issue in DISRUPT CAD. In animal studies, even at 20 times the energy dose used in clinical practice, lithoplasty had no

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Frontline Medical News

Dr. Todd J. Brinton

effect on softer, noncalcified plaque or normal tissue. Vessel temperature increases by about 1.2 degrees C during lithoplasty, which isn’t sufficient to cause injury or drive restenosis.

Elsewhere at EuroPCR, Alberto Cremonesi, MD, who chaired a press conference where Dr. Brinton presented highlights of DISRUPT CAD, declared lithoplasty is “in my mind a real breakthrough, not only for coronary disease but also for PAD.”

Is it possible that stand-alone lithoplasty could reduce the need for multiple stents in longer coronary lesions, instead making possible more focal stenting? asked Dr. Cremonesi of Maria Cecilia Hospital in Cotignola, Italy.

That’s one of several possibilities worthy of future investigation, Dr. Brinton replied. Lithoplasty might also facilitate the results obtainable with bioresorbable coronary scaffolds or drug-coated balloons, he added.

He noted that as cofounder of and a consultant to Shockwave Medical, he has a sizable financial involvement with the company.

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CHEST 2017 Keynote Speaker

Excited to Help Physicians Wake Up and Live Inspired

John O'Leary is a father of four, business owner, speaker, writer, and former hospital chaplain—a fortunate guy. But he attributes the best of everything he has to an unfortunate event that happened back in 1987.

At the age of 9, O'Leary was involved in a house fire that left burns on 100% of his body, 87% of which were third degree. Doctors gave O'Leary less than a 1% chance to live, odds that were overwhelming—but not entirely impossible to beat.

Despite what the health-care professionals told his mother, when

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O'Leary asked her if he was going to die, she responded by asking her son if he wanted to die or if he wanted to live: a question that O'Leary says must have taken lot more courage for a mother to ask than it did for a 9-year-old to answer.

Although he was taken aback, the answer seemed obvious to O'Leary. Of course he wanted to live. And live he did, but only after 5 months in the hospital and the amputation of all of his fingers.

After he returned to school 18 months later with his classmates welcoming him back with a parade, O'Leary didn't see the necessity in sharing his story. "I always knew my story, I just never truly embraced it."

O'Leary's father told him that he wanted to thank the community members who truly helped their family through the tough times and that he planned to do so by writing a book. With the help of O'Leary's mother, 100 copies of *Overwhelming Odds* were originally printed and given to members of the community. Today, over 70,000 copies of their book have been sold.

When some Girl Scouts approached O'Leary and asked him to share his story with their troop and their parents, his life changed. O'Leary says



JOHN O'LEARY

that he now tries to say yes to each person/organization that asks him to share. As a result, he has said yes over 1,500 times and has even made a life of it.

"We confuse being out of bed with being awake, being at work with being fully engaged, or being with a patient with being

actively present for and with that patient," O'Leary says of accidental living. "That's not really awake; that's not alive. It's more of sleep-walking through life."

O'Leary believes that too often we give away the freedom of life to things that are out of our control and that he feels it is his job to remind his listeners that there are a lot of things in our control on which we should be fully living. "We want people to realize they have the ability to be actively present in every engagement and every decision, every thought, and every word, and ultimately, every result in their lives."

CHEST Annual Meeting 2017 is one of the events that O'Leary has recently said "yes" to, and he is very excited about it. "As things continue to change...we can forget why we got into what we got into," O'Leary says. "I am excited to remind everyone at CHEST about the profoundly beautiful nature of their work and how it has the ability to affect both the staff and patients."

Members of O'Leary's medical team, as well as other hospital staff members, were crucial to his survival and improved health. One of his doctors was not only a respected physician and surgeon but also a powerful leader who was capable of reminding every member of the hospital of their purpose and necessity to a patient's life, something that O'Leary hopes can be common in every health-care team.

"When you have the chance to influence men and women who serve patients and teams and impact lives and do it generationally—I think we forget that it is a generational ripple effect; my kids are where and who they are today because doctors, nurses, practitioners, and janitors showed up 30 years ago."

NAMDRC Update

The Growing Need to Mix Pulmonary Medicine and Politics

BY PHIL PORTE

Executive Director, NAMDRRC

The old adage of not wanting to see how laws or sausage is made holds true today, perhaps more so than ever. But certain clinical realities within pulmonary medicine virtually ensure that legislation is actually part of any reasonable solution.

NAMDRC has initiated an outreach to all the key medical, allied health, and patient societies that focus on pulmonary medicine to determine if consensus can be reached on a focused laundry list of issues that, for varying reasons, lean toward Congress for legislative solutions.

Here is a list of some of the issues under discussion:

- Home mechanical ventilation. Under current law, "ventilators" are covered items under the durable medical equipment benefit. In the 1990s, in order to circumvent statutory requirements that ventilators be paid under a "frequent and substantial servicing" payment methodology, HCFA

(now CMS) created a new category – respiratory assist devices and declared that these devices, despite classification by FDA as ventilators, are not ventilators in reality, and the payment methodology, therefore, does not apply.

Over the past several years, the pulmonary medicine community tried its best to convince CMS that its rules were problematic, archaic, and costing the Medicare program tens of millions of dollars in unnecessary expenditures. A formal submission to CMS, a request for a National Coverage Determination reconsideration, was denied with a phrase now echoed throughout health care, "it's complicated." The only effective solution is a legislative one.

- High flow oxygen therapy for ILD patients. Oxygen remains the largest single component of the durable medical equipment benefit and, largely due to competitive bidding, has seen payment drop dramatically since the implementation of competitive bidding. One can easily argue that com-

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This month in CHEST:

Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Editor in Chief, CHEST

GIANTS IN CHEST MEDICINE

Jack Hirsh, MD, FCCP.

By Dr. S. Z. Goldhaber.

ORIGINAL RESEARCH

IVIg for Treatment of Severe Refractory Heparin-Induced Thrombocytopenia.

By Dr. A. Padmanabhan et al.

The Impact of Statin Drug Use on All-Cause Mortality in Patients With COPD:

A Population-Based Cohort Study.

By Dr. A. J. Raymakers et al.

Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis.

By Dr. P. Wang et al.



EVIDENCE-BASED MEDICINE

Etiologies of Chronic Cough in Pediatric Cohorts: CHEST Guideline and Expert Panel Report.

By Dr. A. B. Chang et al, on behalf of the CHEST Expert Cough Panel.

Continued from previous page

petitive pricing is self-inflicted by the DME industry as the rates are set through a complicated formula based on bids from suppliers. But the impact has been particularly hard on liquid systems, the delivery system choice of not only many Medicare beneficiaries but also is the modality of choice for patients with clear need for high flow oxygen. While delivery in the home for high flow needs can be met by some stationary concentrators, the virtual disappearance of liquid systems, attributable to pricing triggered by competitive bidding, results in many ILD patients unable to leave their homes. The only effective solution is a legislative one.

- Section 603. This provision of the Balanced Budget Act of 2015 was designed to inhibit hospital purchases of certain physician practices that were based on aberrations within the Medicare payment system that rewarded hospitals significantly more than the same service provided in a physician office. For example, a physician office-based sleep lab may be able to bill Medicare for a particular service, but if the hospital purchases that physician practice and bills for the same service, it might receive upwards of twice as much payment.

While all involved seem to agree that this provision was not intended to target pulmonary rehabilitation services, it is being hit particularly hard by CMS rules implementing the statute. Any new pulmonary rehab program that is not within 250 yards of the main hospital campus must bill at the physician fee schedule rate, a rate about half of the hospital outpatient rate. Furthermore, existing programs that choose to expand must do so within the confines of their specific current location, unable to move a floor away. Doing so would trigger the reduced payment methodology.

CMS agrees this is clearly an example of unintended consequences, but CMS also acknowledges it does not have the authority to remedy the situation. The agency itself signaled the only way to exempt pulmonary rehabilitation services is to seek Congressional action.

And now to the “sausage” part of the equation. Congressional action on virtually anything except renaming a post office becomes a political, as well as substantive, challenge. Here are just some of the considerations that must be addressed by any legislative strategy.

1. Any “fix” must be clinically sound and supported across a broad cross section of physician and patient groups. And the fix must give some level of flexibility to CMS to implement it in a reasonable way but tie their hands to force changes in policy.
2. Any “fix” must have a strong political strategy that can muster support within key Congressional committees (House Ways & Means Committee and Energy & Commerce Committee, along with the Senate Finance Committee, let alone 218 votes in the

House and 51 votes in the Senate. Given these issues, almost regardless of the political environment, it is time to begin working on substantive solutions so that when the political climate improves, pulmonary medicine is ready to move forward with a coordinated cohesive strategy.

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CHEST Foundation NetWorks Challenge

The CHEST Foundation is proud to announce the winners of the first round of the 2017 NetWorks Challenge! Our first place winner, Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork, and our second place finisher, Women's Health NetWork, both receive session time at CHEST 2017 on a topic of their choice and two travel grants to help their NetWork members attend CHEST 2017.

Our first place NetWork, Home-Based Mechanical Ventilation and Neuromuscular Disease, reached 100% participation from their Steering Committee in the first round of the challenge. At CHEST 2017, they will host a session titled, "Shift Work Sleep Disorders: Effects of Sleep Deprivation on Occupational Performance and Safety" on Tuesday, October 31, 2:45 PM - 4:15 PM.

The Women's Health NetWork was directly behind our first place finish-



ers with more than 90% participation. Their session, "Care of the Critically Ill Pregnant Woman: Balancing Two Patients and Two Lives" will be on Monday, October 30, 1:30 PM - 2:30 PM. This session will focus on identifying the ethical considerations in managing a critically ill patient, foster appreciation of the complex clinical and ethical issues involved in managing the brain-injured or brain-dead pregnant woman, and identify the indications, method, risks, and benefits of perimortem Cesarean section.

Be sure to attend these two sessions while you are at CHEST 2017, and please join us in congratulating the winners of the first round of the NetWorks Challenge.

Don't forget, there is still time to win Round 2 and Round 3 of the NetWorks Challenge.

Learn more about the challenge at chestfoundation.org/networkschallenge.

Round 2

Who: NetWork Steering Committee Members

When: July 1 - Beginning of CHEST 2017

How to Participate: Members will compete by donating or pledging any amount to the CHEST Foundation in 2017.

Where Your Money Goes: Community Service

How to Win: Total amount contributed by top two NetWork Steering Committees

What You Win: New community service initiative and two travel grants to CHEST 2018

Round 3

Who: All NetWork Members

When: During CHEST 2017

How to Participate: Members will compete by donating or pledging any amount to the CHEST Foundation during CHEST 2017.

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NETWORKS

Occupational asthma, lactic acidosis, OSA screening

Occupational and Environmental Health

Gender Disparities in Occupational Health

Over the past few decades, the presence of women in the workforce has changed significantly. According to the US Bureau of Labor Statistics Current Population Survey, in 2015, 46.8% of the workforce included women compared with 28.6% in 1948. Along with this change, there has been an increased focus on gender disparities in occupational health.

For example, a meta-analysis of respiratory health among those exposed to organic and inorganic dust demonstrated that overall, when adjusted for smoking status, age, BMI, ethnicity, atopy, and job duration, women had a higher odds of shortness of breath and asthma compared with men. Men had higher odds of chronic phlegm, occasional wheeze, and FEV₁ <80% (Dimich-Ward et al. *Lung*. 2012;190[2]:147).

Gender differences in occupational asthma were also seen in snow crab processing plant workers. Women were significantly more likely to have occupational asthma than men. However, they found that overall, women had a greater cumulative exposure to crab allergens, which may be a major contributor to this disparity (Howse et al. *Environ Res*. 2006;101[2]:163).

Although several occupational health studies are beginning to highlight gender disparities, a major confounding factor is that of occupational segregation, meaning the

under-representation of one gender in some jobs and over-representation in others. Differences in jobs and tasks even within the same job title between men and women are often major contributors to gender disparities [WHO Dept of Gender, Women and Health, 2006]. Also, several studies suggest that more women should be included in toxicology and occupational cancer studies, since currently, they have included mostly men (Sorrentino et al. *Ann Ist Super Sanità*. 2016;52[2]:190). Perhaps future studies can improve the overall understanding of these important contributing factors to gender disparities in occupational health.

Krystal Clevon, MD
Fellow-in-Training Member

Respiratory Care

Does Beta-agonist Therapy With Albuterol Cause Lactic Acidosis?

Cohen and associates (*Clin Sci Mol Med*. 1977;53:405) suggested that lactic acidosis can occur in at least two different physiologic clinical presentations. Type A occurs when oxygen delivery to the tissues is compromised. Dodda and Spiro (*Respir Care*. 2012;57[12]:2115) indicated that type A lactic acidosis was due to hypoxemia, as seen in inadequate tissue oxygenation during an exacerbation of asthma. In severe asthma, pulsus paradoxus and air trapping (causing intrinsic positive end-expiratory pressure, or PEEP) served to decrease tissue oxygenation by decreasing cardiac output and venous return, leading to type A lactic acidosis. Bates and associates (*Pediatrics*. 2014;133[4]:e1087) considered the role of intrapulmonary arteriovenous anastomoses (IPAVs) when a status asthmaticus patient improved after cessation of beta-agonist therapy. Type B lactic acidosis occurs when lactate production was

increased or lactate removal was decreased even when oxygen was delivered to tissue. Amaducci (<http://www.emresident.org/gasping-air-albuterol-induced-lactic-acidosis/>) explained how high dosages of albuterol, beyond 1 mg/kg, created an increased adrenergic state that, with reduced tissue perfusion, increased glycolysis and pyruvate production, resulting in measurable hyperlactatemia. The authors (*Br J Med Pract*. 2011;4[2]:a420) noted that lactic acidosis also occurs in acute severe asthma due to inadequate oxygen delivery to the respiratory muscles or due to fatiguing respiratory muscles. Ganaie and Hughes reported a case of lactic acidosis caused by treatment with salbutamol. Salbutamol is the most commonly used short-acting beta-agonist. Stimulation of beta-adrenergic receptors leads to a variety of metabolic effects, including increase in glycogenolysis, gluconeogenesis, and lipolysis, thus contributing to lactic acidosis. All authors agreed that the mechanism of albuterol-caused lactic acidosis was poorly understood.

Douglas E. Masini, EdD, FCCP
Steering Committee Member

Sleep Medicine

Withdrawal of OSA Screening Regulation for Commercial Motor Vehicle Operators

Compared with the general US population, the prevalence of sleep apnea (SA) is higher among commercial motor vehicle (CMV) drivers (Berger et al. *J Occup Environ Med*. 2012;54[8]:1017). Additionally, the risk of motor vehicle accidents is higher among individuals with SA compared with those without SA (Tregear et al. *J Clin Sleep Med*. 2009;5[6]:573), and treatment of SA is associated with a reduction in this risk (Mahssa et al. *Sleep*. 2015;38[3]:341).

Undiagnosed sleep apnea has been postulated as an underlying cause of several highway and rail accidents investigated by the US National Transportation Safety Board (NTSB). Therefore, in 2016, the Federal Motor Carrier Safety Administration (FMCSA) and Federal Railroad Administration (FRA) published an advanced notice of proposed rulemaking (ANPRM) seeking public input regarding the

health and economic effects of screening and treating SA among individuals occupying safety-sensitive positions in highway and rail transportation (Federal Register March 2016).

However, after reviewing the public input and data, the FRA and FMCSA recently announced that there was “not enough information available to support moving forward with a



DR. KUNDEL



DR. SHAH

rulemaking action,” and, therefore, they are no longer pursuing the regulation that would require SA screening for truck drivers and train engineers (Federal Register August 2017;49 CFR 391,240,242). See CHEST’s press release at www.chestnet.org/News/Press-Releases/2017/08/American-College-of-Chest-Physicians-Responds-to-DOT-Withdrawal-of-Sleep-Apnea-Screening. The FMCSA endorses existing resources, such as the North American Fatigue Management Program (NAFMP) (www.nafmp.org), which is a web-based program designed to reduce driver fatigue and includes information on SA screening and treatment. The medical examiners, however, will have the ultimate responsibility to screen, diagnose, and treat SA based on their medical knowledge and clinical experience.

Vaishnavi Kundel, MD
NetWork Member
Neomi Shah, MD, MPH, MS
Steering Committee Member

Corrections to previous NetWork articles

July 2017
Clinical Research
Mohsin Ijaz’s name was misspelled.

August 2017
Transplant

The name under Shruti Gadre’s photograph is wrong. It says Dr. Ahya instead of Dr. Gadre.

The authorship of the article at the end of the article is incorrect. It says Vivek Ahya, instead of Shruti Gadre and Marie Budev.



DR. CLEVEN

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¹ Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

² Lin, P., et al., "Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism." *Vascular*, Vol. 17, Suppl. 3, 2009, S137-S147.

³ Nykamp M., et al. "Safety and efficacy of ultrasound-accelerated catheter-directed lytic therapy in acute pulmonary embolism with and without hemodynamic instability." *J Vascular Surgery: Venous and Lymphatic Disorders* 2015; 3(5): 251-7.

⁴ Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. **THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS: Peripheral Vasculature:** The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. **Pulmonary Embolism:** The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥ 50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25mmHg) or echocardiographic evaluation.



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