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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy Dr. Grant W. Waterer

Grant W. Waterer, MBBS, PhD, professor of medicine, University of Western Australia and adjunct professor of medicine, Northwestern University, Chicago.

Most in-hospital pneumonia deaths may not be preventable

BY NICOLA GARRETTM
MDedge News

FROM THE JOURNAL *CHEST*® ▪ Most in-hospital deaths from community-acquired pneumonia are not preventable with current medical therapy, according to an analysis of deaths at five U.S. hospitals with expertise in pneumonia care.

Adults who are hospitalized with community-acquired pneumonia (CAP) are at high risk for short-term mortality but it is unclear whether an improvement in care could lower this risk, noted the study authors led by Grant W. Waterer, MBBS, PhD, professor of medicine, University of Western Australia and adjunct professor of medicine, Northwestern University, Chicago.

"Understanding the circumstances in which CAP patients die could facilitate improvements in the management of CAP by enabling future improvement efforts to focus on common preventable causes of death," they wrote. Their report was published in *CHEST*®.

They therefore performed a secondary analysis of the Etiology of Pneumonia in the Community (EPIC) study involving adults hospitalized with CAP between January 2010 and June 2012 across five tertiary-care hospitals in the United States.

The clinical characteristics of patients who died in the hospital were compared with those of patients who survived to hospital discharge. Chronic heart failure, chronic obstructive pulmonary disease, coronary artery disease, chron-

PNEUMONIA // *continued on page 6*

Breaking the glass ceiling

Barriers and opportunities

BY TARA HAELLE
MDedge News

REPORTING FROM CHEST 2018 ▪ SAN ANTONIO – Women in medicine have made great strides in cracking the glass ceiling, but it's not shattered yet, said Stephanie M. Levine, MD, FCCP, the CHEST President-Elect.

At a session on women in medicine at the annual meeting of the American College of Chest Physicians, Dr. Levine discussed the challenges of breaking through the metaphorical invisible barrier. The "glass ceiling" refers to multiple ways in which women lack equality with men in medicine: leadership roles, positions and titles, progress in academic medicine, gaps in salaries and compensation, and overall gender parity in specialties.

For example, according to data from the American Association of Medical Colleges for 2017-2018, women comprise 50% of medical school graduates but only 34% of the physician workforce and 22% of leadership roles. Women are 13% less likely to be promoted to professor. They receive salaries an average 21% lower than those of their male peers, said Dr. Levine, professor of medicine and director of the pulmonary/critical care fellowship program at the

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THE LINK BETWEEN SUICIDE AND SLEEP

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Rivaroxaban now indicated for CV event prevention

BY CATHERINE HACKETT
MDedge News

The direct oral anticoagulant rivaroxaban is now approved for prevention of major cardiovascular events in patients with chronic coronary or peripheral artery disease when taken with aspirin, Janssen Pharmaceuticals announced on Oct. 11.

The Food and Drug Administration's approval was based on a review of the 27,000-patient COMPASS trial, which showed last year that a low dosage of rivaroxaban (Xarelto) plus aspirin reduced the combined rate of cardiovascular disease events by 24% in patients with coronary artery disease and by 28% in participants with peripheral artery disease, compared with aspirin alone (N Engl J Med. 2017 Oct 5;377[14]:1319-30).

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The flip side to the reduction in COMPASS's combined primary endpoint was a 51% increase in major bleeding. However, that bump did not translate to increases in fatal bleeds, intracerebral bleeds, or bleeding in other critical organs.

COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) studied two dosages of rivaroxaban, 2.5 mg and 5 mg twice daily, and it was the lower dosage that did the trick. Until this approval, that formulation wasn't available; Janssen announced the coming of the 2.5-mg pill in its release.

The new prescribing information states specifically that Xarelto 2.5 mg is indicated, in combination with aspirin, to reduce the risk of major cardiovascular events, cardiovascular death, MI, and stroke in patients with chronic coronary artery disease or peripheral artery disease.

This is the sixth indication for rivaroxaban, a factor Xa inhibitor that was first approved in 2011. It is also the first indication for cardiovascular prevention for any factor Xa inhibitor. Others on the U.S. market are apixaban (Eliquis), edoxaban (Savaysa), and betrixaban (Bevyxxa).

COMPASS was presented at the 2017 annual congress of the European Society of Cardiology. At that time, Eugene Braunwald, MD, of Harvard Medical School and Brigham and Women's Hospital in Boston, commented that the trial produced "unambiguous results that should change guidelines and the management of stable coronary artery disease." He added that the results are "an important step for thrombocardiology."

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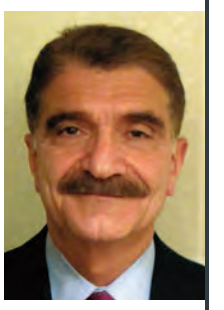
VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: COMPASS was a large double-blind randomized trial involving patients with a history of stable atherosclerotic vascular disease. The definition used for major bleeding in the COMPASS trial differed from the International Society on Thrombosis and Haemostasis (ISTH)[1] definition and "included any bleeding that led to hospitalization with or without an overnight stay, thus including events that would not be considered major bleeding in other trials."[2] Despite a lower rate for the primary outcome with combined low-dose rivaroxaban plus aspirin 24%, there was a 70% higher rate of major bleeding, mostly into gastrointestinal tract. The findings are encouraging and open new avenues for enhancing the care of patients with stable coronary and peripheral arteria disease.

1. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3:692-94.
2. Eikelboom JW et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017 Oct 5;377(14):1319-30.

In-hospital pneumonia deaths // *continued from page 1*

ic liver disease, cerebrovascular disease, cancer (excluding skin cancer), and diabetes were considered as severe chronic comorbidities based on their association with increased mortality and ICU admission in CAP severity scores.

Deaths caused by septic shock, respiratory failure, multisystem organ failure, cardiopulmonary arrest prior to stabilization of CAP, and endocarditis were considered to be directly related to CAP.

Conversely, causes of death indirectly related to CAP included acute cardiovascular disease, stroke, acute renal failure, and secondary infections developed after hospitalization.

Medical notes were assessed to determine whether the patient received management consistent with current recommendations, e.g., antibiotics consistent with guidelines from the Infectious Diseases Society of America.

End-of-life limitations in care, such as patient/family decision not to proceed with full medical treatment, also were considered by the research team.

Results showed that, among the 2,320 patients with radiographically confirmed CAP, 52 died during initial hospitalization, 33 of whom were aged 65 years or older, and 32 of whom had two or more chronic comorbidities.

Most of the in-hospital deaths occurred early in the hospitalization: 35 within the first 10 days of admission, and 5 after 30 days in hospital.

CAP was judged by an expert physician review panel to be the direct cause of death in 27 of the patients, 10 with CAP having an indirect role with major contribution, 9 with CAP having an indirect role with minor contribution, and 6 with CAP having no role in death.

Do-not-resuscitate orders were present at the time of death for 21 of the patients. Forty-five of the patients were admitted to an ICU, with 37 dying in the ICU. The eight patients who died on the ward after transfer out of the ICU had end-of-life limitations of care in place.

The researchers noted that the number of patients dying in the ICU was greater in the United States, possibly because in Europe fewer patients are admitted to an ICU.

"This discrepancy likely reflects cultural differences between the U.S. and Europe in the role of intensive care for patients with advanced age and/or advanced comorbid conditions," they noted.

Two of the patients had end-of-life limitations of care in place, which the authors wrote meant that "only two patients undergoing full medical treatment without end-of-life limitations of care had an identified lapse in quality of in-hospital pneumonia care potentially contributing to in-hospital death, including one with a delay in antibiotics for over an hour in the presence of shock and one with initial antibiotics not consistent with IDSA/ATS guidelines."

The research team concluded that most in-hospital deaths among adult patients admitted with CAP in their study would not have been preventable with higher-quality in-hospital pneumonia care.

"Many of the in-hospital deaths among patients admitted with CAP occurred in older patients with severe comorbidities and end-of-life limitations in care," they noted.

Dr. Waterer reported no conflicts. Two coauthors reported potential conflicts of interest in relation to consulting fees from several pharmaceutical companies.

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SOURCE: Waterer GW et al. CHEST. 2018;154(3):628-35. doi: 10.1016/j.chest.2018.05.021.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: We strive to improve the quality of care in our clinics and hospitals. Waterer and colleagues recently studied the quality of care that we provide to patients hospitalized with community-acquired pneumonia. Factors influencing mortality included older age, multiple co-morbidities, and family decisions to limit the goals of care. The authors concluded that further improvements in this domain would not change patient outcomes. I read of these findings with interest, as they reminded me of something that the great physician William Osler wrote over 100 years ago: "Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old man escapes those 'cold gradations of decay' so distressing to himself and to his friends."[1] Maybe Osler was right!

1. Osler, W. The principles and practice of medicine. 7th Edition, 1909. New York, N.Y.

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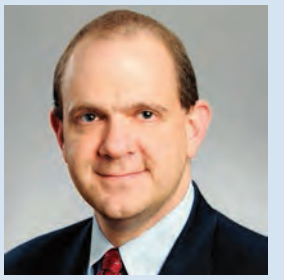

David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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Asthma in children: Close adherence to treatment guidelines means some families can keep their pets

BY ANDREW D. BOWSER
MDedge News

REPORTING FROM CHEST 2018 ▪ SAN ANTONIO – It may not always be necessary to tell parents of children with asthma to get rid of the household pet, a recent study suggests.

Children with uncontrolled asthma who were provided with guideline-appropriate care had significant improvements in a variety of asthma measures, regardless of whether parents reported pets at home, according to results of the 4-year, 471-patient prospective study.

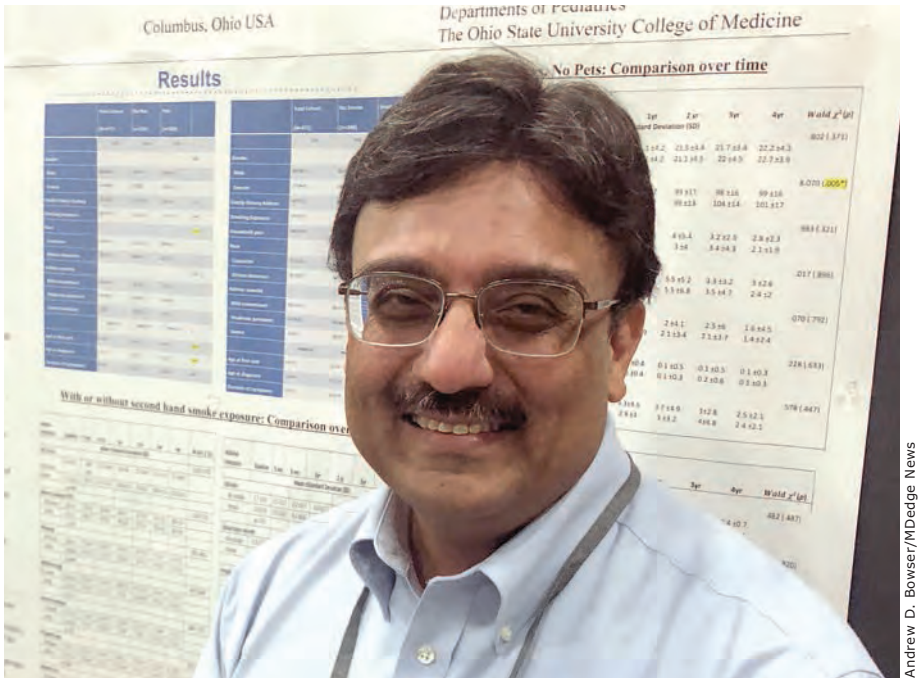
There was no significant difference between the no-pet and pet groups in mean percent of predicted FEV_1, wheezing, nighttime cough, albuterol use, and other factors over the 4 years of follow-up.

Those results suggest that clinicians should be working to make sure the guidelines are being closely followed before, for example, telling parents they need to consider getting rid of the family pet, said Shahid Sheikh, MD, FCCP, of Nationwide Children's Hospital, Columbus, Ohio.

"As the guidelines still work, we need to focus and develop the connections with the family to make sure the patients are on the right treatment, and that they're getting the medications," Dr. Sheikh said in an interview at the annual meeting of the American College of Chest Physicians.

The prospective cohort study by Dr. Sheikh and his colleagues, presented in a poster session, included children referred to a pediatric asthma center with the diagnosis of uncontrolled asthma. All patients received asthma care according to National Asthma Education and Prevention Program Expert Panel Report 3 guidelines.

Medications were changed as needed, and the asthma action plan was revised accordingly and reviewed with the family at each visit, Dr. Sheikh reported. After a baseline evaluation, clinic visits for the study occurred at 3 months, 6 months, and then at 1, 2, 3, and 4 years.



Andrew D. Bowser/MDedge News

Dr. Shahid Sheikh

Out of 471 patients, 258 had pets, according to parent reports.

Asthma control test scores were 15.1 at baseline for children in no-pet households, and 16.5 for those with pets; by the 3-month visit, scores increased to 20.1 and 20.3 for the no-pet and pet groups, and at 4 years, those scores had edged up to 22.2 and 22.7 (P = .371), Dr. Sheikh reported.

Similarly, after care was started, there was no significant difference between the no-pet and pet groups in mean percent of predicted FEV_1, wheezing, nighttime cough, albuterol use, and other factors over the 4 years of follow-up, he said.

Getting rid of the family pet may need to be a consideration for some families, but based on these data, that might not be necessary for the majority of families, Dr. Sheikh said in the interview.

Dr. Sheikh and his coinvestigators disclosed that they had no relationships relevant to the study.

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SOURCE: Sheikh S et al. CHEST 2018. doi: 10.1016/j.chest.2018.08.666.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: The older NAEPP Asthma Guidelines and 2018 Global Initiative for Asthma" (GINA) Guidelines continue to provide information on how to manage pediatric asthma but the nuances of care provided to our patients can be complex. These authors are insightful that a partnership needs to be developed. Demanding that "Oreo" the beloved dog in the family has to be sent to someone else's house is a huge deal and can affect the provider's relationship with the patient and family. This is very interesting research.

Dogs steal the show at CHEST 2018

BY THERESE BORDEN
MDedge News

SAN ANTONIO – Therapy Animals of San Antonio, a nonprofit organization that trains and places therapy pets, delighted the attendees of CHEST 2018 with some specially trained therapy dogs. The organization's philosophy is that pets can bring many benefits to patients, including stress reduction and emotional comfort. Patients with chronic illnesses and those in the ICU find that pets raise the quality of life and provide support through difficult times. Busy clinicians can also benefit from living with a pet. These therapy dogs were trained to be receptive to strangers and hundreds of CHEST 2018 attendees took the opportunity in the middle of the busy meeting to visit with them.

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Courtesy Lisa Baer

Dr. Christopher Carroll (left) and Dr. David Schulman enjoy some face time with the therapy dogs at CHEST 2018.

Men's important role in promoting gender equity

// *continued from page 1*

University of Texas, San Antonio.

Disparities exist particularly within specialties and subspecialties, she said. Women make 85% of what men earn in primary care but, in the specialties, only 75% of what men earn. Among active fellow trainees in the areas of medicine most represented by CHEST, one-third (32%) of critical care physicians and less than a third (29%) of pulmonary physicians are female.

Why the lag in specialty parity?

The reasons for these disparities are complex, Dr. Levine argued, but the problem is not insurmountable. They begin, in a sense, with the problem itself: When there are fewer mentors, role models, sponsors, and leaders, and less overall representation of women in the first place, it is harder for women to advance.

One male audience member, for example, asked how his department could recruit more women, because most turned down interviews despite the fact that more women than men were being invited. "How many women are in your leadership?" Dr. Levine asked. He acknowledged that there were none – and therein lies the likely problem. Applicants are looking for female representation in leadership.

Gender bias and discrimination certainly play a role among peers, leadership, and even patients. Patients referring to female physicians by their first names and asking questions such as "Are you my nurse?" are subtle but cutting examples of the ways in which they reveal implicit bias and reinforce gender stereotypes, Dr. Levine said to weary nods of agreement among the attendees.

Implicit, unconscious bias is also built into the culture of a place and the way things have always been done. Lack of equity in salary, space to work, support, and promotion all compound one another. Work-life integration challenges often do not favor women. Studies have shown that, in the hiring process, CVs with female names do not receive as much attention as do CVs with male names, Dr. Levine noted.

Some of the challenges lie with the way women themselves do or do not advocate for themselves. Research has long shown that women do not negotiate as well – or at all – compared with men. Women tend to be less aggressive in seeking higher compensation and leadership roles, possibly because of existing implicit bias against female assertiveness in general.

The catch-22 is that being more assertive or direct can lead others to interpret a woman as being rude or brusk, as one audience member noted when she described how colleagues perceive her simple, direct tone as seeming "upset."

Conscious bias remains alive and well: The stereotypes that women are caretakers and men are take-charge dominators persist and can reinforce gender disparities in leadership roles.

Women also must make calculations and trade-offs between their academic promotion clocks and their biologic clocks, Dr. Levine explained.

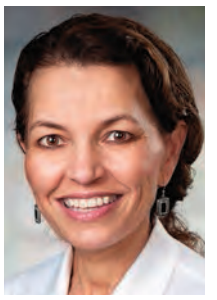
"The 30s are great for both academic and biologic productivity," she told attendees. The typical age for a person's first National Institutes of Health Research Project grant (R01) is in the early 40s.

Can gender equality be improved?

Women bring diverse skills and perspectives to the table, Dr. Levine explained. Women tend to have stronger collaborative skills and greater compassion and empathy, for example. They tend to be less hierarchal and better at mentoring and empowerment, she said.

There are many ways to poke more cracks in the ceiling, starting with diversity and inclusion officers who make it a priority to focus on parity. Formal programs can educate staff and colleagues about implicit bias so that they might more easily recognize it when it kicks in, and training for gatekeepers can lead to more proportional hiring of women at every level.

Institutions should review their policies – salary inequities, diversity in promotion, processes for selecting leaders – and set formal interventional goals that are then evaluated in honest, documented annual reviews.



DR. LEVINE

Some of these policies should address work-life balance as well: Offering part-time and flexible work options during early child-rearing years helps not only mothers, but also fathers who are now taking a more active role in parenting. Slowing or prorating the promotion clock can help those building families, and shifting meetings away from times such as 7:00 a.m. and 6:00 p.m. allows mothers and fathers alike to get their kids to and from school and attend children's events.

Sponsorship of women is an important strategy in breaking the glass ceiling, Dr. Levine said. Sponsors can support women with untapped leadership potential and do the necessary networking and introductions that help make that advance happen. And it must be done by sponsors with power and influence, including men, Dr. Levine said.

Men can play important roles in promoting gender parity by suggesting women for key roles, leadership positions, and committees and also notifying women of upcoming opportunities, such as editorial board spots and other hot jobs. For women who aspire to be leaders, men can seek to convey leadership skills that may be nee ded to chair committees and other groups. Search committees need to expand beyond looking for "token women," she said.

Dr. Levine illustrated her address with her own story. She described how many of these strategies had helped her career and how many male supervisors, mentors, and colleagues helped her, including introducing her to other male leaders who then offered her opportunities to contribute to the American College of Chest Physicians. She ran for CHEST president twice before being elected on her third run in September. She is the fifth woman to lead CHEST.

"Don't give up," she encouraged women in the audience, telling them to advocate for themselves and to encourage, mentor, and sponsor their female fellows and junior faculty.

"This will result in closing the gaps and will help women achieve leadership roles and competitive salaries as well as work-life integration," Dr. Levine said.

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VIEW ON THE NEWS

Together we are stronger

Diversity drives excellence. Creating a more inclusive environment will increase the visibility of our pool of talent, which will facilitate identifying women to take on future leadership roles.

Additionally, we can move beyond looking for a "token woman" by populating environments with a more representative distribution of talent to create truly balanced committees and speaker panels.

CHEST is actively working on enhancing this inclusivity through their Women & Pulmonary program. At the annual meeting this year, we held the Women & Pulmonary Luncheon and Women's Networking Cocktail Hour, and identified several "Women & Pulmonary Approved" sessions that focused on sex differences in disease states. The Women & Pulmonary workgroup also held a live free webinar this past March on how to be successful in pulmonary, critical care, and sleep medicine by learning to break down barriers, fight impostor syndrome, and actively negotiate.

Women are less likely to apply for a position or job due to a sense of having insufficient qualifications, possibly because of impostor syndrome. Having a sponsor to advocate on their behalf or to recommend them for an opportunity can be critical. This is arguably more important than mentorship, which focuses on developing goals and career ambitions, whereas sponsorship involves more aggressive advocacy for opportunities that will help protégés achieve their goals, in part by helping them network with others to further their careers. Involvement in national organizations such as CHEST and taking advantage of networking opportunities created by diversity-oriented bodies, such as the Women & Pulmonary workgroup, can help to facilitate sponsorship among traditionally underrepresented but critical stakeholders.

Aneesa M. Das, MD, FCCP, is Associate Professor of Internal Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University.

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ASPREE: What to do now about aspirin for healthy elderly people

BY ANDREW D. BOWSER
MDedge News

A cross-the-board use of aspirin for primary prevention is "not justified" based on the results of ASPREE as well as the equivocal results from other recent primary prevention trials, according to Prakash C. Deedwania, MD, clinical professor of medicine and chief of the cardiology division at the Veterans Affairs Medical Center/University of California San Francisco Program in Fresno.

Dr. Deedwania said in an interview that many "people have been using aspirin without any medical consultation, without looking at the risks. These studies have shed significant light in showing that even what is considered innocuous could be harmful."

The importance of interpreting these studies lies in the recognition that, while low-risk people don't benefit, patients who are at mid to high cardiovascular (CV) risk clearly might. Aspirin's role in secondary prevention after an initial CV event is clearly established, Dr. Deedwania added.

In ASPREE, a randomized, double-blind, placebo-controlled trial including nearly 20,000 participants, daily aspirin increased rates of major hemorrhage and did not significantly decrease risks of cardiovascular events, death, or other outcomes in healthy elderly individuals.

Aspirin did not prolong disability-free survival, a composite endpoint that included death, dementia, and permanent physical disability, according to one of three separate reports on ASPREE that were published in the New England Journal of Medicine.

Cardiovascular disease rates were likewise not significantly different between aspirin and placebo, with a hazard ratio that ruled out the possibility of a major protective effect, lead author John J. McNeil, MBBS, PhD, of Monash University, Melbourne, said in a second report on ASPREE.

All-cause mortality was actually higher in the aspirin arm versus the placebo arm, attributable largely to an excess of cancer-related deaths, Dr. McNeil and colleagues said in their third full report in the journal. However, that mortality finding needs to be interpreted with caution, they noted, given that previous investigations have shown a protective effect of aspirin on cancer-related death.

Potential harms of "innocuous" drug

The ASPREE (Aspirin in Reducing Events in the Elderly) study evaluated the use of aspirin as primary prevention in 19,114 healthy subjects, with a median age of 74 years, enrolled at 34 centers in Australia and the United States between 2010 and 2014.

The patients, who did not have cardiovascular disease, dementia, or disability at baseline, were randomized to daily 100-mg enteric-coated aspirin or placebo.

DR. DEEDWANIA

The importance of interpreting these studies lies in the recognition that, while low-risk people don't benefit, patients who are at mid to high cardiovascular risk clearly might. Aspirin's role in secondary prevention after an initial CV event is clearly established.

The rate of death, dementia, or disability was 21.5 events per 1,000 person-years in the aspirin group, and 21.2 events per 1,000 person-years in the placebo group, with a hazard ratio of 1.01 (95% confidence interval, 0.92-1.11; $P = .79$), Dr. McNeil and colleagues reported.

The rate of major hemorrhage was 8.6 events per 1,000 person-years for aspirin versus 6.2 events per 1,000 person years for placebo (HR, 1.38; 95% CI, 1.18-1.62; P less than .001), investigators found.

Cardiovascular outcomes: expectations vs. reality

Investigators said they thought they might see a significant cardiovascular benefit of aspirin in ASPREE based on earlier studies and meta-analyses that suggested a benefit in other populations. However, the rate of cardiovascular disease at 4.7 years of follow-up was 10.7 events per 1,000 person-years for aspirin, and 11.3 per 1,000 person-years for placebo (HR, 0.95; 95% CI, 0.83-1.08).

That hazard ratio "rules out the possibility of a major protective effect of aspirin but is compatible with a more modest lowering of risk of up to 17%," Dr. McNeil and colleagues wrote.

The results are consistent with those of a recent meta-analysis including eight primary prevention trials, mainly in adults under 70 years of age. That analysis found a 17% reduction in nonfatal myocardial infarction risk, a 14% reduction in stroke risk, and a higher risk of serious bleeding for aspirin versus control groups.

Results of ASPREE have to be interpreted in light of event rates, which were much lower than the expected 22.4 events per 1,000 person-years, they added. The low event rate probably reflects both the relatively good health of the study subjects, and the declining rates of cardiovascular disease in recent years, they said.

"Because of these factors, the absolute benefit that results from any proportionally lower rate of cardiovascular disease may be less than the benefit observed in studies from previous decades and is less likely than it had been to outweigh the risk of adverse events from aspirin," investigators said in their report.

Current guidelines state that the evidence is limited for use of aspirin as primary prevention of cardiovascular disease in the elderly. "Nevertheless, many millions of relatively healthy older persons in the United States and Australia take low-dose aspirin with the assumption that it will reduce the likelihood of future cardiovascular disease and stroke," study authors said in a discussion of the results.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The findings in the ASPREE study of a daily 100-mg dose of aspirin in healthy elderly patient does not necessarily lower the cardiovascular risks and may, in fact, increase the rate of cancer deaths will have a major impact on the long-standing practice of healthy elderly patients being given aspirin.

Excess deaths studied

There were also no significant differences between arms for the endpoints of death, dementia, or disability evaluated separately. However, the rate of death by any cause was numerically higher in the aspirin group versus the placebo group, at 12.7 and 11.1 events per 1,000 person-years, respectively (HR, 1.14; 95% CI, 1.01-1.29).

Cancer was the major contributor to the imbalance in deaths, ASPREE results show, at 1.6 excess deaths per 1,000 person-years. A total of 3.1% of patients in the aspirin group had cancer-related deaths, compared with 2.3% in the placebo arm of the trial (HR, 1.31; 95% CI, 1.10-1.56).

Mortality related to major hemorrhage contributed "only minimally" to the excess in deaths, investigators added in their report.

The finding of excess deaths in the aspirin arm of ASPREE contrasts with meta-analyses of previous prevention trials. According to investigators, those studies show a protective effect of aspirin on cancer-related death that is apparent after 4-5 years of continuous treatment.

Various cellular and molecular pathways relevant to cancer development, progression, and spread are influenced by aspirin, previous studies show.

"Questions may therefore arise about whether the biology of cancer differs among age groups with regard to the frequency of common molecular patterns, metastatic behavior, and treatment responses," Dr. McNeil and coauthors wrote in their report.

Dr. McNeil reported nonfinancial support from Bayer received during the conduct of the study.

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SOURCE: McNeil JJ et al. N Engl J Med. 2018 Sep 16.

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Study explores link between GERD and poor sleep

BY DOUG BRUNK
MDedge News

ATLANTA – Chronic gastroesophageal reflux disease (GERD) is associated with various sleep disorders that might complicate the response to GERD treatment, results from an ongoing longitudinal analysis demonstrated.

"We have little longitudinal information on GERD in the general population; the last published article on GERD incidence was 20 years ago," lead study author Maurice M. Ohayon, MD, DSc, PhD, said in an interview in advance of the annual meeting of the American Neurological Association. "As a sleep specialist, I am always interested to see how a specific medical condition may affect the sleep quality of the individuals with that condition. How we live our day has an impact on our night; it works together."

In an effort to examine the long-term effects of GERD on sleep disturbances, Dr. Ohayon, director of the Stanford (Calif.) Sleep Epidemiology Research Center, and his colleagues used U.S. Census data to identify a random sample of adults in Arizona, California, Colorado, Idaho, New York, Oregon, Pennsylvania, and Texas. The researchers conducted two waves of phone interviews with the subjects 3 years apart, beginning in 2004. They limited their analysis to 10,930 subjects with a mean age of 43 years who participated in both interviews.

Between wave 1 and wave 2 of phone interviews, the proportion of adults who reported having GERD rose from 10.6% to 12.4% and the prevalence of new GERD cases was 8.5% per year, while the incidence was 3.2% per year. Chronic GERD, defined as that present during both interview periods, was observed in 3.9% of the sample.


DR. OHAYON

The researchers found that 77.3% of GERD subjects were taking a treatment to alleviate their symptoms, mostly proton-pump inhibitors. Those with chronic GERD were more likely to report being dissatisfied with their sleep during wave 2 of the study, compared with wave 1 (24.2% vs. 13.5%; *P* less than .001). In addition, compared with their non-GERD counterparts, those with chronic GERD were more likely to wake up at night (33.9% vs. 28.3%; *P* less than .001) and to have nonrestorative sleep (15.6% vs. 10.5%; *P* less than .001).

"Discomfort related to GERD may happen while you are sleeping," said Dr. Ohayon, who is also a professor of psychiatry and behavioral sciences at Stanford University. "It may wake you up, and if not, it may make you feel unrested when you wake up. We observed both of these symptoms in our GERD participants. Insomnia disorders were also rampant in the chronic GERD group (24.5%, compared with 14.4% in non-GERD participants). An insomnia disorder is more than just having difficulty falling asleep or waking up at night, it means that your daytime functioning is affected by the poor quality of your night."

Dr. Ohayon said other findings from the study were "rather alarming." For example, individuals with GERD, especially those with the chronic form, weighed much more than those with no GERD did. "Over a 3-year period, the chronic GERD individuals gained one point in the body mass index, which for a 6-foot tall man translates into a weight gain of 30 pounds," he said. "Of course, with that follows high blood pressure, high cholesterol, diabetes, chronic pain, and heart disease."

He concluded that GERD has its main manifestations when affected individuals are sleeping on their backs. "The impact of GERD on the quality of sleep is major," he said. "Sleepiness and fatigue during the day are the consequences impacting work, family, and quality of life."

Dr. Ohayon acknowledged certain limitations of the study, including the fact that GERD was based on self-report. The study was supported by an unrestricted grant from Takeda.

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SOURCE: Oyahon MM et al. ANA 2018, Abstract 625.

Digital CBT improves sleep, well-being, quality of life

BY ANDREW D. BOWSER
MDedge News


Hocus Focus Studio/iStockphoto

Digitally delivered cognitive-behavioral therapy not only improved insomnia, but also provided "around-the-clock" health, psychological, and quality-of-life improvements, according to investigators.

Compared with control subjects, patients who used a cognitive-behavioral therapy (CBT) program and associated iPhone app had small improvements in functional health and psychological well-being and large improvements in sleep-related quality of life, the investigators reported.

Those changes were mediated by a large improvement in insomnia, according to Colin A. Espie, PhD, professor of sleep medicine at the University of Oxford (England), and his colleagues.

"These findings indicate that digital CBT improves both daytime and nighttime aspects of insomnia, lending further weight to the clinical guideline recommendation of CBT as the treatment of choice for insomnia," Dr. Espie and his colleagues reported in JAMA Psychiatry.

Their study included 1,711 adults with symptoms of insomnia that were self-reported and a score of 16 or less on the Sleep Condition Indicator (SCI), which has a range of 0-32. A total of 853 were randomized to receive digital CBT, of whom 413 completed six scheduled 20-minute sessions; an additional 276 adults completed at least one session. The control arm included 858 individuals randomized to sleep hygiene education, of whom 759 went on to receive that intervention.

Small but significant improvements were seen in self-reported measures of functional health, Dr. Espie and his colleagues reported. The adjusted differences in mean scores on the Patient-Reported Outcomes Measurement Information System: Global Health Scale were 0.90 in a midtreatment evaluation at 4 weeks after baseline, 1.76 in a posttreatment evaluation at 8 weeks, and 1.76 at a 24-week follow-up assessment (*P* less than 0.001 for all comparisons).

Likewise, adjusted differences in the Warwick-Edinburgh Mental Wellbeing Scale were 1.04, 2.68, and 2.95 at 4, 8, and 24 weeks, respectively.

Adjusted differences in the Glasgow Sleep Impact Index, which measures sleep-related quality of life, were –8.76, –17.60, and –18.72 at 4, 8, and 24 weeks, respectively, indicating a benefit of the digital CBT intervention over the control intervention, the investigators said.

About 45%-84% of these effects were attributable to changes in insomnia symptoms, results of a mediation analysis showed.

Insomnia scores as measured by the eight-item SCI scale were 6.5 and 6.6 at baseline for the digital CBT and control groups, respectively. By week 4, SCI scores were 9.96 and 13.00 for the two groups (*P* less than 0.001), with significant differences also reported at the 8- and 24-week evaluations.

The investigators noted that their findings might not be generalizable because participants were not drawn from patient populations. In addition, although 58% of the participants completed 4 weeks or more of the digital CBT sessions, the dropout rate was "substantial."

Nevertheless, they wrote, these findings, together with results of a recently reported parallel study looking at the effects of sleep on mental health, affirm CBT as the treatment of choice for insomnia. "The mediation analyses in these two studies, with a total of 5,466 participants, provide novel and convincing

Continued on following page

Obesity plays role in sleep-disordered breathing in pregnancy

BY BIANCA NOGRADY
MDedge News

The relationship between hypertension during pregnancy and sleep-disordered breathing may be partly mediated by obesity, new research suggests.

An article published in the Journal of Sleep Research details the results of a case-control study in 80 pregnant women – 40 normotensive and 40 with either gestational hypertension or preeclampsia – who were matched on body mass index.

Nearly half of the women in the study (45%) met the criteria for sleep-disordered breathing – defined as a respiratory disturbance index of 5 or above. The incidence was higher among women with hypertension (53%) than among women in the normotensive control group (38%), but the difference was not statistically significant.

There were also no significant differences in median respiratory disturbance index or apnea-hypopnea index between the hypertension and control groups.

Obesity in pregnancy is defined as a pre-gravid (BMI) of 30 kg/m^2 or greater. Three different classes of obesity exist, ranging from BMI ≥30.0 kg/m^2 to >40 kg/m^2 (Arch. Gynecol. Obstet. 2017; 296:465-68).

However, the incidence of more severe sleep-disordered breathing – a respiratory disturbance index of at least 10 – was significantly greater in the hypertensive group (35% vs. 14%; *P* = .04). The women with pregnancy-related hypertension also had significantly higher respiratory disturbance index during non–rapid eye movement sleep and when they were sleeping on their back.

The severity of hypertensive disease did not affect the prevalence of sleep-disordered breathing.

Danielle L. Wilson of the Institute for Breathing and Sleep at Austin Health in Melbourne and her coauthors wrote that, while previous research has pointed to a link between hypertension in pregnancy and sleep-disordered breathing, this is the first study to explore the potential confounding role of obesity.

"We found SDB [sleep-disordered breathing] to be more common in our control group than in previous studies, confirming that BMI is an important covariate that requires evaluation in future studies exploring the relationship between SDB and HDP [hypertension during pregnancy]," they reported. "SDB may be a mechanism by which obesity and adverse perinatal outcomes are linked, but given the important contribution of obesity to both SDB and HDP, failing to adjust for this covariate will overestimate the strength of association between SDB and HDP."

They acknowledged there was a significant association between moderate to severe sleep-disordered breathing and hypertension in pregnancy. They suggested this might be a means to increase women's uptake of clinical review with a sleep physician, which was very low in the study despite its being offered to all women.

The study was supported by the Austin Medical Research Foundation and the Medical Research Foundation for Women and Babies. One author declared a scholarship from a research funding body, and two declared unrelated research support from private industry. No other conflicts of interest were declared.

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SOURCE: Wilson DL et al. J Sleep Research. 2018 Oct;27(5):e12656.

Continued from previous page

evidence that insomnia may be a legitimate and important target for mental health and well-being."

Dr. Espie reported that he is cofounder and chief medical officer of Big Health. He is a shareholder and receives a salary from the company, which was involved in the design and conduct of the study, interpretation of data, and development of the manuscript appearing in JAMA Psychiatry. The study was funded by Big Health and other sources, including the National Institute for Health Research Oxford Biomedical Research Centre.

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SOURCE: Espie CA et al. JAMA Psychiatry. 2018 Sep 25. doi: 10.1001/jamapsychiatry.2018.2745.

THODONAL/THINKSTOCK

Sexual assault and harassment linked to poor sleep and hypertension

BY BIANCA NOGRADY
MDedge News

Sexual harassment and assault may have significant health impacts on women in midlife, including greater risk of poor sleep, hypertension, depression, and anxiety, research suggests.

In the Oct. 3 online edition of JAMA Internal Medicine, a study of 304 women aged 40-60 years showed that 19% reported a history of workplace sexual harassment, 22% reported a history of sexual assault, and 10% reported both. The report was presented simultaneously at the North American Menopause Society annual meeting in San Diego.

DR. THURSTON

The researchers found that those with a history of sexual assault had more than twofold greater odds of anxiety and poor sleep (odds ratio, 2.26; *P* = .006 and OR, 2.15; *P* = .007, respectively) and almost threefold higher odds of clinically elevated depressive symptoms (OR, 2.86; *P* = .003).

Women who reported experiencing sexual harassment in the workplace – and who were not taking antihypertensive medication – were more than twice as likely to have stage 1 or 2 hypertension, compared with women who had not experienced sexual harassment (OR, 2.36; *P* = .03). They also had 89% higher odds of poor sleep consistent with clinical insomnia (*P* = .03).

These associations all persisted even after adjustment for demographic and biomedical factors such as age, ethnicity, body mass index, snoring, and the use of antihypertensive, antidepressant, and anti-anxiety medications.

"Given the high prevalence of sexual harassment and assault, addressing these prevalent and potent social exposures may be critical to promoting health and preventing disease in women," wrote Rebecca C. Thurston, PhD, of the department of psychiatry at the University of Pittsburgh, and her coauthors.

They noted that the 1-in-5 rate of sexual harassment or assault seen in the study was actually lower than that seen in national samples, which may be have been because of the exclusion of women who smoked, had undergone hysterectomies, or were using common antidepressants or cardiovascular medications.

"Few characteristics distinguished between women who had been sexually harassed and those who had been sexually assaulted, with the exception that women who were sexually harassed were more highly educated yet more financially strained," they wrote. "Notably, women who are younger or are in more precarious employment situations are more likely to be harassed, and financially stressed women can lack the financial security to leave abusive work situations."

The study was supported by the National Institutes of Health, National Heart Lung and Blood Institute, and the University of Pittsburgh Clinical and Translational Science Institute. Dr. Thurston declared consultancies for MAS Innovations, Procter & Gamble, and Pfizer, but no other conflicts of interest were declared.

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SOURCE: Thurston RC et al. JAMA Intern Med. 2018 Oct 3. doi: 10.1001/jamainternmed.2018.4886.

CHEST™ Physician
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Discharge trends for septic shock remain steady

BY ANDREW D. BOWSER
MDedge News

REPORTING FROM CHEST 2018 ▪

SAN ANTONIO – While septic shock mortality has decreased since the Surviving Sepsis Campaign guidelines were introduced, discharge trends for survivors have not changed significantly over time, a recent analysis suggests.

The percentage of survivors discharged to subacute rehab or long-term facilities did not change appreciably over time, according to the 10-year retrospective analysis, presented at the annual meeting of the American College of Chest Physicians.

However, average length of stay did significantly trend downward over the decade analyzed, while total charge per septic shock admission significantly increased, according to investigator Di Pan, DO, Icahn School of Medicine at Mount Sinai, New York, and his colleagues.

The percentage of survivors discharged to subacute rehab or long-term facilities did not change appreciably over time.

This is one of few studies looking at outcomes in survivors of septic shock, as most analyses have primarily focused on mortality outcomes, the investigators said.

Their analysis was based on the 2004 to 2014 National (Nationwide) Inpatient Sample databases and included patients with a primary diagnosis of septic shock at discharge.

Out of nearly 1.8 million patients with septic shock in that cohort, about 1 million survived, according to data Dr. Pan and colleagues provided in an abstract of the presentation.

In-hospital mortality decreased from 51.7% in 2004 to 39.3% in 2014 (P less than .001), the investigators reported.

The proportion of survivors discharged to subacute rehab or long-term acute care facilities was 61.9% in 2004, and similarly, 62.4% in 2014 ($P = .1$), while the percentage discharged home was 17.1% in 2004 and 15.1% in 2014 ($P = 0.55$).

However, there was a small but statistically significant downtick in mean length of stay, from 12.6 days in 2004 to 11.05 days in 2014, the investigators said. Meanwhile, total hospitalization charges surged from $105,776 in 2004 to $134,394 over the same time period.

The first edition of the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock was published in March 2004 in Critical Care Medicine.

Future studies and clinical trials should look beyond mortality outcomes to additionally evaluate morbidity outcomes in septic shock survivors, Dr. Pan and coauthors said in their report.

The researchers had no relationships to disclose relevant to the presented study.

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SOURCE: Pan D et al. CHEST 2018. doi: 10.1016/j.chest.2018.08.339.

In *C. difficile,* metronidazole may not benefit ICU patients on vancomycin

BY M. ALEXANDER OTTO
MDedge News

SAN FRANCISCO – Intravenous metronidazole (Flagyl) did not improve 30-day mortality when it was added to oral vancomycin in adult ICU patients with severe *Clostridium difficile* infections, according to a review of 101 cases at the University of Maryland.

Adding metronidazole is a common move in ICUs when patients start circling the drain with *C. difficile*, in part because delivery to the gut doesn't depend on gut motility. "At that point, you are throwing the kitchen sink at them, but it's" based, like much in *C. difficile* management, on expert opinion, not evidence, said study lead Ana Vega, PharmD, a former resident at the university's school of pharmacy in Baltimore, and now an infectious disease pharmacist at Jackson Memorial Hospital, Miami. The investigators wanted to plug the evidence gap. Forty-seven of the 101 patients in their review – all with signs of *C. difficile* sepsis – had IV metronidazole added to their vancomycin regimens. Thirty-day mortality was 14.9% in the combination group versus 7.4% in the monotherapy arm, and not significantly different ($P = .338$). There were also no significant differences in resolution rates or normalization of white blood cell counts and temperature.

"Our data question the utility of" of adding IV metronidazole to oral vancomycin in patients with severe disease. "It's definitely something to think twice about because metronidazole isn't benign. It makes people feel crummy; you can induce resistance; and it increases the risk of vancomycin-resistant Enterococci colonization," already a risk with vancomycin, Dr. Vega said at an annual scientific meeting on infectious diseases.

"When you get to the point that you are trying combination therapy based on expert opinion, I think fecal transplants are something to consider" because the success rates are so high. "That would be my suggestion," she said, even though "it's much easier to write an order for a drug than to get a fecal transplant."

The issue is far from resolved, and debate will continue. A similar review of ICU patients at Wake Forest University in Winston-Salem, N.C., did find a significant mortality benefit with combination therapy, regardless of *C. difficile* severity (Clin Infect Dis. 2015 Sep 15. doi: 10.1093/cid/civ409).

The Maryland investigators excluded patients with toxic megacolon and other life-threatening intra-abdominal complications requiring surgery, because combination therapy is more strongly recommended in fulminant disease. They were interested in people who were not quite ready for the operating room, when what to do is more in doubt.


M. Alexander Otto/MDedge News

Dr. Ana Vega

Subjects were admitted to the ICU from April 2016 to April 2018 with positive *C. difficile* nucleic acid testing and an order for oral vancomycin. The only statistically significant baseline differences were that patients who got IV metronidazole had higher median white blood cell counts (18,400 versus 13,900 cells/mL; $P = .035$) and were more likely to receive higher than 500-mg doses of vancomycin (36.2% versus 7.4%; P less than .0001).

The Mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score in the combination group was 23 versus 19 in the monotherapy arm ($P = .247$). There was no difference in the probability of receiving metronidazole based on the score.

The study again found no significant 30-day mortality differences among 76 patients matched by their APACHE II scores (15.8% in the combination arm versus 9.7%; $P = .480$).

Severe *C. difficile* infection was defined as either a white cell count above 15,000 or below 4,000 cells/mL, or a serum creatinine at least 1.5 times above baseline, plus at least one other sign of severe sepsis, such as a mean arterial pressure at or below 60 mm Hg. Metronidazole was started within 72 hours of the first vancomycin dose, and subjects on combination therapy were on both for at least 72 hours.

The mean age in the study was about 60 years old, and just over half of the subjects were men.

Dr. Vega said the investigators hope to expand their sample size and see if patients with more virulent strains of *C. difficile* do better on combination therapy.

There was no industry funding for the work, and the investigators didn't have any relevant disclosures.

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SOURCE: Vega A et al. ID Week 2018, Abstract 488.

Severe influenza ups risk of invasive pulmonary aspergillosis

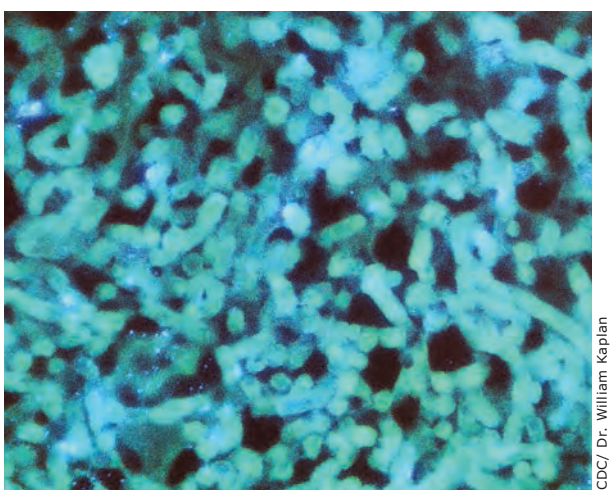
BY TERRY L. KAMPS
MDedge News

Severe influenza is an independent risk factor for invasive pulmonary aspergillosis with an accompanying increased mortality in the ICU, according to a multicenter retrospective cohort study at seven tertiary centers in Belgium and the Netherlands.

The research study was reported by Alexander F.A.D. Schauwvlieghe, MD, of Erasmus MC University Medical Center, Rotterdam, the Netherlands, and his colleagues.

Data were collected from criteria-meeting adult patients admitted to the ICU for more than 24 hours with acute respiratory failure during the 2009-2016 influenza seasons. The included cohort of 432 patients was composed of 56% men and had a median age of 59 years; all participants were diagnosed as having severe type A or type B influenza infection according to positive airway RT-PCR results.

The full cohort was subcategorized into 117 immunocompromised and 315 as nonimmunocompromised individuals using criteria established by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG). To assess influenza as an independent variable in the development of invasive pulmonary aspergillosis, researchers compared the 315 nonimmunocompromised influenza positive individuals with an influenza-negative control group of 315 nonimmunocompromised patients admitted to the ICU that presented similar respiratory insufficiency symptoms with community-acquired pneumonia.


CDC/ Dr. William Kaplan

Determination of other independent risk factors for incidence of invasive pulmonary aspergillosis was achieved by multivariate analysis of factors such as sex, diabetes status, prednisone use, age, and acute physiology and chronic health evaluation (APACHE) II score. The mean APACHE II score was 22, with the majority of patients requiring intubation for mechanical ventilation for a median duration of 11 days.

Influenza is not considered a host factor for invasive pulmonary aspergillosis and will often miss being diagnosed when using strict interpretation of the current EORTC/MSG or AspICU algorithm criteria, according to the researchers. Consequent-

Continued on following page

ICU infections: Chlorhexidine wipes tame MRSA, CRE

BY M. ALEXANDER OTTO
MDedge News

SAN FRANCISCO – The University of Kentucky Medical Center, Lexington, halved the rate of MRSA and CRE infections in the ICU by switching from contact precautions to decolonization with nasal povidone iodine swabs and daily chlorhexidine wipes, according to a report presented at ID Week 2018.

M. Alexander Otto/MDedge News

Dr. Jason Moss

The move prevented an estimated eight methicillin-resistant *Staphylococcus aureus* (MRSA) and three carbapenem-resistant *Enterobacteriaceae* (CRE) infections and saved the medical center more than $150,000 in the year following the November 2016 switch.

The goal was to address the rate of MRSA bacteremia, which was higher than national ICU averages. Contact precautions began to make less sense as MRSA became more common in the surrounding community, and "we just wanted to get rid of contact precautions," said study lead Jason Moss, DO, an infectious disease fellow at the university.

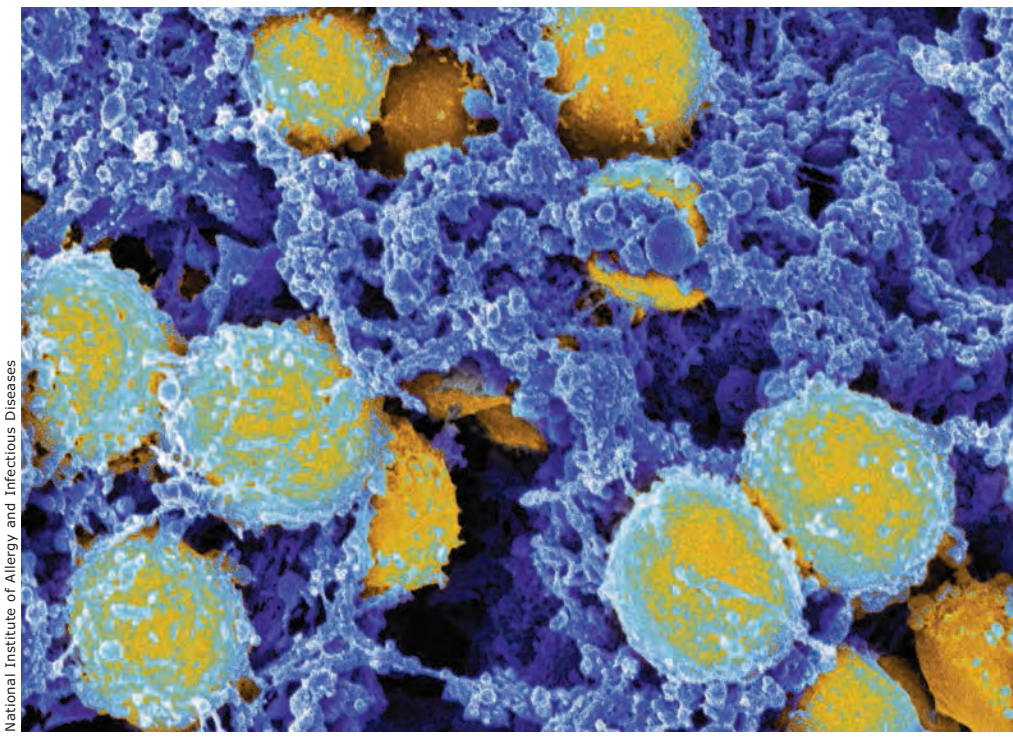
Contact precautions are expensive, make patients feel isolated, and according to some studies, lead to worse outcomes, he said at the annual scientific meeting on infectious diseases.

Decolonization is not routine in most ICUs, but it's gaining traction. Guidelines recommend chlorhexidine bathing with wipes to stop CRE transmission, and chlorhexidine is used to prevent central line–associated bloodstream infections (CLABSI).

A recent analysis of 17 trials found marked decreases in MRSA and CLABSI with decolonization and concluded that chlorhexidine bathing "appears to be of the most clinical benefit when infection rates are high for a given ICU population," as was the case in Kentucky (Crit Care. 2016 Nov 23;20[1]:379).

When researchers compared the year before the change to the year after, "we were pretty surprised at how much the rates of infection and colonization decreased. There have been some people that have been doing this in the ICU, but probably not to our extent. If you want to get rid of contact precautions, this is a great process to do it with," Dr. Moss said.

Rates of colonization with MRSA or CRE fell from about 14 isolates per 10,000 patient-days to fewer than 6 (P = .026). Infection rates fell from 3.9 isolates per 10,000 patient-days to 2 (P = .083). Combined rates of infections and colonizations fell from almost 18 isolates per 10,000 patient-days to fewer than 8 (P = .010).



National Institute of Allergy and Infectious Diseases

Spending on gowns fell from about $153,000 per year to just under $60,000, but spending on wipes went up from about $2,700 to $275,000, and spending on povidone iodine nasal swabs went up to more than $100,000.

Decolonization is now standard practice at the university. Every ICU patient gets a one-time povidone iodine nasal swab at admission, then daily baths with 2% chlorhexidine gluconate applied by impregnated wipe. It usually takes four or five wipes to do the entire body.

When balanced against the money not spent on those 11 prevented infections, however, the program saved the medical center about $152,000 in its first year, according to Dr. Moss and his team.

There was no funding for the work, and the investigators had no disclosures.

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SOURCE: Moss J et al. ID Week 2018, Abstract 32.

Continued from previous page

ly for patients with influenza and the noninfluenza control group with community-acquired pneumonia, the definition of invasive pulmonary aspergillosis was modified from the AspICU algorithm. Stringent mycological criteria, including bronchoaveolar lavage (BAL) culture, a positive *Aspergillus* culture, positive galactomannan test, and/or positive serum galactomannan tests, provided supporting diagnostics for an invasive pulmonary aspergillosis determination.

At a median of 3 days following admission to the ICU, a diagnosis of invasive pulmonary aspergillosis was determined for 19% of the 432 influenza patients. Similar incident percentages of invasive pulmonary aspergillosis occurring for type A and type B, 71/355 (20%) and 12/77 (16%) patients respectively, showed that there was no clear association of the disease development with influenza subtypes that occurred during different annual seasons.

AspICU or EORTC/MSG criteria characterized only 43% and 58% of cases as proven or possible aspergillosis, respectively. On the other hand, stringent mycological tests yielded better invasive pulmonary aspergillosis classification, with 63% of BAL cultures being positive for *Aspergillus*, 88% of BAL galactomannan tests being positive, and 65% of serum galactomannan tests being positive in the 81/83 patients tested.

The study found that, for influenza patients, being immunocompromised more than doubled the incidence of invasive pulmonary aspergillosis, at 32% versus the 14% of those patients who were nonimmunocompromised. In contrast only 5% in the control group developed invasive pulmonary aspergillosis.

For influenza patients, being immunocompromised more than doubled the incidence of invasive pulmonary aspergillosis.

Influenza patients who developed invasive pulmonary aspergillosis in the ICU tended to have their stays significantly lengthened from 9 days (interquartile range, 5-20 days) for those without it to 19 days (IQR, 12-38 days) for those infected (P less than .0001). Likewise, 90-day mortality significantly rose from 28% for those influenza patients without invasive pulmonary aspergillosis to 51% for those with it (P = .0001).

The authors concluded that influenza was "independently associated with invasive pulmonary aspergillosis (adjusted odds ratio, 5.19; P less than.0001) along with a higher APACHE II score, male sex, and use of corticosteroids."

Furthermore, as influenza appears to be an independent risk factor for invasive pulmonary aspergillosis and its associated high mortality, the authors suggested that "future studies should assess whether a faster diagnosis or antifungal prophylaxis could improve the outcome of influenza-associated aspergillosis."

The authors reported that they had no conflicts of interest.

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SOURCE: Schauwvlieghe AFAD et al. Lancet Respir Med. 2018 Jul 31. doi: 10.1016/S2213-2600(18)30274-1.

ACIP okays improved immunization schedule design

BY HEIDI SPLETE
MDedge News

Clinicians consulting the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, vaccination schedules for children, adolescents, and adults in 2019 will find a simpler design and more useful product, according to David Kim, MD, of the Immunization Services Division of the Centers for Disease Control and Prevention, Atlanta.

In a single vote to cover both adult and child/adolescent schedules, the committee voted unanimously in favor of a redesign of the schedules and several clinical updates.

In 2016, the working group for vaccination schedules conducted an ad hoc evaluation of the adult schedule to assess its usability, Dr. Kim said at a meeting of the CDC's ACIP.

The design of the adult schedule was fully evaluated in 2018 via a three-step process – interviews with 48 health care providers, a redesign of the schedule, and a survey after the redesign. Design changes to the child/adolescent schedule were harmonized with the adult schedule, Dr. Kim explained.

The adult vaccination schedule itself includes several updates in ACIP recommendations in addition to the aesthetic design changes.

The 2019 Adult Immunization Schedule includes the option of the live attenuated influenza vaccine (LAIV) for influenza, the addition of homelessness as an indication for hepatitis A vaccination, and the use of CpG-adjuvanted hepatitis B vaccine, Dr. Kim said.

The additions to the 2019 Child and Adolescent Immunization Schedule are the optional use of the LAIV for influenza, the addition of homelessness as an indication for hepatitis A vaccination, the use of CpG-adjuvanted hepatitis B vaccine

(a cytosine phosphoguanosine oligodeoxynucleotide adjuvant), and the addition of the Tdap vaccination of individuals who received Tdap at age 7-10 years.

Some of the key design changes include the use of bright purple on the child/adolescent schedule to more easily distinguish it from the adult version, said Dr. Kim.

Some of the key design changes include the use of bright purple on the child/adolescent schedule to more easily distinguish it from the adult version.

Other changes to both schedules include shorter titles, lists of vaccines and trade names, and compartmentalized information for easier reference. Figures have been replaced by tables, and footnotes are simply "Notes" at the end of the schedule, compartmentalized for easier reading, he said. In addition, the schedules include resources for vaccination in outbreak situations and a section on how to report vaccine-preventable disease outbreaks.

The ACIP committee members had no relevant financial conflicts to disclose.

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What's in that e-cigarette? It may be cannabis

BY BIANCA NOGRADY
MDedge News

Nearly 1 in 11 U.S. middle- and high-school students have used a cannabis product in an e-cigarette, according to a school-based survey of 20,675 students.

The survey found that 8.9% of students in grades 6-12 said they had used an e-cigarette with marijuana, tetrahydrocannabinol or hash oil, or tetrahydrocannabinol wax. Among the students who reported ever using e-cigarettes, 30.6% had used a cannabis product in the device. The findings were published in JAMA Pediatrics.

This translated to around 1.7 million high-school students and 425,000 middle-school students who had ever used cannabis in e-cigarettes; figures the authors said were consistent with or higher than previous reports among U.S. and Canadian students. The investigators noted that this is the first study to assess e-cigarette cannabis use among students more broadly, particularly middle-school students..

Katrina F. Trivers, PhD, and her colleagues from the Centers for Disease Control and Prevention, noted that the U.S. Surgeon General has found e-cigarette aerosol can contain potentially harmful ingredients. Additionally, the National Academies of Sciences has said youth cannabis use can harm learning and memory.

"Strategies to reduce cannabis use in e-cigarettes are critical for protecting young people from these potential health risks," the researchers wrote.

Male students and high-school students were significantly more likely to report using cannabis products in an e-cigarette (10.6% and 12.4%, respectively), compared with female or middle-school students.

Among current users of e-cigarettes, 39.5% reported using cannabis in the e-cigarette, while among those who used other tobacco products, 38.5% used cannabis in e-cigarettes. Higher e-cigarette use was also associated with use of cannabis products in e-cigarettes.

Living with someone who used tobacco products was associated with a higher incidence of cannabis in e-cigarette use (13%). Researchers also saw a higher use of cannabis in e-cigarettes among students of Hispanic ethnicity, compared with other ethnicities.

In 2015, around one-third of U.S. middle- and high-school students said they had used nonnicotine substances in e-cigarettes, but the use of cannabis in e-cigarettes could increase as several states consider legalizing cannabis sales for adults. "Given the high concurrent use of tobacco and other substances, it is important to monitor the substances youth use in e-cigarettes," they wrote.

The researchers reported having no financial disclosures.

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Dupilumab offers extra benefits to asthmatic teens

BY ANDREW D. BOWSER
MDedge News

REPORTING FROM CHEST 2018 ▪ SAN ANTONIO – For adolescents with asthma, treatment with the biologic agent dupilumab provided benefits that were at least comparable with what was seen in adults, results from a retrospective analysis of a randomized, phase 3 study suggest.

Adolescents had reduced asthma exacerbations in line with what was seen in adults and had improvements in lung function that were at a greater magnitude than adults, according to study coauthor Neil M.H. Graham, MD, of Regeneron Pharmaceuticals, Tarrytown, N.Y.

"We think, overall, it's a very good treatment response from this drug in this high-risk population, and it is generally well tolerated, as we've seen in other studies," Dr. Graham said in a podium presentation at the annual meeting of the American College of Chest Physicians.

Dr. Graham presented results of an analysis of the 1,902-patient, phase 3 Liberty Asthma QUEST trial, published in May 2018 in the New England Journal of Medicine.

Andrew D. Bowser/MDedge News

Dr. Neil M.H. Graham

Top-line results of QUEST showed that treatment with dupilumab, a fully human anti–IL-4Ra monoclonal antibody, resulted in significantly lower rates of severe asthma exacerbation, along with improved lung function, in patients aged 12 years and older with moderate to severe asthma.

Top-line results of QUEST showed that treatment with dupilumab, a fully human anti–IL-4Ra monoclonal antibody, resulted in significantly lower rates of severe asthma exacerbation, along with improved lung function, in patients aged 12 years and older with moderate to severe asthma.

This retrospective analysis shows that, in adolescents, improvements from baseline to week 12 in forced expiratory volume in 1 second (FEV_1) were significant and at a greater magnitude than in adults, according to Dr. Graham and his coinvestigators.

The improvement over 12 weeks in FEV_1 for adolescents was 0.36 L and 0.27 L, respectively, for the 200- and 300-mg doses of dupilumab (*P* less than .05 vs. placebo for both), Dr. Graham and his coinvestigators reported. In adults, the improvement was 0.12 L.

The annualized exacerbation rate dropped by 46.4% for those adolescents who received 200 mg dupilumab, though there was no treatment effect versus placebo for dupilumab 300 mg; the investigators said the lack of effect in this retrospective analysis could have been caused by imbalances in prior event rates or the small sample size.

A total of 107 out of 1,902 patients in QUEST were adolescents, and of those, 68 were randomly assigned to dupilumab, according to the report. Injection site reaction was the most common adverse event in adolescents in both dosing groups.

Dr. Graham reported disclosures related to his employment with Regeneron. Study coauthors reported disclosures related to Regeneron, AstraZeneca, Sanofi, Teva Pharmaceutical, GlaxoSmithKline, Boehringer Ingelheim, Merck, Genentech, and others.

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SOURCE: Graham NMH et al. CHEST. 2018 Oct. doi: 10.1016/j.chest.2018.08.022.

FDA expands Orkambi indication to CF patients as young as 2 years

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has expanded the indication for Orkambi (lumacaftor/ivacaftor) to include patients who are aged as young as 2 years with cystic fibrosis (CF), according to its manufacturer, Vertex Pharmaceuticals. Specifically, the drug is meant to treat the most common underlying cause of CF – having two copies of the F508del-CFTR mutation – and is the first drug to treat it.

The approval is based on a phase 3, two-part, open-label, multicenter study that assessed various doses in patents aged 2-5 years. The study demonstrated safety and tolerability in that age group equivalent to that seen in older patients. The drug is expected to be available for this age group within 2-4 weeks of this approval.

Available as oral granules in two doses for weight-based dosing (either lumacaftor 100 mg/ivacaftor 125 mg or lumacaftor 150 mg/ivacaftor 188 mg), the compound targets the defective chloride channels responsible for CF; the two halves work together to increase the number of chloride channels on cell surfaces and also improve their function.

Orkambi should be prescribed only for patients with CF who have the dual F508del-CFTR mutation; it is not indicated for other types of CF.

Patients should not take this drug if they are taking drugs such as rifampin, phenytoin, triazolam, or cyclosporine because of possible drug interactions. It can also lead to worsening liver function and elevated blood liver enzymes, increased blood pressure, or cataracts.

The most common side effects include breathing problems, nausea, fatigue, and rash. Full prescribing information is available on the FDA website.

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Quadrivalent flu vaccine okayed for 6 months and up

BY KARI OAKES
MDedge News

The Food and Drug Administration has extended the indication for a quadrivalent influenza vaccine (Afluria, marketed by Seqirus) to include infants and younger children.

The expanded approval now includes persons aged 6-59 months; the quadrivalent vaccine had previously been approved for ages 5 years and up. A trivalent version of the Afluria influenza vaccine also now is indicated for people aged 6 months and up, according to an Oct. 4 communication from the FDA.

A total of 172 pediatric influenza-related deaths occurred in the United States during the 2017-2018 season, representing a new high in nonpandemic influenza seasons. About half of the pediatric influenza deaths occurred in otherwise healthy children, and about 22% of children who died were fully vaccinated, according to the Centers for Disease Control and Prevention, reporting U.S. data from 2010 to 2016.

"As we enter a new flu season, we are reminded of the enormous impact that influenza can have on public health," Seqirus's vice president of medical affairs Gregg Sylvester, MD, said in a press release announcing the extended indication. "Having another option to fight this disease can translate to saved lives and fewer flu-related hospitalizations this season and going forward."

According to the CDC, the 2018-2019 influenza vaccine has been updated to provide a better match – and more protection against – viruses circulating in this influenza season. Specifically, says the CDC, the influenza B Victoria lineage and the influenza A(H3N2) components were updated.

In addition to providing protection against these two strains of influenza, trivalent vaccines for the 2018-2019 season are recommended to include protection against H1N1 influenza as well. Quadrivalent vaccines protect against a second influenza B lineage.

Most people will receive a quadrivalent vaccine this year, according to the CDC.

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NP discharge support benefited ventilator-dependent children

BY TARA HAELLE
MDedge News

REPORTING FROM CHEST 2018 ▪ SAN ANTONIO – Unplanned readmissions declined among tracheostomy/ventilator-dependent children whose discharge process involved a pulmonary nurse practitioner to coordinate continuity of care, a study of more than 70 patients has found.

Despite an increase over time in the rate of discharges, readmissions fell, Sarah Barry, CRNP, of Children's Hospital of Philadelphia (CHOP), said at the annual meeting of the American College of Chest Physicians.

"The technology-dependent pediatric population who is going home with tracheostomy and ventilator dependence is at risk for hospital readmission, and having an advanced practice provider in a continuity role promotes adherence to our standards of practice and improves transition to home," Ms. Barry said in an interview.

She noted previous research showing that 40% of 109 home mechanical ventilation patients discharged between 2003 and 2009 had unplanned readmissions, 28% of which occurred within the first month after discharge.

Nearly two thirds (64%) of those readmissions were related to a pulmonary and/or tracheostomy problem. That study also found that changes in condition management 1 week before discharge, such as medications, ventilator settings, or feeding regimens, were associated with unplanned readmission.

That research "makes us ask ourselves if our readmissions are avoidable and what can we do to get these kids home safe and to keep them home," Ms. Barry told attendees, adding that CHOP was unhappy with their readmission rates.

"Kids were often not making it to their first pulmonary appointment, and it was a burden for these families," she said. "We questioned whether or not having a nurse practitioner in a role to promote adherence to our standards would have a positive impact on our unplanned route."

They evaluated the effect of such an NP on unplanned readmissions among tracheostomy/ventilator-supported children. The NP's role was to track patients, mostly from the progressive care unit, who required a tracheostomy and ventilator and were expected to be discharged home or to a long-term care facility. The NP provided continuity for medical management and coordinated care at discharge.

Tara Haelle/MDedge News

Sarah Barry

"We also do not make changes for 2 weeks before discharge so that we can focus on all the other coordination that goes into getting these kids home," Ms. Barry said.

She reviewed the patients' electronic charts to record time to scheduled follow-up visit, days until hospital readmission, admitting diagnosis

Continued on following page

Community-based therapy improved asthma outcomes in African American teens

BY MADHU RAJARAMAN
MDedge News

A family- and community-based treatment program significantly improved outcomes in African American adolescents with moderate to severe persistent asthma, according to results published in Pediatrics.

In a study of 167 African American patients aged 12-16 years, the 84 randomly assigned to Multisystemic Therapy–Health Care (MST-HC) had greater improvement in forced expiratory volume in 1 second (FEV_1) over time, compared with the 83 patients randomly assigned to family support (FS) therapy (beta = 0.097, $t[164.27] = 2.52$; $P = .01$). Improvements in secondary outcomes also were observed in this group, reported Sylvie Naar, PhD, of Florida State University, Tallahassee, and her coauthors.

They studied African American adolescents with moderate to severe persistent asthma who resided in a home setting with a caregiver and were at high risk for poorly controlled asthma. Families were randomized to either MST-HC (84 patients) or FS (83 patients) based on severity of urgent care use, and follow-up was completed 7 and 12 months after baseline assessment. Families were paid $50 for each assessment.

FEV_1 was the primary outcome. Secondary outcomes were medication adherence, symptom severity and frequency, inpatient hospitalizations, and ED visits. Medication adherence was evaluated via the Family Asthma Management System Scale (FAMSS) and the Daily Phone Diary (DPD). Other outcomes were confirmed via medical records.

Patients in the FS control group received weekly home-based counseling for up to 6 months. Patients in the MST-HC treatment group were first engaged in a motivational session with a therapist and evaluated for asthma management with interviews and observations within the home and community. Once possible contributing factors to poor asthma management (such as medication underuse or low parental monitoring) were identified, targeted interventions such as skills training, behavioral and family therapy, or communication training with school and medical staff were chosen, and treatment goals continually monitored and modified, the authors said.

The mean length of treatment until termination in the MST-HC group was 5 months, and the mean number of sessions was 27. In the FS group, mean length of treatment was 4 months, and the mean number of sessions was 11.

FEV_1 for the MST-HC group improved from 2.05 at baseline to 2.25 at 7 months (a 10% improvement), and to 2.37 (a 16% improvement) at 12 months, compared with an improvement from 2.21 to 2.31 at 7 months (a 4% improvement) and 2.33 (a 5% improvement) at 12 months in the control group, the authors reported.

At 12 months, FAMSS adherence scores improved from 4.19 to 5.24 in the MST-HC group and from 4.61 to 4.72 in the control group.

DPD adherence scores improved from a mean of 0.33 at baseline to 0.69 for the MST-HC group, and from 0.43 to 0.46 in the FS group.

At 12 months, the mean frequency of asthma symptoms in the MST-HC group improved from 2.75 at baseline to 1.43, compared with a decline from 2.67 to 2.58 in the control group. The mean number of hospitalizations in the MST-HC group improved from 0.87 to 0.24, compared with a change from 0.66 to 0.34 in the control group.

The study results are "especially noteworthy because African American adolescents experience greater morbidity and mortality from asthma than white adolescents even when controlling for socioeconomic variables," Dr. Naar and her associates wrote.

Future research should focus on the "transportability" of MST-HC treatment to community settings, which is "ready to be studied in effectiveness and implementation trials."

The study was supported by a National Institutes of Health grant. Coauthor Phillippe Cunningham, PhD, is a co-owner of Evidence-Based Services, a network partner organization that is licensed to disseminate Multisystemic Therapy for drug court and juvenile delinquency settings. The other authors said they have no potential conflicts of interest.

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SOURCE: Naar S et al. Pediatrics. 2018. doi: 10.1542/peds.2017-3737.

Pediatric OSA linked to abnormal metabolic values

BY TARA HAELLE
MDedge News

REPORTING FROM CHEST 2018 ▪

SAN ANTONIO – Obstructive sleep apnea (OSA) in children is associated with an abnormal metabolic profile, but not with body mass index, according to new research.

"Screening for metabolic dysfunction in obese children with obstructive sleep apnea can help identify those at risk for cardiovascular complications," Kanika Mathur, MD, of the Albert Einstein College of Medicine and the Children's Hospital at Montefiore, both in New York, told attendees at the annual meeting of the American College of Chest Physicians. Dr. Mathur explained that no consensus currently exists regarding routine cardiac evaluation of children with OSA.

"The American Academy of Pediatrics does not mention any sort of cardiac evaluation in children with OSA while the most recent guidelines from the American Heart Association and the American Thoracic Society recommend echocardiographic evaluation in children with severe obstructive sleep apnea, specifically to evaluate for pulmonary hypertension and right ventricular dysfunction," Dr. Mathur said.

OSA's association with obesity, diabetes, and hypertension is well established in adults. It is an independent risk factor for coronary artery disease, heart failure, stroke, and atrial fibrillation, and research has suggested OSA treatment can reduce cardiovascular risk in adults, Dr. Mathur explained, but few data on children exist.

"Despite similar degrees of obesity and systemic blood pressure, pediatric patients with OSA had significantly higher diastolic blood pressure, heart rate, and abnormal metabolic profile, including elevated alanine transaminase, aspartate transaminase, triglycerides and hemoglobin A_{1c}," they found.

Their study included patients aged 3-21 years with a BMI of at least the 95th percentile who had undergone sleep study and an echocardiogram at the Children's Hospital at Montefiore between November 2016 and November 2017.

They excluded those with comorbidities related to cardiovascular morbidity: heart disease, neuromuscular disease, sickle cell disease, rheumatologic diseases, significant cranial facial abnormalities, tracheostomy, and any lung disease. However, 7% of the patients had trisomy 21.

Among the 81 children who met their criteria, 37 were male and 44 were female, with an average age of 14 years old and a mean BMI of 39.4 kg/m^2 (mean BMI *z* score, 2.22). Most of the patients (53.1%) had severe OSA (apnea-hypopnea index of at least 10), 21% had moderate OSA (AHI, 5-9.9), 12.3% had mild OSA (AHI. 2-4.9), and 13.6% did not have OSA. The median AHI of the children was 10.3.


Tara Haelle/MDedge News
Dr. Kanika Mathur

BMI, BMI *z* score, systolic blood pressure *z* score, oxygen saturation and cholesterol (overall and both HDL and LDL cholesterol levels) did not significantly differ between children who had OSA and those who did not, but diastolic blood pressure and heart rate did. Those with OSA had a diastolic blood pressure of 65 mm Hg, compared with 58 mm Hg without OSA (P = .008). Heart rate was 89 bpm in the children with OSA, compared with 78 bpm in those without (P = .004).

The children with OSA also showed higher mean levels of several other metabolic biomarkers:

- Alanine transaminase 26 U/L with OSA vs. 18 U/L without (P = .01).
- Aspartate transaminase 23 U/L with OSA vs. 18 U/L without (P = .03).
- Triglycerides 138 mg/dL with OSA vs 84 mg/dL without (P = .004).
- Hemoglobin A_{1c} 6.2% with OSA vs. 5.4% without (P = .002).

Children with and without OSA did not have any significant differences in left atrial indexed volume, left ventricular volume, left ventricular ejection fraction, or left ventricular mass (measured by M-mode or 5/6 area length formula). Though research has shown these measures to differ in adults with and without OSA, evidence on echocardiographic changes in children has been conflicting, Dr. Mathur noted.

The authors also conducted subanalyses according to OSA severity, but BMI, BMI *z*-score, systolic or diastolic blood pressure *z*-score, heart rate, and oxygen saturation did not differ between those with mild OSA vs moderate or severe OSA.

The study had several limitations, including its retrospective cross-sectional nature at a single center and its small sample size. "We have a wide variety of ages, which could represent different pathophysiology of the associated metabolic dysfunction in these patients," she said.

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SOURCE: CHEST 2018. https://journal.chestnet.org/article/S0012-3692(18)31935-4/fulltext.

Continued from previous page

at readmission, and length of stay after readmission. With consideration for the time needed for transition into this new process, the population studied was assessed within three cohorts.

The first cohort comprised the 22 children discharged between April 2016 and March 2017, the full year before a pulmonary NP began coordinating the discharge process. These patients averaged 1.8 discharges per month with an initial follow-up of 2-12 weeks.

Just over a quarter (27%) of the first cohort were readmitted before their scheduled follow-up, ranging from 2 to 25 days after discharge. Five percent were readmitted within a week of discharge, and 27% were readmitted within a month; their average length of stay was 13 days after readmission. Most (83%) of these discharges were respiratory related while the other 17% were gastrointestinal related.

The second cohort involved the 11 patients discharged between April 2017 and August 2017, the first 5 months after a pulmonary NP began overseeing the discharge readiness process.

An average 2.2 discharges occurred monthly with 2-8 weeks of initial postdischarge follow-up. Though nearly half these children (45%) were readmitted before their scheduled follow-up, their length of stay was shorter, an average of 11 days.

Readmission within a week after discharge occurred among 27% of the children, and 45% of them were readmitted within a month of discharge. Sixty percent of these patients were readmitted for respiratory issues, compared with 40% with GI issues.

The third cohort included all 38 patients discharged from September 2017 to August 2018, the year after a pulmonary NP had become fully established in the continuity role, with an average 3.2 discharges occurred per month. Readmission rates were considerably lower: Eighteen percent of patients were readmitted before their scheduled follow-up appointment, which ranged from 1 to 13 weeks after discharge.

Five percent were readmitted within a week of discharge, and 24% were readmitted within a month, ranging from 1 to 26 days post discharge. But length of stay was shorter still, at an average of 9 days.

Ms. Barry's colleague, Howard B. Panitch, MD, also on the staff of CHOP, noted during the discussion that the NP's role is invaluable in "keeping the inpatient teams honest.

"She reminds her colleagues in critical care that you can't make that ventilator change when on your way out the door or very close to discharge."

Ms. Barry had no disclosures. No external funding was noted.

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SOURCE: Barry S et al. CHEST 2018 Oct. doi: 10.1016/j.chest.2018.08.743.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: I am giving a standing ovation for this study from CHOP! The home ventilator population is extremely fragile and our group at Helen DeVos Children's Hospital also has many criteria for a new ventilator discharge, including no ventilator changes for 2 weeks prior to discharge. This group of patients has become increasingly complex and on higher ventilator settings than a decade ago (in my opinion). There is also a crisis regarding a shortage of qualified private duty nurses because their salaries are woefully inadequate.

COPD: Triple trumps dual therapy regardless of reversibility

BY ANDREW D. BOWSER
MDedge News

REPORTING FROM CHEST 2018 ▪ SAN ANTONIO – Regardless of COPD patients' bronchodilator reversibility at baseline, triple therapy with fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) significantly reduced the exacerbation rate versus dual therapies, according to a recent retrospective analysis of a randomized, double-blind study.

Andrew D. Bowser/MDedge News

Dr. Robert Wise

FF/UMEC/VI, a triple-therapy combination of an inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting beta$_2$ agonist (ICS/LAMA/LABA), was superior to both LAMA/LABA and ICS/LABA combinations in reducing the rate of moderate to severe exacerbation and lung function, the analysis showed.

The ICS/LAMA/LABA combination, compared with LAMA/LABA, also significantly reduced the rate of severe exacerbations and time to first moderate to severe exacerbations in both reversible and nonreversible patients, Robert Wise, MD, FCCP, of Johns Hopkins University, Baltimore, said at the annual meeting of the American College of Chest Physicians.

The analysis was based on data from IMPACT, an international, randomized, 52-week study that included more than 10,000 patients with symptomatic COPD, of whom 18% demonstrated reversibility at screening.

"The results across both reversibility subgroups are consistent with those observed in the intention-to-treat or overall study population and show a similar benefit-to-risk profile of the triple therapy across different subtypes based on bronchodilator reversibility," Dr. Wise told attendees in a podium presentation.

Reversibility was defined as a difference between pre- and postalbuterol assessment of FEV_1 of equal to or greater than 12% and equal to or greater than 200 mL at screening, Dr. Wise said.

Reversible patients had a 40% reduction in the rate of moderate to severe exacerbations for FF/UMEC/VI versus UMEC/VI, while nonreversible patients had a 21% reduction, according to data reported in the meeting abstract.

Severe exacerbation rates dropped by 44% and 31%, respectively, in the reversible and nonreversible patients for triple versus dual therapy, he added.

Triple therapy reduced time to first moderate to severe exacerbation versus dual therapy by 25.6% in reversible and 13.6% in nonreversible COPD patients, the data showed.

The FF/UMEC/VI combination also demonstrated improvements versus UMEC/VI in time to first severe exacerbation for both the reversible and nonreversible groups, as well as improved quality of life in both groups as measured by the St. George Respiratory Questionnaire (SGRQ) in both groups.

Results were somewhat different when comparing the FF/UMEC/VI combination with the FF/VI – the ICS/LABA combination – in this post hoc analysis.

Triple therapy did reduce moderate to severe exacerbations and improved lung function regardless of baseline reversibility. However, for the reversible patients, ICS/LAMA/LABA versus ICS/LABA did not significantly reduce risk specifically of severe exacerbations, time to first moderate to severe exacerbation, or increase odds of being an SGRQ responder, Dr. Wise said.

Nonetheless, these findings taken together imply that this ICS/LAMA/LABA combination provides clinically relevant improvements versus dual therapy across a range of important outcomes regardless of baseline reversibility, according to Dr. Wise and colleagues.

Dr. Wise and coinvestigators provided disclosures related to Boehringer Ingelheim, BTG, Chiesi, GlaxoSmithKline, Mereo, Novartis, PneumRx, Prometic, and Pulmonx.

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SOURCE: Wise R et al. Chest. 2018 Oct. doi: 10.1016/j.chest.2018.08.662.

Suicide risk doubled in COPD patients taking benzodiazepines

BY NICOLA GARRETT
MDedge News

Patients with chronic obstructive pulmonary disease who are taking benzodiazepines have a more than doubled risk of suicide, compared with similar patients not taking the medications, according to the results of research published in the Annals of the American Thoracic Society.

Benzodiazepines were often prescribed for people with COPD to manage chronic symptoms of anxiety, dyspnea, and insomnia, Lucas M. Donovan, MD, of the division of pulmonary, critical care, and sleep medicine at the University of Washington, Seattle, and his colleagues noted.

However, there were documented concerns that the class of medications could lead to respiratory depression and increase the risk of exacerbations. One particular area of controversy was the long-term use of benzodiazepines, with up to 40% of COPD patients using them on a long-term basis against the advice of clinical guidelines.

They noted that benzodiazepines were often used to treat dyspnea, a fact which had the potential to introduce confounding into research as the symptom was linked to increased mortality, nonfatal respiratory events, and suicidal ideation.

"One strategy to reduce confounding is to examine risks of benzodiazepines in a sample of patients who are likely to be prescribed benzodiazepines to manage nonrespiratory symptoms, and patients with comorbid posttraumatic stress disorder (PTSD) provide one such opportunity," they wrote.

The research team used data from a nationwide cohort of patients with comorbid COPD and PTSD identified from the Veteran's Health Administration administrative data between 2010 and 2012. Of 44,555 patients with COPD and PTSD included in the analysis, 29,237 had no benzodiazepine use, 4,782 patients had short-term use (less than 90 days' supply), and 10,536 patients had long-term use (equal to or more than 90 days).

With a matched sample of 19,552 patients who did not receive benzodiazepines, the risk of all-cause mortality was not significantly different among those with long-term benzodiazepine use relative to those without use (hazard ratio, 1.06; 95% confidence interval, 0.95-1.18).

Among matched and unmatched patients, short-term benzodiazepine use (HR, 1.16; 95% CI, 1.05-1.28), but not long-term use (HR, 1.03; 95% CI, 0.94-1.13) was associated with increased mortality.

They saw a substantially greater risk for death by suicide among those with long-term benzodiazepine use (HR, 2.33; 95% CI, 1.14-4.79). After adjustment of all analyses by propensity score for any benzodiazepine exposure, individuals with both short-term and long-term use of benzodiazepines were at a greater risk of suicide (short-term: HR, 2.46; 95% CI, 1.16-5.26; long-term: HR, 2.35; 95% CI, 1.33-4.16).

Concomitant opioid use was associated with increased risk of overall mortality (HR for every 10 days of exposure, 1.02; 95% CI, 1.01-1.02) and accidental overdose (HR, 1.11; 95% CI, 1.04-1.18). Individuals with long-term benzodiazepine use also had a higher rate of psychiatric admissions (incidence rate ratio, 1.37; 95% CI, 1.14-1.65).

The researchers concluded that, overall, their results did not suggest that discontinuation of long-term benzodiazepines would reduce overall mortality or death related to obstructive lung disease or overdose.

However, they advised that providers consider discontinuing benzodiazepines in patients already at high suicide risk as well as avoiding the concomitant use of opioids.

The study was funded by several National Institutes of Heath grants, the ASPIRE Fellowship, and a VA grant.

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SOURCE: Donovan LM et al. Ann Am Thorac Soc. 2018 Oct 12. doi: 10.1513/AnnalsATS.201802-145OC.

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Pulmonary circulation disorders predict need for NIV

BY TARA HAELLE
MDedge News

FROM THE JOURNAL *CHEST*® ▪ COPD patients with pulmonary circulation disorders were more than four times more likely to need invasive ventilation after noninvasive ventilation (NIV) failed for acute exacerbations, found a new study.

Patients with fluid and electrolyte abnormalities or alcohol abuse also had a greater risk of escalating beyond NIV for exacerbations, according to the findings.

"Patients with these underlying conditions should be monitored closely, especially individuals with existing pulmonary disorders as they are at highest risk," Di Pan, DO, of Icahn School of Medicine at Mount Sinai, New York, reported at annual meeting of the American College of Chest Physicians.

The researchers used the 2012-2014 Nationwide Inpatient Sample database to retrospectively analyze data from 73,480 patients, average age 67.8 years, who had a primary diagnosis of COPD exacerbation and who had received initial treatment with NIV in their first 24 hours after hospitalization. The report is in CHEST (2018 Oct. doi: 10.1016/j.chest.2018.08.340).

The researchers examined associations between NIV failure and 29 Elixhauser comorbidity measures to identify what clinical characteristics might predict the need for invasive ventilation. They defined NIV failure as requiring intubation at any time within 30 days of admission.

Pulmonary circulation disorders emerged as the strongest predictor of the need for intubation, with a fourfold increase in relative risk (hazard ratio 4.19, *P* less than .001). Alcohol abuse (HR 1.85, *P* = .01) and fluid and electrolyte abnormalities (HR 1.3, *P* less than .001) followed as additional factors associated with NIV failure. The latter included irregularities in potassium or sodium, acid-base disorders, hypervolemia and hypovolemia.


DR. PAN

Among the 3,740 patients with alcohol abuse, additional statistically significant associations with intubation included a slightly higher mean age, female sex, and the mean Charlson comorbidity index. Mean age of those requiring intubation in this group was 62.28 years, compared 61.47 years among those in whom NIV was adequate (*P* = .03). Among those intubated, 30.2% of the patients were female, compared with 26.3% female patients in the nonintubated group.

Among the 26,150 patients with fluid, electrolyte, and acid-base disturbances, younger patients were more likely to require intubation: The average age of those needing intubation was 67.23 years, compared with 69.3 years for those nonintubated (*P* less than .001). While a higher Charlson index (2.83 vs. 2.53) was again correlated with greater risk of needing intubation (*P* less than .001), males were now more likely to require intubation: 58.1% of those without intubation were female, compared with 53.9% of those needing intubation (*P* less than .001).

Within the 890 patients with pulmonary circulation disorders, mean age was 68.03 years for intubation and 70.77 years for nonintubation (*P* less than .001). In this group, 56.4% of the patients requiring intubation were female, compared to 47.9% of patients not intubated. The average Charlson index was lower (3.11) among those requiring intubation than among those not needing it (3.57, *P* less than .001).

The findings were limited by the lack of disease severity stratification and use of now-outdated ICD-9 coding. The researchers also lacked detailed clinical data, such as lab values, imaging results, and vital signs, and there was a broad variation within the diagnoses of the also-broad Elixhauser comorbidity index.

"For the next steps, we can do a stratified analysis" to identify which specific pulmonary circulation diseases primarily account for the association with intubation, Dr. Pan said.

No external funding was noted. The authors reported having no disclosures.

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SOURCE: Pan D et al. CHEST 2018. https://doi.org/10.1016/j.chest.2018.08.340.

FDA approves Xofluza for treatment of influenza

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza in people aged 12 years or older who have been symptomatic for 48 hours or less.

The FDA approval is based on results from two randomized, clinical trials. In both trials, patients who received Xofluza experienced a shorter duration until alleviation of symptoms, compared with patients who received a placebo. In the second trial, patients who received Xofluza and patients who received another approved antiviral influenza medication experienced similar durations until symptom alleviation.

"When treatment is started within 48 hours of becoming sick with flu symptoms, antiviral drugs can lessen symptoms and shorten the time patients feel sick Having more treatment options that work in different ways to attack the virus is important because flu viruses can become resistant to antiviral drugs," Debra Birnkrant, MD, director of the Division of Antiviral Products in the FDA's Center for Drug Evaluation and Research, said in a press release.

The most common adverse events associated with Xofluza were diarrhea and bronchitis.

"This is the first new antiviral flu treatment with a novel mechanism of action approved by the FDA in nearly 20 years," said FDA Commissioner Scott Gottlieb, MD.

"With thousands of people getting the flu every year, and many people becoming seriously ill, having safe and effective treatment alternatives is critical. This novel drug provides an important, additional treatment option," Gottlieb added.

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Adjuvanted flu vaccine reduces hospitalizations in oldest old

BY JIM KLING
MDedge News

SAN FRANCISCO – An adjuvanted trivalent flu vaccine cuts the risk of hospitalizations in nursing home residents by about 6%, according to a new study presented at an annual scientific meeting on infectious diseases.

"It's one thing to say you have a more immunogenic vaccine; it's another thing to be able to say it offers clinical benefit, especially in the oldest old and the frailest frail," says Stefan Gravenstein, MD, professor of medicine and health services, policy and practice at the Brown University School of Public Health, Providence, R.I. Dr. Gravenstein presented a poster outlying a randomized, clinical trial of the Fluad vaccine in nursing homes.

The study randomized the nursing homes so that some facilities would offer Fluad as part of their standard of care. The design helped address the problem of consent. Any clinical trial that requires individual consent would likely exclude many of the frailest patients, leading to an unrepresentative sample. "So if you want to have a generalizable result, you'd like to have it applied to the population the way you would in the real world, so randomizing the nursing homes rather than the people makes a lot of sense," said Dr. Gravenstein.

Dr. Gravenstein chose to test the vaccine in nursing home residents, hoping to see a signal in a population in which flu complications are more common. "If you can get a difference in a nursing home population, that's clinically important, that gives you hope that you can see it in all the other populations, too," he said.

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SOURCE: Gravenstein S et al. IDWeek 2018, Abstract 996.

New valve to treat emphysema-related hyperinflation improved lung function, dyspnea

BY TED BOSWORTH
MDedge News

PARIS – A one-way endobronchial valve placed in the lungs of emphysema patients with hyperinflation provides acceptable safety and clinically significant improvement in lung function at 12 months, according to results from a multicenter trial presented as a late-breaker at the annual congress of the European Respiratory Society.

Six-month results have been presented previously, but the 12-month results suggest that lung volume reduction associated with placement of the valves provides "durable effectiveness in appropriately selected hyperinflated emphysema patients," according to Gerard Criner, MD, FCCP, chair of the thoracic medicine department at Temple University, Philadelphia.

In this randomized controlled trial, called EMPROVE, 172 emphysema patients with severe dyspnea were randomized in a 2:1 fashion to receive a proprietary endobronchial valve or medical therapy alone. The valve, marketed under the brand name Spiration Valve System (SVS), is currently indicated for the treatment of air leaks after lung surgery.

"The valve serves to block airflow from edematous lungs with the objective of blocking hyperinflation and improving lung function," Dr. Criner explained. The valves are retrievable, if necessary, with bronchoscopy.

High-resolution computed tomography (HRCT) was used to identify emphysema obstruction and target valve placement to the most diseased lobes. The average number of valves placed per patient was slightly less than four.

When reported at 6 months, the responder rate, defined as at least 15% improvement in forced expiratory volume in 1 second (FEV_1) was 36.8% and 10% in the SVS and control groups, respectively, a difference of 25.7% that Dr. Criner reported as statistically significant although he did not provide *P* values. At 12 months, the rates were 37.2% and 5.1%, respectively.

Thoracic adverse events were higher at both 6 months (31% vs. 11.9%) and 12 months (21.4% vs. 10.6%) in the treatment group relative to the control group. At 6 months, pneumothorax, which Dr. Criner characterized as "a recognized marker of target lobe volume reduction," was the only event that occurred significantly more commonly (14.2% vs. 0%) in the SVS group.

Between 6 and 12 months, there were no pneumothorax events in either arm. The higher numerical rates of thoracic adverse events in the treatment arm were acute exacerbations (13.6% vs. 8.5%) and pneumonia in nontreated lobes (7.8% vs. 2.1%), not statistically different.

At 6 months, there was a numerically higher rate of all-cause mortality in the treatment group (5.3% vs. 1.7%) but the rate was numerically lower between 6 and 12 months (2.9% vs. 6.4%).

A significant reduction in hyperinflation favoring valve placement was accompanied by improvement in objective measures of lung function, such as FEV_1, and dyspnea, as measured with the Modified Medical Research Council (mMRC) Dyspnea Scale, at 6 and 12 months. These improvements translated into persistent quality-of-life benefits as measured with the St. George Respiratory Questionnaire (SGRQ). At 12 months, the SGRQ changes from baseline were a 5.5-point reduction and a 4-point gain in the treatment and control groups, respectively. This absolute difference of 9.5 points is slightly more modest than the 13-point difference at 6 months (–8 vs. +5 points), but demonstrates a durable effect, Dr. Criner reported.

According to Dr. Criner, EMPROVE reinforces the principle that HRCT is effective "for selecting the lobe for therapy and which patients may benefit," but the most important message from the 12-month results is persistent clinical benefit.

Dr. Criner reports financial relationships with Olympus, the sponsor of this trial.

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Achieving meaningful functional and patient-centered outcomes using minimally invasive lung volume reduction techniques may prove extremely beneficial in the lives of many patients with heterogenous emphysema. The outcomes of this trial, as well as the Zephyr valve trial published earlier, suggest that this concept is becoming a reality. There are several cautionary points to recognize: (1) Patient selection is extremely important, with special emphasis on offering this treatment only to patients without signs of significant collateral ventilation to the target lobe; and (2) as with many new therapies with the potential for adverse outcomes, postapproval surveillance for adverse events should be encouraged given that these event rates in the general population are often much higher than in the controlled setting of a clinical study.

COPD opposites: Utah and West Virginia

BY RICHARD FRANKI
MDedge News

New estimates of chronic obstructive pulmonary disease (COPD) prevalence may have Utah and six other states breathing a sigh of relief.

West Virginia was at the other end of the continuum with the highest prevalence of COPD in the country.

The Beehive State has the lowest prevalence of COPD in the country at 2,710 per 100,000 population, while the Mountain State tops the charts at 11,130 cases of COPD per 100,000, according to estimates from the American Lung Association. (Crude rates were calculated by MDedge News using the ALA's estimates for total persons with COPD in each state and Census Bureau estimates for population.)

Other states with freer-breathing residents include Minnesota, which was just behind Utah with an estimated rate of 3,000 per 100,000 population, Hawaii (3,182), Colorado (3,334), and California (3,409). West Virginia's rate, however, seems to be an outlier.

The state with the next-highest rate, Kentucky, has a calculated COPD prevalence of 8,890 per 100,000 population, followed by Tennessee at 7,880, Alabama at 7,400, and Arkansas at 7,330, using the ALA's estimates, which were based on data from the 2016 Behavioral Risk Factor Surveillance System survey.

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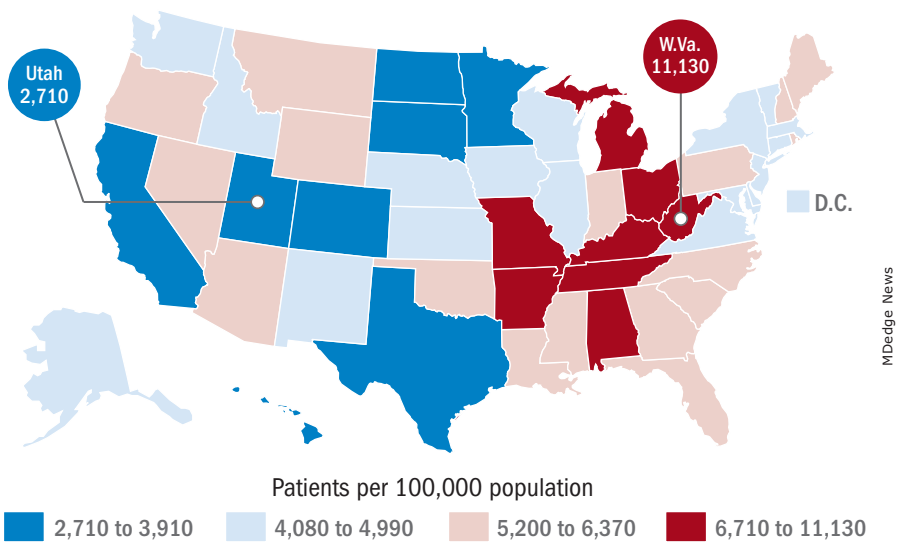
Estimated chronic obstructive pulmonary disease prevalence



Note: Based on data from the 2016 Behavioral Risk Factor Surveillance System survey.
Source: American Lung Association

Oral drug successful in preventing angioedema attacks

BY JENNIE SMITH
MDedge News

An experimental agent reduced swelling episodes markedly in patients with hereditary angioedema, according to results from a phase 2 randomized, dose-ranging, placebo-controlled trial.

The drug BCX7353, developed by BioCryst Pharmaceuticals, is taken orally and works by inhibiting plasma kallikrein, an enzyme overexpressed in hereditary angioedema, a rare genetic disease that causes severe tissue swelling. In research published July 26 in the New England Journal of Medicine (2018;379:352-62), Emel Aygören-Pürsün, MD, of Goethe University in Frankfurt, Germany, and colleagues, randomized 77 patients with type 1 or II hereditary angioedema and a pattern of frequent attacks to one of four doses of daily BCX7353, or placebo, for 28 days.

Dr. Aygören-Pürsün's group found significant reductions in the number of monthly attacks for the three doses used in the study, with the best response seen in the group receiving the second-lowest dose of 125 mg. These patients saw a reduction of 73.8% (*P* less than .001) in monthly attacks from baseline, and 43% of patients receiving that dose had no attacks during the study period. The higher-dose groups saw more adverse events and apparently less efficacy, with the 250-mg dose associated with a reduction in attacks of 44.6% (*P* = .01), and for the 350-mg group, a 45.5% reduction (*P* = .006).

Patients receiving the lowest dose in the study, 62.5 mg, saw a small (about 10%) reduction in attacks that did not reach statistical significance. Gastrointestinal adverse events were reported in the two highest-dose groups, and three patients in the 350-mg group dropped out after reporting serious adverse events, including one liver disorder considered likely related to the trial regimen.

The efficacy of the highest doses "was probably masked by gastrointestinal adverse events that may have been misattributed as early symptoms of abdominal angioedema attacks," the investigators wrote in their analysis. Improvements in angioedema-related quality of life scores, a secondary trial endpoint, reached statistical significance for the 125- and 250-mg doses.

The drug BCX7353 is taken orally and works by inhibiting plasma kallikrein, an enzyme overexpressed in hereditary angioedema, a rare genetic disease that causes severe tissue swelling.

The authors cautioned that the safety of long-term dosing would need to be studied in longer-term trials.

The study was sponsored by the drug manufacturer, BioCryst Pharmaceuticals. All of the study's authors, including the lead author, disclosed financial relationships in the form of grant support, fees, or employment with the study sponsor.

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SOURCE: Aygören-Pürsün E et al. N Engl J Med. 2018;379:352-62.

Early supportive care cuts costs for cancer patients

BY ANDREW D. BOWSER
MDedge News

PHOENIX – By starting supportive measures early in the care of cancer patients undergoing curative treatment, a cancer center cut costs, emergency department visits, and admissions, a researcher said at symposium on quality care sponsored by the American Society of Clinical Oncology.

The supportive care pathway resulted in double-digit decreases in admissions and an opportunity cost savings of $1,500 per patient, reported Christopher D. Koprowski, MD, MBA, of Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System, Newark, Del.

Although satisfaction hasn't been measured yet, anecdotal reports suggest the patient experience has

improved because of the multidisciplinary program, which included mandatory supportive care screening and enhancements to computer systems, said Dr. Koprowski, who is director of quality and safety at the cancer center.

"From all outward signs, the patients are extraordinarily grateful in this program," Dr. Koprowski said in an interview. "I just had one who said that being seen at the same time by all these people just makes things so much easier."

The Supportive Care of Oncology Patients (SCOOP) clinical pathway, introduced in November 2016, includes palliative and supportive care service screening that occurs during the multidisciplinary visit. The pathway incorporates a checklist integrated into a nurse navigator information system to support care standardization, according to Dr. Koprowski.

Also added were "flags" in the inpatient information system that trigger alerts to navigators, oncologists, and the supportive care service whenever a patient in the SCOOP pathway is admitted, discharged, or seen in the emergency room, he said.

Enrollment in SCOOP was limited to lung, esophageal, head and neck, and colorectal cancer patients receiving concurrent radiation and chemotherapy. Out of approximately 200 eligible patients in the first year, about half entered the clinical pathway, according to Dr. Koprowski.

The supportive care pathway resulted in double-digit decreases in admissions and an opportunity cost savings of $1,500 per patient. Admissions were 25% for the SCOOP patients and 34% of non-SCOOP patients, and readmissions were seen in 20% versus 32% of those groups.

For that first year, 32% of SCOOP patients had ED visits, compared with 54% of combined modality patients who did not enter the pathway, Dr. Koprowski reported.

Similarly, admissions were 25% for the SCOOP patients and 34% of non-SCOOP patients, and readmissions were seen in 20% versus 32% of those groups, respectively.

These findings are much like what has been seen when early supportive care is introduced in patients with more advanced disease, according to Dr. Koprowski.

He said the SCOOP program was partly inspired by a study in the New England Journal of Medicine showing that patients with advanced non–small cell lung cancer who received early palliative care had longer survival despite less-aggressive care, including reduced use of chemotherapy, at the end of life.

"Early-stage patients aren't that much different if they are being treated very aggressively with combined modality chemotherapy and radiation," he said. "The treatment is very, very tough on people."

Dr. Koprowski and his coinvestigators had no relationships to disclose relevant to the research presented at the ASCO symposium.

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SOURCE: Koprowski CD et al. 2018 ASCO Quality Care Symposium, Abstract 142.

NELSON trial: CT screening reduces lung cancer deaths

BY SHARON WORCESTER
MDedge News

TORONTO – Computed tomography screening among asymptomatic men at high risk for lung cancer reduced lung cancer deaths by a highly statistically significant 26% at 10 years, according to the results of the NELSON trial.

The findings from this large trial in 15,792 individuals at risk for lung cancer support those of the National Lung Screening Trials [NLST], published in 2011," said Harry de Koning, MD, who presented the findings at the World Conference on Lung Cancer.

Participants (majority men) from the Netherlands and Belgium aged 50-74 years with at least a 20–pack-year smoking history were randomized to CT screening at baseline, 1, 3, and 5.5 years after randomization, or to a control group that received usual care.

Sharon Worcester/MDedge News

Dr. Harry de Koning, Erasmus Medical Center

Overall 157 lung cancer deaths occurred in the screening arm vs. 250 in the control arm. Detection rates varied between 0.8% and 1.1% across screenings (0.9% overall), and the positive predictive value of screening was 41%, Dr. de Koning of Erasmus Medical Center, Rotterdam, the Netherlands, reported at the recent by the International Association for the Study of Lung Cancer.

Notably, 69% of the 243 lung cancers detected by screening were stage 1A or 1B, compared with 10%-12% detected at stage 4 in about 50% of control patients based on registry data in the Netherlands. Additionally, an analysis of a subset of those patients with lung cancer showed a significant threefold increase in surgical treatment among the screened patients vs. those in the control arm who developed lung cancer (67.7% vs. 24.5%).

"There's huge importance of this early detection in the screening arm," Dr. de Koning said.

CT screening reduced the risk of death from lung cancer by 9%-41% in men over the course of the study, with an overall reduction of 26% at 10 years, and in women, the relative mortality reduction varied from 39% to 61% at different years of follow-up, he said, noting that this suggests a "significant and even larger reduction" in women.

Participants' records were linked with national registries with 100% coverage regarding cancer diagnosis and date and cause of death, and medical records for deceased lung cancer patients were reviewed by a blinded expert panel through 2013, and for the remaining study years cause of death as reported by Statistics Netherlands was used. Compliance among those randomized to the screening group was 86%, Dr. de Koning said.

"These findings show that CT screenings are an effective way to assess lung nodules in people at high risk for lung cancer, often leading to detection of suspicious nodules and subsequent surgical intervention at relatively low rates and with few false positives, and can positively increase the chances of cure in this devastating disease," Dr. de Koning said in a press statement.

He noted, "It is the second-largest trial in the world, with an even more favorable outcome than the first trial, the NLST, showed. These results should be used to inform and direct future CT screening in the world."

During a press briefing, in response to a question about whether lung cancer screening should be offered more widely, he said that yes, countries – including the United States – should take note that "now two large-scale trials show large benefit."

Dr. de Koning reported having no disclosures.

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VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: While the National Lung Cancer Screening Trial (NLST) demonstrated relative reduction in lung cancer mortality for patients undergoing low-dose CT scanning, uptake of lung cancer screening (LCS) in the US has been very low. The very much anticipated results of the NELSON trial were reported in abstract form at the recent World Lung Conference in Toronto and not only did the results confirm the benefits of LCS in high-risk individuals, it showed even larger reductions in lung cancer mortality.

The trial enrolled 15,792 patients, 84% men, with slightly younger age and less tobacco history at start of screening compared with NLST. The interval of screening was different (not yearly as in the NLST) and the follow-up was longer (10 years). Reduction in lung cancer mortality was seen in both men and women, 26% and 39%-61% respectively. Several important aspects of the trial included centralized reading of CT images, monitoring of lung nodule volume and nodule doubling time, and follow-up through national registries.

The results are impactful because now there is irrefutable evidence for realization of LCS based on two large randomized controlled trials. LCS implementation remains challenging due to multiple barriers at various levels including provider, patient, and healthcare system. Multiple interventions including but not limited to ongoing education for providers and eligible individuals, improved access to screening facilities/programs, decreased stigma and nihilism, structured guideline-based management of screen-detected nodules to minimize harms, and institutional/hospital support for the multidisciplinary infrastructure are needed.

Without doubt, if implemented correctly, LCS is the intervention, along with tobacco cessation, that is likely to have the greatest impact on lung cancer mortality.

NELSON: Scanning for lung cancer

windcatcher/Thinkstock

"CT screenings are an effective way to assess lung nodules in people at high risk for lung cancer ... and can positively increase the chances of cure in this devastating disease."

Source: Harry de Koning, MD

MDedge News

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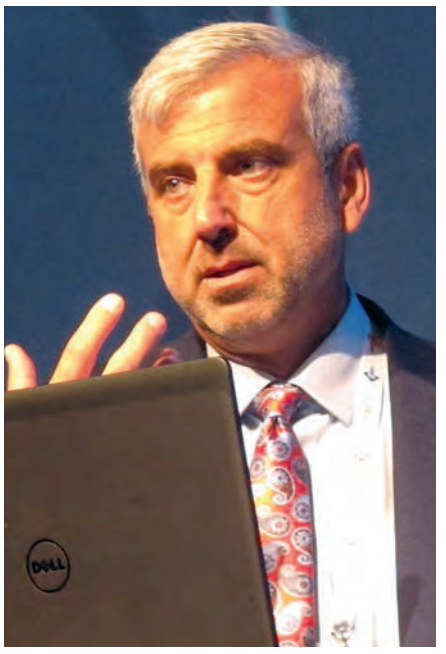
PACIFIC trial: Durvalumab improves both overall and progression-free survival in stage III NSCLC

BY SHARON WORCESTER
MDedge News

TORONTO – The programmed death-ligand 1 (PD-L1) inhibitor durvalumab significantly improves overall survival in patients with stage III unresectable non–small cell lung cancer without progression after chemoradiotherapy, according to updated results from the global phase 3 PACIFIC study.

The findings, presented at the World Conference on Lung Cancer, follow a prior report from the study showing improved progression-free survival (PFS) in durvalumab-treated patients (stratified hazard ratio, 0.52), and together these survival benefits mark the first major advance in this disease setting in decades," Scott J. Antonia, MD, reported at the conference, sponsored by the International Association for the Study of Lung Cancer.

"The fact is this is a new standard-of-care treatment for the patients with this disease," he said, adding that "in all likelihood we are improving the cure rate for the patients with this disease."



Dr. Scott J. Antonia

Dr. Frances Shepherd

Photos Sharon Worcester/MDedge News

The findings were published simultaneously in the New England Journal of Medicine.

Overall survival at a median follow-up of 25.2 months in 473 patients randomized to receive durvalumab was significantly greater than among 236 who received placebo (stratified HR, 0.68; median survival not reached vs. 28.7 months in the groups, respectively), said Dr. Antonia of the H. Lee Moffitt Cancer Center and Research Institute, and professor of oncologic sciences at the University of South Florida, Tampa.

Durvalumab also improved overall survival in all prespecified subgroups, and PFS was similar to that in previous reports (stratified HR, 0.51; median of 17.2 vs. 5.6 months with durvalumab and placebo, respectively), he said, noting that "interestingly, patients who were nonsmokers did benefit from durvalumab."

This is notable because prior research suggests that never-smokers with advanced-stage cancer have less of a chance of responding to immunotherapy (although they should still be offered immunotherapy), he explained.

"Also interestingly, it appears as if cisplatin was the better drug to use in the conventional therapy portion of the treatment," he said.

Durvalumab also provided continued improvement vs. placebo in time to death or distant metastasis (stratified HR, 0.53), time to second progression (stratified HR, 0.58), time to first subsequent therapy or death (stratified HR, 0.58), and time to second subsequent therapy or death (stratified HR, 0.63).

Study subjects were patients with World Health Organization Performance Status scores of 0 or 1 with any PD-L1 tumor status, who received at least two cycles of conventional standard-of-care platinum-based chemoradiotherapy (CRT). They were randomized between May 2014 and April 2016 – at 1-42 days after CRT – to receive intravenous durvalumab at a dose of 10 mg/kg given intravenously every 2 weeks or placebo, and were stratified by age, gender, and smoking history.

Durvalumab was well tolerated; 30.5% and 26.1% of treatment and placebo patients, respectively, had grade 3/4 adverse events, and 15.4% and 9.8%, respectively, discontinued because of adverse events.

"There were no new safety signals with this longer follow-up," Dr. Antonia said.

After study treatment ended, 41% and 54% in the groups, respectively, received additional anticancer therapy, and 8% and 22.4%, respectively, received additional immunotherapy, he noted.

The results are not only statistically significant, but clinically meaningful, and they offer new hope for patients with a disease that, in those who receive chemoradiotherapy, has a 3-year survival rate of only about 27%, he said.

During a press briefing at the conference, moderator Frances Shepherd, MD, a medical oncologist at Princess Margaret Cancer Centre in Toronto and a past president of the International Association for the Study of Lung Cancer, called the results "very exciting" given that this type of cancer represents about a third of all lung cancers and therefore affects an "enormous number of patients in Canada and globally."

The PACIFIC trial was sponsored by AstraZeneca. Dr. Antonia reported being a speaker or advisory board member or receiving funding support from AstraZeneca and numerous other companies. Dr. Shepherd reported receiving honoraria and support from AstraZeneca and others. She is a speaker or advisory board member for Eli Lilly, AstraZeneca, and Merck, and she has ownership Interest in Eli Lilly and AstraZeneca.

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SOURCE: Antonia S et al. WCLC 2018, Abstract PL02.01.

IMpower133: Atezolizumab plus standard chemotherapy boosted survival in ES-SCLC

BY SHARON WORCESTER
MDedge News

TORONTO – Adding the humanized monoclonal programmed death-ligand 1 (PD-L1) antibody atezolizumab to standard first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) significantly improved overall and progression-free survival in the phase 1/3 IMpower133 trial.

The combination may represent a new standard-of-care regimen for patients with untreated ES-SCLC, which is highly lethal – with 5-year survival of about 1%-3% – and represents about 13% of all lung cancers, Stephen V. Liu, MD, reported at the World Conference on Lung Cancer.

The findings were published simultaneously in the New England Journal of Medicine.

The median overall survival in 201 patients randomized to receive atezolizumab in addition to carboplatin and etoposide was 12.3 months, compared with 10.3 months in 202 patients who received placebo plus carboplatin and etoposide (hazard ratio, 0.7), Dr. Liu of Georgetown University, Washington, and a member of the trial steering committee said at the meeting, sponsored by the International Association for the Study of Lung Cancer.

"That translates to a 30% reduction in the risk of patient death," he said at a press briefing during the conference. "Patients receiving atezolizumab had a much greater likelihood of being alive at 1 year, with a 1-year survival rate of 51.7% versus 38.2%."


DR. LIU

Median progression-free survival (PFS) also improved with atezolizumab (5.2 months vs. 4.3 months with placebo; HR, 0.77), as did 6-month PFS. At 12 months there was more than a doubling of PFS in the atezolizumab group (5.0% vs. 12.6%), he said.

Participants in the double-blind trial were treatment-naive all-comers with measurable ES-SCLC and good performance status. They received four 21-day cycles of intravenous carboplatin (area under the curve, 5 mg/mL per minute) on day 1 plus intravenous etoposide (100 mg/m^2) on days 1-3 with either concurrent 1,200 mg of atezolizumab on day 1 or placebo, followed by maintenance therapy with atezolizumab or placebo until intolerable toxicity or disease progression.

The atezolizumab safety profile was as expected with no new safety signals and did not compromise patients' ability to complete four treatment cycles, Dr. Liu noted.

The findings are exciting in that they represent the first in decades to show a significant improvement in survival in patients with ES-SCLC, he said. Although most patients have an initial response to standard-of-care chemotherapy, that response isn't durable. "As much as we expect a response, we also know that it's transient. We expect a response; we expect relapse. There hasn't been a change really in the past 20 years, at least, with this regimen that we've been using since the 1980s." More than 40 phase 3 studies have looked at more than 60 different drugs since the 1970s and have "failed to move the needle."

Immunotherapy, however, has dramatically improved the therapeutic landscape in non–small cell lung cancer, and preclinical data and clinical experience suggest "a possible synergy between checkpoint inhibition and chemotherapy," which led to this global study, he explained.

"This is the first study in over 20 years to show a significant improvement in survival and progression-free survival in initial treatment of small cell lung cancer. The concurrent administration of atezolizumab with chemotherapy helped people live longer, compared to chemotherapy alone," Dr. Liu concluded.

IMpower133 was sponsored by F. Hoffman–La Roche. Dr. Liu is a speaker or advisory board member for Genentech, Pfizer, Takeda, Celgene, Eli Lilly, Taiho Pharmaceutical, Bristol-Myers Squibb, AstraZeneca, and Ignyta, and has received research or grant support from Genentech, Pfizer, Threshold Pharmaceuticals, Clovis Oncology, Corvus Pharmaceuticals, Esanex, Bayer, OncoMed Pharmaceuticals, Ignyta, Merck, Lycera, AstraZeneca, and Molecular Partners.

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SOURCE: Liu SV et al. WCLC 2018, Abstract PL02.07.

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: Small cell lung cancer accounts for about 10%-15% of all new lung cancers diagnosed yearly with over 60% of patients diagnosed with extensive-stage disease (ES-SCLC). Carboplatin/etoposide chemotherapy has remained the standard of care for years. While the majority of patients with ES-SCLC will respond to first-line chemotherapy, inevitably, recurrence rates are very high and responses to second-line treatment are poor. Progress in therapeutic options in small cell lung cancer has until recently been at a standstill, and the overall prognosis of ES-SCLC remained dismal, with a reported 5-year survival rate of 1%-2%. Immunotherapy, however, is finally making an entrance in small cell lung cancer. Recent trials evaluating immunotherapy in the second-line setting demonstrated improved outcomes, compared with chemotherapy, and nivolumab was recently approved by the FDA for patients with ES-SCLC who progress after chemotherapy. The recent results of the Impower133 study further highlight the expanding role of immunotherapy in the treatment of ES-SCLC. In this study, the combination of atezolizumab and chemotherapy resulted in improved progression-free survival at 12 months, compared with chemotherapy alone with acceptable toxicity profile. The improvement resulted in a 30% reduction in the risk of death from small cell. These results provide real hope for patients with small cell lung cancer, a disease that for more than 2 decades had not been associated with any improvement in treatment options or outcomes.

Pulmonary artery denervation helped with walking capacity in left heart failure

BY SUSAN LONDON
MDedge News

SAN DIEGO – Pulmonary artery denervation is efficacious for treating combined pre- and postcapillary pulmonary hypertension attributable to left heart failure, based on results of the Chinese PADN-5 trial reported at the Transcatheter Cardiovascular Therapeutics annual meeting.

This ablative treatment has been studied among patients with pulmonary hypertension attributable to other etiologies, but not in randomized fashion among this population, noted lead investigator Shao-Liang Chen, MD, of Nanjing (China) First Hospital, Nanjing Medical University. The treatment is an attractive one, as medications recommended for pulmonary arterial hypertension are not recommended for joint pre- and postcapillary pulmonary hypertension (group II pulmonary hypertension).

In PADN-5, 98 patients were randomized to pulmonary artery denervation or to sham denervation plus open-label sildenafil (Viagra), which at the time of trial initiation was thought to be safe and potentially beneficial.

The trial's main outcome, 6-minute walk distance at 6 months, improved in both groups, according to data reported at the meeting and simultaneously published in JACC Cardiovascular Interventions. But the improvement was about four times greater in the pulmonary artery denervation group. Secondary efficacy outcomes also favored that group, and the rate of fatal pulmonary embolism did not differ for the two groups.

Susan London/MDedge News

Dr. Shao-Liang Chen

"The PADN-5 trial demonstrates the benefits of pulmonary artery denervation for patients with combined pre- and postcapillary pulmonary hypertension. Patients with preserved and with reduced ejection fraction equally benefited."

"The PADN-5 trial demonstrates the benefits of pulmonary artery denervation for patients with combined pre- and postcapillary pulmonary hypertension. Patients with preserved and with reduced ejection fraction equally benefited," summarized Dr. Chen, who pioneered this procedure about 7 years ago. "There was no sign of any harm of sildenafil in patients with combined pre- and postcapillary pulmonary hypertension."

Trial critique

"This is a very difficult study to conduct, being able to recruit patients and actually have these procedures done," commented press conference moderator Ori Ben-Yehuda, MD, professor of clinical medicine and director, coronary care unit, UC San Diego Medical Center.

At the same time, he expressed some reservations about the trial. "Sildenafil in the control group might actually be expected to ... decrease your effect size. Also, particularly in men, perhaps even in women, it might unblind them to which group they are in and undermine your sham design," he noted. In addition, some hemodynamic changes after pulmonary artery denervation – a decrease in wedge pressure and an increase in ejection fraction – were puzzling.

"We need a lot more data here. There are some issues with this trial in terms of design, and we haven't even gotten into the issue of whether there were core labs, whether the echoes, the hemodynamics, were read blindly," Dr. Ben-Yehuda maintained. "This issue of secondary or group II pulmonary hypertension due to left heart failure is one that has been very frustrating in terms of actual PA-specific therapies. So this is an important step further, but it needs confirmation in truly sham-controlled trials that have no potential for unblinding."

The catheter used in PADN-5 is available in China but has not received clearance in the United States, he pointed out. "There are alternative or competing technologies, one using ultrasound, for example, that has a very similar approach. … We'll have to see how it ends up [performing]."

Trial details

Patients in the PADN-5 pulmonary artery denervation group underwent ablation only in the periconjunctional area between the distal main trunk and the left ostial branch with a multifunction catheter having premounted electrodes. Those in the control group underwent a sham procedure, with catheter positioning at the target sites and connection to a generator but no ablation, and were given open-label sildenafil. All additionally received standard heart failure medical therapy. (No sildenafil placebo was used in the denervation group.)

Trial results reported at the meeting, which is sponsored by the Cardiovascular Research Foundation, showed that most echocardiographic and hemodynamic measures improved more in the pulmonary artery denervation group.

The greater improvement in 6-minute walk test with denervation versus sham and sildenafil at 6 months was evident in a variety of measures: absolute median distance walked (432.5 m vs. 358 m) and mean distance walked (434.6 m vs. 359.4 m), and absolute increase (80 m vs. 17.5 m) and relative increase (21.4% vs. 4.9%) The difference was significant for all measures at P less than .001.

The denervation group had a comparatively greater reduction of pulmonary vascular resistance (29.8% vs. 3.4%; P less than .001) and were less likely to experience clinical worsening (16.7% vs. 40.0%; $P = .014$).

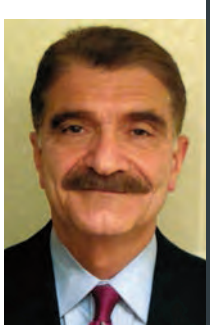
There was a single fatal pulmonary embolism in each treatment group. Of the seven total deaths, two occurred in the denervation group (one attributable to pump failure, one a sudden death) and five occurred in the sham with sildenafil group (all but one attributable to pump failure).

Dr. Chen disclosed that he had no relevant conflicts of interest. The trial was sponsored by Nanjing First Hospital, Nanjing Medical University.

chestphysiciannews@chestnet.org

SOURCE: Chen S-J et al. TCT 2018. JACC Cardiovasc Interv. 2018 Sep 23.

VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: The results of this report are interesting and potentially promising provided further studies with a true "sham control" group, as stated by the moderator of the session Dr. Ben-Yehuda, confirm the findings.

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Two distinct SLE-linked pulmonary arterial hypertension subtypes identified

BY BIANCA NOGRADY
MDedge News

Patients with pulmonary arterial hypertension as a consequence of systemic lupus erythematosus can be classified into two different subtypes, one of which shows significantly greater mortality, new research suggests.

Systemic lupus erythematosus–associated pulmonary arterial hypertension (SLE-PAH) has a poor prognosis with 3-year mortality ranging from 45% to 88%, leading the first author of the study Fangfang Sun of the School of Medicine at Shanghai (China) Jiaotong University and coauthors to seek "to further differentiate among SLE-PAH patterns to better understand the disease and optimize its management,

In a letter published online in Annals of the Rheumatic Diseases, the researchers presented data from a retrospective study of a derivation cohort of 108 Chinese patients with SLE-PAH and a validation cohort of 87 patients.

Using clinical and laboratory characteristics, the researchers classified the derivation cohort into two clusters, which they labeled as the vasculitic and vasculopathic subtypes.

Patients with the vasculitic subtype of SLE-PAH had higher levels of SLE disease activity and manifestations, such as pericarditis, rash, arthritis, nephritis, and neuropsychiatric lupus, while those with the vasculopathic subtype showed "purer" PAH and lower lupus disease activity.

The researchers found that the vasculitic subtype had around a threefold higher 3-year mortality than did the vasculopathic subtype (34.5%-40.2% vs. 13.0%-18.6%; hazard ratio, 2.84-3.15; *P* less than .05), even after adjusting for differences in treatments.

Patients with the vasculitic subtype of SLE-PAH had higher levels of SLE disease activity and manifestations, such as pericarditis, rash, arthritis, nephritis, and neuropsychiatric lupus, while those with the vasculopathic subtype showed "purer" PAH and lower lupus disease activity.

Patients who developed pulmonary arterial hypertension less than 2 years after being diagnosed with SLE were significantly more likely to have the vasculitic subtype of SLE-PAH (*P* less than .0001). A SLE disease activity index score greater than nine was also significantly associated with the vasculitic subtype (*P* = .001).

The prediction model developed based on these two factors had a sensitivity of 98.5% and a specificity of 74.4% (area under the curve, 0.94; *P* less than .0001), for a weighted score of two or more, in identifying patients with the vasculitic subtype of SLE-PAH.

Dr. Sun and colleagues suggested that the existence of two distinct clinical subtypes of SLE-PAH points to different underlying pathophysiologic mechanisms; one that is autoimmune mediated and one that involves noninflammatory vascular remodeling. However, the authors stressed that their findings needed confirmation in prospective studies.

"The next key question that remains unanswered is how to balance the utility of immunosuppressants and PAH-targeted drugs in patients with different phenotypes," the investigators wrote.

Two authors declared research funding from academic and government agencies. No conflicts of interest were declared.

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SOURCE: Sun F et al. Ann Rheum Dis. 2018 Sep 19. doi: 10.1136/annrheumdis-2018-214197.

DVT diagnostic aid is simple and inexpensive

BY BRUCE JANCIN
MDedge News

NEW ORLEANS – Both the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio proved to be better predictors of the presence or absence of deep vein thrombosis than the ubiquitous D-dimer test in a retrospective study, Jason Mouabbi, MD, reported at the annual meeting of the American College of Physicians.

What's more, both the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) can be readily calculated from the readout of a complete blood count (CBC) with differential. A CBC costs an average of $16, and everybody that comes through a hospital emergency department gets one. In contrast, the average charge for a D-dimer test is about $231 nationwide, and depending upon the specific test used the results can take up to a couple of hours to come back, noted Dr. Mouabbi of St. John Hospital and Medical Center in Detroit.

"The NLR and PLR ratios offer a new, powerful, affordable, simple, and readily available tool in the hands of clinicians to help them in the diagnosis of DVT," he said. "The NLR can be useful to rule out DVT when it's negative, whereas PLR can be useful in ruling DVT when positive."

Investigators in a variety of fields are looking at the NLR and PLR as emerging practical, easily obtainable biomarkers for systemic inflammation. And DVT is thought to be an inflammatory process, he explained.

Dr. Mouabbi presented a single center retrospective study of 102 matched patients who presented with lower extremity swelling and had a CBC drawn, as well as a D-dimer test, on the same day they underwent a lower-extremity Doppler ultrasound evaluation. In 51 patients, the ultrasound revealed the presence of DVT and anticoagulation was started. In the other 51 patients, the ultrasound exam was negative and they weren't anticoagulated. Since the study purpose was to assess the implications of a primary elevation of NLR and/or PLR, patients with rheumatic diseases, inflammatory bowel disease, recent surgery, chronic renal or liver disease, inherited thrombophilia, infection, or other possible secondary causes of altered ratios were excluded from the study.

A positive NLR was considered 3.4 or higher, a positive PLR was a ratio of 230 or more, and a positive D-dimer level was 500 ng/mL or greater. The NLR and PLR collectively outperformed the D-dimer test in terms of sensitivity, specificity, positive predictive value, and negative predictive value.

In addition, 89% of the DVT group were classified as "double positive," meaning they were both NLR and PLR positive. That combination provided the best diagnostic value of all, since none of the controls were double positive and only 2% were PLR positive.

While the results are encouraging, before NLR and PLR can supplant D-dimer in patients with suspected DVT in clinical practice a confirmatory prospective study should be carried out, according to Dr. Mouabbi. Ideally it should include the use of the Wells score, which is part of most diagnostic algorithms as a preliminary means of categorizing DVT probability as low, moderate, or high. However, the popularity of the Wells score has fallen off in the face of reports that the results are subjective and variable. Indeed, the Wells score was included in the electronic medical record of so few participants in Dr. Mouabbi's study that he couldn't evaluate its utility.

He reported having no financial conflicts regarding his study, which was conducted free of commercial support.

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DVT diagnosis showdown: CBC vs. D-dimer

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
NLR	90.2%	80.4%	82.1%	89.1%
PLR	62.7%	89%	97%	72.5%
Double-ratio positive	88.6%	100%	100%	90.9%
D-dimer	88.2%	35.3%	57.7%	75%

Notes: Based on data from a single-center retrospective study involving 102 patients. Positive NLR = 3.4 or higher, positive PLR = 230 or more, positive D-dimer = 500 ng/mL or greater.
Source: Dr. Mouabbi

MDEDGE NEWS

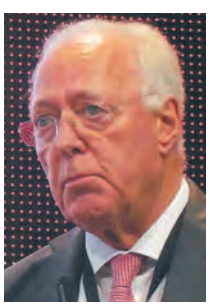
GARFIELD-AF registry: DOACs cut mortality 19%

BY MITCHEL L. ZOLER
MDedge News

MUNICH – Treatment of real-world patients newly diagnosed with atrial fibrillation using a direct oral anticoagulant led to benefits that tracked the advantages previously seen in randomized, controlled trials of these drugs, based on findings from more than 26,000 patients enrolled in a global registry.

Atrial fibrillation patients enrolled in the GARFIELD-AF (Global Anticoagulant Registry in the Field) study who started treatment with a direct oral anticoagulant (DOAC) had a 19% relative risk reduction in all-cause mortality during 2 years of follow-up, compared with patients on an oral vitamin K antagonist (VKA) regimen (such as warfarin), a statistically significant difference after adjustment for 30 demographic, clinical, and registry variables, A. John Camm, MD, said at the annual congress of the European Society of Cardiology. The analysis also showed trends toward lower rates of stroke or systemic thrombosis as well as major bleeding events when patients received a DOAC, compared with those on VKA, but these differences were not statistically significant, reported Dr. Camm, a professor of clinical cardiology at St. George's University of London.

The analyses run by Dr. Camm and his associates also confirmed the superiority of oral anticoagulation. There was an adjusted 17% relative risk reduction in all-cause mortality during 2-year follow-up in patients on any form of oral anticoagulation, compared with patients who did not receive anticoagulation, a statistically significant difference. The comparison of patients on any oral anticoagulant with those not on treatment also showed a significant lowering of stroke or systemic embolism, as well as a 36% relative increase in the risk for a major bleeding episode that was close to statistical significance.


DR. CAMM

These findings in a registry of patients undergoing routine care "suggest that the effectiveness of oral anticoagulants in randomized clinical trials can be translated to the broad cross section of patients treated in everyday practice," Dr. Camm said. However, he highlighted two important qualifications to the findings.

First, the analysis focused on the type of anticoagulation patients received at the time they entered the GARFIELD-AF registry and did not account for possible changes in treatment after that. Second, the analysis did not adjust for additional potential confounding variables, which Dr. Camm was certain existed and affected the findings.

"I'm concerned that a confounder we have not been able to account for is the quality of medical care that patients received," he noted. "The substantial reduction in mortality [using a DOAC, compared with a VKA] is not simply due to reductions in stroke or major bleeding. We must look at other explanations, such as differences in quality of care and access to care."

The analyses have also not yet looked at outcomes based on the specific DOAC a patient received – apixaban, dabigatran, edoxaban, or rivaroxaban – something that Dr. Camm said is in the works.

GARFIELD-AF enrolled nearly 35,000 patients with newly diagnosed atrial fibrillation and at least one stroke risk factor in 35 countries from April 2013 to September 2016. The analysis winnowed this down to 26,742 patients who also had a CHA2DS2-VASc score of at least 2 (which identifies patients with a high thrombotic risk) and had complete enrollment and follow-up data.

GARFIELD-AF was funded in part by Bayer. Dr. Camm reported being an adviser to Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer/Bristol-Myers Squibb.

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CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

A year in review with CHEST President, John Studdard, MD, FCCP

BY JOHN STUDDARD, MD, FCCP

Wow, what an incredible year this has been! Serving as CHEST President from the end of CHEST 2017 until the CHEST Annual Meeting in San Antonio—in early October 2018—means I've served one of the shortest presidencies in CHEST history. I must say, however, that it has been a phenomenal year for me personally, highlighted not only by the accomplishments outlined below, but by the opportunity to meet so many new people and to grow existing relationships both for myself and for CHEST.

I am so proud and excited by the meaningful work being done by our volunteers, staff, and leadership. Thank you for the incredibly humbling opportunity to work with you and to serve CHEST this year.

Since joining CHEST in 1982, I've had the opportunity to observe and learn from so many great leaders, each with different strengths and styles of leadership. I also have learned so much from members of our staff at all levels, as well as members of our leadership who serve as committee chairs, NetWork leaders, faculty representatives, and more, all giving so unselfishly of their time and talent to this organization. In addition, I

Dr. John Studdard

was blessed this year to work with a special Board of Regents—experienced, engaged, professional in their approach, supportive, strategic, representing diversity of thought and passionate about this organization.

Throughout the 2017-2018 fiscal year, CHEST's Board of Regents worked tirelessly to refine CHEST's mission and vision and to develop goals, strategies, and key performance indicators to develop a new, 5-year strategic plan.

Our organizational goals going forward are focused on several broad areas of achievement. To achieve these goals, we need to continue investing in and expanding our efforts in key areas like Membership, Education, and Publishing. We need to focus our attention on key groups like clinician educators, young leaders and young members, and embracing diversity of thought and meaningful inclusion, paying attention to gaps, barriers, and opportunities.

As I look to our updated CHEST mission—"To champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research"—as I look at the areas of achievement over the past year, and as I look to the strategic plan and what lies ahead, in my opinion there is no finish line, and there will always be more work to do.

Thank you to the CHEST volunteers, staff, leadership, and partners for your unwavering support of CHEST and our mission. We could not be successful without you.

First released as a Thought Leaders Blog on chestnet.org, September 30, 2018.

This month in the journal *CHEST*®

Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

ORIGINAL RESEARCH

Effectiveness of Reprocessing for Flexible Bronchoscopes and Endobronchial Ultrasound Bronchoscopes.
By Dr. C. L. Ofstead, et al.

Lower Glucose Target Is Associated With Improved 30-Day Mortality in Cardiac and Cardiothoracic Patients.
By Dr. A. M. Hersh, et al.

Sarcoidosis Diagnostic Score: A Systematic Evaluation to Enhance the Diagnosis of Sarcoidosis.
By Dr. A. N. Bickett, et al.

EVIDENCE-BASED MEDICINE

Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report.
By Dr. G. Y. H. Lip, et al.

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SLEEP STRATEGIES

The link between suicide and sleep

BY JACQUELINE LOCROTONDO, DO; AND WILLIAM V. McCALL, MD, MS

According to the Centers for Disease Control and Prevention, suicide is the 10th leading cause of mortality in the United States, with rates of suicide rising over the past 2 decades. In 2016, completed suicides accounted for approximately 45,000 deaths in the United States (Ivey-Stephenson AZ, et al. *MMWR Surveill Summ*. 2017;66[18]:1). While progress has been made to lower mortality rates of other leading causes of death, very little progress has been made on reducing the rates of suicide. The term "suicide," as referred to in this article, encompasses suicidal ideation, suicidal behavior, and suicide death.

Researchers have been investigating potential risk factors and prevention strategies for suicide. The relationship between suicide and sleep disturbances, specifically insomnia and nightmares, has been well documented in the literature. Given that insomnia and nightmares are potentially modifiable risk factors, it continues to be an area of active exploration for suicide rate reduction. While there are many different types of sleep disorders, including excessive daytime sleepiness, parasomnias, obstructive sleep apnea, and restless legs syndrome, this article will focus on the relationship between insomnia and nightmares with suicide.

Insomnia

Insomnia disorder, according to the American Psychiatric Association's DSM-5, is a dissatisfaction of sleep quantity or quality that occurs at least three nights per week for a minimum of 3 months despite adequate opportunity for sleep. This may present as difficulty with falling asleep, staying asleep, or early morning awakenings. The sleep disturbance results in functional impairment or significant distress in at least one area of life (American Psychiatric Association. Arlington, Virginia: APA; 2013). While insomnia is often a symptom of many psychiatric disorders, research has shown that insomnia is an independent risk factor for suicide, even when controlling for mental illness. Studies have shown that there is up to a 2.4 relative risk of suicide death with insomnia after adjusting for depression severity (McCall W, et al. *J Clin Sleep Med*. 2013;32[9]:135).

Nightmares

Nightmares, as defined by the American Psychiatric Association's DSM-5, are "typically lengthy, elaborate, story-like sequences of dream imagery that seem real and incite anxiety, fear, or other dysphoric emotions" (American Psychiatric Association. Arlington, Virginia: APA; 2013). They are common symptoms in posttraumatic stress disorder (PTSD), with up to 90% of individuals with PTSD experiencing nightmares following a traumatic event (Littlewood DL, et al. *J Clin Sleep Med*. 2016;12[3]:393). Nightmares have also been shown to be an independent risk factor for suicide when controlling for mental illness. Studies have shown that nightmares are associated with an elevated risk factor of 1.5 to 3 times for suicidal ideation and 3 to 4 times for suicide attempts. The data suggest that nightmares may be a stronger risk factor for suicide than insomnia (McCall W, et al. *Curr Psychiatr Rep*. 2013;15[9]:389).

Proposed mechanism

The mechanism linking insomnia and nightmares with suicide has been theorized and studied by researchers. A couple of the most noteworthy proposed psychological mechanisms involve dysfunctional beliefs and attitudes about sleep, as well as deficits in problem solving capability.

Dysfunctional beliefs and attitudes about sleep (DBAS) are negative cognitions pertaining to sleep, and they have been shown to be related to the intensity of suicidal ideations. Many of the DBAS are pessimistic thoughts that contain a "hopelessness flavor" to them, which lead to the perpetuation of insomnia. Hopelessness has been found to be a strong risk factor for suicide. In addition to DBAS, insomnia has also shown to lead to impairments in complex problem solving. The lack of problem solving skills in these patients may lead to fewer quantity and quality of solutions during stressful situations and leave suicide

as the perceived best or only option.

The biological theories focus on serotonin and hyperarousal mediated by the hypothalamic-pituitary-adrenal (HPA) axis. Serotonin is a neurotransmitter that is involved in the induction and maintenance of sleep. Of interesting note, low levels of serotonin's main metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have been found in the cerebrospinal fluid of suicide victims. Evidence has also shown that sleep and the HPA axis are closely related. The HPA axis is activated by stress leading to a cascade of hormones that can cause susceptibility of hyperarousal, REM alterations, and suicide. Hyperarousal, shared in context with PTSD and insomnia, can lead to hyperactivation of the noradrenergic systems in the medial prefrontal cortex, which can lead to decrease in executive decision making (McCall W, et al. *Curr Psychiatr Rep.* 2013;15[9]:389).

Treatment strategies

The benefit of treating insomnia and nightmares, in regards to reducing suicidality, continues to be an area of active research. Many of the previous studies have theorized that treating symptoms of insomnia and nightmares may indirectly reduce suicide. Pharmaceutical and nonpharmaceutical treatments are currently being used to help treat patients with insomnia and nightmares, but the benefit for reducing suicidality is still unknown.

Dr. Jacqueline Locrotondo

Dr. William V. McCall

One of the main treatment modalities for insomnia is hypnotic medication; however, these medications carry their own potential risk for suicide. Reports of suicide death in conjunction with hypnotic medication has led the FDA to add warnings about the increased risk of suicide with these medications. Some of these medications include zolpidem, zaleplon, eszopiclone, doxepin, ramelteon, and suvorexant. A review of research studies and case reports was completed in 2017 and showed that there was an odds ratio of 2 to 3 for hypnotic use in suicide deaths. However, most of the studies that were reviewed reported a potential confounding bias of the individual's current mental health state. Furthermore, many of the suicide case reports that involved hypnotics also had additional substances detected, such as alcohol. Hypnotic medication has been shown to be an effective treatment for insomnia, but caution needs to be used when prescribing these medications. Strategies that may be beneficial when using hypnotic medication to reduce the risk of an adverse outcome include using the lowest effective dose and educating the patient on not combining the medication with alcohol or other sedative/hypnotics (McCall W, et al. *Am J Psychiatry*. 2017;174[1]:18).

For patients who have recurrent nightmares in the context of PTSD, the alpha-1 adrenergic receptor antagonist, prazosin, may provide some benefit; however, the literature is divided. There have been several randomized, placebo-controlled clinical trials with prazosin, which have shown a moderate to large effect for alleviating trauma-related nightmares and improving sleep quality. Some of the limitations of these studies were that the trials

SLEEP AND SUICIDE // *continued on following page*

AMA insights

BY NEERAJ R. DESAI, MD, MBA, FCCP; AND D. ROBERT McCAFFREE, MD, MSHA, MASTER FCCP

While the American Medical Association (AMA) is the oldest and largest national medical association, many physicians, both CHEST members and nonmembers, have limited understanding of the policies, processes, and strategic foci of the AMA. It is our goal to inform our membership about the workings of the AMA and how those interact with the goals of CHEST and our members. We hope to do this by publishing periodic articles in *CHEST® Physician*. One of the authors (DRM) was the CHEST delegate to the AMA for more than 20 years, and the other (NRD) is CHEST's new AMA delegate.

The American Medical Association (AMA) had its Annual Meeting of the House of Delegates (HOD) from May 9-13. This meeting was attended by over 1,000 physicians who are delegates from all geographic societies, ie, state societies and specialties and subspecialties, as well as the uniformed services.

Policy and resolutions

Process:

Policies originate via resolutions submitted by individuals or societies. These resolutions then go to one of several Reference Committees for open discussion. These committees then report their recommendations back to the HOD, which then discusses and votes on the recommendations. In some instances, the question is referred for further studies by one of several Councils, whose reports go to the Board of Trustees or back to the House. The diagram below explains the flow of resolutions to policies.

Chest/Allergy Section Council (which is composed of CHEST, ATS, SCCM, AASM, and several allergy specialty organizations) meets prior to the voting in the House to discuss the pending business. The Specialty and Service Society (SSS) is the largest caucus in the AMA's House of Delegates and is composed of all the delegates from the specialty societies, as well as the uniformed services.

There are two categories of groups in the SSS: those societies that have seats in the HOD and those seeking admission to the house.

SSS groups in the HOD include:

- 119 national medical specialties
- 2 professional interest medical associations
- 5 military or uniformed service groups (the Public Health Service is "uniformed" but not "military" or "armed")

The compendium of policies covers the entire range of topics impacting the practice of medicine – ethics, legislation, regulation, public health, individual health, and medical education, among them. The full range of policies can be found in the AMA's Policy Manual available on the website, AMA-assn.org

Some of the issues discussed at the HOD are as follows:

- Health care as a "right." In response to a resolution asking the AMA to support health care as a "right," the Board of Trustees reaffirmed current policy supporting expanded access to health care for all but stopped short of calling health care a "right."
- POLST forms. The Board of Trustees will work with state organizations and others to recognize Physician Orders for Life Sustaining Treatment (POLST) forms and allow for reciprocity between states.
- Influenza vaccination. The HOD enacted as AMA policy that no health-care worker should be terminated from employment due solely to their refusal to be vaccinated for influenza.
- e-Cigarettes and tobacco.

A. The AMA was instructed to urge federal officials, including but not limited to the US Food and Drug Administration (FDA), to prohibit the sale of any e-cigarette cartridge that does not include a complete list of ingredients on its packaging, in the order of prevalence (similar to food labeling). We will also urge federal officials, including but not limited to the FDA, to require that accurate nicotine content of e-cigarettes be prominently displayed on the product alongside a warning of the addictive quality of nicotine (new HOD policy).

B. Develop a report on the individual health

SLEEP AND SUICIDE

Continued from previous page

were small to moderate in size, and the length of the trials was 15 weeks or less. In 2018, Raskin and colleagues completed a follow-up randomized, placebo-controlled study for 26 weeks with 304 participants and did not find a significant difference between prazosin and placebo in regards to nightmares and sleep quality (Raskind MA, et al. *N Engl J Med*. 2018;378[6]:507).

Cognitive behavioral therapy for insomnia (CBT-I) and image rehearsal therapy (IRT) are two sleep-targeted therapy modalities that are evidence based. CBT-I targets dysfunctional beliefs and attitudes regarding sleep (McCall W, et al. *J Clin Sleep Med*. 2013;9[2]:135). IRT, on the other hand, specifically targets nightmares by having the patient write out a narrative of the nightmare, followed by re-scripting an alternative ending to something that is less distressing. The patient will rehearse the new dream narrative before going to sleep. There is still insufficient evidence to determine if these therapies have benefit in reducing suicide (Littlewood DL, et al. *J Clin Sleep Med*. 2016;12[3]:393).

While the jury is still out on how best to target and treat the risk factors of insomnia and nightmares in regards to suicide, there are still steps that health-care providers can take to help keep their patients safe. During the patient interview, new or worsening insomnia and nightmares should prompt further investigation of suicidal thoughts and behaviors. After a thorough interview, treatment options, with a discussion of risks and benefits, can be tailored to the individual's needs. Managing insomnia and nightmares may be one avenue of suicide prevention.

Dysfunctional beliefs and attitudes about sleep are negative cognitions pertaining to sleep, and they have been shown to be related to the intensity of suicidal ideations.

Drs. Locrotondo and McCall are with the Department of Psychiatry and Health Behavior at the Medical College of Georgia, Augusta University, Augusta, Georgia.

and public health implications of a low nicotine standard for cigarettes. Such a report should consider and make recommendations on scientific criteria for selection of a nicotine standard that is nonaddictive, regulatory strategies to ensure compliance with an established standard, and how a low-nicotine standard should work with other nicotine products in a well-regulated nicotine market. American Medical Association consider joining other medical organizations in an amicus brief supporting the American Academy of Pediatrics legal action to compel the US Food and Drug Administration to take timely action to establish effective regulation of e-cigarettes, cigars, and other nicotine tobacco products (Directive to Take Action).

- Prior authorization for durable medical equipment. The AMA will advocate that denials of prior authorization for durable medical equipment must be based on true medical necessity not arbitrary time limits or other paperwork issues and will continue to work to improve the prior authorization process for Medicare Managed Care Plans (Directive to Take Action).
- Medical training (including IMG, medical students, residents, and fellows).

A. EHR and business training during med ed and residency

B. Fellowship start date. The AMA will survey physicians who have experienced a fellowship start date of August 1 to further evaluate the benefits and drawbacks from this transition (Directive to Take Action).

- Opioid abuse. Surgeon General Jerome Adams addressed the HOD about several topics but focused on opioid crisis.
- Physician burnout and organizational efficiency. Physician burnout is a health-care crisis in all specialties, and critical care has a very high rate of physician burnout. The AMA has several tools available that can help with physician burnout both in the ICU and outpatient medicine. (https://www.stepsforward.org)

This is just a small sampling of the activities at the HOD. More information, including reports from the various Councils, are available on the AMA website, http://ama-assn.org.

There are two categories of groups in the SSS: those societies that have seats in the HOD and those seeking admission to the house.

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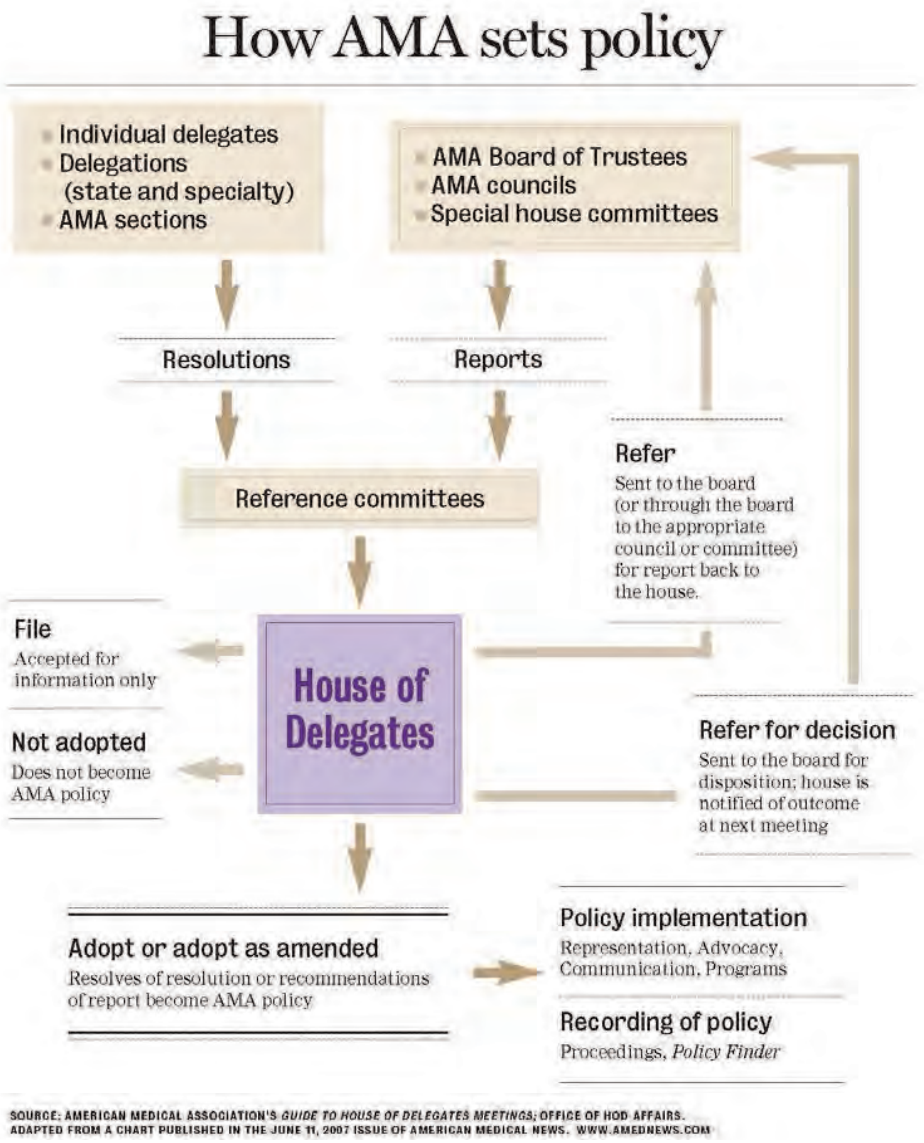


CHEST Foundation awards grants to scholars, young investigators, and community service volunteers

Each year, the CHEST Foundation offers grants to worthy research candidates, generous community service volunteers, and distinguished scholars. More than 1,000 recipients worldwide have received more than $10 million in support and recognition of outstanding contributions to chest medicine.

In 2018, the Foundation awarded more than $500,000 to researchers who were honored during Sunday's Opening Session at CHEST 2018.

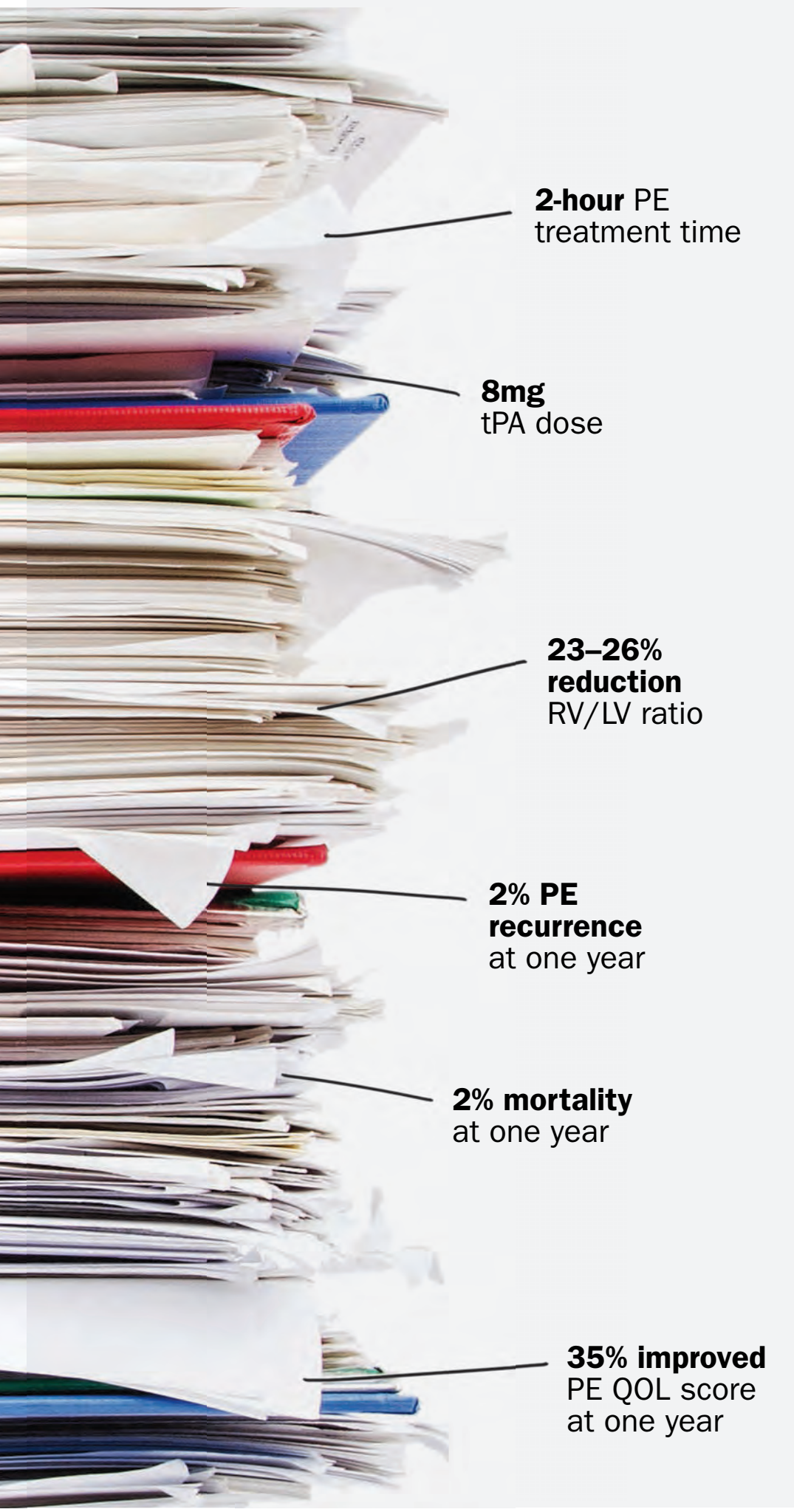
Robert C. Hyzy, MD, FCCP, director of the Critical Care Medicine Unit at the University of Michigan, was awarded the 2018 Eli Lilly and Company Distinguished Scholar in Critical Care Medicine grant for his research titled "The Use of Electrical Impedance Tomography to Assess Mechanical Ventilation in Acute Respiratory Distress Syndrome." The grant, sponsored by Eli Lilly, will further Dr. Hyzy's research into vetting electrical impedance tomography (EIT).

"EIT is essentially a belt that's worn around a patient's chest that creates an image through a low, imperceptible electronic current," Dr. Hyzy said, noting CT scanners can also be used to see how air gets into the lungs, but those are not a practical tool in the ICU. "EIT creates some images, and the images change with regard to how air gets into the lungs, particularly when the patient has ARDS. So the idea here, with this generous grant, would be to build a better mousetrap—to explore this technology as a means to see various ways to push air through the lungs. It's using the images you get to guide the way mechanical ventilation is provided."

The Foundation's grants have made a difference in patients' lives by aiding young investigators. Many of the supported projects have led to breakthroughs in the treatment of chest diseases and in patient care. The Foundation encourages members to apply for grants to ensure these continued outstanding contributions to chest medicine and patient care.

Congratulations to all of our 2018 CHEST Foundation grant winners!

Watch for the list of all CHEST 2018 winners in the December issue of *CHEST® Physician*.



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*Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL. Feb 2018.

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

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