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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Bruce Jancin/Frontline Medical News

Dr. Javier Bermejo, a cardiologist at Gregorio Marañón University Hospital in Madrid.

Avoid sildenafil for PH after valvular heart disease correction

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Off-label use of the phosphodiesterase-5 inhibitor sildenafil to treat residual pulmonary hypertension after successful correction of valvular heart disease is not merely ineffective, it's counterproductive, according to the results of the randomized, placebo-controlled SIOVAC study.

"We believe based upon our results that off-label use of sildenafil in patients with left heart disease-pulmonary hypertension due to valvular disease should be discouraged," Javier Bermejo, MD, declared at the annual congress of the European Society of Cardiology.

Sildenafil is approved with a solid, evidence-based indication for treating some other types of pulmonary hypertension. Many cardiologists also prescribe the drug off label for residual pulmonary hypertension in patients with corrected valve disease, hoping that it will be of benefit, since there is currently no approved treatment for this common and serious condition associated with increased mortality. But because the anecdotal literature on sildenafil for this specific type of pulmonary hypertension is mixed, Dr. Bermejo and his coinvestigators in the Spanish Network Center for Cardiovascular Research decided to conduct a multicenter randomized trial.

CONTROLS FARED BETTER THAN TREATED // *continued on page 4*

Phrenic nerve stimulator shows benefits in heart failure patients

BY MITCHEL L. ZOLER
Frontline Medical News

DALLAS – Heart failure patients with central sleep apnea who received treatment with a transvenous phrenic nerve–stimulating device showed dramatic improvement in their global self-assessment, compared with control patients, in a subgroup analysis of 80 patients enrolled in the device's pivotal trial.

The Remede System, which consists of a battery pack and small, thin wires placed under the skin in the upper chest area, monitors respiratory signals and causes normal breathing to be restored by stimulating the phrenic nerve to communicate with the diaphragm. Among 35 patients with heart failure enrolled in the Remede System pivotal trial and treated for 6 months with the phrenic nerve stimulator, 57% reported that they had "markedly" or "moderately" improved, compared with a 9% rate for this self-rating among 44 control heart failure patients in the trial, a statistically significant difference, Lee R. Goldberg, MD, said at the annual scientific meeting of the Heart Failure Society of America.

NO SIGNAL OF HARM SEEN // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Meet Debasree Banerjee, MD, MS winner of a CHEST Foundation grant.

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Controls fared better than treated // *continued from page 1*

SIOVAC (Sildenafil for Improving Clinical Outcomes After Valvular Correction) comprised 200 patients with residual pulmonary hypertension after corrected valvular heart disease at 17 Spanish general hospitals. The patients were randomized to receive sildenafil at 40 mg t.i.d. or placebo for 6 months in this double-blind trial.

The primary endpoint was a standardized composite clinical score widely used in heart failure trials. It consists of all-cause mortality, hospital admission for heart failure, worsening exercise tolerance, and deterioration in a global self-assessment rating.

The shocker for the investigators – who had expected a positive study – was that 33% of patients in the sildenafil group worsened significantly on the composite clinical score at 6 months, compared with 14% of placebo-treated controls, said Dr. Bermejo, a cardiologist at Gregorio Marañón University Hospital in Madrid.

Moreover, only 27% of the sildenafil group improved, compared with 44% of controls. About one-third of patients in both groups re-

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mained unchanged over the course of the 6-month trial.

Dr. Bermejo noted that valvular disease is considered the next cardiac epidemic because of its strong association with advancing age and the rapid aging of the population worldwide. Pulmonary hypertension occurs is virtually all patients with severe mitral disease and in up to two-thirds of those with asymptomatic aortic stenosis. Regression of the pulmonary hypertension is often incomplete after successful surgical or transcatheter correction of the valvular lesion.

Discussant Irene M. Lang, MD, called SIOVAC "a very clear study." It convincingly establishes that sildenafil – a vasodilator – is ineffective for the treatment of what the current ESC/European Respiratory Society guidelines on pulmonary hypertension call isolated post-capillary pulmonary hypertension, a condition defined hemodynamically by a diastolic pulmonary vascular pressure gradient of less than 7 mm Hg and/or a pulmonary vascular resistance below 3 Wood units (Eur Heart J. 2016 Jan 1;37[1]:67-119.)

The SIOVAC findings underscore the strong IIIC recommendation in the European guidelines that the use of approved therapies for pulmonary arterial hypertension is not recommended in patients with left heart disease-pulmonary hypertension, added Dr. Lang, a coauthor of the guidelines and professor of vascular biology at the Medical University of Vienna.

The Spanish government funded SIOVAC. Dr. Bermejo reported having no financial conflicts of interest.

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NEWS

Sepsis response team not beneficial

BY LUCAS FRANKI
Frontline Medical News

FROM CHEST ▪ A sepsis response team did not have a positive effect on mortality or organ dysfunction in septic patients, compared with standard treatment by a primary care team, according to a study abstract from the CHEST annual meeting.

The study, by Chhaya Patel, MD, and colleagues, covers a retrospective analysis of 517 septic patients in an inpatient ward at a tertiary care academic center from June 2014 until December 2016. Of this group, 302 were treated by a sepsis response team, while the others were treated by the normal primary care team.

Compared with the primary care team, the sepsis team was more likely to intervene on patients with a quick Sepsis-Related Organ Failure Assessment score greater than 1 (33.8% vs. 22.8%), change or initiate antibiotics within 3 hours (64.6% vs. 37.2%), and obtain blood cultures on time (66.4% vs 45.2%). An additional difference between the two groups was that the sepsis team had better compliance with the 3-hour bundle (15.2% vs 8.4%).

Despite the sepsis team's higher level of compliance with certain protocols, the combined outcome measure of mortality and organ dysfunction within 28 days was not significantly higher for patients treated by the sepsis team (11.3% vs. 9.8%; $P = .6$). In fact, there was at least one downside to being treated by the sepsis team, which was having a 14% longer hospital stay.

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No signal of harm seen

// *continued from page 1*

This analysis of the 80 heart failure patients enrolled in the pivotal trial, (which also included 71 patients with central sleep apnea but without heart failure) also showed that, during the first 6 months of phrenic nerve stimulation, patients had a 5% incidence of first heart failure hospitalization, compared with a 17% rate among controls who received no stimulation, a difference that fell slightly short of statistical significance. The results also showed no signal of harm – including no suggestion of increased mortality – an important observation, because a prior study of another approach for treating central sleep apnea, adaptive servo-ventilation, showed clear evidence for increased mortality in the SERVE-HF trial (N Engl J Med. 2015 Sep 17;373 [12]:1095-105).

'There is no treatment option right now for central sleep apnea ... we treated some patients' with fairly advanced HF who did fine.

DR. GOLDBERG

Further analysis focused on echocardiographic examinations after 12 months in 23 of the heart failure patients who entered the study with a left ventricular ejection fraction of 45% or less and received 12 months of phrenic nerve stimulation. The average LVEF rose in these patients from 30% at baseline to 35%, a statistically significant difference, and left ventricular end systolic volume fell by an average of almost 11 mL from baseline, a difference just short of statistical significance, findings Dr. Goldberg called "a little exciting."

"It is very encouraging to see some evidence for ventricular remodeling," commented Lynne W. Stevenson, MD, professor of medicine and a heart failure specialist at Vanderbilt University in Nashville, Tenn.

"There is no treatment option right now for central sleep apnea, and during the phrenic nerve–stimulation pivotal trial we treated some patients [at our center] with fairly advanced heart failure who did fine on the treatment," noted Dr. Goldberg, medical director of the heart failure and transplantation program at the University of Pennsylvania in Philadelphia.

The FDA approved the use of this device for the treatment of moderate to severe central sleep apnea on Oct. 6 . "I think we would use it" in heart failure patients with intolerable symptoms from central sleep apnea, Dr. Goldberg said in an interview during the meeting.

"There is a tight connection between sleep-disordered breathing, sleep apnea, heart failure, and cardiovascular disease, and we have been pretty aggressive in trying to treat the sleep apnea. Even if phrenic nerve stimulation just improves patients' quality of life and is neutral for other outcomes," it would be reasonable to offer it to patients, he said. "But many of us think there is a bigger connection that results in a therapeutic benefit [to heart failure patients] by treating their central sleep apnea."

Continued on following page

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: Among the encountered categories of central sleep apnea, such as idiopathic CSA, treatment-emergent CSA, and Cheyne-Stokes respiration (CSR) in association with heart failure (HF), the latter has received most attention in the last decade because of its association with increased mortality in HF patients. While the role of CSR in sympathetic activation and arrhythmogenesis in heart failure patients has been debated, attempts to treat CSR with adaptive servo-ventilation have been associated with increased mortality in patients with lower left ventricular ejection fraction. Transvenous phrenic nerve pacing is a novel modality that appears to be well tolerated. Despite treating only central apneas, it appears to reduce the apnea-hypopnea index by more than 50% in HF patients with central-predominant AHI greater than 20. Other improvements were noted in global functioning and oxygen saturations without worsening of obstructive apneas. Given what we have previously seen with adaptive servo-ventilation, longer-term trials to examine mortality with this treatment will be important.

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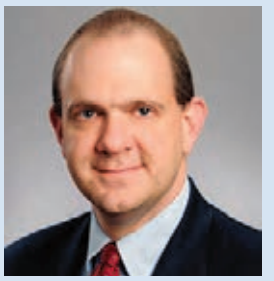

David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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Ideal intubation position still unknown

BY ANDREW D. BOWSER
Frontline Medical News

FROM CHEST ▪ In critically ill adults undergoing endotracheal intubation, the ramped position does not significantly improve oxygenation compared with the sniffing position, according to results of a multicenter, randomized trial of 260 patients treated in an intensive care unit.

Moreover, "[ramped] position appeared to worsen glottic view and increase the number of attempts required for successful intubation," wrote Matthew W. Semler, MD, of Vanderbilt University Medical Center, Nashville, Tenn., and his coauthors (Chest. 2017 Oct. doi: 10.1016/j.chest.2017.03.061).

The ramped and sniffing positions are the two most common patient positions used during emergent intubation, according to investigators. The sniffing position is characterized by supine torso, neck flexed forward, and head extended, while ramped position involves elevating the torso and head.

Some believe the ramped position may offer superior anatomic alignment of the upper airway; however, only a few observational studies suggest it is associated with fewer complications than the sniffing position, the authors wrote.

Accordingly, they conducted a multicenter randomized trial with a primary endpoint of lowest arterial oxygen saturation, hypothesizing that the endpoint would be higher for the ramped position: "Our primary outcome of lowest arterial oxygen saturation is an established endpoint in ICU intubation trials, and is linked to periprocedural cardiac arrest and death," they wrote.

The investigators instead found that median lowest arterial oxygen saturation was not statistically different between groups, at 93% for the ramped position, and 92% for the sniffing position ($P = 0.27$), published data show.

Further results showed that the ramped position appeared to be associated with poor glottic view and more difficult intubation. The incidence of grade III (only epiglottis) or grade IV (no visible glottis structures) views were 25.4% for ramped vs. 11.5% for sniffing ($P = .01$), while the rate of first-attempt intubation was 76.2% for ramped vs. 85.4% for sniffing ($P = .02$).

While the findings are compelling, the authors were forthcoming about the potential limitations of the study and differences compared with earlier investigations. Notably, they said, all prior controlled trials of patient positioning during endotracheal intubation were conducted in the operating room, rather than in the ICU.

Also, the operators' skill levels may further explain differences in this study's outcomes from those of similar studies, the researchers noted. Earlier studies included patients intubated by one or two senior anesthesiologists from one center, while this trial involved 30 operators across multiple centers, with the average operator having performed 60 previous intubations. "Thus, our findings may generalize to settings in which airway management is performed by trainees, but whether results would be similar among expert operators remains unknown," the investigators noted.

The authors reported no potential conflicts of interest. One coauthor reported serving on an advisory board for Avisa Pharma.

VIEW ON THE NEWS

Valuable new data amid sparse literature

Editorialists praised the multicenter, randomized design of this study, and its total recruitment of 260 patients. They also noted several limitations of the study that "could shed some light" on the group's conclusions (Chest. 2017 Oct. doi: 10.1016/j.chest.2017.06.002).

"The results diverge from [operating room] literature of the past 15 years that suggest that the ramped position is the preferred intubation position for obese patients or those with an anticipated difficult airway." This may have been caused by shortcomings of this study's design and differences between it and other research exploring the topic of patient positioning during endotracheal intubation, they wrote.

The study lacked a prespecified algorithm for preoxygenation and the operators had relatively low amounts of experience with intubations. Finally, the beds used in this study could contribute to the divergences between this intensive care unit experience and the operating room literature. The operating room table is narrower, firmer, and more stable, while by contrast, the ICU bed is wider and softer, they noted. This "may make initial positioning, maintenance of positioning, and accessing the patient's head more difficult."

Nevertheless, "[this] important study provides ideas for further study of optimal positioning in the ICU and adds valuable data to the sparse literature on the subject in the ICU setting," they concluded.

James Aaron Scott, DO, Jens Matthias Walz, MD, FCCP, and Stephen O. Heard, MD, FCCP, are in the department of anesthesiology and perioperative medicine, UMass Memorial Medical Center, Worcester, Mass. The authors reported no conflicts of interest. These comments are based on their editorial.

Continued from previous page

The pivotal trial enrolled a total of 151 patients with central sleep apnea at 31 centers in Germany, Poland, and the United States who were selected based on having an apnea-hypopnea index of at least 20 events per hour. All participants received a transvenous phrenic nerve–stimulator implant, and then randomization assigned 73 patients to have the device turned on for the first 6 months while 78 device recipients had their devices left off to serve as controls. The study's primary efficacy endpoint was the percentage of patients having at least a 50% cut in their apnea-hypopnea index, which happened in 51% of evaluable patients in the active treatment arm and in 11% of the evaluable controls. The FDA's approval of this device is based on these specific findings, according to a statement from the agency. This device is not intended for use in patients with obstructive sleep apnea. Adverse events reported in the study included concomitant device interaction, implant site infection, and swelling and local tissue damage or pocket erosion. The Remede System is contraindicated for patients with active infection or who are known to require an MRI. The primary study results were published last year (Lancet. 2016 Sep 3;388[10048]974-82).

'It is very encouraging to see some evidence for ventricular remodeling.'

DR. STEVENSON

"We hope this treatment will have the collateral effect of improving cardiovascular disease outcomes, but we don't know that yet. The initial target will be patients with apnea-hypopnea episodes that affect their quality of life," Dr. Goldberg said.

The apparent safety of this approach for treating central sleep apnea may relate to its mechanism of action, he suggested. The mortality-boosting effect of adaptive servo-ventilation may correlate with the positive pressure it creates in a patient's chest that perhaps causes myocardial stress or hemodynamic problems. In contrast, phrenic nerve stimulation produces diaphragm motion that mimics normal breathing and creates negative chest pressure. "A lot of hypothesis generation needs to happen to better understand the underlying physiology," Dr. Goldberg conceded.

At the end of the 6-month period that compared active treatment with control, the heart failure subgroup also showed statistically significant benefits from treatment for several sleep metrics, including apnea-hypopnea index, the central apnea index, and oxygen desaturation, and also for daytime sleepiness measured on the Epworth Sleepiness Scale. After 12 months on active treatment, patients also showed a significant improvement over baseline in their score on the Minnesota Living With Heart Failure Questionnaire, Dr. Goldberg reported.

The trial was sponsored by Respicardia, the company developing the Remede System. Dr. Goldberg has been a consultant to and has received research funding from Respicardia. Dr. Stevenson had no relevant disclosures.

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Cases of Legionnaires' continue to rise in U.S.

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Rates of reported Legionnaires' disease nearly quadrupled in the United States between 2000 and 2015, and it is likely underdiagnosed, said Laura A. Cooley, MD.

"Improved testing and surveillance are needed to improve understanding of disease and outbreak burden," she said at an annual scientific meeting on infectious diseases. "There is more to learn about environmental sources of *Legionella* for cases not associated with known outbreaks and about the distribution of *Legionella* in the environment."

Dr. Cooley, a medical epidemiologist at the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention, Atlanta, said that between 2000 and 2015, the rate of reported cases in the United States increased by about 350%, from 0.42 cases per 100,000 people to 1.89 cases per 100,000, "and this is likely an underestimate due to underdiagnosis." Reasons for the increase are likely multifactorial, she said, including increased susceptibility of the population. "The population is aging, and there are more people in the United States on immunosuppressive medications. There also may be more *Legionella* in the environment." There also are improved diagnostic capabilities, with the urinary antigen test, improved diagnosis and reporting due to increased awareness and testing, and increased surveillance capacity.


Dr. Laura A. Cooley

A Gram-negative bacillus, *Legionella* is an intracellular parasite of free-living protozoa primarily found in freshwater. "It can live and grow in biofilm, and there are more than 60 species of the bacterium," she said at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

Cases are higher in the warmer months, and the rates are highest among the elderly, men, and those of black race. Currently, *L. pneumophila* accounts for about 90% of cases in the United States. "Once it's transmitted, it has to hit a susceptible population to cause disease, generally older individuals and people with underlying conditions," Dr. Cooley said.

According to a CDC analysis of

27 building-associated *Legionella* outbreaks in the United States between 2000 and 2014, common settings included hotels, long-term care facilities, and hospitals. Common sources of transmission were aerosolizing devices such as showers and faucets, cooling towers, hot tubs, and decorative fountains (MMWR 2016;65[22]:576-84). The median number of cases per outbreak ranged from 3 to 82. Cooling tower outbreaks affected a median of 22 people, while potable water outbreaks affected a median of 10 people.

A separate analysis evaluated *Legionella* cases reported among U.S. residents between 2005 and 2009 (MMWR. 2011;60[32]:1083-6). It found that only 4% were associated with outbreaks, and 96% were sporadic. "That doesn't mean that [the cases] weren't associated with the same kind of source, they just weren't identified as an outbreak," Dr. Cooley said. "It shows that there is a lot to learn about transmission of *Legionella*."

The U.S. case definition of Legionnaires' disease consists of clinical or radiologic pneumonia plus confirmatory laboratory testing, either by urinary antigen test (UAT), lower respiratory culture, or appropriate serological testing. Polymerase chain reaction can be used as a presumptive test for a suspect case. "UAT is easy and it detects *L.*

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pneumophila serogroup 1 (Lp1), but it has some gaps," Dr. Cooley said. "It isn't completely sensitive for Lp1, and it doesn't detect any other species or serogroups. That's why we also recommend that a culture of respiratory secretions on selective media be performed at the same time. That being said, in the U.S., nearly all reported cases of *Legionella* are diagnosed by UAT only."

A 2016 CDC MMWR and Vital Signs report found that almost all *Legionella* outbreaks could be prevented with effective water management, and the CDC has published a step-by-step guide to creating a water management program to reduce *Legionella* growth and spread in buildings. The 2017 MMWR Report found that definite health care–associated Legionnaires' disease is deadly for one in four people who get it. The report also found that this issue is widespread; 76% of complete reporting jurisdictions reported at least one definite case of health care–associated *Legionella* disease in 2015. More recently, the Centers for Medicare & Medicaid Services issued a requirement to reduce risk in health care facility water systems to prevent cases and outbreaks. It applies to hospitals, skilled nursing facilities, and critical access hospitals.

Dr. Cooley reported having no financial disclosures.

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Pneumococcal vaccines knock out many serotypes

BY LUCAS FRANKI
Frontline Medical News

The introduction of pneumococcal conjugate vaccines 7 (PCV7) and 13 (PCV13) has significantly reduced pneumococcal colonization of the serotypes targeted by the vaccines, but serotypes not covered by these vaccines have picked up the slack, according to an analysis of more than 6,000 young Massachusetts children tested at well child or acute care visits over 15 years.

In the past 15 years, use of pneumococcal vaccines in the United States has led to dramatic declines in invasive pneumococcal disease (IPD) in young children, reductions in pneumonia hospitalizations, and herd protection in older adults against disease that otherwise would be caused by the vaccinated serotypes, studies have found. But not all serotypes of *Streptococcus pneumoniae* are covered by the vaccines.

The data used in the Massachusetts study included results from nasopharyngeal swabs taken from 6,537 children younger than 7 years of age in various Massachusetts communities during six respiratory illness seasons during 2000-2001, 2003-2004, 2006-2007, 2008-2009, 2010-2011, and 2013-2014. The highest rate of pneumococcal colonization was in 2011 at 32%, and the lowest was in 2004 at 23%, Grace M. Lee, MD, MPH, of the Harvard Medical School and Harvard Pilgrim Health Care Institute, both in Boston, and her associates reported (Pediatrics. 2017;140[3]:e20170001).

"Replacement with nonincluded serotypes remains a risk with vaccines that do not cover the full range of serotype diversity. As new selective pressures are applied, such as the introduction of a vaccine into a community, the void may be filled by nontargeted serotypes," as was observed after PCV7.

In 2001, PCV7 serotypes were the most common, but after the rapid introduction of the vaccine, infection rates for those serotypes quickly declined, nearly disappearing by 2007. Serotype 19A became the most common serotype in 2004, but after the introduction of PCV13 in 2010, it and other serotypes targeted by PCV13 also began to decline. In 2014, the most common serotypes were 15B/C, 35B, 23B, 11A, and 23A.

Non-PCV13 serotypes accounted for about a third of observed *Streptococcus pneumoniae* colonizations in 2001, but by 2014 they accounted for nearly all colonizations. In addition, the overall rate of infection did not decrease over

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the study period. While a reduction was seen from 2011 to 2014, it remains to be seen whether this drop is transient.

"Replacement with nonincluded serotypes remains a risk with vaccines that do not cover the full range of serotype diversity. As new selective pressures are applied, such as the introduction of a vaccine into a community, the void may be filled by nontargeted serotypes," as was observed after PCV7, Dr. Lee and her fellow researchers noted.

Nonsusceptibility to erythromycin was most common in 2014, with 35% of pneumococcal isolates displaying either moderate susceptibility or resistance. Nonsusceptibility to ceftriaxone (12%), clindamycin (9%), and penicillin (6%) was significantly less common, and no isolates were found to have vancomycin resistance.

"First-line penicillins continue to be the most frequently prescribed antibiotic across all age groups among young children in Massachusetts, which may result in the continued success of 19A associated with penicillin resistance," the researchers said.

Risk factors associated with colonization by either PCV13 serotypes or non-PCV13 serotypes include younger age, more hours of child care exposure, and having a respiratory tract infection on the day of sampling. The presence of a smoker in the house and recent usage of antibiotics was associated with colonization by PCV13 serotypes but not by non-PCV13 serotypes.

"As newer pneumococcal vaccines are developed, there will continue to be a need for monitoring both the intended and unintended consequences of altering the nasopharyngeal niche through immunization," Dr. Lee and her associates concluded.

This work was funded by a National Institute of Allergy and Infectious Diseases grant and the National Institutes of Health. Marc Lipsitch, PhD; William P. Hanage, PhD; Ken Kleinman; Stephen Pelton, MD; and Susan S. Huang, MD, MPH, reported various conflicts of interest. Dr. Lee and the remaining investigators indicated that they had no potential conflicts of interest.

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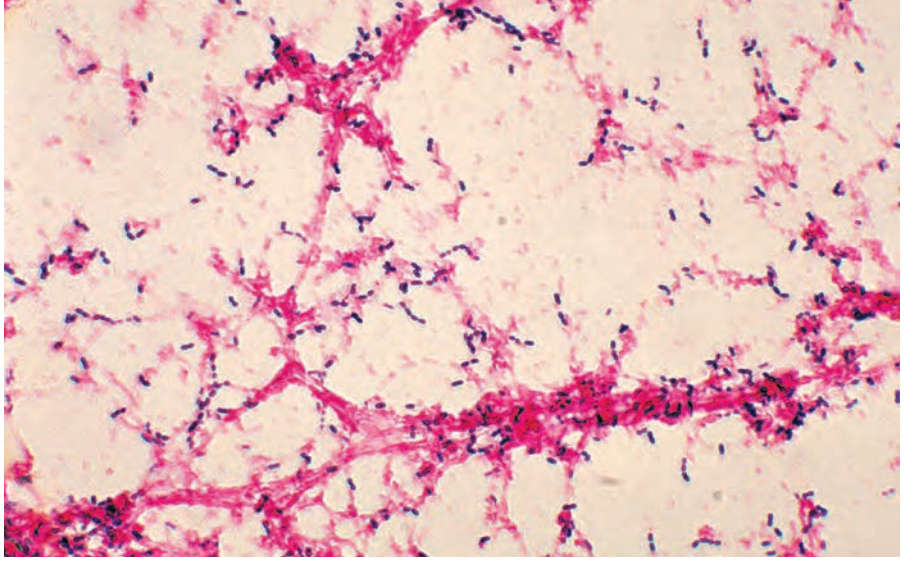

CDC/Dr. Mike Miller

Streptococcus pneumoniae

VIEW ON THE NEWS

Playing pneumococcal serotype elimination 'whack-a-mole'

"The hope that IPD and antibiotic resistance would disappear after widespread use of PCV vaccines has yet to be realized," Douglas S. Swanson, MD, and Christopher J. Harrison, MD, wrote in an accompanying editorial (Pediatrics. 2017;140[5]:e20172034).

While some invasive pneumococcal diseases, such as occult bacteremia and meningitis, have been significantly reduced due to PCV7 and PCV13, "one concern is whether some replacement serotypes could have invasive disease potential. For example, post-PCV7, there was increased severity of IPD from non-PCV7 serogroup organisms among children in the Intermountain West of the United States," the authors noted. Newly dominant strains, such as post-PCV13 serotype 35B, could cause increased IPD in vulnerable populations, becoming the equivalent of a post-PCV7 serotype 19A.

While addressing emerging serotypes in additional PCVs is possible, reformulating the vaccine and obtaining Food and Drug Administration approval would take time and resources, with no clear guarantee of ultimate success, making "this strategy seem like playing a game of whack-a-mole. To overcome the phenomenon of serotype replacement, vaccine strategies need to expand beyond serotype specificity by identifying antigens common to all *Streptococcus pneumoniae*, regardless of serotype," Dr. Swanson and Dr. Harrison said.

"Shifts back to less penicillin resistance may soon preclude the need for high dose amoxicillin for acute otitis media, and the near absence of occult *Streptococcus pneumoniae* bacteremia may drastically reduce empirical ceftriaxone for fever without a focus. To assist providers in ongoing vigilance for the now less frequent IPD, algorithms based on new epidemiologic data are in development and should decrease the number of 'sepsis work-ups' performed," they said.

On-time PCV13 vaccination would help address the risk factor of young age, and judicious antibiotic use could further reduce antibiotic resistance. Social engineering approaches, although difficult, also might help. These approaches include continued parent education to restrict secondhand smoke exposure and the risk of *S. pneumoniae* nasopharyngeal colonization, as well as having young children spend fewer hours in day care in order to reduce two other risk factors – pathogen exposure and frequency of viral upper respiratory tract infections.

Dr. Swanson and Dr. Harrison are with the division of infectious diseases at Children's Mercy Kansas City, University of Missouri-Kansas City. Both reported conducting pneumococcal research supported by funding from Pfizer.

Pertussis resurgence is real, but possible solutions exist

BY BRUCE JANCIN
Frontline Medical News

MADRID – The explanation for the ongoing resurgence in pertussis in adolescents and adults in the United States and other developed countries lies largely in the waning effectiveness of current acellular pertussis vaccines as early as 2-3 years post boosters, according to Stanley A. Plotkin, MD, chair of the steering committee for the Global Pertussis Initiative.

"The problem seems to lie in the lack of persistence of immunity after vaccination using the acellular pertussis vaccines. To say that this is not controversial would clearly be wrong, but that is my view," he declared at the annual meeting of the European Society for Paediatric Infectious Diseases.

It's a view supported by persuasive evidence, added Dr. Plotkin, emeritus professor of pediatrics at the University of Pennsylvania, Philadelphia.

There are other reasons for the resurgence of pertussis, he noted. Better diagnosis and improved surveillance are certainly factors. So is increased virulence of pertussis strains in response to vaccine immunity. There is intriguing preliminary evidence from a study in baboons conducted by scientists at the Food and Drug Administration that suggests acellular vaccine doesn't protect against pertussis infection and transmission, even though symptoms are prevented (Proc Natl Acad Sci USA. 2014 Jan 14;111[2]:787-92). If that work is confirmed in humans, it would mean that circulation of *Bordetella pertussis* is intensified in the United States and other countries using acellular vaccine.

In the United States, investigators at Northern California Kaiser Permanente have shown that the effectiveness of acellular pertussis in the Tdap vaccine wanes rapidly in adolescents. Indeed, it plunged from 69% effectiveness in the first year after vaccination to less than 9% by year 4 (Pediatrics. 2016 Mar;137[3]:e20153326).

In contrast, whole-cell pertussis vaccines provide roughly 6-10 years of protection against infection, and native infection provides persistent

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protection against reinfection for 7-20 years, Dr. Plotkin noted.

He was senior coauthor of a recent study that addresses why acellular pertussis vaccine immunity wanes so quickly. He and his coinvestigators demonstrated that while whole-cell pertussis vaccines promote vigorous Th1 and Th17 responses, which discourage pharyngeal colonization, acellular pertussis vaccines orient the immune system toward a less salutary Th1/Th2 response (Cold Spring Harb Perspect Biol. 2017 Mar 13. doi: 10.1101/cshperspect.a029454).

In addition, other investigators have shown that repeated booster doses of acellular pertussis vaccine generate higher levels of antigen-specific IgG4, which doesn't bind complement and results in impaired phagocytosis and a suboptimal inflammatory response. In contrast, priming of the immune system via administration of a whole-cell pertussis vaccine at birth followed by acellular pertussis boosters results in improved phagocytosis and complement-mediated microbial killing via preferential induction of IgG1(Cold Spring Harb Perspect Biol. 2017 Mar 13. doi: 10.1101/cshperspect.a029553).

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Pertussis

Possible solutions to the pertussis problem

The long-term solution is clear, Dr. Plotkin said: "I think a new vaccine for adolescents and adults is badly needed."

Infants don't need a new vaccine; that's not where the vaccine failures are occurring. "Again, I stress that the problem so far has not been in infants, it has been in adolescents and adults," he said.

A new vaccine is a daunting prospect. Given the huge investment vaccine manufacturers made in the 1990s to bring the current acellular vaccines to the market, they are hardly eager to launch development programs for new pertussis vaccines. They have other vaccine development priorities.

Moreover, the regulatory challenges are huge unless the Food and Drug Administration and other licensing authorities are willing to forgo the large, long, and expensive clinical trials that have traditionally been required. In lieu of such efficacy studies, they would need to consider studies demonstrating better immunogenicity based upon antibody titers, or animal studies.

"The possibility of a human challenge study in adults is an idea I like; I'm not sure about the FDA," the pediatrician said.

Until a new or improved vaccine becomes available, the most important strategy to control the resurgence of pertussis is acellular vaccination of pregnant women in their third trimester to provide passive protection to the newborn via transplacental antibody. That practice is already recommended in the United States and many other countries. And while it reduces the risk of pertussis in early infancy – the most serious form of the disease – that strategy won't have any real impact on the adult burden of disease, which Dr. Plotkin estimated at more than 600,000 cases annually.

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Stanley A. Plotkin, chair of the steering committee for the Global Pertussis Initiative.

Cocooning – a strategy of vaccinating all of a newborn's family contacts – has been promoted in guidelines but has proved difficult to implement. "I think cocooning strategies by and large have been a failure," he declared.

More frequent boosters of current acellular pertussis vaccines would presumably increase effectiveness, but that would be costly and tough to put in place on a public health scale.

A return to using conventional whole-cell pertussis vaccines would be a tough sell to the public and is probably flat out unacceptable. Developing a less reactogenic whole-cell vaccine might be a work-around, but it hasn't been done yet.

The easiest way to improve acellular pertussis vaccine for adolescents and adults is to improve the pertussis toxin antigen component. Increasing the dose of pertussis toxin could generate more and longer-lasting antibodies to it. An even more exciting possibility is based upon evidence more than a decade old that genetic inactivation of pertussis toxin results in antibody levels far higher and presumably more bactericidal than the formalin-inactivated pertussis toxin included in current vaccines, according to Dr. Plotkin.

Adding stronger adjuvants to a Tdap vaccine for adolescents is another appealing strategy.

The Global Pertussis Initiative is sponsored by Sanofi Pasteur. Dr. Plotkin reported serving as a consultant to that vaccine manufacturer and numerous others but declared he had no financial conflicts regarding his presentation.

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New pertussis vaccine may solve immunogenicity problem

BY BRUCE JANCIN
Frontline Medical News

MADRID – A novel, monovalent, acellular pertussis vaccine containing a recombinant, genetically inactivated pertussis toxin displayed markedly greater sustained immunogenicity than the widely used Sanofi Pasteur Tdap, known as Adacel, which is used as a booster vaccination of adolescents and young adults, in a pivotal phase 3, randomized trial, Simonetta Viviani, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

A Tdap containing the same proprietary genetically detoxified pertussis toxin (PT) also outperformed the conventional, acellular pertussis–containing Adacel in the pivotal three-arm study. Both novel vaccines were similar to Adacel in terms of safety. Based on these results, the novel monovalent vaccine, known as Pertagen, and the novel Tdap, known as Boostagen, are now licensed and marketed in Thailand.

"Our interpretation of these results is that they open up a new way to approach pertussis vaccination," declared Dr. Viviani, director of clinical development at BioNet-Asia, a Bangkok-based biotech vaccine company.

DR. VIVIANI

The impetus for developing new acellular pertussis vaccines is the documented resurgence of pertussis.

"One suggested approach has been to replace chemically inactivated PT with a genetically inactivated PT," Dr. Viviani explained.

The significant phase 3 trial included 450 Thai 12- to 17-year-olds who were randomized to a single 0.5-mL dose of Pertagen, Boostagen, or Adacel. Both Pertagen and Boostagen contain 5 mcg of the genetically inactivated PT and 5 mcg of filamentous hemagglutinin.

The seroconversion rate, defined as the proportion of subjects who reached at least a fourfold increase in titers of PT and filamentous-hemagglutinin antibodies over baseline, was far superior at both 28 days and 1 year in subjects who got Pertagen or Boostagen, compared with those who received Adacel.

The fast-waning immunity that is a major limitation of conventional acellular pertussis vaccines was amply illustrated by the difference in falloff of PT-neutralizing antibody over time. The PT-neutralizing antibody titer was 278 IU/mL at 1 month and 77 IU/mL at 1 year in the Pertagen group, 216 IU/mL at 1 month and 67 IU/mL at 1 year with Boostagen, and a mere 36 IU/mL at 1 month and 12 IU/mL at 1 year with Adacel.

The study was sponsored by BioNet-Asia and Mahidol University.

Dr. Viviani is a BioNet employee.

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FDA advisory committee rejects opioids in children's cough syrup

BY IAN LACY
Frontline Medical News

ROCKVILLE, MD. – The majority of a Food and Drug Administration advisory panel agreed the benefit versus risk of prescription opioid cough suppressants for pediatric patients was not favorable.

The voting was broken into multiple votes based on age range of patients and the specific opioid present in the cough syrup. Unlike other advisory committee meetings, this meeting did not focus on the treatment of a disease state, but rather on the treatment of a symptom.

On Sept. 11, 2017, the FDA's Pediatric Advisory Committee voted 21-2, with one abstention, that the benefit versus the risk of opioid cough suppressants for pediatric patients was not favorable.

This vote was preceded by two previous votes specifically questioning the use of codeine and hydrocodone in medications for pediatric patients. For codeine, the committee voted unanimously that the benefit versus risk was not favorable in pediatric patients aged 12 years to less than 18 years.

For hydrocodone, the committee asked two questions: 1) Was the benefit versus risk favorable for pediatric patients aged 6 years to less than 12 years? and 2) Was the benefit versus risk favorable for pediatric patients aged 12 years to less than 18 years? On the vote for patients aged 6 years to less than 12 years, the committee voted 23-1, with no abstention, that it was not favorable. The committee likewise voted 23-1 that it wasn't favorable in patients aged 12 to less than 18 years.

Due to the wide scope of this committee, the voting was based on presentations from pharmaceutical company representatives presenting the results of industry-led studies and independent researchers.

According to Sharon Levy, MD, MPH, adolescents are the most at-risk population for opioid misuse. This susceptibility is due to the developmental neurobiology of adolescent brains. A region of the brain associated with the reward pathway, nucleus accumbens, is developing in adolescents and plays a role in salience. Salience, or the differentiation between important versus unimportant rewards, varies widely by age group. Young children show little salience with rewards, and treat rewards equivocally. Adults have a proportional response to rewards with accurate salience. Adolescents, on the other hand, are unhappy with small rewards, but receive a massive return with large rewards. This type of neurobiological feedback makes adolescents "vulnerable to develop substance use disorders."

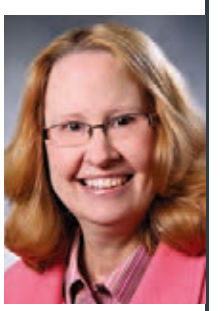
Dr. Levy also noted a correlation between prescribed opioid use and alcohol, marijuana, and tobacco use as contributing factors to opioid misuse. When opioids are prescribed for pain management, there is an adjusted odds ratio (AOR) of 1.33, indicating a high likelihood of misuse. Similar AORs are seen in adolescents who have used marijuana, cigarettes, and alcohol: 2.44, 1.25, and 1.23, respectively.

Sovereign pharmaceuticals representative Leonard Lawrence presented the findings of a pharmacokinetic study for hydrocodone and guaifenesin in 25-35 pediatric patients evenly divided into groups aged 6 years to less than 12 years, and 12 years to less than 18 years. According to Mr. Lawrence, codeine appears "to be a greater risk in children younger than 12 years, and should not be used" because of difficulty breathing. Mr Lawrence

Continued on following page

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Pediatric pulmonologists talk about this all the time but it is usually primary care and urgent care providers who give children cough suppressants that don't work and are potentially dangerous. I don't understand why they aren't taken off the market.



CHEST Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Faster multiplex PCR led to faster hospital discharges

BY AMY KARON
Frontline Medical News

SAN DIEGO – Switching to a faster, more comprehensive multiplex PCR viral respiratory assay enabled a hospital to discharge young children with acute respiratory illnesses sooner, prescribe oseltamivir more often, and curtail the use of antibiotics and thoracic radiography, Rangaraj Selvarangan, PhD, reported at an annual meeting on infectious disease.

The study shows how rapid multiplex PCR testing can facilitate antimicrobial stewardship, said Dr. Selvarangan, who is a professor at the University of Missouri Kansas City School of Medicine and director of the microbiology laboratory at Children's Mercy Kansas City. "Our antimicrobial stewardship programs monitor these test results daily, add notes, and make recommendations on antibiotic choices," he said.

Acute respiratory illness is a leading reason for pediatric hospitalization, is usually viral in nature, and continues to fuel the overuse of antibiotics. Multiplex PCR respiratory panel assays have been available in the United States for about a decade, but uptake has varied. "As one of the early adopters of the technology, we wanted to see how it might affect patient care," Dr. Selvarangan said.

For the study, the researchers compared hospital records from December 2008 through May 2012, when Children's Mercy hospital used the Luminex xTAG Respiratory Viral Panel, with records from August 2012 through June 2015, after the hospital had switched over to the BioFire FilmArray Respiratory Panel. FilmArray targets the same 17 viral pathogens as the Luminex panel, but also targets *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, seasonal influenza A, parainfluenza type 4, and four coronaviruses.

The study included children aged up to 2 years who were not on immunosuppressive medications, in the

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Continued from previous page

went on to say that these effects were exacerbated in obese children with lung disease or obstructive sleep apnea.

Victor S. Sloan, MD, of UCB in Brussels, presented an internal review of Tussionex, a combination cough medicine (hydrocodone/chlorpheniramine). This review took into account modern pharmacovigilance methods, changes in clinical practice, and a literature review. "Upon annual review, UCB determined that benefit risk balance for use of Tussionex for cough in children was no longer favorable," said Dr. Sloan. Based on the results of the review, UCB has filed a label supplement to limit use of Tussionex to patients aged 18 years or older.

"Codeine, in particular, is an antiquated drug," said Kathleen Neville, MD, pediatrics and clinical pharmacology section chief of Arkansas Children's Hospital, Little Rock.

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NICU, or hospitalized for more than 7 days. For this population, the two panels yielded similar rates of positivity overall (about 60%) and for individual viruses, Dr. Selvarangan said. A total of 810 patients tested positive for at least one virus on the Luminex panel, and 2,096 patients tested positive on FilmArray. Results for FilmArray were available within a median of 4 hours, versus 29 hours for Luminex (*P* less than .001). The prevalence of empiric antibiotic therapy was 44% during the Luminex era and 28% after the hospital switched to FilmArray (*P* less than .001). Rates of antibiotic discontinuation rose from 16% with Luminex to 23% with FilmArray (*P* less than .01). Strikingly, oseltamivir prescriptions rose fivefold (from 17% to 85%; *P* less than .001) after the hospital began using FilmArray, which covers seasonal influenza. Finally, use of chest radiography fell significantly in both infants and older children after the hospital began using FilmArray instead of Luminex.

This study is one of the first to directly compare clinical outcomes

Continued on following page

AMY KARON/FRONTLINE MEDICAL NEWS

Dr. Rangaraj Selvarangan, PhD

Continued from previous page

between two assays, Dr. Selvarangan noted.

"For the individual patient, having more rapid diagnostic methods for viral infections not only allows for the prompt initiation of the correct therapy, but helps to avoid the incorrect prescription of antibiotics for viral disease," said Vera A. De Palo, MD, FCCP. "For community health in general, the authors indicate the important antimicrobial stewardship benefits of the more comprehensive multiplex PCR viral respiratory assay."

Dr. Selvarangan disclosed grant support from both Biofire Diagnostics and Luminex, and an advisory relationship with BioFire.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: I have found film arrays to be incredibly useful in certain situations. I also prefer it over ordering a mycoplasma IgM for the diagnosis of mycoplasma. The blood tests can cross-react with viral respiratory tract illnesses leading a clinician to treat with a macrolide, for example, when the illness was really precipitated by a respiratory virus.

Guidelines cut ACS hospital returns in sickle cell disease

BY HEIDI SPLETE
Frontline Medical News

Children with sickle cell disease who experience acute chest syndrome benefit from the current guideline-recommended antibiotic regimen, based on data from more than 7,000 patients.

Although acute chest syndrome (ACS) is among the most common complications of sickle cell disease (SCD), data on the effectiveness of the recommended antibiotic therapies (macrolides and cephalosporins) are lacking, wrote David G. Bundy, MD, of the Medical University of South Carolina, Charleston, and colleagues. ACS often leads to intensive hospital care and 1%-2% morbidity, they noted.

The most recent guidelines from the National Heart, Lung, and Blood Institute call for "an intravenous cephalosporin and an oral macrolide antibiotic," the researchers said.

To determine the impact of antibiotic use as directed on reducing hospital readmissions in young SCD patients, the researchers reviewed data from 14,480 hospitalizations for ACS involving 7,178 children and young adults aged 0-22 years seen at 41 hospitals in the United States (JAMA Pediatr. 2017 Sep 11. doi: 10.1001/jamapediatrics.2017.2526).

'This high level of interhospital variation also suggests possible clinician disagreement regarding the ideal antibiotic treatment for children with ACS.'

Overall, 74% of the patients were treated with antibiotics according to the guidelines, but use of guideline-recommended antibiotics ranged from 24% to 90% across the participating hospitals.

"This high level of interhospital variation also suggests possible clinician disagreement regarding the ideal antibiotic treatment for children with ACS," the researchers wrote.

Rates of all-cause readmission and 30-day ACS-related readmission were significantly lower among patients who received the recommended antibiotics (odds ratio, 0.50 and 0.71, respectively). Children aged 5-9 years were most likely to receive the recommended antibiotics (80%), while young adults aged 19-22 years were the least likely (64%).

The findings were limited by several factors, including coding errors and incomplete clinical information, the researchers noted. But the results suggest that the guideline-recommended antibiotics are effective, "so more robust dissemination and implementation of existing treatment guidelines may reduce readmissions in this high-risk population," they said.

The researchers had no financial conflicts to disclose.

Study coauthor Staci Arnold, MD, was supported in part by the Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program.

Preterm bronchopulmonary dysplasia rate maintained

BY BIANCA NOGRADY
Frontline Medical News

Inhaled nitric oxide (NO) therapy does not appear to achieve reduction in the incidence of bronchopulmonary dysplasia in preterm infants, according to data published online Sept. 25 in JAMA Pediatrics.

Shabih U. Hasan, MD, from the Cumming School of Medicine at the University of Calgary, and his coauthors wrote that inhaled nitric oxide is currently approved for the treatment of hypoxic respiratory failure in infants with pulmonary hypertension. Animal studies have prompted interest in its potential to prevent bronchopulmonary dysplasia in preterm infants, but randomized trials so far have shown mixed results (JAMA Pediatrics. 2017 Sep 25. doi: 10.1001/jamapediatrics.2017.2618).

In this study, researchers recruited 451 preterm infants of less than 30 weeks' gestation, with a birth weight below 1,250 g, and who were receiving ventilation or respiratory support. They were randomized either to inhaled NO (229 infants), starting at 20 ppm then decreasing to 10 ppm after 3-4 days and finally to 5 ppm on day 10 or 11 until day 24, or to nitrogen placebo (222 infants).

The dosage selected was higher, and the treatment was given for a longer period and initiated later than in some previous studies, which the authors hypothesized might improve outcomes.

However, there was no significant difference between the placebo and inhaled NO groups in the primary outcome of survival to 36 weeks postmenstrual age without bronchopulmonary dysplasia (31.5% vs. 34.9%).

Similarly, the rate of severe bronchopulmonary dysplasia was similar for placebo and inhaled nitric oxide (26.6% vs. 20.5%), as was the rate of postnatal corticosteroid use (41.0% vs. 41.5%), mean days of positive pressure respiratory support (55 vs. 54), mean days of oxygen therapy (88 vs. 91) and mean days of hospitalization (105 vs. 108).

The subgroup analysis revealed that characteristics such as birth weight, gestational age, sex, postnatal age at study entry, maternal race or mode of respiratory support also did not influence the outcomes.

While the rates of severe bronchopulmonary dysplasia were similar between the placebo and inhaled nitric oxide groups, the inhaled NO group had a larger number of infants whose mothers were white and a higher rate of rupture of mem-

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Nitric oxide is an expensive but sometimes important therapy for critically ill infants in the NICU and PICU. However, I don't know anyone who believes it will prevent BPD. BPD prevention is the holy grail of neonatology and as elusive as looking for a therapy for the common cold!

branes for more than 7 days. The two groups had similar incidence of prematurity complications, such as sepsis, patent ductus arteriosus, necrotizing enterocolitis, retinopathy, intraventricular hemorrhage, and pulmonary air leak.

There were also no significant differences in neurodevelopmental or respiratory outcomes at 18-24 months postmenstrual age.

The authors commented that they had hoped their results would be similar to the earlier NO CLD trial, which hinted at a substantial increase in survival without bronchopulmonary dysplasia, compared with placebo in infants aged 7-14 days at the start of treatment.

"The NO CLD trial was not powered to assess the primary outcome in the subgroup enrolled between ages 7 and 14 days, whereas our study was powered specifically for that purpose and included twice as many infants in each treatment arm," the authors wrote.

Despite this, and a lack of any obvious differences between the study populations, the authors could not identify a reason for the lack of efficacy seen in their own study, compared with this earlier study.

The study was sponsored by Mallinckrodt Pharmaceuticals. Four authors declared honorarium, speaking engagements, advisory positions or consultancies with Mallinckrodt Pharmaceuticals.

Wait two days to replace CVCs in candidemia

BY AMY KARON
Frontline Medical News

SAN DIEGO – Wait at least 2 days before replacing central venous catheters (CVC) in patients with catheter-associated candidemia, according to the results of a single-center retrospective cohort study of 228 patients.

Waiting less than 2 days to replace a CVC increased the odds of 30-day mortality nearly sixfold among patients with catheter-related bloodstream infections due to candidemia, even after controlling for potential confounders, Takahiro Matsuo, MD, said at an annual scientific meeting on infectious diseases. No other factor significantly predicted mortality in univariate or multivariate analyses, he said. "This is the first study to demonstrate the optimal timing of central venous catheter replacement in catheter-related [bloodstream infection] due to *Candida*."

Invasive candidiasis is associated with mortality rates of up to 50%, noted Dr. Matsuo, who is a fellow in infectious diseases at St. Luke's International Hospital, Tokyo. Antifungal therapy improves outcomes, and most physicians agree that removing a CVC does, too. To better pinpoint optimal timing of catheter replacement, Dr. Matsuo and his associates examined risk factors for 30-day mortality among patients with candidemia who were treated at St. Luke's between 2004 and 2015.


DR. MATSUO

Among 228 patients with candidemia, 166 had CVCs, and 144 had their CVC removed. Among 71 patients who needed their CVC replaced, 15 died within 30 days. Central venous catheters were replaced less than 2 days after removal in 87% of patients who died and in 54% of survivors ($P = .04$). The association remained statistically significant after the researchers accounted for potential confounders (adjusted odds ratio, 5.9; 95% confidence interval, 1.2-29.7; $P = .03$).

Patients who died within 30 days of CVC replacement also were more likely to have hematologic malignancies (20% versus 4%), diabetes (13% vs. 11%), to be on hemodialysis (27% vs. 16%), and to have a history of recent corticosteroid exposure (20% versus 11%) compared with survivors, but none of these associations reached statistical significance. Furthermore, 30-day mortality was not associated with gender, age, *Candida* species, endophthalmitis, or type of antifungal therapy, said Dr. Matsuo, who spoke at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

The findings ideally should be confirmed in a larger randomized controlled trial, Dr. Matsuo said.

Negative nasal swabs reliably predicted no MRSA infection

BY AMY KARON
Frontline Medical News

SAN DIEGO – Only 0.2% of intensive care unit patients developed MRSA infections after testing negative on nasal surveillance swabs, said Darunee Chotiprasitsakul, MD, of Johns Hopkins Medicine in Baltimore.

But physicians often prescribed vancomycin anyway, accumulating nearly 7,400 potentially avoidable treatment days over a 19-month period, she said during an oral presentation at an annual meeting on infectious diseases.

Current guidelines recommend empiric vancomycin to cover MRSA infection when ill patients have a history of MRSA colonization or recent hospitalization or exposure to antibiotics. Patients whose nasal screening swabs are negative for MRSA have been shown to be at low risk of subsequent infection, but guidelines don't address how to use swab results to guide decisions about empiric vancomycin, Dr. Chotiprasitsakul said.

Therefore, she and her associates studied 11,882 adults without historical MRSA infection or colonization who received nasal swabs for routine surveillance in adult ICUs at Johns Hopkins. A total of 441 patients (4%) had positive swabs, while 96% tested negative.

Among patients with negative swabs, only 25 (0.22%) developed MRSA infection requiring treatment. Thus, the negative predictive value of a nasal swab for MRSA was 99%, making the probability of infection despite a negative swab "exceedingly low," Dr. Chotiprasitsakul said.

But clinicians seemed not to use negative swab results to curtail vancomycin therapy, she found. Rates of empiric vancomycin use were 36% among patients with positive swabs and 39% among those with negative swabs. Over 19 months, ICU patients received 7,371 avoidable days of vancomycin, a median of 3 days per patient.

Matching patients by ICU and days at risk identified no significant predictors of MRSA infection, Dr. Chotiprasitsakul said. Johns Hopkins Medicine has robust infection control practices, high compliance with hand hygiene and contact precautions, and low rates of nosocomial MRSA transmission, she noted. The predictive value of a negative MRSA nasal swab could be lower at institutions where that isn't the case, she said.

Johns Hopkins is working to curtail unnecessary use of vancomycin, said senior author Sara Cosgrove, MD, professor of medicine in infectious diseases and director of the department of antimicrobial stewardship. The team has added the findings to its guidelines for antibiotic use, which are available in an app for Johns Hopkins providers, she said in an interview.

The stewardship also highlights the data when discussing starting and stopping vancomycin in patients at very low risk for MRSA infections, she said. "In general, providers have responded favorably to acting upon this new information," Dr. Cosgrove noted.

Johns Hopkins continues to track median days of vancomycin use per patient and per 1,000 days in its units. "[We] will assess if there is an impact on vancomycin use over the coming year," said Dr. Cosgrove.


Frontline Medical News

Dr. Darunee Chotiprasitsakul

The investigators had no conflicts of interest. The event marked the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

No benefit seen for routine low-dose oxygen after stroke

BY KARI OAKES
Frontline Medical News

Routine use of low-dose oxygen supplementation in the first days after stroke doesn't improve overall survival or reduce disability, according to a large new study.

The poststroke death and disability odds ratio was 0.97 for those receiving one of two continuous low-dose oxygen protocols, compared with the control group (95% confidence interval, 0.89-1.05; $P = .47$).

The Stroke Oxygen Study (SO_2S) was a single-blinded, randomized, controlled trial that recruited 8,003 adults with a diagnosis of acute stroke within 24 hours of hospital admission, drawing from 136 centers in the United Kingdom, according to an article in JAMA (2017;318[12]:1125-35). A total of 7,677 participants (96%) had data available for analysis of the primary outcome measure, a composite of death and disability 90 days post stroke.

Participants, who were not hypoxic at enrollment, were randomized 1:1:1 to receive continuous oxygen supplementation for the first 72 hours after stroke, to receive supplementation only at night, or to receive oxygen when indicated by usual care protocols. The average participant age was 72 years and 55% were men in all study arms, and all stroke severity levels were included in the study.

Patients in the two intervention arms received 2 L of oxygen by nasal cannula when their baseline oxygen saturation was greater than 93%, and 3 L when oxygen saturation at baseline was 93% or less. Participation in the study did not preclude more intensive respiratory support when clinically indicated.

Nocturnal supplementation was included as a study arm for two reasons: Poststroke hypoxia is more common at night, and night-only supplementation would avoid any interference with early rehabilitation caused by cumbersome oxygen apparatus and tubing.

Not only was no benefit seen for patients in the pooled intervention arm cohorts, but no benefit was seen for nighttime versus continuous oxygen as well. The odds ratio for a better outcome was 1.03 when comparing those receiving continuous oxygen to those who only received nocturnal supplementation (95% CI, 0.93-1.13; $P = .61$).

First author Christine Roffe, MD, and her collaborators in the Stroke Oxygen Study Collaborative Group also performed subgroup analyses and did not see benefit of oxygen supplementation for older or younger patients, or for patients with chronic obstructive pulmonary disease, heart failure, or more severe strokes.

"Supplemental oxygen could improve outcomes by preventing hypoxia and secondary brain damage but could also have adverse effects," according to Dr. Roffe, consultant at Keele (England) University and her collaborators.

A much smaller SO_2S pilot study, they said, had shown improved early neurologic recovery for patients who received supplemental oxygen after stroke, but the pilot also "suggested that oxygen might adversely affect outcome in patients with mild strokes, possibly through formation of toxic free radicals," wrote the investigators.

These were effects not seen in the larger SO_2S study, which was designed to have statistical power to detect even small differences and to do detailed subgroup analysis. For patients like those included in the study, "these findings do not support low-dose oxygen in this setting," wrote Dr. Roffe and her collaborators.

Dr. Roffe reported receiving compensation from Air Liquide. The study was funded by the United Kingdom's National Institute for Health Research.

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Correction

An article titled "Changes to CPT® codes coming January 2018," published in October on page 62, misidentified the CPT code that should be utilized when a therapeutic bronchoscopy procedure is performed in the nonhospital setting and later repeated. CPT code **31645** is the correct code for this scenario.

LVAD use soars in elderly Americans

BY MITCHEL L. ZOLER
Frontline Medical News

DALLAS – The percentage of left ventricular assist devices placed in U.S. heart failure patients at least 75 years of age jumped sharply during 2003-2014, and concurrently the short-term survival of these patients improved dramatically, according to data collected by the National Inpatient Sample.

During the 12-year period examined, the percentage of left ventricular assist devices (LVADs) placed in U.S. heart failure patients aged 75 years and older rose from 3% of all LVADs in 2003 to 11% in 2014, Aniket S. Rali, MD, said at the annual scientific meeting of the Heart Failure Society of America.

Mitchel L. Zoler/Frontline Medical News

Dr. Aniket S. Rali

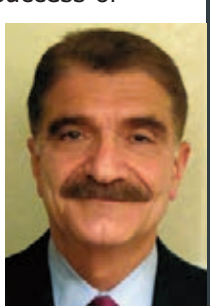
In actual numbers, LVAD placement into elderly patients jumped from 23 in 2003 to 405 in 2014, a greater than 17-fold increase. During the same period, total U.S. LVAD use rose from 726 placed in 2003 to 3,855 placed in 2014, about a fivefold increase.

The U.S. national numbers also showed that throughout the period studied, elderly U.S. patients who received an LVAD were increasingly sicker, with steadily increasing numbers of patients with a Charlson Comorbidity Index score of 4 or greater. Despite this, in-hospital mortality rates of elderly patients receiving an LVAD plummeted, dropping from 61% of elderly LVAD recipients in 2003 to 18% in 2014. During the same time, the percentage of elderly patients with a Charlson Comorbidity Index score greater than 4 doubled from 33% in 2003 to 66% in 2014, said Dr. Rali, a cardiologist at the University of Kansas Medical Center in Kansas City.

"If the Charlson Comorbidity Index score is increasing but in-hospital mortality is decreasing, then increased LVAD use is not a bad

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The success of LVAD use as a destination therapy for patients not candidates for transplantation has changed the paradigm for the treatment of patients with end stage heart failure. This report is a confirmation of this paradigm shift.



trend," Dr. Rali said in an interview. He hopes that future analysis of longitudinal data from patients could identify clinical factors that link with better patient survival and help target LVAD placement to the patients who stand to gain the most benefit.

"We may be able to give these elderly patients not just longer life but improved quality of life" by a more informed targeting of LVADs, he suggested. "I think these numbers will help convince people that all is not lost," he noted, for elderly heart failure patients who receive an LVAD as destination therapy. Patients at least 75 years old are not eligible for heart transplantation, so when these patients receive an LVAD it is, by definition, destination therapy.

The data also showed a marked sex disparity in LVAD use, with LVAD placement in men at least 75 years old rising from 1.4/1,000 patients in 2003 to 2.78/1,000 patients in 2014. In contrast, among women these rates rose from 0.8/1,000 patients in 2003 to 1.36/1,000 patients in 2014.

The average age for elderly U.S. LVAD recipients for the entire 12-year period studied was 77.6 years among a total of 2,090 recipients. For all 21,323 U.S. LVAD recipients during 2003-2014 the average age was 51.5 years old.

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Closure of left atrial appendage slashes stroke risk

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Routine surgical closure of the left atrial appendage during open heart surgery provides long-term protection against cerebral ischemic events, according to the findings of the first-ever randomized controlled trial to address the issue.

"I think we can say, based on our study, that it would be advisable to routinely add surgical closure of the left atrial appendage to planned open heart surgery," Jesper Park-Hansen, MD, said at the annual congress of the European Society of Cardiology.

New-onset atrial fibrillation is common following cardiac surgery. That's one of the reasons why 1%-3% of patients have a stroke within the first year following coronary artery bypass graft (CABG) surgery. A clot kicked loose from the left atrial appendage (LAA) is the source of most ischemic strokes.

In light of the demonstrated success of percutaneous closure of the LAA using the Watchman and other devices for stroke prevention in patients with atrial fibrillation, Dr. Park-Hansen and his coinvestigators at the University of Copenhagen organized LAACS (the Left Atrial Appendage Closure Study). The goal was to generate solid, randomized trial evidence as to whether preemptive routine surgical closure of the LAA at the time of cardiac surgery is of benefit. Some cardiac surgeons already do this routinely; many others don't because of the lack of Level 1 supporting evidence.

LAACS included 141 patients randomized to surgical LAA closure or not at the point of first-time open heart surgery. The study population included patients with and without a history of atrial fibrillation. LAA closure was accomplished via a purse string closure with a silk

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VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This report on prophylactic closure of left atrial appendage (LAAC) during the first heart operation in preventing subsequent cerebrovascular accident (CVA) events is the first of its kind, and, although the treated group had a lower rate of CVA compared with the control group, the difference did not reach statistical significance. Both open and closed atrial appendage groups had a high rate of perioperative atrial fibrillation, 60.5% and 50%, respectively. Only 10% of the treated group had follow-up transesophageal echocardiography for confirmation of complete appendage closure. Nonetheless, the results reported are encouraging for cardiac surgeons in considering LAAC in high-risk patients undergoing cardiac operations.

Hearts from HCV-infected patients successfully transplanted

BY MITCHEL L. ZOLER
Frontline Medical News

GRAPEVINE, TEXAS – The heart transplant team at Vanderbilt University has successfully placed hearts from deceased, hepatitis C virus–positive patients into recipients, and then eradicated the subsequent infection that appeared in most recipients using a standard, direct-acting antiviral regimen.

So far, five of nine heart transplant recipients who developed a post-transplant hepatitis C virus (HCV) infection had the infection eradicated using one of the highly effective HCV drug regimens, and an additional three patients from the series are nearing their 12th week without detectable virus following treatment that marks a sustained response, Kelly H. Schlendorf, MD, said at the annual scientific meeting of the Heart Failure Society of America. The ninth patient died after developing a pulmonary embolism during the 7th week on antiviral therapy.

The team has also placed hearts from HCV-positive donors into an additional four patients who have not developed HCV infection, for a total of 13 heart transplants performed using hearts that until now have been routinely beyond consideration.

The recipients have been patients in a marginal clinical state and facing a long projected wait on the heart-recipient queue of the United Network for Organ Sharing (UNOS), Dr. Schlendorf said in an interview.

These have been "patients with a morbidity and mortality risk from waiting that can be mitigated by expanding the donor pool." She gave an example of a patient with a left ventricular assist device that required replacement by either a second device or transplant, "so getting the transplant quickly was a good thing," said Dr. Schlendorf, a cardiologist at Vanderbilt in Nashville.

Based on her analysis of UNOS data, "upwards of 100" and perhaps as many as 300 additional donor hearts could be available annually for U.S. transplants if the organs weren't excluded because of HCV infection.

The Vanderbilt team has so far approached 15 patients in their program wait-listed for hearts about the possibility of accepting an HCV-positive organ, and all 15 have given their consent, she said. "We spend a lot of time talking with patients and their caregivers about the risks and benefits and possible complications."

The 13 recipients, starting in September 2016, included 12 patients who were HCV naive and 1 patient with a history of HCV exposure. All 13 received the program's standard three-drug regimen for immunosuppression.

During close surveillance, 9 of the 13 developed an infection. Patients with genotype 1 HCV received 12 weeks of treatment with ledipasvir plus sofosbuvir. Those infected with genotype 3 received 12-24 weeks of treatment with sofosbuvir plus velpatasvir. Treatment with these direct-acting antivirals meant that patients had to adjust the time when they took their proton-pump inhibitors, and they needed to stop treatment with diltiazem and statins while on the antivirals.

"In the era of direct-acting antivirals, HCV-positive donors may provide a safe and effective way to expand the donor pool and reduce wait-list times," Dr. Schlendorf said. She noted that in recent years an increased number of potential organ donors have been HCV positive. She also cautioned that so far follow-up has been relatively brief, with no patient yet followed as long as 1 year after transplant.

The direct-acting HCV antivirals are expensive, and some payers established clinical criteria that patients must meet to qualify for coverage of these regimens. "We have not encountered difficulties getting insurers to pay," Dr. Schlendorf said. Despite the antivirals' cost there are significant cost savings from fewer days in the ICU waiting for heart transplantation and a reduced need for mechanical support as a bridge to transplant, she noted.

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MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS
Dr. Kelly H. Schlendorf

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: With the shortage of donor hearts, many patients on the transplant waiting list either do not survive or remain on cardiac assist devices, which may require replacement. The report from the Nashville group is an attempt to expand the donor pool for the high-risk and very ill patients on the transplant list. This is an early report on a small series of 13 patients. Longer follow-up beyond 1 year is needed to prove the viability of this strategy as an effective option for cardiac transplant candidates.

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string around the neck of the appendage backed up by an additional single running suture. Transesophageal echocardiography performed in 10 patients a mean of 520 days post closure showed no signs of leakage or incomplete closure.

The primary composite outcome was comprised of clinical stroke or transient ischemic attack diagnosed by a neurologist, or a silent cerebral infarct detected on MRI performed 2-4 weeks post discharge and again at least 6 months later. At a mean follow-up of 3.7 years and a maximum of 6 years, this outcome had occurred in 6.3% of the LAAC group, significantly lower than the 18.3% rate in controls. All but one patient with a cerebral ischemic event in the control group had atrial fibrillation. The risk of an event was unrelated to whether or not a patient had a history of atrial fibrillation prior to surgery or to CHA_2DS_2-VASc score.

Dr. Park-Hansen emphasized that he and his coinvestigators don't consider LAACS to be the final word on routine prophylactic appendage closure.

"This is the first randomized study. We are eager to move on to another randomized study on a larger scale. That is the next step for us," he said.

"The challenge now – and what we will be discussing with our surgeons – is to agree on a feasible safe and effective means of left atrial appendage closure. My personal opinion is the Lariat suture delivery device or some other easily reproducible method of closure could be a good way to go," Dr. Park-Hansen added.

The research group's cardiac surgeons already have ruled out excision and stapling because of concerns about bleeding risk and the additional cost imposed by stapling.

Discussant Volkmar Falk, MD, commented that LAACS was too small, probably severely underpowered, should have included a preoperative MRI so investigators could reliably capture perioperative silent cerebral infarcts, and the double suture purse string is "probably not the best method" to occlude the LAA.

"LAACS addresses an important question, but alas, it does not provide the answer," declared Dr. Falk, professor and director of the department of cardiothoracic and vascular surgery at Charité Medical University in Berlin.

Dr. Park-Hansen and Dr. Falk reported having no financial conflicts of interest.

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BRUCE JANCIN/FRONTLINE MEDICAL NEWS
Dr. Jesper Park-Hansen

MACRA: Screening for hypertension

If you haven't started reporting quality data for the Merit-Based Incentive Payment System (MIPS), there's still time to avoid a 4% cut to your Medicare payments.

Under the Pick Your Pace approach being offered this year, the Centers for Medicare & Medicaid Services allows clinicians to test the system by reporting on one quality measure for one patient through paper-based claims. Be sure to append a Quality Data Code (QDC) to the claim form for care provided up to Dec. 31, 2017, in order to avoid a penalty in payment year 2019.

Consider this measure:

Measure #317: Preventive Care and Screening: Screening for High Blood Pressure and Follow-Up Documented

This measure is aimed at capturing the percentage of patients aged 18 years and older who were screened for high blood pressure and given a follow-up plan.

What you need to do: Check the patient's blood pressure and recommend follow-up care – lifestyle modifications, additional testing, or medication, as appropriate – and document that plan.

Eligible cases include patients aged 18 years and older on the date of the encounter and a patient encounter during the performance period. Applicable codes include (CPT or HCPCS): 90791, 90792, 90832, 90834, 90837, 90839, 90845, 90880, 92002, 92004, 92012, 92014, 96118, 99201, 99202, 99203, 99204, 99205, 99212, 99213, 99214, 99281, 99282, 99283, 99284, 99285, 99215, 99304, 99305, 99306, 99307, 99308, 99309, 99310, 99318, 99324, 99325, 99326, 99327, 99328, 99334, 99335, 99336, 99337, 99341, 99342, 99343, 99344, 99345, 99347, 99348, 99349, 99350, D7140, D7210, G0101, G0402, G0438, G0439 without telehealth modifier: GQ or GT.

To get credit under MIPS, be sure to include a QDC that shows that you successfully performed the measure or had a good reason for not doing so. For instance, code G8783 indicates that a normal blood pressure reading was documented and follow-up is not required, while code G8950 indicates that the patient had a pre-hypertensive or hypertensive blood pressure reading documented and the appropriate follow-up was documented. Exclusion code G9744 should be used if the patient is not eligible due to an active diagnosis of hypertension.

CMS has a full list measures available for claims-based reporting at qpp.cms.gov. The American Medical Association has also created a step-by-step guide for reporting on one quality measure.

Certain clinicians are exempt from reporting and do not face a penalty under MIPS:

- Those who enrolled in Medicare for the first time during a performance period.
- Those who have Medicare Part B allowed charges of $30,000 or less.
- Those who have 100 or fewer Medicare Part B patients.
- Those who are significantly participating in an Advanced Alternative Payment Model (APM).

MIPS: It's time to get started

BY GREGORY TWACHTMAN
Frontline Medical News

David O. Barbe, MD, president of the American Medical Association, is urging physicians to participate in the Medicare Quality Payment Program, even if the business case isn't quite there.

QPP is the value-based payment system created by the Medicare Access and CHIP Reauthorization Act (MACRA). It promotes high-value care through Medicare payment increases. But for some practices, the investment in personnel and technology needed to earn those increases may be more than the increases themselves, leading doctors to do just enough to avoid being penalized.

"I think that many physicians don't feel they are ever going to get a bonus but sure would like to avoid

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a penalty," Dr. Barbe, said in an exclusive interview. "I am afraid many will simply perform at the lowest level that keeps them out of the penalty. Because many of them find that making the investment it takes to perform highly, there is not a business case for that."

Full participation in QPP's Merit-based Incentive Payment System (MIPS) could run small practices an additional $10,000 to $30,000 a year, he said. "If you've got $200,000 in Medicare receipts, if you get adjusted even the maximum of 4%, that is $8,000. You can't cover $20,000 with $8,000. The math doesn't work. There is not a business case there for it."

That said, Dr. Barbe still spoke in favor of QPP and noted that the AMA is working with the Centers for Medicare & Medicaid Services as well as Congress to make the program more valuable and meaningful for physicians.

"We understand where we need to go as a profession, as an industry," he said. "How we get there is the key, it's the challenge and it requires flexibility. ... CMS has been accommodating but there are limits to how long they can go."

The AMA is urging doctors who have missed the 90-day window for full participation – which effectively closed for most on Oct. 2 – to consider the Pick Your Pace option offered by the CMS.

Pick Your Pace allows physicians and practices to submit data on one measure for one patient to avoid a reduction in Medicare pay, even though they would not be eligible for a bonus.

DR. BARBE

"AMA has put out a lot of tools to help physicians assess their readiness, assess the gap between what they are able to do in their practice now and what they need to do to be successful under [the MIPS] primarily down to and including a video that would walk a physician step-by-step through the one patient, one measure, no penalty," Dr. Barbe said.

He also encouraged doctors to pick a measure that is meaningful to their practice if only to get the ball rolling and get their feet wet in the QPP pool.

"What I tell physicians is pick something that is relevant for your practice," he said."If I see a lot of diabetes patients in my practice but I don't see many people on anticoagulants, it doesn't make sense for me to pick an anticoagulant measure."

And if all a practice can do this year is one patient, one measure, Dr. Barbe urged physicians to look toward the next reporting year with an eye to do more, as that will ultimately lead to better quality of care delivered.

"Report on one patient and one measure this year ... but look at next year to say 'that's going to be a 90-day project for me,' and get in on that. There is a pretty long laundry list of conditions and metrics that you can report on."

And if practices start capturing relevant data, it opens the door to improving their practice if they also take the time to analyze what they are collecting.

"That is the purpose," Dr. Barbe said. "As you measure yourself along the way, if the threshold for performance is here, and you find yourself working at this [lower] level for the first 30 days or whatever, then you stop and take stock of that" and react accordingly.

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Ruling: Apologies can't be used against doctors

BY ALICIA GALLEGOS
Frontline Medical News

The Ohio Supreme Court has ruled that apologies by physicians that include an admission of fault cannot be used against them in court, upholding a lower court decision that spared a doctor's comments from being heard at trial.

In a Sept. 12 decision, state Supreme Court justices concluded that Ohio's apology statute protects both expressions of regret for an unanticipated outcome and acknowledgments that the patient's treatment fell below the standard of care. The decision resolves a split among Ohio appeals courts over whether expressions of fault are admissible.

The decision declaring Ohio's apology statute "unambiguous" is an important and clarifying ruling for physicians and settles the differing opinions of some lower courts, said Reginald Fields, director of external and professional relations for the Ohio State Medical Association.

"We applaud the high court's decision," Mr. Fields said in an interview. "Even the two dissenting justices agreed that the apology law is clear; they just questioned whether it applied in this particular case. This ruling likely means pending legislation thought to be needed to clarify the law is now unnecessary. The OSMA will now focus on other aspects of tort reform, such as 'loss of chance' claims and further elimination of frivolous lawsuits."

The Ohio Association for Justice, the state's plaintiffs' bar did not respond to a request for comment.

The case of Stewart v. Vivian resulted from a lawsuit filed by Dennis Stewart against Cincinnati psychiatrist Rodney Vivian, MD, after the death of Mr. Stewart's wife by suicide. Michelle Stewart was admitted to the emergency department of Mt. Orab MediCenter in February 2010 after attempting suicide and was later transferred to the psychiatric unit at Mercy Hospital Clermont in Batavia, Ohio. After consulting with nurses, Dr. Vivian ordered that a staff member of the psychiatric unit visually observe Ms. Stewart every 15 minutes, according to court documents. The next evening, Mr. Stewart arrived at the psychiatric unit to visit his wife and found her unconscious as a result of hanging.

Two days later, Dr. Vivian went to Ms. Stewart's room in the intensive care unit to speak with family members. The content of the conversation between Dr. Vivian and family members is disputed. Family members allege that Dr. Vivian expressed that it was a "terrible situation" and that the patient had told Dr. Vivian that she "wanted to be dead" would "keep trying" to kill herself. Dr. Vivian testified that he told the family he was "sorry this has happened." Ms. Stewart was later taken off life support and died.

In 2011, Mr. Stewart sued Dr. Vivian and Mercy Hospital Clermont for medical malpractice, loss of spousal consortium, and wrongful death. Dr. Vivian argued that his statements to family members in the ICU room were inadmissible under the state's apology law because they were "intended to express commiseration, condolence, or sympathy." Mr. Stewart countered that Dr. Vivian's statements were admissible because they were not "pure expressions of apology, sympathy, commiseration, condolence, compassion, or a general sense of benevolence." The trial court sided with Dr. Vivian and his statements were kept from trial testimony. The jury returned a verdict in favor of Dr. Vivian, concluding that he was not negligent in his assessment, care, or treatment.

The 12th District Court of Appeals ruled that Dr. Vivian's statements were properly excluded, finding that the Ohio's apology law is ambiguous because according to the term's dictionary definition, "apology" may or may not include an admission of fault. But the decision conflicted with the case of Davis v. Wooster Orthopaedics & Sports Medicine, Inc. in which the Court of Appeals for the 9th District in Ohio determined Ohio's apology statute protects from admission "pure expressions of apology, sympathy, commiseration, condolence, compassion, or a general sense of benevolence," but not "admission of fault."

Resolving the split, the Ohio Supreme Court concluded that the state law is unambiguous and that its legislative intent is to shield expressions of regret for unexpected outcomes that may include acknowledgments that the patient's medical care fell below the standard of care.

Ohio Supreme Court Chief Justice Maureen O'Connor and Justice William M. O'Neill partially dissented. While they agreed with the majority's holding regarding the intent of Ohio's apology law, Justice O'Connor wrote that the Dr. Vivian's statements fell outside the law's protection.

"Dr. Vivian's statements were not an apology nor did they express regret or a type of shared sadness associated with sympathy or commiseration," she wrote in her dissent.

At least 36 states have apology laws that shield against certain statements, expressions, or other evidence related to disclosures being used against physicians in court.

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CMS alerts physicians of payment reductions for PQRS noncompliance

BY GREGORY TWACHTMAN
Frontline Medical News

Doctors who did not adequately meet Physician Quality Reporting System (PQRS) requirements in 2016 will soon be receiving notification letters alerting them that their Medicare Part B physician fee schedule payments will be reduced by 2%.

Officials from the Centers for Medicare & Medicaid Services said in a statement that "the majority" of eligible professionals "successfully reported to PQRS and avoided the downward payment adjustment," but did not state how many doctors are expected to receive letters.

Physicians who are flagged for the payment reduction, but who believe they successfully complied with PQRS requirements, will have the opportunity to challenge the finding. They must submit an informal review request online here within 60 days of the release of the 2016 PQRS feedback report.

The CMS noted that there are no hardship exemptions to avoid the payment reduction for 2018.

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Riociguat may benefit subset of PAH patients

BY DOUG BRUNK
Frontline Medical News

Switching to riociguat may be an effective strategy for pulmonary arterial hypertension (PAH) patients who respond inadequately to phosphodiesterase-5 inhibitors, results from a small open-label study demonstrated.

"This study represents an important step towards determining if this new treatment strategy is an effective approach to the management of patients with PAH, although additional data from larger, randomised, controlled studies are needed to further establish the safety and efficacy of this approach," researchers led by Marius M. Hoeper, MD, wrote in a study published online Sept. 9, 2017, in the European Respiratory Journal (Eur Respir J. 2017 Sep 9. doi: 10.1183/13993003.02425-2016).

Current clinical data indicate that many patients with PAH who receive phosphodiesterase-5 inhibitors do not reach treatment goals. "For example, in the AMBITION study, 73% of patients with PAH receiving tadalafil monotherapy and 61% of those receiving tadalafil in combination with ambrisentan did not achieve a satisfactory clinical response at week 24 of the study (N Engl J Med. 2015;373:834-44)," Dr. Hoeper of the Clinic for Respiratory Medicine at Hannover Medical School Germany and his associates wrote. "Furthermore, in the SERAPHIN study, event-free survival of patients receiving [phosphodiesterase-5 inhibitors] monotherapy was approximately 50% at 3 years (N Engl J Med. 2013;369:809-18)."

For the current trial, known as RESPITE, investigators from nine countries in Europe and North America enrolled 61 PAH patients in a 24-week, open-label uncontrolled analysis to investigate the safety, feasibility, and benefit of switching them from phosphodiesterase-5 inhibitors to riociguat. The patients underwent 1-3 days free of phosphodiesterase-5 inhibitors before receiving riociguat in a maximum dose of up to 2.5 mg t.i.d. Most patients (74%) were female, and 92% were Caucasian. In all, 51 patients (84%) completed all 24 weeks of treatment, while the remaining 10 discontinued treatment, 4 of whom due to adverse events.

Among those who completed all 24 weeks of the trial, their mean 6-minute walking distance had increased by a mean of 31 meters and their N-terminal pro b-type natriuretic peptide level decreased by a mean of 347 pg/mL. Additionally, 54% of the patients studied experienced an improvement in their the World Health Organization Functional Class. However, 32 patients (52%) experienced study drug–related adverse events and 10 (16%) experienced serious adverse events, two of which were related to the drug being studied. Six patients (10%) experienced clinical worsening, including death in two, though the deaths were deemed to be unrelated to the drug being studied.

"Although not mechanistically studied, the findings of RESPITE support the hypothesis that a defective [nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate] pathway might explain why some patients have no sufficient or sustained response to [phosphodiesterase-5 inhibitors] therapy," the researchers noted. "In such patients, direct stimulation of [soluble guanylate cyclase] may be more effective than inhibition of [phosphodiesterase-5], but this hypothesis is still unproven."

They acknowledged certain limitations of the study, including its prospective design and the relatively homogenous patient population. "Other limitations include the lack of a long-term continuation phase, and the absence of mechanistic data allowing identification of patients likely to respond or not respond to switching," they wrote. "Two deaths were observed in this study, which might raise concerns, although neither of the deaths (one due to pneumonia and one due to subdural haematoma) was considered by the investigators to be study drug-related or due to worsening PAH. Given the lack of a control group and the rate of study withdrawals and clinical worsening events, further evaluation to clarify the safety of switching is required."

The study was funded by Bayer AG, Berlin.

Dr. Hoeper and his coauthors disclosed having financial ties to numerous pharmaceutical companies, including Bayer, which makes riociguat.

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Risk factors for PAH identified in lupus patients

BY JEFF EVANS
Frontline Medical News

FROM CHEST ▪ The presence of specific autoantibodies may help to identify the small percentage of patients with systemic lupus erythematosus (SLE) who are at higher risk of developing pulmonary arterial hypertension after SLE diagnosis and may also detect those at lower risk of death, according to findings from a retrospective study of French patients.

Eric Hachulla, MD, of the University of Lille (France) and his coinvestigators reported that 51 SLE patients in the French Pulmonary Hypertension Registry who had a diagnosis of pulmonary arterial hypertension (PAH) confirmed by right heart catheterization were more likely to have the condition if they had anti-SSA and anti-SSB antibodies, compared with a control group of 101 SLE patients without known PAH who were selected from SLE expert centers participating in the registry. Overall, anti-SSA antibodies were present in 62% of PAH patients vs. 40% of non-PAH patients, and anti-SSB antibodies were detected in 27% with PAH, compared with 8% of those without.

Following SLE diagnosis, the 51 SLE patients had a median delay in diagnosis of PAH by about 5 years. Their survival was 89% at 3 years and 84% at 5 years. "Survival appeared to be substantially better than that still observed today in [PAH associated with systemic sclerosis], where estimated 3-year survival is about 50%. Our survival rates are comparable to those reported by Sobanski et al. in the recently published study for the U.K. SLE-PAH cohort (85% at 5 years)," the authors wrote.

In the current study, mortality during 10 years of follow-up was significantly lower among patients who had anti–U1-RNP antibodies than among those who did not (0% vs. 25%; $P = .04$). This finding of improved survival in patients with anti–U1-RNP antibodies mirrored the results reported in the British SLE-PAH cohort study and a 2016 Chinese study, indicating that "the presence of anti–U1-RNP antibodies appears to be a protective factor in terms of survival."

Treatment with hydroxychloroquine followed a trend toward increased survival, but was not statistically significant (hazard ratio, 0.31; 95% confidence interval, 0.09-1.11; $P = .07$).

"These findings must be interpreted with caution due to the small number of untreated patients and require further investigations in other cohorts," the investigators wrote.

But "based on our results on the potential effect of hydroxychloroquine, this treatment might be used in association with the immunosuppressive strategy for SLE-PAH patients."

Read more of the findings in CHEST (2017 Aug 26. doi: 10.1016/j.chest.2017.08.014).

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Prescription-strength ibuprofen worse for BP

BY BRUCE JANCIN
Frontline Medical News

BARCELONA – Prescription-strength ibuprofen has a bigger adverse effect on blood pressure than celecoxib or naproxen, a finding that suggests a likely mechanism for the worse cardiovascular event rate documented in ibuprofen-treated arthritis patients in the PRECISION trial, Frank Ruschitzka, MD, said at the annual congress of the European Society of Cardiology.

"Prescription-strength ibuprofen is under pressure – it has a high incidence of new-onset hypertension, particularly when compared to the more selective COX-2 inhibitor celecoxib. Before we did this study, many would have said it's the other way around," observed Dr. Ruschitzka, professor of cardiology at the University of Zurich.

He presented the results of PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement).

"These results will have impact on your daily practice when you go home," the cardiologist said.

PRECISION-ABPM was a prespecified double-blind, randomized, 60-center substudy of the published PRECISION trial, which included 24,081 U.S. patients who needed daily NSAIDs for arthritis and were also at increased cardiovascular risk. They were randomized to the COX-2 inhibitor celecoxib at 100-200 mg b.i.d. or the nonselective NSAIDs ibuprofen at 600-800 mg three times a day or naproxen at 375-500 mg twice daily. Participants also received a proton pump inhibitor to protect against NSAID-related GI bleeding. In the on-treatment analysis, the ibuprofen group was significantly more likely to experience cardiovascular and all-cause mortality and renal events than were those on celecoxib (N Engl J Med. 2016 Dec 29;375[26]:2519-29).

The PRECISION-ABPM substudy included 444 arthritis patients, 92% of whom had osteoarthritis. During the 4-month study, investigators amassed roughly 60,000 automated blood pressure measurements across the three study arms.

The primary outcome was change

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from baseline in mean 24-hour systolic blood pressure (SBP). It increased by 3.7 mm Hg in the ibuprofen group and declined by 0.3 mm Hg in the celecoxib group, while the naproxen group occupied the middle ground with a 1.6–mm Hg increase.

The nearly 4-mm Hg increase in mean 24-hour SBP at 4 months in the ibuprofen group is of sufficient magnitude to be clinically important, Dr. Ruschitzka noted. Fully 23.2% of ibuprofen-treated patients who had normal baseline blood pressure developed hypertension as defined by a mean 24-hour SBP of at least 130 and/or a diastolic blood pressure of at least 80 mm Hg. In contrast, incident hypertension occurred in only 10.3% of the celecoxib group and 19% of naproxen-treated patients. Thus, the likelihood of developing hypertension was 61% less with celecoxib than ibuprofen and 51% less with celecoxib than naproxen.

Not treating chronic arthritic pain to avoid the cardiovascular risk of NSAIDs is not a legitimate option.

"Pain is a cardiovascular risk factor," Dr. Ruschitzka emphasized. "It's unethical not to treat it. If you don't treat pain, the patient's blood pressure goes up, heart rate goes up, and you're driving patients into inactivity."

Although he's convinced there's no such thing as a safe NSAID from a

cardiovascular risk standpoint, the PRECISION and PRECISION-ABPM data show celecoxib is less unsafe than ibuprofen. And as for the oft-heard statement that naproxen is the safest NSAID for the heart, Dr. Ruschitzka commented, "What an urban legend."

Discussant Scott Solomon, MD, director of noninvasive cardiology at Brigham and Women's Hospital, Boston, said that, although PRECISION-ABPM doesn't support the notion that conventional NSAIDs such as naproxen or ibuprofen are any safer than celecoxib, it would be wrong to conclude from the study that celecoxib doesn't affect blood pressure and is safer than the others from a cardiovascular standpoint. That's because the three study drugs weren't compared in an equipotent way. Because of safety concerns, the Food and Drug Administration required that the daily dose of celecoxib be capped at the low end of the therapeutic range, while no such constraints were placed on the two nonselective NSAIDS.

Dr. Ruschitzka discussed his findings in a video interview on www.mdedge.com/chestphysician.

PRECISION-ABPM was sponsored by Pfizer.

Dr. Ruschitzka and Dr. Solomon, who is also a professor of medicine at Harvard Medical School, reported having no financial conflicts of interest regarding their presentations.

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Distinguished CHEST Educators

In keeping with the commitment of the American College of Chest Physicians (CHEST) to be the home of the clinician educator, and supporting CHEST's strategic vision of advancing best patient outcomes through innovative chest medicine education, a new designation intended to provide national-level recognition of excellence in continuing medical education has been established—the innovation award-winning Distinguished CHEST Educator.

Distinguished CHEST Educators are within the top 5% of CHEST's faculty and are recognized for their achievements in making significant and long-term contributions to the design and delivery of CHEST education. With more than 108 ways to educate, these faculty members have exceeded expectations by serving as CHEST committee chairs, vice-chairs, faculty, and peer reviewers for programs such as the CHEST Annual Meeting.

"The greatest achievement I can imagine is seen in the people we train—as that lives on. Real values in medicine live only by being handed down to others. Over the past decade, CHEST has afforded me the privilege to represent the organization on a national platform, and, in doing so, I have been able to refine my own skills and those of my peers, as well as adding both quality and detail to my understanding of how young physicians learn," says Nader Kamangar, MD, FCCP, of UCLA, CHEST member since 2000, and Distinguished CHEST Educator.

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This Month in *CHEST:* Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, CHEST

ORIGINAL RESEARCH

Burden of Adult Community-Acquired, Health-care-Associated, Hospital-Acquired, and Ventilator-Associated Pneumonia: New York City, 2010 to 2014. *By R. E. Corrado, et al.*

Hyperbaric Oxygen Therapy Is Associated With Lower Short- and Long-Term Mortality in Patients With Carbon Monoxide Poisoning. *By C-C Huang, et al.*

EVIDENCE-BASED MEDICINE

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold: CHEST Expert Panel Report. *By M. A. Malesker, et al, on behalf of the CHEST Expert Cough Panel.*

Cough in Ambulatory Immunocompromised Adults: CHEST Expert Panel Report. *By M. J. Rosen, et al, on behalf of the CHEST Expert Cough Panel.*

Learn About a CHEST Foundation Research Grant Winner

In 2015, Debasree Banerjee, MD, MS, received the CHEST Foundation Research Grant in Pulmonary Arterial Hypertension. She was also a 2016 NetWorks Challenge Travel Grantee as a member of the Women's Health NetWork, allowing her to attend the 2016 CHEST Annual Meeting and network with peers and leaders in chest medicine. Read our follow-up interview with Dr. Banerjee on her research progress and how the grants she's received have impacted her and the work she is doing.

What is the project you have been working on?

I have been researching the role of the specific sodium channel in the heart, how it affects the conductance in patients with pulmonary arterial hypertension, and how it might affect RV function. We know in some sources that about 25% of patients with PAH can die of sudden cardiac death, and sudden cardiac death is more common in patients with left-sided heart disease.

Instead of dying of sudden death or end stage heart failure, we wanted a way to see, just based on a physical exam, if there's evidence of heart pump function not working well. With the funding, I've been able to more than double the sample size of the original pilot data and add in two more large objectives to complement my original aim.

What has receiving the grant meant to you?

One of the reasons I was able to stay at Brown was because of winning this grant from the CHEST Foundation. It was able to cement my interest in fully pursuing a physician scientist career, which is huge, because it is not what I had planned on doing. Because of this grant, I had an 80% protected research position in my first year. Winning the grant gave me a feeling of affirmation and validation, and that certainly motivates me to continue on this path.

Going into fellowship, if you had asked me what I had envisioned myself doing, I would have said I'd be a medical educator. I think I was surprised by my research year in fellowship when I was working on this project, because the grant created so much excitement. I felt like I could actually do this, and obtaining the grant uped the ante of investment and kept me excited. Plus, the grant allowed me to do everything, see the whole process, the full arc, and I'm not even done.

What barriers have you encountered with your research?

Not having all the control, like unplanned hospitalizations or advanced sickness in the patients. There are also things cost-wise that are needed for the research that I wouldn't have had access to without the grant. I didn't do much research in medical school and residency, since I was more focused on teaching, so I hadn't been prepared for the administrative legwork. But, it's something I'm learning.

Being able to follow up with the CHEST Foundation and attend the CHEST annual meeting are exciting ways to overcome any slumps or doubts, because you see the interest and encouragement for the work you're doing. Receiving the travel grant and coming to the annual meeting as a new faculty member, it was the most high-yield conference I've ever attended. Every day, there is something new and interactive for development.

What advice would you give to someone who hasn't received a grant before but is considering applying?

If they can get a good mentor, that's invaluable. It takes perseverance, persistence, and passion, and if you believe your work is having an impact, it's absolutely worth doing. Even if you apply and don't get it the first time, try, try again. I have so much more faith in CHEST because of the positivity I see from the investment in my own mentor, who was a past foundation grant recipient and encouraged me to apply. CHEST gives ample opportunity to network and help to be steered in the right way. As a grant recipient and being folded into the CHEST community, you start to think, "I want this feeling again. Someone thinks this is important work."

Continued from previous page

This designation will be granted to select clinical educators each year. The inaugural class of Distinguished CHEST Educators was honored at the end of October at CHEST 2017 in Toronto, as will be the tradition for the classes that follow.

Distinguished CHEST Educator

Congratulations to the inaugural class of Distinguished CHEST Educators.

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A Visit With Stephen J. Welch

CHEST Executive Vice President and CEO

Stephen J. Welch was officially appointed Executive Vice President and CEO in April after serving as the interim for both positions since May 2016. Here's a little "inside look" at what Steve is all about.

What is one major accomplishment you hope to achieve as Executive Vice President & Chief Executive Officer?

My goal as EVP/CEO is fairly simple and straightforward: to ensure the organization remains relevant and viable as a leader in providing clinically focused, innovative educational programs and content. I don't really have one accomplishment that I'm focused on, but I do want to ensure that we achieve our annual organizational goals that support CHEST's strategic plan. That may sound a little vague, but it's true. We have so many outstanding programs and initiatives that I'd be doing a disservice to identify a single goal.

How does your previous experience with CHEST help you successfully lead the organization?

With CHEST being a not-for-profit organization, which relies on volunteer leadership and faculty, I think the relationships I've built over the past 23 years within the organization and the chest medicine community are invaluable. I personally know so many of our leadership because I've been part of the organization at the executive level working with them for those 23 years. They know me and how I approach opportunities, address issues, and handle challenges, which has helped build an immediate level of mutual respect, trust, and confidence between the staff and leadership. In addition, there was no disruption from having someone come in from the outside and have to get up to speed. It made the transition pretty seamless for the staff, as well.

During my time at CHEST, I've seen how the organization operates, from the journal, to the annual meeting and board reviews, to the simulation and hands-on skills training, to operational activities like the management of our finances and new global headquarters and training center. I've also had the opportunity to meet with many of our international members and sister societies. Those experiences have allowed me to work closely with many of our faculty, authors, and educators to understand their educational and professional needs, so we can ensure that we meet them.

CHEST is only as good as the education we provide, and it's our subject matter experts who drive that content engine. In my previous role leading the Publishing Division and working on our journal *CHEST*® and programs like SEEK, I've had the honor and pleasure of working with some of the greatest minds in pulmonary, critical care, and sleep medicine. It's humbling.

What will be some of the underlying themes as you work to outline the strategic plan for the next 5 years?

We are in the final stages of planning for 2018 and beyond, and although our proposed roadmap isn't significantly different than what we have been doing, there's some greater emphasis on a few key areas. For example, we're looking at innovations in educational delivery. We've got some very forward thinking faculty educators and staff who are collaborating to develop innovations like gamification of educational and simulation programs, and augmented reality. Globalization and growth are also a key part of our strategic plan, and we are committed to the broad delivery of our educational programs and content both here and around the world. Finally, we have invested

in a data analytics project that is maturing, and we'll be leveraging that information to provide more personalized education plans – not just for the physician but for the entire health-care team. It's important for us to stay relevant and viable.

Why has CHEST shifted to an interdisciplinary, team-focused approach?

I look at it as simply an evolution that reflects how health care is changing. It's a team sport now, and our advanced practice providers (APPs) play a huge role in patient management and care. To be as effective and efficient as possible, and ensure the best patient outcomes, the whole team needs to be on the same page, and we believe that providing education for the interdisciplinary care team will help ensure that the best patient care is delivered.

There's also a need for this education, and we want to fill it. Our APPs tell us that there is no formal pulmonary training or post-masters fellowship in pulmonary medicine for them. They are often left on their own to fill any gaps in knowledge and skills. That's where our CHEST programs, such as our CHEST Annual Meeting, come in. We have an Interprofessional NetWork made up of APPs and physicians, and they were integral in working with the CHEST 2017 Program Committee to ensure plenty of relevant content was offered. Moving forward, we will continue to offer and build interdisciplinary programs designed for the entire team, as well as programs that address clinical issues across disciplines.

What are some of the critical skills CHEST physicians need to keep the population healthy during the ever-evolving field?

Educationally, we recognize that conferences like the annual CHEST meeting must provide more than just talking heads. We've invested heavily in high-fidelity medical simulation through small group, hands-on skill training in critical care techniques, airway management, EBUS, critical care ultrasound, bronchoscopy, and other chest medicine content. It's like the old adage about fishing: instead of telling people how to fish, we teach them to fish.

Any final thoughts?

I always encourage our members to get involved with CHEST and experience the camaraderie and connectivity of the CHEST family. Ask any of our leadership, and you will surely hear their story of that special person who first introduced them to the College. Reach out and tell a colleague about CHEST.

We are focused on clinically relevant education that our members can take back and put into action immediately. At the end of the day, it's about providing state-of-the-art education via high fidelity medical simulation, hands-on skills training, clinically focused courses, case-based programming, and more—all intended to be immediately implemented to improve patient care and patient outcomes. That's what the CHEST organization is all about.

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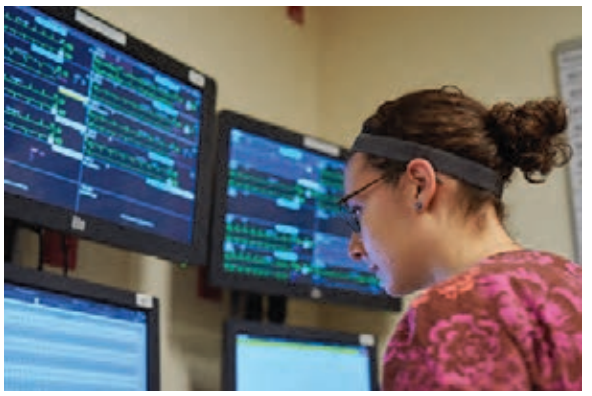

SLEEP STRATEGIES

Lessons Learned From SERVE-HF

BY JAIRO H. BARRANTES, MD

Great attention has been paid to the SERVE-HF trial ("Treatment of Sleep-disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure"), which showed increased all-cause mortality and cardiovascular mortality in the Adaptive Servo-ventilation (ASV) group compared with the control group of conventional heart failure management alone. The results of this trial led to the recommendation by multiple ASV manufacturers and medical societies to withdraw clinical use of ASV from patients with heart failure and a reduced ejection fraction (HFrEF) less than 45%.

Sleep-disordered breathing is common in patients with HFrEF with prevalence rates of 50% to 75%. Central sleep apnea (CSA) is associated with increased mortality in heart failure (HF) and is found in 25% to 40% of this subpopulation. It is estimated that the severity of CSA increases in parallel with the severity of the HF. For several years, treatment of CSA with positive pressure ventilation was believed to favor outcomes in HFrEF with a protective effect.

In the Canadian Positive Airway Pressure for Patients with CSA and HF (CANPAP) trial, subjects were randomized to treatment with CPAP or no CPAP. This trial was terminated early; it did not show an advantage of CPAP in morbidity or mortality. A post-hoc analysis suggested that mortality might be reduced if the frequency of respiratory events per hour or apnea hypopnea index (AHI) is reduced to 15/hour or less while using CPAP.

Hoping to improve the outcomes of HF, SERVE-HF was the first randomized, large scale, multinational trial directed to treat CSA in patients with HFrEF < 45% and concomitant clinically significant sleep apnea with AHI > 15/hour of central predominance (CSA index >10/hour). Treatment arms compared the addition the ASV, one of the most effective noninvasive positive pressure ventilation technologies for central apneas that offers automated inspiratory pressure support in addition to expiratory positive pressure vs conventional medical treatment alone in the control group.

Dr. Barrantes is an assistant professor, Department of Pulmonary, Critical Care, and Sleep Medicine, Baylor College of Medicine, Houston, Texas.

The study published in the *New England Journal of Medicine* in September 2015 was designed in an intention-to-treat basis with the primary end point of time to first event, a composite of death from any cause, lifesaving cardiovascular intervention (heart transplant, implantation of LVAD, resuscitation after sudden cardiac arrest, or defibrillation for ventricular arrhythmia), or unplanned hospitalization for heart failure. The study did not show significant differences in the primary end point between the ASV and control group (54.1% and 50.8%, respectively; hazard ratio, 1.13; 95% confidence interval, 0.97 to 1.31; P=.10).[1]

The most interesting and unexpected outcome was an increase in the all cause mortality and cardiovascular mortality in the ASV group (hazard ratio for death from any cause, 1.28; 95% CI, 1.06 to 1.55; P=.01; and hazard ratio from cardiovascular death, 1.34; 95% CI, 1.09 to 1.65; P=.006).[1] These findings led to the above recommendations from manufacturers, as well as a position statement from the American Academy of Sleep Medicine. These findings cannot be extrapolated to the obstructive sleep apnea population with concomitant HFrEF or to patients with HF with preserved ejection fraction, where positive pressure ventilation has offered an advantage[1] likely by a different physiologic mechanism not fully uncovered at this time, believed to be an overall effect of afterload reduction.

Selection and self-selection bias in this study was addressed in a new analysis by the same SERVE-HF investigator group published August 2017, where a time-dependent model of on-treatment analysis (done to tease out if the original results were related to the treatment assignment or to poor adherence) was conducted to understand potential causes of the initial findings in the original study. It showed patients randomized to ASV who crossed over to the control group were at higher risk of cardiovascular death than control subjects; also the control patients with crossover to ASV had a signal of lower risk of cardiovascular death risk compared with patients assigned to ASV.[2]

Reduced adherence to ASV treatment during SERVE-HF was a concern, since it resulted in a reduced exposure to the treatment. The on-treatment analysis showed again an increase of cardiovascular death in HFrEF patients with predominant CSA treated with ASV in addition to conventional heart failure treatment compared with the control group.[2] There was no increase in cardiovascular death risk associated with ASV use intervals (dose effect). This effect is not related to the amount of hours used per night.

The effect of the recommended withdrawal of treatment in HFrEF patients with EF<45% and moderate to severe central predominant sleep apnea is being addressed in smaller studies. A single center retrospective analysis observed the effects after ASV discontinuation in this population. Thirteen out of 126 patients treated with ASV who met SERVE-HF criteria were followed for at least a year; 93% of the subjects who met criteria had ASV removed; immediate recurrence of the central apnea was observed in most (except two patients), while adverse events were

not identified (defined as need for emergency hospitalization). Day and nighttime symptoms were reported by 61% of the group, and they were started on alternative treatments.[3] At 1 year after ASV removal, 88% of patients were still alive, overall cardiac function did not change in 1 year (P=0.17), and seven patients required adjustment of medications for heart failure. Symptomatic patients were treated with oxygen supplementation for nocturnal symptoms or CPAP if they had daytime sleepiness. None was treated with bi-level PAP, acetazolamide, or phrenic nerve stimulation. Four patients insisted on continuation of ASV despite understanding physician concerns. [3] This study helps to demonstrate that ASV discontinuation is feasible but requires close follow-up. However, larger, long-term prospective reviews are required to draw statistically meaningful conclusions about the consequences and safety of ASV removal; these studies will be difficult to conduct under the current indications for ASV in the interest group.

At this time, investigators have shifted to further understand the causes of the increase in cardiovascular mortality, overall mortality, and the understanding of the pathophysiologic processes associated with ASV use in HFrEF. It is not known whether the effect in mortality is related to the specific ASV device/algorithm used to suppress CSA or is related to the ASV principle itself. Upcoming studies will assist in clarifying these details. Currently, there is an ongoing trial looking at the effect of ASV on survival and hospital admissions in heart failure (ADVENT–HF) using a different ASV device; this study will hopefully elucidate the impact of class effect vs device effect. It may also provide better insight of the etiology of mortality and the impact of improved ASV compliance, first addressed by the on-treatment analysis of the SERVE-HF.[4]

Although the reasons for increased mortality related to ASV are unclear, proposed hypotheses include: central apnea is an adaptive mechanism to HFrEF and the reversal of central apneas might adversely affect the underlying disease process,[1] low adherence to ASV may impact outcomes, and specific devices may induce hyper-/hypoventilation generated by the algorithm designs of the specific ASV device and this may result in electrolyte abnormalities that generate arrhythmias.

The ADVENT-HF trial, although similar in design, has significant differences from SERVE-HF: different ASV devices may have a different impact on cardiac output and ventilation, recruited patients included those with less daytime sleepiness, and the potential to assess the effect of ASV in patients with OSA and low daytime sleepiness in patients with reduced EF.[5,6] This ongoing study may help us to further understand why there is increased mortality and what effect ASV has on the treatment of sleep apnea in patients with HFrEF.

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