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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

*“Every 5 years someone  
says we’re 5 years away,  
and then 5 years go by and  
we’re still 5 years away.  
So I’m not making any  
predictions on that.”*

Dr. Edward A. Belongia

## Obstacles remain in the way of developing better flu vaccines

BY BRUCE JANCIN

MDedge News

LJUBLJANA, SLOVENIA – An improved, more reliably effective influenza vaccine may not be on the horizon in the near future.

That was a key cautionary message provided by vaccine expert Edward A. Belongia, MD, at the annual meeting of the European Society for Paediatric Infectious Diseases.

The effectiveness of seasonal influenza vaccine varies from 10% to 60% year by year, leaving enormous room for improvement. But many obstacles exist to developing a more consistent and reliably effective version of the seasonal influenza vaccine. And the lofty goal of creating a uni-

versal vaccine is even more ambitious, although the National Institute of Allergy and Infectious Diseases has declared it to be a top priority and mapped out a strategic plan for getting there (J Infect Dis. 2018 Jul 2;218[3]:347-54).

“Ultimately the Holy Grail is a universal flu vaccine that would provide pan-A and pan-B protection that would last for more than 1 year, with protection against avian and pandemic viruses, and would work for both children and adults. We are nowhere near that. Every 5 years someone says we’re 5 years away, and then 5 years go by and we’re still 5 years away. So I’m not making any predictions on that,” said Dr. Belongia, director of the Center for Clinical Epide-

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## OSA prevalence in North and South America estimated at 170 million

BY DOUG BRUNK

MDedge News

The estimated prevalence of obstructive sleep apnea in North and South America stands at 170 million, results from a novel epidemiologic analysis showed.

“I would not have thought that there are 170 million people in the Americas with clinically important sleep apnea based on our conservative estimates,” the study’s first author, Atul Malhotra, MD, FCCP, said in an interview in advance of the annual meeting of the Associated Professional Sleep Societies. “Even if we restrict the conversation to moderate to severe sleep apnea, we still see 81 million people afflicted in the Americas alone. We have recently estimated almost 1 billion patients afflicted with OSA worldwide.”

In an effort to estimate the Americas’ prevalence of adult OSA using existing data from epidemiologic studies, Dr. Malhotra, director of sleep medicine at the University of California, San Diego, senior author Adam V. Benjafield, PhD, and their colleagues contacted authors of important analyses on the topic following an

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# COPD rates reflect current smoking prevalence

BY STEVE CIMINO  
*MDedge News*

Chronic obstructive pulmonary disease (COPD) prevalence among adults is strongly cor-

related with their state's current smoking prevalence, according to a Centers for Disease Control and Prevention analysis of respondents to a behavioral risk factor survey. "Population-based strategies for

smoking prevention and control have the potential to decrease the prevalence of COPD in the United States," wrote Anne G. Wheaton, PhD, of the CDC's National Center for Chronic Disease Prevention and

Health Promotion and coauthors. The study was published in the Morbidity and Mortality Weekly Report. Dr. Wheaton and her fellow researchers analyzed data from

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418,378 adult respondents to the 2017 Behavioral Risk Factor Surveillance System survey. Responses came from all 50 states and Washington, D.C.; respondents who had smoked less than 100 lifetime cigarettes were categorized as “never smoked,” while those who had smoked at least 100 cigarettes but

no longer smoked were categorized as “former smokers.” Anyone who had smoked at least 100 cigarettes and currently smoked was categorized as a “current smoker.”



The age-adjusted prevalence of COPD among U.S. adults was 6.2% (95% confidence interval, 6.0%-6.3%) in 2017. Current cigarette smokers had a prevalence of 15.2% (95% CI, 14.7%-15.7%); this dipped to 7.6% (95% CI, 7.3%-8.0%) among former smokers and 2.8% (95% CI, 2.7%-2.9%) among adults

who had never smoked. Patterns were visible within states: Current smokers had a state-level prevalence of COPD that was strongly correlated with state-level current smoking prevalence (Pearson correlation coefficient, 0.69;  $P$  less than .001). State-level COPD prevalence among former smokers (Pearson correlation coefficient, 0.71;  $P$  less than .001) and those who never smoked (Pearson correlation coefficient, 0.64;  $P$  less than .001) were also strongly correlated with the

*“Population-based strategies for smoking prevention and control have the potential to decrease the prevalence of COPD in the United States.”*

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current smoking prevalence, indicating secondhand smoke as a risk factor for COPD.

The findings on populations at higher risk for COPD were not unexpected. The higher COPD prevalences observed among women, older adults, American Indians/Alaska Natives, adults with less education, those with a history of asthma, and those residing in rural areas were consistent with results from previous studies.

Smoking prevention policies including tobacco product price increases, mass media antismoking campaigns, comprehensive smoke-free laws, and barrier-free access to evidence-based cessation interventions all could attack COPD prevalence in the United States, the report suggests. In addition, policies to help protect nonsmokers from secondhand smoke exposure can also make an impact on COPD prevalence.

The coauthors acknowledged the study's limitations, including relying on self-reporting for both COPD and smoking status. They also noted that there was no way to measure exposure to secondhand smoke, other indoor or outdoor air pollutants, or respiratory infection history, “all of which might contribute to COPD risk.”

No conflicts of interest were reported.

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**SOURCE:** Wheaton AG et al. MMWR Morb Mortal Wkly Rep. 2019 Jun 21;68(24):533-8.

# AMA names recipients of Reimagining Residency initiative

BY LUCAS FRANKI

MDedge News

The American Medical Association has announced the final eight recipients of the Reimagining Residency initiative, who will receive a total of \$14.4 million to support residency innovation projects led by medical schools, residency programs, and health systems.

"After establishing a framework for creating the medical schools of the future, the AMA is now supporting innovation projects that will better align residency training with the evolving needs of patients and communities," AMA CEO and Executive Vice President James L. Madara, MD, stated.

The projects include curricular innovations to address workforce shortages and address social determinants of health. Other projects will be developed within the framework of innovations and concepts developed and implemented in medical schools over the past 6 years by the AMA's consortium.

The projects were chosen through a competitive grant process by an advisory panel made up of leading experts in medical education, and selection was based on how well each program met the goals of the initiative.

Each of the following projects will receive \$1.8 million over 5 years:

- California Oregon Medical Partnership to Address Disparities in Rural Education and Health – Oregon Health & Science University, Portland, and the University of California, Davis
- Fully Integrated Readiness for Ser-

vice Training: Enhancing the Continuum from Medical School to Residency to Practice – University of North Carolina at Chapel Hill

- NYU Transition to Residency Advantage – New York University
- Promotion in Place: Enhancing Trainee Well-Being and Patient Care Through Time-Variable Graduate Medical Education – Partners HealthCare System, Massachusetts General Hospital, and Brigham and Women's Hospital, Boston
- Reimagining Residency: Ensuring Readiness for Practice Through Growing Interprofessional Partnerships to Advance Care and Education – Maine Medical Center, Portland
- Residency Training to Effectively Address Social Determinants of Health: Applying a Curricular Framework Across Four Primary Care Specialties – Montefiore Health System, New York
- The Graduate Medical Training "Laboratory": An Innovative Program to Generate, Implement, and Evaluate Interventions to Improve Resident Burnout and Clinical Skill – Johns Hopkins University, Baltimore; Stanford (Calif.) University; and the University of Alabama at Birmingham
- The GOL2D Project (Goals of Life and Learning Delineated): Collaboration Across Academic Health Systems to Better Align GME with Learner, Patient, and Societal Needs – Vanderbilt University, Nashville, Tenn., and the University of Mississippi, Jackson.

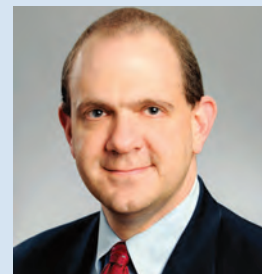
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David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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## VIEW ON THE NEWS

**David A. Schulman, MD, FCCP, comments:** It is refreshing to see additional attention (and funding) being deployed to helping our residents see more of what medicine has to offer. Studies show that the vast majority of people entering medical school continue to do so with the primary goal of helping the public, and yet burn-out rates for postgraduate trainees climb year after year, related to nonclinical aspects of the job (like documentation), long work hours, the growing debt associated with pursuit of medical training, and the emotionally stressful task of treating patients with severe and premorbid medical conditions. There's much ongoing discussion about maintaining the well-being of physicians-in-training, but I would opine that projects like the ones being funded by the AMA, that allow us to be creative in what and how we teach these doctors, are far more likely to rekindle the residents' flame of enthusiasm for medicine than free food or social gatherings.

## Flu vaccines against H3N2 remain less effective for younger children // continued from page 1

miology and Population Health at the Marshfield (Wisc.) Clinic Research Institute, which is part of the U.S. Influenza Vaccine Effectiveness Network.

One of the big problems in creating a more effective flu vaccine, particularly for children, is the H3N2 virus subtype. Dr. Belongia was first author of a systematic review and meta-analysis of studies of more than a dozen recent flu seasons showing that although vaccine effectiveness against H3N2 varied widely from year to year, it was consistently lower than against influenza type B and H1N1 (Lancet Infect Dis. 2016 Aug;16[8]:942-51).

And that's especially true in children and adolescents. Notably, in the 2014-2015 U.S. flu season, vaccine effectiveness against H3N2 in children aged 6 months to 8 years was low at 23%, but shockingly lower at a mere 7% in the 9- to 17-year-olds. Whereas in the 2017-2018 season, vaccine effectiveness against H3N2 in the 9- to 17-year-olds jumped to 46% while remaining low but consistent at 22% in the younger children.

"We see a very different age pattern here for the older children compared to the younger children, and quite frankly we don't really understand what's doing this," said Dr. Belongia.

What is well understood, however, is that the problematic performance of influenza vaccines when it comes to protecting against H3N2 is a complicated matter stemming from three sources: the virus itself; the current egg-based vaccine manufacturing methodology, which is now 7 decades old; and host factors.

### That troublesome H3N2 virus

Antigenic evolution of the H3N2 virus occurs at a 5- to 6-fold higher rate than for influenza B virus and roughly 17-fold faster than for H1N1. That high mutation rate makes for a moving target that's a real problem when trying to keep a vaccine current. Also, the globular head of the virus is prone to glycosylation, which enables the virus to evade immune detection.

### Vaccine-related factors

It's likely that the availability of the flu vaccine for the upcoming 2019-2020 season is going to be delayed because of late selection of the strains for inclusion. The World Health Organization ordinarily selects strains for vaccines for the Northern Hemisphere in February, giving vaccine manufacturers 6-8 months to produce their vaccines and ship them in time for administration from September through November. This year, however, the WHO delayed selection of the H3N2 component until March because of the high level of antigenic and genetic diversity of circulating strains.

"This hasn't happened since 2003 – it's a very rare occurrence – but it does increase the potential that there's going to be a delay in the availability of the vaccine in the fall," he explained.

Eventually, the WHO selected a new clade 3C.3a virus called A/Kansas/14/2017 for the 2019-2020 vaccine. It should cover the circulating strains of H3N2 "reasonably well," according to the physician.

Another issue: H3N2 has become adapted to the mammalian environment, so growing the virus in eggs introduces strong selection pressure for mutations leading to reduced vaccine effectiveness. Yet only two flu vaccines licensed in the United States are manufactured without eggs: Flucelvax, marketed by Seqirus for patients aged 4 years and up, and Sanofi's Flublok, which is licensed for individuals who are 18 years of age or older. Studies are underway looking at the relative effectiveness of egg-based versus cell culture–manufactured flu vaccines in real-world settings.

### Host factors

Hemagglutinin imprinting, sometimes referred to as "original antigenic sin," is a decades-old concept whereby early childhood exposure to influenza viruses shapes future vaccine response.

"It suggests there could be some birth cohort effects in vaccine responsiveness, depending on

what was circulating in the first 2-3 years after birth. It would complicate vaccine strategy quite a bit if you had to have different strategies for different birth cohorts," Dr. Belongia observed.

Another host factor issue is the controversial topic of negative interference stemming from repeated vaccinations. It's unclear how important this is in the real world, because studies have been inconsistent. Reassuringly, Dr. Belongia and coworkers found no association between prior-season influenza vaccination and diminished vaccine effectiveness in 3,369 U.S. children aged 2-17 years studied during the 2013-2014 through 2015-2016 flu seasons (JAMA Netw Open. 2018 Oct 5;1[6]:e183742. doi: 10.1001/jamanetworkopen.2018.3742).

"We found no suggestion at all of a problem with being vaccinated two seasons in a row," according to Dr. Belongia.

### How to build a better influenza vaccine for children

"I would say that, even before we get to a universal vaccine, the next generation of flu vaccines that are more effective are not going to be manufactured using eggs, although we're not real close to that. But I think that's eventually where we're going," he said.

"I think it's going to take a systems biology approach in order to really understand the adaptive immune response to infection and vaccination in early life. That means a much more detailed understanding of what is underlying the imprinting mechanisms and what is the adaptive response to repeated vaccination and infection. I think this is going to take prospective infant cohort studies; the National Institutes of Health is funding some that will begin within the next year," Dr. Belongia added.

Dr. Belongia reported having no financial conflicts regarding his presentation.

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## OSA prevalence in the United States estimated at 54 million // continued from page 1

exhaustive review of the literature. For countries where no measurement had been made, they used publicly available data to obtain estimates of age, sex, race, and body mass index. Next, they developed an algorithm to match countries without prevalence estimates with countries from which OSA epidemiologic studies exist. "The situation was complicated given the variable age of the existing studies, the differences in technology used (e.g., nasal pressure vs. thermistor), the changing scoring criteria, and other sources of variability," the researchers wrote in their abstract.

Dr. Malhotra reported on data from 38 of 40 countries in the Americas. Drawing from American Academy of Sleep Medicine 2012 criteria and using what they characterized as a "somewhat conservative" approach, the researchers estimated the prevalence of adult OSA in the Americas to be 170 million, or 37% of the population. In addition, they estimate that 81 million adults, or 18% of the population, suffer from moderate to severe OSA based on an apnea hy-



Dr. Atul Malhotra

popnea index of 15 or more per hour. The countries with the greatest burden of OSA are the United States (54 million), Brazil (49 million), and Colombia (11 million).

"The findings will hopefully help to raise awareness about the disease but also encourage a strategic conversation regarding how best to

address this large burden," Dr. Malhotra said. "We are unaware of prior efforts to estimate OSA prevalence on a large scale."

He acknowledged certain limitations of the study, including that the methods, equipment, definitions, and criteria used in existing studies in the medical literature varied widely. "We did our best to harmonize these methods across studies but obviously we can't change the equipment that was used in previous studies," he said. "Thus, we view our findings as an estimate requiring further efforts to corroborate."

The research stemmed from an academic/industry partnership with ResMed, which provided a donation the UCSD Sleep Medicine Center. Dr. Malhotra reported having no financial disclosures. Dr. Benjafield is an employee of ResMed, a medical equipment company that specializes in sleep-related breathing devices.

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**SOURCE:** Malhotra A et al. SLEEP 2019, Abstract 0477.

# Cost of physician burnout estimated at \$4.6 billion per year

BY RICHARD FRANKI

MDedge News

**P**hysician burnout costs the U.S. health care system approximately \$4.6 billion a year in physician turnover and reduced productivity, according to the results of a cost-consequence analysis.

In 2015, the burnout-attributable cost per physician was \$7,600 – an estimate occupying the conservative middle ground between the \$3,700 and \$11,000 extremes produced by the study's mathematical model.

“Traditionally, the case for ameliorating physician burnout has been made primarily on ethical grounds.” This study, believed to be the first to look at the system-wide costs of burnout, “provides tools to evaluate the economic dimension of this problem,” wrote Shasha Han, MS, of the National University of Singapore and her associates in *Annals of Internal Medicine*.

Individual burnout-attributable costs were higher for physicians in the younger age group (less than 55 years) in all three specialty categories: \$7,100 versus \$5,900 for those aged at least 55 years among primary care physicians, \$10,800 versus \$9,100 for surgical specialists, and \$7,800 versus \$6,100 for other specialists, the investigators reported.

The mathematical model used in the study focused on two produc-

tivity metrics related to burnout – cost associated with physician replacement and lost income from unfilled physician positions. “Estimated turnover costs were generally higher than costs of reduced productivity across all” the various segments of age and specialty, Ms. Han and associates wrote.

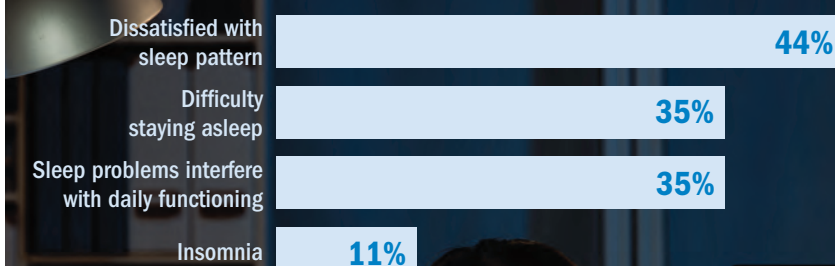
“Burnout is a problem that extends beyond physicians to nurses and other health care staff. Future work holistically investigating the costs associated with burnout in health care organizations would be valuable. Studies focusing on differences in burnout-attributable costs across provider segments other than the ones investigated in this study, including academic versus private settings, or across a finer segmentation of physician specialties also might be fruitful,” they wrote.

One investigator has received grants from the American Medical Association Accelerating Change in Medical Education Consortium, the Physicians Foundation, and the National Institutes of Health. Another received a startup grant from the National University of Singapore. Ms. Han said that she had no financial conflicts to disclose. All of the investigators' disclosures are available online.

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**SOURCE:** Han S et al. *Ann Intern Med*. 2019 May 28. doi: 10.7326/M18-1422.

## Prevalence of sleep disturbances among physicians



Note: Based on data for 417 physicians who completed the Insomnia Severity Index.

Source: Medisauskaitė A, Kamau C. *BMJ Open*. 2019 May 15;9(5):e027362

# Vaping among teens shot up from 2017 to 2018

BY RICHARD FRANKI

MDedge News

**V**aping among teens aged 16-19 years rose significantly in the United States and Canada from 2017 to 2018 but did not change in England, according to data from national cross-sectional surveys.

The prevalence of vaping in the past 30 days rose from 11% to 16% in the United States and from 8% to 14.6% in Canada, while use in England showed a nonsignificant increase of 8.7% to 8.9%, David Hammond, PhD, of the University of Waterloo (Canada) and associates said in the *BMJ*.

Embedded in those U.S. and Canadian increases is the recent evolution of the vaping market brought about by “the growth of JUUL e-cigarettes and similar products [that use] benzoic acid and nicotine salt technology to deliver higher concentrations of nicotine than conventional e-cigarettes,” they explained.

In England, the JUUL system is limited to less than half the nicotine concentration, at 20 mg/mL, compared with more than 50 mg/mL in the United States and Canada, and it was not available at all types of retail outlets at the time of the surveys. That situation changed in March 2019, when the company expanded to convenience stores, the investigators noted.

In the United States, JUUL was the second-most popular product among past-30-day vapers who had a usual brand in 2017, with

9% reporting use. In 2018, JUUL was the most popular brand and use was up to 28%. In Canada, the brand was not among the top five in 2017, but was third in 2018 at 10% in those who reported vaping in the past 30 days. The leading Canadian brand in 2018 was Smok, which released a nicotine-salt version in March of 2018, Dr. Hammond and associates reported.

“Before 2018, there was relatively little evidence of regular vaping among adolescents that might be indicative of nicotine addiction; however, the emergence of JUUL and nicotine salt-based products might signal a change,” they wrote.

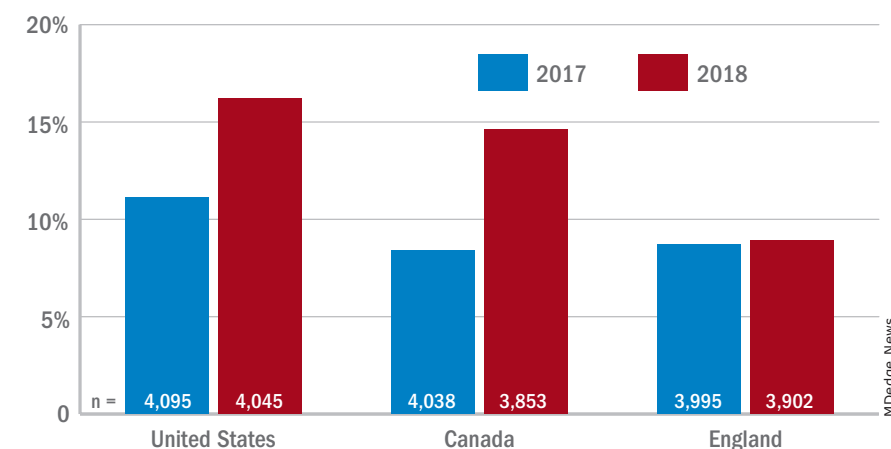
The International Tobacco Control Policy Evaluation Project's Youth Tobacco and Vaping Survey was conducted online in each country in two waves – July to August 2017 and August to September 2018 – with a sample size of approximately 12,000 for each.

The study was funded by the U.S. National Institutes of Health. Dr. Hammond is supported by a Canadian Institutes of Health Research–Public Health Agency of Canada applied public health research chair. The investigators said that they had no other financial disclosures to report, but several have served as paid witnesses in legal challenges against tobacco companies.

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**SOURCE:** Hammond D et al. *BMJ*. 2019 Jun 19. doi: 10.1136/bmj.l2219.

## Vaping prevalence in the past 30 days among 16- to 19-year-olds



Note: Based on data from the International Tobacco Control Policy Evaluation Project's Youth Tobacco and Vaping Survey, conducted in Jul-Aug 2017 and Aug-Sept 2018.

Source: *BMJ* 2019 Jun 19;365:l2219

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# Nintedanib cut lung function decline in interstitial lung disease caused by systemic sclerosis

BY MICHELE G. SULLIVAN

MDedge News

DALLAS – Nintedanib, a tyrosine kinase inhibitor, decreased by 44% the annual rate of lung function decline among patients with interstitial lung disease associated with systemic sclerosis, a year-long study has found.

In a placebo-controlled 52-week trial, forced vital capacity (FVC) in patients who took nintedanib (Ofev) declined by a mean of 52 mL – significantly less than the mean 93-mL decline seen among those who were given placebo, Oliver Distler, MD, said at the annual meeting of the American Thoracic Society.

*“These are people in their mid-40s and -50s. They have a long time to go. If there is an annual preservation of lung function by 40%, if you have that every year, it becomes very surely clinically significant. A decline in FVC is also a good surrogate marker of mortality in interstitial lung disease associated with systemic sclerosis.”*

“These are people in their mid-40s and -50s,” said Dr. Distler of the University of Zürich. “They have a long time to go. If there is an annual preservation of lung function by 40%, if you have that every year, it becomes very surely clinically significant. A decline in FVC is also a good surrogate marker of mortality in interstitial lung disease associated with systemic sclerosis. Assuming the effects are ongoing above the 1 year we looked at, then indeed these results are clinically important.”

The study was simultaneously published in the New England Journal of Medicine. Nintedanib is already approved for idiopathic pulmonary fibrosis. But some data suggest that it also exerts antifibrotic and anti-inflammatory effects in animal models of systemic sclerosis and inflammatory lung disease (ILD). SENSICIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) investigated the molecule's use in patients with ILD associated with systemic sclerosis.

Conducted in 32 countries, SENSICIS comprised 576 patients with the disorder, whose sclerosis affected at least 10% of their lungs. They were assigned to 52 weeks of either placebo or 150 mg nintedanib twice weekly. However, patients stayed on their blinded treatment until the last patient enrolled had finished the year of treatment; some patients took the drug for 100 weeks, Dr. Distler said.

The primary endpoint was annual rate of decline in the forced vital capacity (FEV). Secondary endpoints included changes of the modified Rodnan skin score and in the total score on the St. George's Respiratory Questionnaire.

Patients were a mean of 54 years old, with a mean disease duration of about 3 years. About half had diffuse cutaneous systemic sclerosis; the sclerosis was limited in the remainder. The mean extent of lung fibrosis was about 36%. Half were taking mycophenolate at baseline, which was allowed as background treatment, along with up to 10 mg/day of prednisone. Any patient who experienced clinically significant lung function deterioration could receive additional therapy at the investigator's discretion.

The mean baseline FEV for these patients was 72.5% of predicted value. The mean diffusing capacity of the lungs for carbon monoxide was 53% of expected capacity.

Most patients completed the study (80% of the active group and 89% of the placebo group). The mean drug exposure duration was 10 months in the active group and 11 in the placebo group.

Improvement began early in treatment, with the efficacy curves separating by week 12 and continuing to diverge. After 52 weeks of therapy, the annual rate of change was 41 mL less in the active group than in the placebo group (–54.4 mL vs. –93.3 mL). The mean adjusted absolute change from baseline was –54.6 mL in the active group and –101 mL in the placebo at week 52. Significantly fewer patients taking nintedanib also lost more than 10% of FVC by week 52 (16.7% vs. 18%).

The St. George's Respiratory Questionnaire score improved about one point in the active group and declined about one point in the placebo group.



Dr. Oliver Distler

Nintedanib was equally effective across a number of subgroups, including those divided by sex, age, and race. Antitopoisomerase antibodies and so-called antitopoisomerase I antibody status did not affect nintedanib's action. Nintedanib also significantly improved scores on the Health Assessment Questionnaire Without Disability Index and Dyspnea.

More patients in the active group than on placebo discontinued treatment because of a serious adverse event (16% vs. 8.7%). The most common of these were diarrhea (75.7% vs. 31%), nausea (31.6% vs. 13.5%), and vomiting (24.7% vs. 10.4%).

Skin ulcers occurred in about 18% of each group. Patients in the active group were significantly more likely to develop elevated alanine and aspartate aminotransferase of up to three times normal levels (4.9% vs. 0.7%).

The trial had some limitations. Patients with clinically significant pulmonary hypertension were excluded so the data cannot be applied to patients with this comorbidity.

The nintedanib and placebo groups showed no difference in patient-reported outcomes and health-related quality of life. No treatment effect was observed with respect to skin fibrosis, as assessed with the use of the modified Rodnan skin score.

In addition, treatment did not significantly affect mortality rates. Over the treatment period, 10 patients in the nintedanib group and 9 in the placebo group died (3.5% vs. 3.1%). In addition, researchers stated, “The lower rate of decline in FVC in the nintedanib group was not accompanied by a benefit with respect to health-related quality of life. ... An uncontrolled open-label extension study (NCT03313180) is ongoing and will provide long-term data on nintedanib therapy in patients with ILD associated with systemic sclerosis.”

The study was sponsored by Boehringer Ingelheim. Dr. Distler was the primary investigator on the trial.

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**Daniel R. Ouellette, MD, FCCP, comments:** She had traveled a long way to come and see me. The young pharmacist in her 30s had struggled for several years to balance her symptoms of systemic sclerosis with the demands of a busy profession. Upon learning that she might have lung disease, she had sought a referral to a tertiary center specialty clinic in the geographically diffuse medical system where we both worked. Thus began regular visits with pulmonary function tests, CT scans, and discussions about immunosuppressive regimens, interspersed with friendly chit-chat. Over time, her interstitial lung disease steadily worsened. She died years ago waiting for her transplant. It is good to think that in nintedanib we might have a medicine that would slow progression of this terrible disease. We need more research to confirm these findings and to learn if other important outcomes are improved as well.



**SOURCE:** Distler O et al. ATS 2019, Abstract A7360.



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# Cannabis vaping among teens tied to tobacco use

BY HEIDI SPLETE

MDedge News

One in 10 high school students has used an e-cigarette device to vaporize (vape) cannabis and that practice is associated with cigar, waterpipe, and e-cigarette use, findings from a survey of nearly 3,000 adolescents have shown.

“Although the prevalence of e-cigarette use among youth has increased dramatically in the past decade, little epidemiologic data exist on the prevalence of using e-cigarette devices or other specialised devices to vaporise (‘vape’) cannabis in the form of hash oil, tetrahydrocannabinol (THC) wax or oil, or dried cannabis buds or leaves,” wrote Sarah D. Kowitt, PhD, of the University of North Carolina, Chapel Hill, and colleagues. “This is surprising given that (1) cannabis (also referred to as marijuana) and e-cigarettes are the most commonly used substances by adolescents in the USA, (2) evidence exists that adolescents dual use both tobacco e-cigarettes and cannabis, and (3) longitudinal research suggests that use of e-cigarettes is associated with progression to use of cannabis.”

In a study published in *BMJ Open*, the researchers used data from the 2017 North Carolina Youth Tobacco Survey, a school-based survey of students in grades 6-12. The study population included 2,835 ad-

olescents in grades 9-12.

Overall, 9.6% of students reported ever vaping cannabis. In multivariate analysis, cannabis vaping was significantly more likely among adolescents who reported using e-cigarettes (adjusted odds ratio 3.18), cigars (aOR 3.76), or water pipes (aOR 2.32) in the past 30 days, compared with peers who didn’t use tobacco.



The researchers found no significant association between smokeless tobacco use or traditional cigarette use in the past 30 days and vaping cannabis.

In a bivariate analysis, vaping cannabis was significantly more common among males vs. females (11% vs. 8.2%) and among non-Hispanic white students (11.3%), Hispanic students (10.5%), and other

non-Hispanic students (11.8%) compared with non-Hispanic black students (5.0%).

In addition, prevalence of cannabis vaping increased with grade level, from 4.7% of 9th graders to 15.5% of 12th graders.

The health impacts of vaping cannabis are not well researched, but the researchers note that among the

bis behavior, lack of data on specific products, and lack of data on whether teens used specialized devices or e-cigarettes for cannabis vaping. However, the findings are consistent with studies on prevalence of cannabis vaping in other states such as Connecticut and California. “No studies to our knowledge have examined how adolescents who vape cannabis use other specific tobacco products (i.e., cigarettes, cigars, waterpipe, smokeless tobacco),” the researchers wrote.

The findings confirm that a large number of adolescents who use tobacco products have vaped cannabis as well, and this growing public health issue “is likely to affect and be affected by tobacco control and cannabis policies in states and at the federal level in the USA,” the researchers concluded.

“Increased research investigating how youth use e-cigarette devices for other purposes beyond vaping nicotine, like the current study, is needed,” they added.

The study was supported in part by the National Cancer Institute and the Food and Drug Administration’s Center for Tobacco Products. The researchers had no financial conflicts to disclose.

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**SOURCE:** Kowitt SD et al. *BMJ Open*. 2019 Jun 13. doi: 10.1136/bmjopen-2018-028535.

## Eosinophil-guided therapy reduces corticosteroid use in COPD

BY BIANCA NOGRADY

MDedge News

Using eosinophil levels to guide steroid treatment in patients with chronic obstructive pulmonary disease (COPD) was found to be noninferior to standard treatment in terms of the number of days out of hospital and alive, new research has found.

Writing in the *Lancet Respiratory Medicine*, researchers reported the outcomes of a multicenter, controlled, open-label trial comparing eosinophil-guided and standard therapy with systemic corticosteroids in 318 patients with COPD.

Pradeesh Sivapalan, MD, of the respiratory medicine section of Herlev and Gentofte Hospital at the University of Copenhagen, and coauthors wrote that eosinophilic inflammation had been seen in 20%-40% of patients with acute exacerbations of COPD. Patients with higher eosinophilic blood counts were at increased risk of acute exacerbations but were also more likely to benefit from corticosteroid treatment.

In the eosinophil-guided therapy arm of the

study, 159 patients received 80 mg of intravenous methylprednisolone on day 1, then from the second day were treated with 37.5 mg of prednisolone oral tablet daily – up to 4 days – only on days when their blood eosinophil count was at least  $0.3 \times 10^9$  cells/L. In the control arm, 159 patients also received 80 mg of intravenous methylprednisolone on day 1, followed by 37.5 mg of prednisolone tablets daily for 4 days.

After 14 days, there were no significant differences between the two groups for mean days alive and out of hospital.

There were 12 more cases of readmission with COPD, including three fatalities, in the eosinophil-guided group within the first month. However the authors said these differences were not statistically significant, but “because the study was not powered to detect differences in this absolute risk range, we cannot rule out that this was an actual harm effect from the interventional strategy.”

The eosinophil-guided therapy group did show more than a 50% reduction in the median duration of systemic corticosteroid therapy, which was 2 days in the eosinophil-guided group, com-

pared with 5 days in the control group ( $P$  less than .0001), and the differences between the two groups remained significant at days 30 and 90.

“The tested strategy was successful in reducing the exposure to systemic corticosteroids, but we cannot exclude the possibility that a more aggressive algorithm, such as a single dose of systemic corticosteroid, might have been more effective,” the authors wrote.

At the 90-day follow-up, there were no differences in the number of infections requiring antibiotic treatment, nor in dyspepsia, ulcer complications, or initiation of new proton-pump inhibitor treatment.

The study was supported by the Danish Regions Medical Fund and the Danish Council for Independent Research. Two authors declared personal fees from pharmaceutical companies outside the submitted work. No other conflicts were declared.

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**SOURCE:** Sivapalan P et al. *Lancet Respir Med*. 2019 May 20. doi: 10.1016/S2213-2600(19)30176-6.

# Peanut desensitization comes at cost of anaphylaxis

BY HEIDI SPLETE

MDedge News

**O**ral immunotherapy reduced sensitivity to peanuts in allergic individuals, but at the cost of increased risk of anaphylaxis and other reactions, based on a meta-analysis from more than 1,000 patients published in the *Lancet*.

In the Peanut Allergen Immunotherapy, Clarifying the Evidence (PACE) systematic review and meta-analysis, Derek K. Chu, MD, of McMaster University, Hamilton, Ont., and colleagues reviewed 12 trials conducted between 2011 and 2018 with a total of 1,041 patients (median age, 9 years).

Overall, the risk of anaphylaxis was significantly higher among children who received oral immunotherapy, compared with no therapy (risk ratio, 3.12) as was anaphylaxis frequency (incidence rate ratio, 2.72) and use of epinephrine (RR, 2.21).

In addition, oral immunotherapy increased serious adverse events, compared with no therapy (RR, 1.92). Nonanaphylactic reactions also went up among oral immunotherapy patients, with increased risk for vomiting (RR, 1.79),

angioedema (RR, 2.25), upper respiratory tract reactions (RR, 1.36), and lower respiratory tract infections (RR, 1.55).

Quality of life scores were not significantly different between patients who did and did not receive oral immunotherapy, the researchers noted.

The oral immunotherapy consisted of defatted, lightly roasted peanut flour in 10 studies, and a combination of peanut paste, peanut extract, or ground and defatted peanut in the other studies.

The oral immunotherapy did induce desensitization to peanuts in support of earlier studies including the subcutaneous immunotherapy trial, but “this outcome does not translate into achieving the clinical and patient-desired aim of less allergic reactions and anaphylaxis,” Dr. Chu and associates wrote.

However, “rather than take the view that these data denounce current research in oral immunotherapy as not successful, we instead suggest that this research has reached an important milestone in mechanistic but not clinical efficacy. From a clinical or biological perspective, the apparently paradoxical desensitization versus longitudinal clinical findings show the lability and unreliabil-

ity of allergen thresholds identified during oral food challenges because patients often unpredictably reacted to previously tolerated doses outside of clinic,” they emphasized.

The findings were limited by several factors including the small sample size, compared with similar studies for asthma or cardiovascular conditions, and by incomplete or inconsistent data reporting, the researchers noted. However, the results are the most comprehensive to date, and support the need for food allergy treatments with better safety profiles, using peanut allergy immunotherapy as a model for other food allergies.

Dr. Chu and two other authors reported being investigators on a federally funded ongoing peanut oral immunotherapy trial. Two authors reported receiving a variety of grants from organizations such as the National Institutes of Health; the American Academy of Allergy, Asthma, & Immunology; or pharmaceutical companies.

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**SOURCE:** Chu DK et al. *Lancet*. 2019 Jun 1;393:2222-32.

## COPD exacerbations associated with poor sleep quality

BY AMY KARON

MDedge News

### FROM THE JOURNAL CHEST®

Poor subjective sleep quality was associated with subsequent symptomatic exacerbations of chronic obstructive pulmonary disease in an 18-month prospective study of 480 patients.

“Poor sleep quality in COPD has previously been associated with reduced health-related quality of life and reduced physical activity during the day,” wrote Matthew Shorofsky, MD, of McGill University, Montreal, and associates. Their report is in *CHEST*. “However, to our knowledge, this is the first population-based longitudinal study evaluating exacerbation risk in relation to subjective sleep disturbances and assessing previously diagnosed and undiagnosed COPD.”

The study included participants enrolled in the Canadian Respiratory Research Network and the Canadian Cohort Obstructive Lung Disease (CanCOLD) study who had COPD, available baseline PSQI scores, and 18 months of follow-up data. The PSQI includes 19 questions on sleep quality, latency, duration, efficiency, disturbances, use of sleep medications, and daytime dysfunction. Total score ranges between 0 and 21, and a score above 5 is considered poor sleep. Online patient surveys and



quarterly phone interviews were used to track symptom-based exacerbations (at least 48 hours of increased dyspnea, sputum volume, or sputum purulence) and event-based exacerbations (a symptom-based exacerbation plus the use of antibiotics or corticosteroids or health services).

At baseline, 203 patients met the PSQI threshold for poor sleep quality. During follow-up, 185 patients had at least one COPD exacerbation. Poor sleep at baseline was significantly more prevalent among patients with symptoms-based COPD exacerbations (50.3%) than among patients without symptoms-based exacerbations (37.3%;  $P = .01$ ). Poor baseline sleep quality remained a significant risk factor for symptom-based exacerbations of COPD even after the researchers accounted

for the effect of age, gender, body mass index, smoking, depression, angina, baseline inhaled respiratory medications, forced expiratory volume in 1 second %predicted, and modified Medical Research Council (mMRC) dyspnea scale (adjusted risk ratio, 1.09; 95% confidence interval, 1.01-1.18;  $P = .02$ ).

Patients with at least one symptomatic exacerbation of COPD were significantly more likely to meet the threshold for poor sleep quality on the Pittsburgh Sleep Quality Index and have significantly higher median PSQI scores compared with patients without exacerbations (6.0 [interquartile range, 3.0 to 8.0] vs. 5.0 [2.0 to 7.0];  $P = .01$ ). Poor baseline sleep quality also was associated with event-based exacerbations and with a shorter time to symptoms-based

exacerbations. Sleep disturbances, such as rising to void or experiencing respiratory issues or pain during sleep, correlated most strongly with symptoms-based exacerbations.

Sleep disruption can impede immune function and increase systemic inflammation, which might worsen COPD control and increase exacerbation risk. The researchers acknowledged limitations to their study design. “Individuals with asthma or other obstructive lung diseases could not be definitively excluded; methacholine challenges were not performed. However, analyses excluding self-reported asthma were consistent with our main results. Second, because definitions of COPD exacerbation vary among studies, comparison may be limited.”

The CanCOLD study has received funding from the Canadian Respiratory Research Network, Astra Zeneca Canada, Boehringer Ingelheim Canada, GlaxoSmithKline Canada, Novartis, Merck Nycomed, Pfizer Canada, and Theratechnologies. Dr. Shorofsky had no disclosures. Several coinvestigators reported ties to GlaxoSmithKline, Novartis, Boehringer Ingelheim, Merck, Almirall, and Theratechnologies.

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**SOURCE:** Shorofsky M et al. *CHEST*. 2019 May 28. doi: 10.1016/j.chest.2019.04.132.

# Study IDs factors contributing to sleep clinic no-shows

BY DOUG BRUNK

MDedge News

SAN ANTONIO – Key determinants of no-show rates to a sleep clinic include being a new patient and lacking health insurance coverage, results from a single-center study showed.

“There are lots of people with sleep problems,” one of the study’s authors, Alvan Nzewuihe, MD, said

*“Patients who are new to the clinic or have no insurance coverage have a higher odds of not showing up to their appointment and delaying their care.”*

in an interview at the annual meeting of the Associated Professional Sleep Societies. “However, we have to identify these patients to be able to help them. If they don’t come to the sleep clinic [for assessment], we are going nowhere.”

In an effort to better understand determinants of no-show rates among sleep clinics, Dr. Nzewuihe and colleagues performed a 10-month, retrospective chart review of 2,532 patients scheduled at Saint Louis University’s SLUCare

Sleep Disorders Center during the months of July and October 2017 and April 2018. A no-show was determined if the patient failed to show up at their scheduled appointment on time or if they canceled their appointment. The researchers used multivariable logistic regression to determine which factors were independently associated with no-show rates.

Dr. Nzewuihe, a sleep medicine physician at the university, reported that the overall no-show rate during the study period was 21.2% and did not change with age, sex, or appointment factors such as time of day, day of week, or season of the year. Significant determinants of no-show rates included being a new patient (39.1% vs. 28.8% among established patients;  $P$  less than .0001) and having no health insurance (47.5% vs. public 28.3% vs private 24.2%;  $P$  less than .0001). Multivariate logistic regression confirmed the associations. New patients were 1.96 times more likely to not show up to the sleep clinic, compared with established patients, while patients with no health insurance coverage were 1.55 times more likely to not show up, compared with those with public health insurance.

The researchers wrote in their



Dr. Alvan Nzewuihe

poster abstract, “Patients who are new to the clinic or have no insurance coverage have a higher odds of not showing up to their appointment and delaying their care. Efforts to prioritize high-risk patients of nonadherence will help contribute to better care and outcomes. Further studies are needed to develop methods to decrease no-show rates once high-risk appointments have been identified.”

Dr. Nzewuihe acknowledged certain limitations of the study, includ-

ing its retrospective design and the fact that other possible contributing factors were not evaluated such as literacy level, employment status, and length of time between appointment booking and appointment date. The study’s first author was Julie Sahrman, DO. The researchers reported having no financial disclosures.

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**SOURCE:** Sahrman J et al. Sleep 2019, Abstract 0965.

# Insomnia common among transgender college students

BY DOUG BRUNK

MDedge News

SAN ANTONIO – Compared with their cisgender counterparts, transgender college students are nearly three times more likely to be diagnosed with and treated for insomnia symptoms, results from a large national population-based survey showed.

“That was a stronger association than we expected,” one of the study’s researchers, Lisa B. Matlen, MD, said during an interview at the annual meeting of the Associated Professional Sleep Societies.

According to Dr. Matlen, a fellow in the division of sleep medicine at the University of Michigan, Ann Arbor, the transgender population is “extremely understudied” when it comes to research on sleep disturbances. In an effort to examine the prevalence of sleep disturbances and the association between transgender identity and sleep disturbances among transgender college students in the United States, she and her colleagues drew from the 2016 and 2017 American College Health Association National College Health Assessment II, a confidential, voluntary, electronically administered survey of college and university students. In all, 224,233 students were polled, and the researchers analyzed their re-



Dr. Lisa B. Matlen

sponses to questions about gender identity, sleep symptoms, and diagnoses.

The mean age of the respondents was 23 years, and most (82%) were undergraduate students. Of the 224,233 students, 3,471 (1.6%) self-identified as transgender. More than half of the transgender students (61.9%) were white, 10.6% were Hispanic/Latino, 10.5% were Asian or Pacific Islander, 6.3% were biracial or multiracial, 4.6% were black, and the rest were from other ethnicities. Compared with cisgender students, transgender students had

*Transgender students were nearly three times more likely to have an insomnia diagnosis and treatment, compared with their cisgender counterparts.*

increased odds of having sleep disturbances (odds ratio, 1.6), not feeling well rested on 4 or more days per week (OR, 1.8), going to bed early on 3 or more days per week due to sleepiness (OR, 1.3), and having insomnia 3 or more days per week (OR, 1.7). In addition, transgender students were nearly three times more likely to have an insomnia

diagnosis and treatment, compared with their cisgender counterparts (OR, 2.9).

Dr. Matlen acknowledged certain limitations of the study, including the fact that it drew from a population-based sample and that the survey was based on self-reported information. The study’s first author was Ronald R. Gavidia Romero, MD. The researchers reported having no financial disclosures.

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**SOURCE:** Matlen LB et al. Sleep 2019.

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# Lemborexant: Sex-based dosing not anticipated

BY DOUG BRUNK

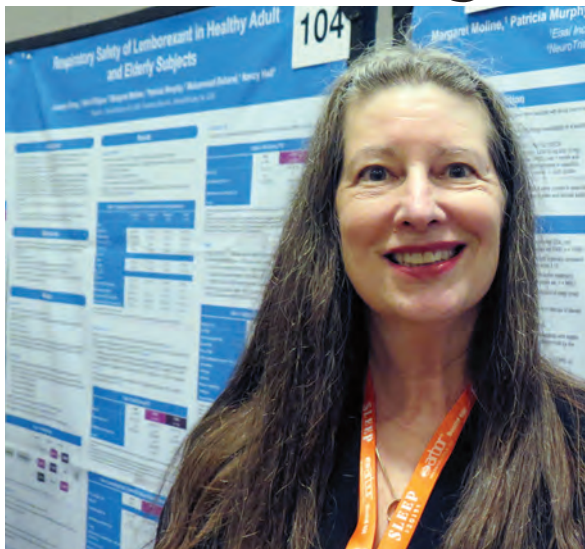
MDedge News

SAN ANTONIO – Lemborexant was effective in treating both sleep onset and maintenance variables in male and female subjects with insomnia, and it was well tolerated by both sexes, results from a pooled analysis showed.

A dual orexin receptor antagonist developed by Eisai, lemborexant is being studied as a treatment for insomnia disorder and irregular sleep-wake rhythm disorder. Early in 2019, the Food and Drug Administration accepted for review the New Drug Application for lemborexant for the treatment of insomnia. A target Prescription Drug User Fee Act date is set for Dec. 27, 2019.

“We evaluated early on whether exposure to lemborexant was going to be different between men and women,” lead study author Margaret Moline, PhD, said during an interview at the annual meeting of the Associated Professional Sleep Societies. “With some drugs, like zolpidem and other so-called Z drugs, because exposure is different, clinical studies could involve different dosing for different sexes. Because we knew the exposure to lemborexant wasn’t different between the sexes, we expected to see similar results in both sexes. That was the case.”

Dr. Moline, executive director of the Neurology Business Group and International Project Team Lead for the lemborexant clinical development program at Eisai, and colleagues presented pooled analyses of subject-reported sleep-onset latency (sSOL) and subject-reported wake after sleep onset (sWASO) from lemborexant phase 3 studies, SUNRISE-1 and SUNRISE-2. SUNRISE-1 was a 1-month, double-blind, placebo- and active-controlled, parallel-group study in 1,006 subjects. Participants were females aged



Dr. Margaret Moline

55 years and older and males aged 65 years and older with a primary complaint of sleep maintenance difficulties and an Insomnia Severity Index (ISI) total score of 13 or higher. SUNRISE-2 was a placebo-controlled, 6-month, active treatment, double-blind, parallel-group study in 949 subjects with insomnia disorder. Participants were females and males aged 18 years and older with a primary complaint of sleep onset and/or sleep maintenance difficulties and an ISI total score of 15 or higher. Both analyses included subjects randomized to placebo, lemborexant 5 mg, or lemborexant 10 mg. Each study included a single-blind placebo run-in period prior to randomization.

The pooled analysis of 1,693 subjects included 402 (23.7%) men and 1,291 (76.3%) women. Results on sSOL and sWASO were consistent with the significant results on sleep diary in the individual studies. In both sexes, sSOL for lemborexant 5 mg and lemborexant 10 mg was

significantly reduced versus that for placebo during the first 7 days and end of month 1 ( $P$  less than .05 for all comparisons). In women, the researchers observed significantly greater reductions in sWASO placebo for both lemborexant doses versus that with placebo (first 7 days and end of month 1;  $P$  less than .0001 for all comparisons). In males, sWASO decreased significantly, compared with placebo, for the first 7 days (lemborexant 5 mg and lemborexant 10 mg;  $P$  equal to or less than .0001) and at end of month 1 (lemborexant 10 mg only;  $P$  = .0032). For placebo, lemborexant 5 mg, and lemborexant 10 mg, the overall incidence of treatment-emergent adverse events was similar across sexes. Incidence of treatment-emergent serious adverse events was low for both sex subgroups; most events occurred in one subject each. Treatment-emergent adverse events leading to study drug withdrawal or interruption were few and similar across sexes for all treatments and was highest in males receiving lemborexant 10 mg. The most frequent treatment-emergent adverse events reported in males were somnolence, fatigue, and headache, while the most common in females were somnolence, headache, and urinary tract infection. About 3% of females (no males) reported a urinary tract infection; the incidence in females was similar across treatment groups.

“Overall, sleep diary outcomes in males and females were consistent with the significant results observed in the total populations of the individual studies,” Dr. Moline concluded. “A dose adjustment based on sex is not anticipated.”

The research was supported by Eisai. Dr. Moline is an employee of the company.

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**SOURCE:** Moline M et al. Sleep 2019, Abstract 0368.

## CPAP for infants with OSA is effective, with high adherence

BY TARA HAELE

MDedge News

DALLAS – Continuous positive airway pressure (CPAP) is an effective, feasible treatment for infants with obstructive sleep apnea (OSA), according to a study.

“Positive airway pressure is a common treatment for OSA in children,” wrote Christopher Cielo, DO, of Children’s Hospital of Philadelphia Sleep Center, and his colleagues. But the authors note that treating infants with CPAP can be more challenging because infants have less consolidated sleep, may have greater medical complexity, and have smaller faces that make mask fit, titration, and adherence difficult.

The researchers therefore compared use of CPAP for OSA on 32 infants who began the therapy before age 6 months and 102 school-

age children who began the therapy between ages 5 and 10 years, all treated at a single sleep center between March 2013 and September 2018.

Only one of the infants (mean age 3 months) had obesity, compared with 37.3% of the school-age children (mean age 7.7 years), but more of the infants (50%) had a craniofacial abnormality compared with the older children (8.9%) ( $P$  less than .001).

None of the infants had had an adenotonsillectomy, whereas the majority of the older children (80.4%) had ( $P$  less than .001). Rates of neurological abnormality and genetic syndromes (including Down syndrome) were similar between the groups.

In baseline polysomnograms, infants had a higher mean obstructive apnea-hypopnea index (AHI) compared with older children (22.6 vs. 12;  $P$  less than .001) and a slightly,

but significantly, lower oxygen saturation nadir (81% vs. 87%;  $P$  = .002).

Only 9.8% of the children and none of the infants used autotitrating. Similar proportions of both groups – 90.6% of infants and 93.1% of children – achieved a mean AHI below 5 with CPAP treatment, and both CPAP pressure and mean oxygen saturation nadir at final pressure were similar in both groups.

Adherence was higher in infants than in children: Infants used CPAP for at least some time for 93.3% of nights compared with children (83.4%) ( $P$  = .009), and infants used CPAP for more than 4 hours for 78.4% of nights, compared with 59.5% of nights among children ( $P$  = .04).

Barriers to adherence reported by caregivers were similar between both groups. The most common barrier was child behavior, such as crying or refusing the CPAP, which

25% of infant caregivers and 35.3% of child caregivers reported. While a higher proportion of caregivers reported a poor mask fit for infants (15.6%) than for children (10.8%), the difference was not significant ( $P$  = .47). Rates of skin irritation also did not significantly differ between the groups.

In addition to the limitations accompanying any retrospective analysis from a single center, another study limitation was the inability to account for differences in total sleep time between infants and school-age children in comparing CPAP usage.

The National Institutes of Health and the Francis Family Foundation funded the research. The authors had no disclosures.

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**SOURCE:** Cielo C et al. ATS 2019, Abstract A2786.

# Briefest flash of light can alter the circadian system

BY DOUG BRUNK

MDedge News

SAN ANTONIO – The human circadian system can be phase shifted by flashes of dim light that last as little as 10 microseconds, results from a novel study showed.

“This becomes a complementary way to help people with various kinds of circadian phase disorders,” the study’s first author, Jamie M. Zeitzer, PhD, said during an interview at the annual meeting of the Associated Professional Sleep Societies. “Right now under ideal laboratory circumstances, you can change someone’s circadian timing by about 3 hours. That’s not happening in the real world; that’s what you do in a lab. That’s with very bright light for 6 hours and very dim light the rest of the time.”

In an effort to build on previous literature related to circadian phase shifting and continuous light exposure in rodents and in humans, Dr. Zeitzer, of the department of psychiatry and behavioral sciences at Stanford (Calif.) University, and colleagues enrolled 56 healthy young men and women in their 20s and 30s to take part in two parallel 16-day studies. For the first 14 days, study participants maintained a regular sleep/wake cycle at home as

confirmed through actigraphy and sleep logs. They spent the final 2 days in a specialized time-isolation laboratory, during which the phase of the circadian pacemaker (salivary melatonin onset) was determined in constant routine conditions on



Dr. Jamie M. Zeitzer

evening one and two; light exposure occurred between these two phase determinations on night one.

Light exposure consisted of 1 hour of a sequence of light flashes delivered through a pair of modified welding goggles during enforced wake starting 2 hours after habitual bedtime. Flashes were presented every 15 seconds and varied either by duration (from 10 microseconds

to 10 seconds at a fixed intensity of 2,200 lux) or intensity (a range between 3 and 9,500 lux, with a duration fixed at 2 milliseconds).

Dr. Zeitzer and colleagues observed no significant difference in the phase shift created between flashes that were given at 10 microseconds and flashes that were given at 10 seconds. “That’s a six-log unit variation,” he said during a presentation of the results at the meeting. “There are a million times more photons given in 10-second flashes over the hour than there are in the 10-microsecond flashes. Despite the fact that there are a million more photons, you get the exact same phase shift in both of these conditions. You need very little light in order to generate these phase shifts. You’re talking about less than 1 second of light stretched out over 1 hour.”

The researchers also observed that flash intensity showed a sigmoidal relationship with phase shifting, with a half-maximal shift observed at 8 lux and 90% of the maximal shift occurring after exposure to flashes as dim as 50 lux. None of the flash sequences caused acute suppression of melatonin.

“We did not anticipate the invariance, that anything from 10 microseconds to 10 seconds gives us no difference [in phase shift-

ing],” Dr. Zeitzer said. “That was surprising. I thought that more light would be slightly less effective in terms of photons but still give a bigger [phase] shift, but that didn’t happen. In the intensity response, we see things are more sensitive to light flashes than they are to continuous light, which is also surprising. It implies that a different part of the eye is responding to light flashes than it is to continuous light. It provides more information about how to minimize the amount of light we’re using and maximize the amount of shift.”

Which photoreceptors underlie the responses remains unclear, he continued, “but given the characteristics of photoreceptors, our hypothesis is that flashes are being mediated through a cone cell response, while the response to continuous light is being primarily mediated through a melanopsin response. A future question we plan to investigate is, can selective sequential simultaneous activation of different photoreceptors create enhanced phase shifts?”

The study was supported by the Department of Defense. Dr. Zeitzer reported having no financial disclosures.

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**SOURCE:** Zeitzer JM et al. SLEEP 2019.

## Sleep quality linked to gut microbiome biodiversity

BY DOUG BRUNK

MDedge News

SAN ANTONIO – Better sleep quality and less sleepiness, but not sleep duration, are significantly associated with greater species richness and diversity of the gut microbiota, according to results from a population sample of adults.

“These findings are preliminary and very early in the growth of this field,” lead study author Erika W. Hagen, PhD, said during an interview at the annual meeting of the Associated Professional Sleep Societies

According to Dr. Hagen, an epidemiologist at the University of Wisconsin–Madison, experimental studies in mice have shown that disturbed sleep is associated with gut microbiota composition, and a few small experimental studies in humans have found associations between curtailed sleep and measures of gut microbiota richness and diversity.

In an effort to examine associations of subjectively and objectively assessed sleep metrics with indices of gut microbiome richness and diversity, Dr. Hagen and colleagues assessed 482 individuals who participated in the Survey of the Health of Wisconsin and completed in-home study visits in 2016. They provided fecal samples, partici-

pated in a week-long wrist actigraphy protocol to measure sleep, and completed questionnaires about sleep, diet, and other health and sociodemographic factors, and an assessment of physical activity by waist-worn actigraphy.

Metrics of species richness included the Chao1 and the ACE, which estimate the number of species. Metrics of the diversity of the gut microbiome included the Inverse Simpson index and the Shannon index. All metrics were regressed on self-reported sleep duration, extreme daytime sleepiness, the Epworth Sleepiness Scale (ESS), and actigraphy-measured sleep duration and wake after sleep onset (WASO). Next, the researchers estimated associations between each of the sleep and diversity measures separately, adjusting for age and sex and then additionally adjusting for body mass index, moderate-vigorous physical activity, and dietary fat and fiber.

The mean age of the 482 subjects was 56 years, 57% were female, and the mean body mass index was 30 kg/m<sup>2</sup>. After the researchers adjusted for gender and age, they found that greater WASO was statistically significantly associated with lower richness and alpha diversity (*P* less than .05). These associations remained significant on the Chao1 measure and borderline significant on the

ACE and Shannon measures after further adjustment for BMI, physical activity, and dietary fiber and fat. For example, 60 minutes greater WASO was associated with an approximate 26% population standard deviation reduction in microbial richness as measured by Chao1. In fully-adjusted models, greater daytime sleepiness was associated with lower richness and diversity on all indices (*P* = .01-.06).

“Our results suggest that sleep quality is associated with gut microbiome richness and diversity,” Dr. Hagen said. “Our results are in line with other research on this topic. What’s interesting is how your sleep over a period of time is affecting these measures of your microbiome. That’s something people can do something about with [eating] habits over time.”

She acknowledged certain limitations of the study, including the small sample size and the cross-sectional design. The study was supported by the University of Wisconsin School of Medicine and Public Health through the Wisconsin Partnership Program.

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**SOURCE:** Hagen EW et al. SLEEP 2019, Abstract 0106.

# Lung disease + screen time impact sleep quality

BY TARA HAELE

MDedge News

DALLAS – Children with cystic fibrosis or asthma report sleep interruptions 1 or 2 nights a week caused by their symptoms, but nighttime use of technology may contribute more to sleep problems, according to a new study.

“Routinely addressing sleep concerns, sleep hygiene, and mental health is important in the care of pediatric patients with chronic illness,” concluded Lauren Greenawald, DO, and colleagues at the Alfred I. duPont Hospital for Children in Wilmington, Del. The researchers presented their findings on sleep quality and mental health of children with asthma or cystic fibrosis (CF) at the American Thoracic Society’s international conference.

Dr. Greenawald’s team screened 31 children (aged 7-17 years) with CF and 34 children with asthma for anxiety, depression, and ADHD. The researchers also assessed the children’s sleep hygiene, sleep quality, and physical and emotional symptoms. Instruments included the validated Pediatric Daytime Sleepi-

ness Scale (PDSS), Pediatric Quality of Life Inventory, and Patient-Reported Outcomes Measurement Information System Pediatric Anxiety Survey, plus an investigator-designed survey about sleep habits.

Just over half the children with CF (52%) and 14% of children with asthma had mental health diagnoses (*P* less than .01). The same proportion of patients with CF (52%) and nearly a third of patients with asthma (30%) reported they often or always felt they needed more sleep based on the PDSS.

Further, 42% of children with CF and 55% of children with asthma said their symptoms kept them awake 1-2 nights a week. Only 6% of asthma patients and no CF patients said their symptoms keep them awake often, 3-4 nights a week. Just over a third of children with CF (36%) and 46% of those with asthma thought they would sleep better if they didn’t have a medical condition.

Yet, for the vast majority of children, the sleeping problems did not appear to result from worry about their illness: 85% of those with CF and nearly all of those with asthma

(97%) did not have trouble sleeping as a result of anxiety about their medical condition.

The researchers identified nighttime use of technology that may affect the children’s sleep in ways similar to that of the general population. Many of the participants – 68% of those with CF and 47% of those with asthma – reported texting or using social media or other technology an hour before going to bed. In addition, 55% of those with CF and 25% of those with asthma said they use their phone after the lights are out at least 5 nights a week. One in five of those with CF (20%) said they go to bed later than they planned at least 5 days a week because of social media or texting, though only 6% of those with asthma said the same.

Despite the children’s reports of inadequate sleep, very few – 3.2% of children with CF and 5.9% of children with asthma – reported feeling low daytime energy.

The use of child self-reporting in the presence of family members is a study limitation, including potentially introducing social

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP,**  
**comments:** Every day,

parents are giving their BABIES cell phones in my exam room to “entertain” or “pacify” them with videos or Youtube. And when I talk to adolescents about no screen time 1 hour prior to bedtime, they comment “it’s okay because I have it on the dimmer light at night.” This report is extremely important!



desirability bias.

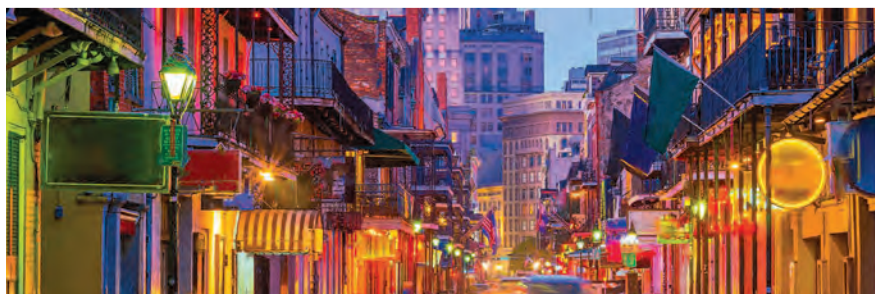
The research was funded by the Nemours Summer Undergraduate Research Program. The authors reported no disclosures.

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**SOURCE:** Greenawald L et al. ATS 2019, Abstract A2788.

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# CF drug picks up indication for children as young as 6

BY M. ALEXANDER OTTO

MDedge News

The Food and Drug Administration has expanded the indication for an oral tezacaftor/ivacaftor combination for cystic fibrosis (Symdeko), to include children as young as 6 years old.

The drug was approved in 2018 for patients aged 12 years and older who have the most common cause of the disease, two alleles for the F508del mutation in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, or at least one other CFTR mutation responsive to the combination, as listed in labeling.

The original approval was based on three phase 3, double-blind, placebo-controlled trials, which demonstrated improvements in lung function and other key measures of the disease. One trial that found a 6.8% mean improvement in lung function testing over placebo at 8 weeks, and another that found a 4% improvement at 24 weeks, with few-

er respiratory exacerbations and improved respiratory-related quality of life. A third trial in patients without the indicated genetic mutations was ended early for futility.

The efficacy in children under 12 years was extrapolated from those trials, plus an open-label study that found similar effects.

Labeling warns of elevated liver enzymes and cataracts in children, and notes that the drug should be taken with food that contains fat. Labeling also recommends against use with strong cytochrome P450 3A4 (CYP3A) inducers – rifampin, phenobarbital, St. John’s wort, among others – because they might reduce efficacy, and against use with CYP3A inhibitors – ketoconazole, clarithromycin, Seville oranges, grapefruit juice, etc. – because of the risk of increased exposure.

The most common side effects are headache, nausea, sinus congestion, and dizziness. The FDA has cleared a CF gene test to check for the required mutations. Symdeko is marketed by Vertex Pharmaceuticals.

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# Penicillin-susceptible *Streptococcus pneumoniae* most common cause of bacteremic CAP

BY JILL D. PIVOVAROV

MDedge News

A study found that only 2% of children hospitalized with community-acquired pneumonia (CAP) actually had any causative pathogen in their blood culture results, despite national guidelines that recommend blood cultures for all children hospitalized with moderate to severe CAP.

The guidelines are the 2011 guidelines for managing CAP published by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) (Clin Infect Dis. 2011 Oct;53[7]:617-30).

Cristin O. Fritz, MD, of the Children's Hospital of Colorado, Aurora, and associates conducted a data analysis of the EPIC (Etiology of Pneumonia in the Community) study to estimate prevalence, risk factors, and clinical outcomes in children hospitalized with bacteremic CAP and to evaluate the relationship between positive blood culture results, empirical antibiotics, and changes in antibiotic treatment regimens.

Data were collected at two Tennessee hospitals and one Utah hospital during Jan. 1, 2010–June 30, 2012. Of the 2,358 children with CAP enrolled in the study, 2,143 (91%) with blood cultures were included in Dr. Fritz's analysis. Of the 53 patients presenting with positive

blood culture results, 46 (2%; 95% confidence interval: 1.6%-2.9%) were identified as having bacteremia. Half of all cases observed were caused by *Streptococcus pneumoniae*, with *Staphylococcus aureus* and *Streptococcus pyogenes* noted less frequently, according to the study published in Pediatrics.

A previous meta-analysis of smaller studies also found that children with CAP rarely had positive blood culture results, a pooled prevalence of 5% (Pediatr Infect Dis J. 2013;32[7]:736-40). Although it is believed that positive blood culture results are key to narrowing the choice of antibiotic and predicting treatment outcomes, the literature – to date – reveals a paucity of data supporting this assumption.

Overall, children in the study presenting with bacteremia experienced more severe clinical outcomes, including longer length of stay, greater likelihood of ICU admission, and invasive mechanical ventilation and/or shock. The authors also observed that bacteremia was less likely to be detected in children given antibiotics after admission but before cultures were obtained (0.8% vs 3%;  $P = .021$ ). Pleural effusion detected with chest radiograph also consistently indicated bacteremic pneumonia, an observation made within this and other similar studies.

Also of note in detection is the biomarker procalcitonin, which

is typically present with bacterial disease. Dr. Fritz and colleagues stressed that, because the procalcitonin rate was higher in patients presenting with bacteremia, “this information could influence decisions around culturing if results are rapidly available.”

Compared with other studies reporting prevalence ranges of 1%-7%, the prevalence of bacteremia in this study is lower at 2%. The authors attributed the difference to a possible potential limitation with the other studies, for which culture data were only available for a median 47% of enrollees. Dr. Fritz and her colleagues caution that, “because cultures were obtained at the discretion of the treating clinician in a majority of studies, blood cultures were likely obtained more often in those with more severe illness or who had not already received antibiotics.”

The authors observed that penicillin-susceptible *S. pneumoniae* was the most common cause of bacteremic CAP. They further acknowledged that their study and findings by Neuman et al. in 2017 give credence to the joint 2011 PIDS/IDSA guideline recommending narrow-spectrum aminopenicillins specifically to treat children hospitalized due to suspected bacterial CAP.

Despite its small sample size, the results of this study clearly demonstrate that children with bacteremia because of *S. pyogenes* or *S. aureus*

experience increased morbidity, compared with children with *S. pneumoniae*, they said

While this is acknowledged to be one of the largest studies of its kind to date, a key limitation was the small number of observable patients with bacteremia, which prevented the researchers from conducting a more in-depth analysis of risk factors and pathogen-specific differences. That one-fourth of patients received inpatient antibiotics before cultures could be collected also likely led to an underestimation of risk factors and misclassification bias.

“In an era with widespread pneumococcal vaccination and low prevalence of bacteremia in the United States, children admitted with CAP that have pleural effusion or require ICU admission may represent a high-yield population for identifying bacteremia,” they wrote.

Dr. Fritz had no conflicts of interest to report. Some coauthors cited multiple sources of potential conflict of interest related to consulting fees, grant support, and research support from various pharmaceutical companies and agencies. The study was funded by the National Institutes of Health and in part by a grant from the National Institute of Allergy and Infectious Diseases.

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**SOURCE:** Fritz CO et al. Pediatrics. 2019;144(1):e20183090.

## 10-valent pneumococcal vaccine effective in boys and girls

BY LUCAS FRANKI

MDedge News

A 10-valent pneumococcal conjugate vaccine appeared equally effective against pneumococcal disease in boys and girls, according to Heta Nieminen, MD, of the National Institute for Health and Welfare in Tampere, Finland, and associates.

For the study, published in Vaccine, the investigators conducted a post hoc analysis of the phase 3/4, cluster-randomized, double-blind FinIP trial, in which more than 30,000 infants received the PHiD-CV10 vaccine or a placebo. Patients were aged less than 7 months when they received their first vaccination, and received two or three primary doses, plus a booster shot after the age of 11 months.

In term infants, vaccine effectiveness was similar in boys and girls; while the vaccine worked marginally better in girls, the difference was not



significant. Infants who received the 2 + 1 schedule had vaccine effectiveness similar to that of those who received the 3 + 1 schedule. In a smaller subanalysis of 1,519 preterm infants, outcomes of pneumonia were more common, but the vaccine seemed to confer protection, although the

sample size was not large enough for statistical significance to be reached.

“The point estimates of vaccine effectiveness suggest protection in both sexes, and also among the preterm and low-birth-weight infants. ... There were no significant differences between the 2 + 1 and 3 + 1 schedules in any of the subgroups analyzed. Based on this study, the 2 + 1 or “Nordic” schedule is sufficient also for the risk groups such as the preterm or low-birth-weight infants,” the investigators concluded.

Five study authors are employees of the National Institute for Health and Welfare, which received funding for the study from GlaxoSmithKline. Four coauthors are employees of GlaxoSmithKline; three of them own shares in the company.

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**SOURCE:** Nieminen H et al. Vaccine. 2019 May 20. doi: 10.1016/j.vaccine.2019.05.033.

# Cardiovascular burden driven by unmet social needs

BY JENNIFER REISING

MDedge News

WASHINGTON – Having unmet social needs plays a key role in raising the risk of cardiovascular disease among immigrant, socially isolated, and low-income populations, according to a study.

“Although there have been great medical interventions and our technology keeps improving, we can’t prevent the burden of cardiovascular disease. It’s the social factors that are playing this role,” said Ana Palacio, MD, MPH, of the Uni-

*“The most surprising finding was how much weight the social factors have in adding to the Framingham risk score, in taking a patient from a medium score to a higher score because of their social environment.”*

versity of Miami during her presentation of the study findings at the annual meeting of the Society of General Internal Medicine.

“We need to address issues at the patient’s home, such as food, isolation, and transportation, to help them prevent cardiovascular risk,” she added.

The study was designed to determine how patient-reported social determinants of health (SDH) had an effect on the Framingham risk score (FRS). Researchers also wanted to assess the relationship between the SDH score and individual risk factors for cardiovascular health, including blood pressure, hemoglobin A<sub>1c</sub>, LDL cholesterol, body mass index, tobacco use,

and physical activity.

Results showed that several SDH factors significantly increase the FRS score, including being born outside of the United States, living alone, having a high social isolation score, and having a low geocoded-based median household income (*P* less than .01). The calculated SDH score ranged from 0 to 59.

Higher SDH scores were associated with high FRS scores in the areas of poor blood pressure and diabetes control. Additionally, those who had financial strain, poor health literacy, stress, lack of education, and a low median household income were more likely to have a sedentary lifestyle. Black or Hispanic patients who were born outside the United States and had low median household income were at a higher risk of obesity.

The study also shows the prediction of poor blood pressure and diabetes control was superior through the 11,153 SDH self-survey responders, compared with census data. In the self-reported SDH survey, the predicted blood pressure was 0.74 (0.71-0.76) and the diabetes predictor was 0.77 (0.75-0.80). While the census-based deprivation index predicted blood pressure was 0.68 (0.64-0.70) and diabetes control was 0.73 (0.71-0.76). The retrospective cohort study originally involved 11,113 primary care patients who received care at the University of Miami Health System between Sept. 16, 2016, and Sept. 10, 2017, and answered an SDH survey. Of this group, 2,876 patients completed the electronic health record data to compile a score. This population had a mean age of 53.8 years and was 61% female; 38% were Hispanic and 9% were black. The mean household income was \$53,677 and 87% reported speaking English.

The study examined a total of 11 self-reported and census-based SDH factors. The self-reported

## VIEW ON THE NEWS

**G. Hossein Almassi, MD, FCCP, comments:**

This is a timely report adding science behind the well-known impact of poverty and lack of social resources on the well-being of the underserved minorities. It is in line with a published report from the University of Virginia group on the impact of these social factors on surgical outcomes after cardiac surgery (Ann Thorac Surg. Jun 2019;107:1706-12). The challenge for physicians is how to optimize the care of these patients to improve their outlook.



factors were race/ethnicity, education, financial strain, stress, tobacco use and physical activity, social isolation, years living in the United States, health literacy, and delayed care. The remaining factors were based on an area deprivation index and census-driven median household income.

“The most surprising finding was how much weight the social factors have in adding to the Framingham risk score, in taking a patient from a medium score to a higher score because of their social environment,” said Dr. Palacio.

The study was funded by the Precision Medicine and Health Disparities Collaborative and was supported by the National Institute on Minority Health and Health Disparities and National Human Genome Research Institute of the National Institutes of Health.

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## Long-term antibiotic use may heighten stroke, CHD risk

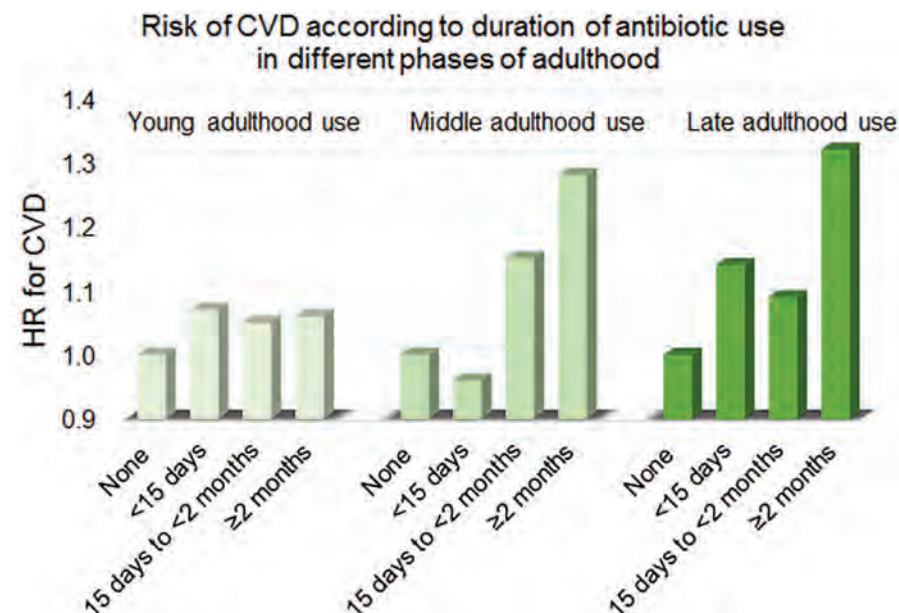
BY JAKE REMALY

MDedge News

**A**mong middle-aged and older women, 2 or more months’ exposure to antibiotics is associated with an increased risk of coronary heart disease or stroke, according to a study in the European Heart Journal.

Women in the Nurses’ Health Study who used antibiotics for 2 or more months between ages 40 and 59 years or at age 60 years and older had a significantly increased risk of cardiovascular disease, compared with those who did not use antibiotics. Antibiotic use between 20 and 39 years old was not significantly related to cardiovascular disease.

Prior research has found that antibiotics may have long-lasting effects on gut microbiota and relate to cardiovascular disease risk.



“Antibiotic use is the most critical factor in altering the balance of microorganisms in the gut,” said lead investigator Lu Qi, MD, PhD, in a

news release. “Previous studies have shown a link between alterations in the microbiotic environment of the gut and inflammation and narrow-

ing of the blood vessels, stroke, and heart disease,” said Dr. Qi, who is the director of the Tulane University Obesity Research Center in New Orleans and an adjunct professor of nutrition at Harvard T.C. Chan School of Public Health in Boston.

To evaluate associations between life stage, antibiotic exposure, and subsequent cardiovascular disease, researchers analyzed data from 36,429 participants in the Nurses’ Health Study. The women were at least 60 years old and had no history of cardiovascular disease or cancer when they completed a 2004 questionnaire about antibiotic usage during young, middle, and late adulthood. The questionnaire asked participants to indicate the total time using antibiotics with eight categories ranging from none to 5 or more years.

The researchers defined incident

Continued on following page

Continued from previous page

cardiovascular disease as a composite endpoint of coronary heart disease (nonfatal myocardial infarction or fatal coronary heart disease) and stroke (nonfatal or fatal). They calculated person-years of follow-up from the questionnaire return date until date of cardiovascular disease diagnosis, death, or end of follow-up in 2012.

Women with longer duration of antibiotic use were more likely to use other medications and have unfavorable cardiovascular risk profiles, including family history of myocardial infarction and higher body mass index. Antibiotics most often were used to treat respiratory infections. During an average follow-up of 7.6 years, 1,056 participants developed cardiovascular disease.

In a multivariable model that adjusted for demographics, diet, lifestyle, reason for antibiotic use, medications, overweight status, and other factors, long-term antibiotic use – 2 months or more – in late adulthood was associated with significantly increased risk of cardiovascular disease (hazard ratio, 1.32), as was long-term antibiotic use in middle adulthood (HR, 1.28).

Although antibiotic use was self-reported, which could lead to misclassification, the participants were health professionals, which may mitigate this limitation, the authors noted. Whether these findings apply to men and other populations requires further study, they said. Because of the study's observational design, the results "cannot show that antibiotics cause heart disease and stroke, only that there is a link between them,"

Dr. Qi said. "It's possible that women who reported more antibiotic use might be sicker in other ways that we were unable to measure, or there may be other factors that could affect the results that we have not been able to account of."

"Our study suggests that antibiotics should be used only when they

are absolutely needed," he concluded. "Considering the potentially cumulative adverse effects, the shorter time of antibiotic use the better."

The study was supported by National Institutes of Health grants, the Boston Obesity Nutrition Research Center, and the United States-Israel Binational Science Foundation. One

author received support from the Japan Society for the Promotion of Science. The authors had no conflicts of interest.

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**SOURCE:** Heianza Y et al. *Eur Heart J*. 2019 Apr 24. doi: 10.1093/eurheartj/ehz231.

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not available for the digital edition.

#### VIEW ON THE NEWS

**G. Hossein Almassi, MD, FCCP, comments:** This large observational study provides evidence for a link between long-term use of antibiotics and the increased risk of cardiovascular disease in older women. This challenges the physicians in being more selective in their prescription of antibiotics for their patients. In support of the authors' suggestion on the potential role of gut microbiome on dietary metabolites, some recent publications on this topic are worth reading (*Eur Heart J*. 2019 Apr 23; <https://doi.org/10.1093/eurheartj/ehz259>; *JAMA*. 2019;321[22]:2149-51; *J Am Heart Assoc*. 2017;6[7]:e004947).

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# Dexmedetomidine fails to reduce 90-day mortality in ICU patients supported by mechanical ventilation

BY JEFF CRAVEN

MDedge News

**D**exmedetomidine fell short for reducing 90-day mortality as the primary sedative for patients on mechanical ventilation, according to results of the randomized, controlled, open-label SPICE III trial, which was presented at the annual meeting of the American Thoracic Society and simultaneously published in the *New England Journal of Medicine*.

“Among patients undergoing mechanical ventilation in the ICU, those who received early dexmedetomidine for sedation had a rate of death at 90 days similar to that in the usual-care group and required supplemental sedatives to achieve the prescribed level of sedation,” Yahya Shehabi, PhD, of Monash University in Clayton, Australia,

and colleagues wrote.

The study was conducted in 74 ICUs in eight countries. Researchers randomly assigned 4,000 patients who were critically ill, had received ventilation for less than 12 hours, and were likely to require mechanical ventilation for at least the next day to either dexmedetomidine or usual care (propofol, midazolam, or another sedative).

The sedation goal was a Richmond Agitation and Sedation Scale (RASS) score of -2 (lightly sedated) to +1 (restless), and was assessed every 4 hours. Intravenous dexmedetomidine was administered at 1 mcg/kg of body weight per hour without a loading dose and adjusted to a maximum dose of 1.5 mcg/kg per hour to achieve a RASS score in the target range. Use was continued as clinically required for up to 28 days.

The modified intention-to-treat analysis included 3,904 patients. The 90-day mortality rate was 29.1% (556 of 1,948 patients) for patients who received dexmedetomidine and 29.1% (569 of 1,956 patients) for those who received usual care. There was no significant difference for patients with suspected or proven sepsis at randomization and those without sepsis. Mortality did not vary based on country, cause of death, or discharge destination.

Dr. Shehabi and colleagues noted that, for 2 days after randomization, patients who received dexmedetomidine were also given propofol (64% of patients), midazolam (3%), or both (7%) as supplemental sedation. In the control group, 60% of the patients received propofol, 12% received midazolam, and 20% received both. About 80% of patients in both groups received fentanyl.

The use of multiple agents may reflect sedation requirements during the acute phase of critical illness.

With regard to adverse events, the patients receiving dexmedetomidine more commonly experienced bradycardia and hypotension than the usual-care group.

SPICE III was funded in part by a grant from the National Health and Medical Research Council of Australia and the National Heart Institute of Malaysia. Dr. Shehabi reports grants from the National Health and Medical Research Council of Australia, nonfinancial and other support from Pfizer, and nonfinancial and other support from Orion Pharma.

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**SOURCE:** Shehabi Y et al. *N Engl J Med*. 2019 May 19. doi: 10.1056/NEJMoa1904710.

## Elevated monocyte count predicted poor outcomes in idiopathic pulmonary fibrosis

BY JAKE REMALY

MDedge News

**A**n increased monocyte count at the time of diagnosis predicts poor outcomes among patients with idiopathic pulmonary fibrosis and other fibrotic diseases, including hypertrophic cardiomyopathy, systemic sclerosis, and myelofibrosis, according to research published in *The Lancet Respiratory Medicine*.

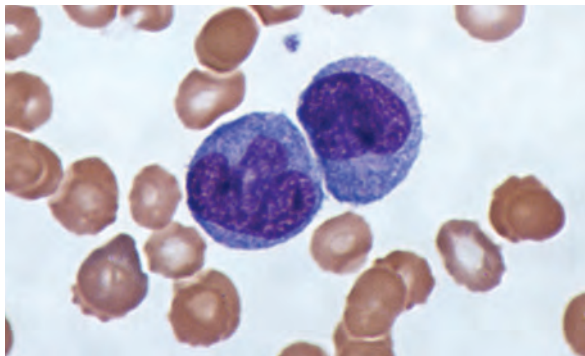
The data indicate that “a single threshold value of absolute monocyte counts of 0.95 K/mcL could be used to identify high-risk patients with a fibrotic disease,” said Madeleine K.D. Scott, a researcher at Stanford (Calif.) University, and coauthors.

While other published biomarkers – including gene panels and multicytokine signatures – may be expensive and not readily available, “absolute monocyte count is routinely measured as part of a complete blood count, an inexpensive test used in clinical practice worldwide,” the authors said.

### A retrospective multicenter cohort study

To assess whether immune cells may identify patients with idiopathic pulmonary fibrosis at greater risk of poor outcomes, Ms. Scott and her collaborators conducted a retrospective multicenter cohort study.

They first analyzed transcriptome data from 120 peripheral blood mononuclear cell samples of patients with idiopathic pulmonary fibrosis, which they obtained from the Gene Expression Omnibus at the National Center for Biotechnology Information. They used statistical deconvolution to



GRAHAM BEARDS/WIKIPEDIA CREATIVE COMMONS

estimate percentages of 13 immune cell types and examined their associations with transplant-free survival. Their discovery analysis found that estimated CD14+ classical monocyte percentages above the mean correlated with shorter transplant-free survival times (hazard ratio, 1.82), but percentages of T cells and B cells did not.

The researchers then validated these results using samples from patients with idiopathic pulmonary fibrosis in two independent cohorts. In the COMET validation cohort, which included 45 patients with idiopathic pulmonary fibrosis whose monocyte counts were measured using flow cytometry, higher monocyte counts were significantly associated with greater risk of disease progression. In the Yale cohort, which included 15 patients with idiopathic pulmonary fibrosis, the 6 patients who were classified as high risk on the basis of a 52-gene signature had more CD14+ monocytes than the 9 low-risk patients did.

In addition, Ms. Scott and her collaborators looked at complete blood count values in the

electronic health records of 45,068 patients with idiopathic pulmonary fibrosis, systemic sclerosis, hypertrophic cardiomyopathy, or myelofibrosis in Stanford, Northwestern, Vanderbilt, and Optum Clinformatics Data Mart cohorts.

Among patients in the COMET, Stanford, and Northwestern datasets, monocyte counts of 0.95 K/mcL or greater were associated with mortality after adjustment for forced vital capacity (HR, 2.47) and the gender, age, and physiology index (HR, 2.06). Data from 7,459 patients with idiopathic pulmonary fibrosis “showed that patients with monocyte counts of 0.95 K/mcL or greater were at increased risk of mortality with lung transplantation as a censoring event, after adjusting for age at diagnosis and sex” in the Stanford (HR, 2.30), Vanderbilt (HR, 1.52), and Optum (HR, 1.74) cohorts. “Likewise, higher absolute monocyte count was associated with shortened survival in patients with hypertrophic cardiomyopathy across all three cohorts, and in patients with systemic sclerosis or myelofibrosis in two of the three cohorts,” the researchers said.

The study was funded by grants from the Bill & Melinda Gates Foundation, U.S. National Institute of Allergy and Infectious Diseases, and U.S. National Library of Medicine. Ms. Scott had no competing interests. Coauthors disclosed grants, compensation, and support from foundations, agencies, and companies.

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**SOURCE:** Scott MKD et al. *Lancet Respir Med*. 2019 Jun. doi: 10.1016/S2213-2600(18)30508-3.

## FROM THE EVP/CEO

# Opportunities for CHEST to broaden its reach across the globe

BY BOB MUSACCHIO, PHD

In order to have a greater impact on the way that lung diseases, critical care conditions, and sleep disorders are diagnosed and treated, CHEST has been actively expanding its reach and the way it plans, develops, and executes its international educational strategy.

Our recent congress in Bangkok, Thailand, was just the beginning of our plans to expand the CHEST brand and share our innovative education across the globe.

The congress held this past April served as a successful launchpad that included attendance of over 1,000 delegates who represented 57 countries and featured innovative and diverse educational opportunities that incorporated the best of the CHEST Annual Meeting, including interactive lectures, recent advances in clinical practice and science, guided poster presentations, and hands-on simulation opportunities.

The exceptional program is attributed to the partnership with the Thoracic Society of Thailand; the Chair, Dr. David Schulman; the faculty, for delivering such an innovative and engaging educational event; and many others who planned, supported, and participated in this impressive event.

This was CHEST's first venture into a new model designed around hosting one large congress outside of the United States and one smaller

regional congress each year. This year, Athens, Greece, followed in June as the site of the regional congress. In subsequent years, we hope to increase the offerings and the options for these regional international events.



Dr. Musacchio

Newly announced, the CHEST Congress 2020 will be held in Bologna, Italy, June 25-27, in collaboration with the CHEST delegation from Italy, led by Dr. Francesco de Blasio. The program chairs for this event are Dr. de Blasio and Dr. William Kelly.

We are excited to broaden our international educational reach through this plan. By refining, growing, and building upon this new model and developing more live learning, hands-on simulation, CHEST gamification, and other interactive components, we continually provide the most cutting-edge learning opportunities available across the globe.

We are accomplishing this through partnering with global societies and CHEST delegations to identify unmet educational needs by region and patient base. Through this expansion, we hope to continue our fight to "Crush" lung disease wherever it exists.



CHEST faculty getting ready for the CHEST Congress 2019 Thailand, which was held in Bangkok, April 10-12.



## 2019 Education Calendar



CHEST Innovation, Simulation, and Training Center in Glenview, Illinois

Learn More [livelearning.chestnet.org](http://livelearning.chestnet.org)

July 25 - 27	Mechanical Ventilation: Advanced Critical Care Management
August 8 - 10	Cardiopulmonary Exercise Testing (CPET)
September 5 - 7	Difficult Airway Management
September 12 - 14	Ultrasonography: Essentials in Critical Care
September 19 - 21	Comprehensive Bronchoscopy With Endobronchial Ultrasound
November 7-9	Extracorporeal Support for Respiratory and Cardiac Failure in Adults
November 14 - 16	Critical Care Ultrasound: Integration into Clinical Practice
November 22 - 23	Comprehensive Pleural Procedures
December 5 - 7	Ultrasonography: Essentials in Critical Care
December 13 - 14	Advanced Critical Care Echocardiography Board Review Exam Course



### CHEST Board Review 2019

August 16-24 | Phoenix, Arizona

SLEEP

CRITICAL CARE

PULMONARY



October 19-23 | New Orleans, LA

Calendar subject to change. For most current course list and more information, visit [livelearning.chestnet.org](http://livelearning.chestnet.org).

## CHEST NetWORKS

# Biologics. NetWork name change. Rapid sequence intubation. Competitive bidding. Genomic classifier.

## Airways disorders

### Asthma biologics: which patients?

Biologic therapies targeting specific inflammatory pathways promise “precision” medicine for severe asthma. Because these therapies are expensive and have different mechanisms of action, appropriate patient selection is crucial. To date, the biologics have been primarily used in severe asthma.

Severe asthma has been defined as “asthma which remains uncontrolled on high-dose inhaled corticosteroids plus a second controller for the previous year or systemic corticosteroids (for 50% or more of the previous year) to prevent it from becoming uncontrolled, or which remains uncontrolled despite this therapy” (Chung, et al. *Eur Respir J*. 2014;43:[2]343).

Severe asthma is an infrequent to rare occurrence. Only 5% to 10 % of patients have severe asthma (Varsa-



Dr. Conroy



Dr. Garay

no, et al. *Respir Med*. 2017;123:131). Indeed, one study suggests that only 3.6% of patients meet criteria for it (Hekking, et al. *J Allergy Clin Immunol*. 2015;135[4]:896).

Not all difficult to control asthma is severe. With aggressive management of comorbidities and appropriate assessment of medication adherence/inhaler technique, up to 50% of uncontrolled asthmatics can reach therapeutic goals with traditional stepwise inhaler-based therapies (Tay, et al. *J Allergy Clin Immunol Pract*. 2017;5[4]:956; Hekking, et al. *J Aller-*

*gy Clin Immunol*. 2015;135[4]:896). Yet, incorrect inhaler technique (MDI and DPI) is unacceptably frequent and has not improved over the past 40 years (Sanchis, et al. *Chest*. 2016;150[2]:394). Furthermore, correct inhaler technique was found in only 15.5% of health-care providers and has worsened in recent years (Plaza, et al. *J Allergy Clin Immunol Pract*. 2018;6[3]:987).

After establishing appropriate diagnosis, control of comorbidities, proper inhaler technique, and medication adherence, evaluation of a severe asthmatic's inflammatory phenotype is necessary. Several phenotypes have emerged, including the severe allergic asthma phenotype and the severe eosinophilic asthma phenotype. Molecular phenotyping allows stratification into type-2-high vs type-2-low patients, which helps guide selection of the appropriate biologic. Options include: (1) anti-IgE (omalizum-

ab); (2) anti-interleukin-5 (mepolizumab and reslizumab); (3) anti-interleukin-5 receptor alpha (benralizumab); and (4) anti-interleukin-4 receptor alpha and interleukin-13 (dupilumab).

Targeted biologics for specific severe asthma phenotypes may be cost effective long-term. However, long-term side effects need to be assessed and pharmaco-economic studies need to be performed.

Megan Conroy, MD

Steering Committee Fellow-in-Training

Stuart M. Garay, MD, FCCP

Steering Committee Chair

## Clinical research and quality improvement Anew, redefined, and enriched

CHEST Physician readers may not know that the Clinical Research NetWork recently changed its name to include quality improvement

**NEW** | at CHEST Annual Meeting 2019—An Inaugural Event

# FISH BOWL

## AN INNOVATION COMPETITION



Do you have an innovative idea pertaining to pulmonary, critical care, or sleep medicine technology or education? Submit your pitch between **June 15 and July 31** to be considered for presentation at the inaugural FISH Bowl event at CHEST 2019 in New Orleans, Louisiana.

**Finalists will receive complimentary CHEST 2019 registration.**

[chestmeeting.chestnet.org/fish-bowl](http://chestmeeting.chestnet.org/fish-bowl)

 **CHEST**



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Recently reviewed sleep content is now eligible for up to 57.5 CME/MOC in the CHEST SEEK™ Library Sleep Medicine - CME/MOC collection. This reviewed content includes more than 200 questions—all eligible for CME/MOC.

Use CHEST SEEK education to test and improve your clinical skills in recall, interpretation, and problem-solving. Case-based questions reflect the content of board certification exams.

\*CME/MOC-eligible SEEK sleep medicine collection questions are only available in the online library.

 **CHEST**

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(QI). Its new mission is “to provide a forum for clinical research, QI, research ethics, and regulatory aspects, as topics of multidisciplinary discussion and collaboration.” Medical education has become a natural addition to our NetWork’s scope,



**Dr. Ioachimescu**

as this field of scholarly activity has emerged and grown tremendously in the past decade. Interestingly, the number of session submissions to CHEST 2019 increased by a whopping 32%

vs 2018, while our NetWork saw an even more impressive increase of 42% in submissions deemed Clinical, Education Research, or QI.

The initial concept of a CHEST Clinical Research NetWork was narrower, aiming to fill gaps between our members’ interests and activities with those of pharmaceutical industry partners and equipment and device manufacturers. Its scope evolved, and our NetWork became the home of all clinical research endeavors not pinned to a specific condition, disease class, or membership category.

QI emerged in other industries long ago, using scientific methods and known to be foundational for any organization’s capacity to survive in competitive environments, become more efficient, satisfy customers, improve outcomes, and develop better work flows and conditions for employees and business partners.

If the QI world strives to achieve certainty with confidence levels less than 0.0001, it is interesting that in our scientific quest we settle for *P* less than .05. Self-indulgence? Simplistically speaking, are we tolerating “defect rates” of 5%, while others aim for 6 sigma thresholds? These are a few thoughts on how health care can learn from other industries and apply more stringent standards for scholarly activities in clinical research, education, and QI.

In conclusion, while it continues to strive to build the infrastructure of future CHEST clinical research nodes for randomized or observational multicentric studies, Clinical Research and QI NetWork enthusiastically embraces the fields of medical education and QI into its enriched activity scope and scale.

*Octavian C. Ioachimescu, MD, PhD, FCCP  
Steering Committee Member*

### Critical care Rapid sequence intubation

Casey and colleagues recently published a study (*N Engl J Med.* 2019;380[9]:811) that challenges the long-held view that rapid sequence



**Dr. Gaillard**

intubation (RSI) should not include ventilation attempts between induction and laryngoscopy. Airway management purists will say that true RSI is pre-oxygenate, give a sedation agent

followed immediately by a paralytic agent, and immediate laryngoscopy as soon as the patient is paralyzed. However, RSI has come to mean the use of a sedation agent and a paralytic agent without specific timing of when to give the paralytic.

Purists would also say RSI is done for patients who are at a high risk for aspiration. In this study, the amount of subjectively reported aspiration was actually lower in the YES BVM group: 2.5% vs 4.0%. The presence of a new opacity on chest radiograph within 48 hours was 16% vs 15%, suggesting that there is no significant difference in the incidence of aspiration.

In this study, 40% in the NO BVM group and 30% in the YES BVM group had O<sub>2</sub> desaturations below 90%. These statistics highlight the fact that it is imperative to pre-oxygenate all patients who will undergo intubation. Critically ill patients have little reserve. These patients are on the steep portion of the oxygen dissociation curve. The saturations will drop quickly. It is better to avoid any desaturation, if possible.

This study demonstrates that bag-mask ventilation between induction and laryngoscopy can help prevent severe desaturation with a number needed to treat to prevent one severe hypoxic event is nine.

*John Gaillard, MD, FCCP  
Steering Committee Member*

### Home-based mechanical ventilation and neuromuscular disease Pressures of competitive bidding process

Advancements in invasive and non-invasive ventilator technology have allowed patients with neuromuscular conditions and severe COPD to transition from institutional care to living at home. Ventilator support is reserved for severe or progressive

respiratory impairment where interruption would lead to serious negative consequences. Access to this technology does entail significant cost, as monthly rental fees range from \$660 to \$1,352, and yearly ventilator claims for chronic respira-



**Dr. Brown**

tory failure have increased from 29% in 2009 to 85% in 2015 (US Dept HHS, OIG Data brief 2016). There is a current proposal to include home mechanical ventilators with oxygen and other

services in competitive bidding programs (CBP). Since oxygen was included in CBP, access to liquid oxygen systems and payments for oxygen have decreased significantly. Of patients using home oxygen since July 1, 2016, 59% reported difficulties with access to oxygen-related equipment and services (American Association for Respiratory Care: Comment on Federal policies, aarc.org).

Ventilator-dependent patients should not be subjected to the pressures of CBP when trying to obtain the equipment, supplies, and access to experienced medical providers that are necessary to remain in their homes. Beyond denying ventilatory support to some, CBP may also result in other unintended consequences, including the increased use of otherwise avoidable tracheostomies to ensure coverage for appropriate services. CHEST, including the Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork and other patient groups, has advocated that home mechanical ventilators should be permanently excluded from the CBP to protect these fragile and vulnerable patients.

*Jeanette Brown, MD, PhD  
Steering Committee Member*

### Interstitial and diffuse lung disease New genomic classifier

A confident diagnosis of idiopathic pulmonary fibrosis (IPF) relies on the radiographic pattern of usual interstitial pneumonitis (UIP), although in some cases, histologic confirmation is warranted. Transbronchial biopsy (TBBx) does not provide adequate tissue for diagnosis, thus patients are subjected to the risk of a surgical biopsy. A promising new test can increase confidence in the diagnosis of IPF.

The Envisia Genomic Classifier (Veracyte) is a recently approved test to aid in the diagnosis of IPF. It utilizes 190 genes and RNA sequencing, combined with machine learning, to create an algorithm that determines the presence of



**Dr. D'Annunzio**

UIP on samples derived from TBBx.

A proof-of-principle study described the characteristics of the genomic classifier in distinguishing UIP for 53 training subjects and 31

test subjects. To ensure validation, this new test was compared with a diagnosis determined by histopathologic review from expert pathologists. Specificity was 86% and sensitivity 63% in distinguishing UIP vs non-UIP patterns. Although false-negatives were a concern due to IPFs heterogeneous involvement of the lung, combining multiple specimens from a single patient increased accuracy.

The recently-published BRAVE study was a validation and utilization study, proving the test’s success in identifying UIP on TBBx samples. The test was again compared with diagnostic histopathology, demonstrating 88% specificity and 70% sensitivity. In addition, two multidisciplinary teams had an 86% agreement on diagnoses when using pathology vs the genomic classifier. The classifier is commercially available and is covered by Medicare in the United States.

As with all new technology, it is expected that its use will increase in the future and that we will learn more about how, and in whom, to best utilize this tool.

*Samantha D'Annunzio, MD  
Steering Committee Member*

### References

- Pankratz DG, et al. *Ann Am Thorac Soc.* 2017;14[11]:1646.
- Raghu G, et al. *Lancet Respir Med.* 2019 Jun;7(6):487.

## In memoriam

CHEST has been notified of the following deaths. We extend our sincere condolences.

**John W. Thomas, MD (2018)**  
**Frederick J. Curley, MD (2018)**

## Fill your day in New Orleans

No matter if you're only in New Orleans during #CHEST2019 for a day or for the entire meeting, we've got you covered on how to spend your time in the Big Easy outside of sessions and CHEST events!

**CHEST®**  
Annual Meeting  
2019

**Rise and shine!** If breakfast is the most important meal of the day, we've got the perfect way to start your morning before heading over to the Ernest N. Morial Convention Center to begin a day of learning. For a quick bite, try the ever popular Cafe du Monde Riverwalk next to the convention center for a light breakfast of beignets and café au lait, or Fulton Street Cafe.

**Lunchtime:** For something a little more hearty, head to Green Goddess in the French Quarter for southern comfort food. There's something for everyone, as you'll even find some vegan dishes on the menu. If you have time for a longer

mid-day break, check out a Garden District Tour, Steam Boat on the River, or relax in Jackson Square.

**Evening:** You've had a long day of sessions, lectures, and exploring the exhibit hall, and now you want to wind down with a good meal (and maybe a drink!). For a slower vibe and space to linger and enjoy yourself, take an Uber/Lyft over to La Petite Grocery on Magazine Street for some tasty, traditional dishes.

If you're a night owl or looking for a late-night activity with a group of your friends and peers, there are plenty of places to find a cocktail on Bourbon Street, or listen to live jazz music along Frenchman Street.

There are many more things you can check out in New Orleans, and we hope you enjoy your stay during CHEST 2019.

*\*Note: If you're staying in the hotel block near the convention center, many of the attractions, including the Convention Center, will be a short walking distance. Otherwise, we suggest taking an Uber or Lyft to reach your destination.*



**Cardiopulmonary Exercise Testing**  
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and MOC Points  
**20.50**

Join prominent exercise experts as they discuss high-level interpretive strategies that can be used to better support your exercise laboratory, as well as exercise training program design, exercise testing evidence-based data, exercise prescriptions, rehabilitation, sports medicine, cardiopulmonary exercise testing (CPET) guidelines, and current controversies in the field.

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- Data interpretation, including report creation and how to make informed CPET study recommendations
- Required skills for performing CPET, including:
  - Calibration
  - Maneuvers
  - Testing
  - Biologic controls

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## CHEST Clinical Perspectives™ explores the emerging field of precision medicine

For clinicians seeking to provide a pathway to treatment or diagnosis that is individualized to the patient, a recent study found that the issues go beyond awareness or a patient's degree of comfort – there remains the question of something as simple as: what should we call it?

Clinicians remain uncertain whether to name the new field precision or personalized medicine according to the new *CHEST Clinical Perspectives™* white paper, "Precision Medicine: Adoption of Emerging Methods of Evaluation and Therapy." A survey of leading community clinicians from among CHEST membership found that only 35 % called tailoring medical treatment to the individual characteristics of each patient "precision medicine," with 24% preferring "personalized" medicine. Thirty-six percent of respondents used the terms interchangeably.

Beyond the communication issues, the study found that most

clinicians surveyed did not know enough about precision medicine to adopt it into their practice. Those surveyed reported that they wanted to see more published studies on the effectiveness of the newly available tools before discussing these options with their patients.

The majority of the respondents were general pulmonologists with intensivists and interventional pulmonologists also responding. The study was led by Nichole T. Tanner, MD, MSCR, FCCP, of the Medical University of South Carolina. Dr. Tanner will be hosting a webinar to review the conclusions of this paper at 10:00 AM CT on Tuesday, July 30.

More information about *CHEST Clinical Perspectives™*, part of the CHEST Analytics program, can be found at [insights.chestnet.org](https://insights.chestnet.org). To suggest a topic to be covered in a future issue, contact Linda Tomczynski, [ltomczynski@chestnet.org](mailto:ltomczynski@chestnet.org) or +1 (224) 521-9593. Register today at <https://hubs.ly/H0jqCGb0>.

## This month in the journal CHEST®

### Editor's picks

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

### EDITORIAL

**The CHEST Editorial Team: Serving Our Contributors and Readers**  
By Dr. P. J. Mazzone

### ORIGINAL RESEARCH

**Pulmonary Arterial Histologic Lesions in Patients With COPD With Severe Pulmonary Hypertension**  
By Dr. V. Bunel, et al.

**Pulmonary Edema Following Initiation of Parenteral Prostacyclin Therapy for Pulmonary Arterial**



**Hypertension: A Retrospective Study**  
By Dr. N. A. Khan, et al.

**Lung Allocation Score Thresholds Prioritize Survival After Lung Transplantation**  
By Dr. S. S. Li, et al.

**EVIDENCE-BASED MEDICINE**  
**Chronic Cough and Gastroesophageal Reflux in Children: CHEST Guideline and Expert Panel Report**  
By Dr. A. B. Chang, et al.

# Environmental Scan: Drivers of change in health care

Chest physicians are witnessing a revolution within the environment in which they practice. Information technology, changing consumer behavior, and the social imperative to contain costs are coming together to transform health care.

Innovation in the prevention, diagnosis, and treatment of health-related issues is being fueled by the emergence of accessible and affordable technology-based solutions and changes in patient approaches to health care. Consumers and employers are increasingly motivated to look for cost-effective options for health in care delivery and for economical access to innovations.<sup>1</sup> Organizations will need to respond with a strategy that aligns with the changing environment and position physicians to lead these trends in the direction of improved patient care.<sup>2</sup>

Enabling technologies like electronic health records, blockchain, and artificial intelligence will increase connectivity among all the stakeholders in the health-care system. The exponential increase in connectivity means growing engagement of health systems, health plans, patients, and families in all aspects of health care. For health-care providers, these technologies will mean an acceleration of the requirement to generate data in clinical settings and utilize data for clinical decision making. Easily available data on outcomes and, most importantly, cost of treatment will be expected at point of service.<sup>3</sup>

Access to information will continue to empower consumers to take an active role in their own health care. More patients will be comfortable with delivery of some health care via digital devices, apps, and virtual access to treatment. The market will respond with technology that helps consumers navigate health-care systems, explore options, and communicate directly with providers. The use of apps and virtual encounters is expected to transform the role of primary care providers: patients will increasingly utilize non-physician resources in outpatient settings, bypassing primary care physicians and reaching out to specialty care as needed.<sup>4</sup>

David A. Schulman, MD, FCCP, Professor of Medicine, Division of Pulmonary, Aller-

gy, Critical Care and Sleep Medicine, Emory University School of Medicine, Atlanta, and Editor in Chief of *CHEST Physician*, has seen the transformation of patient behavior and attitudes in his own practice.

"In general, they have done far more research about their health problems before seeking my counsel than patients did previously. Many use the internet not just to read about their symptoms and diseases, but also to connect with others having similar issues, sharing experiences, treatments, outcomes, and emotions; in some ways, this is the new 'crowdsourcing' of medicine."

Patients who do their own "research" can present a challenge for physicians. Dr. Schulman noted, "I am often surprised about the misconceptions about disease that derive from information gleaned from a web-based source. One need not look any farther than the groundswell of misinformation being spread about vaccinations to see the potential downside of the pervasive availability of medical 'facts' online. Since we are unlikely to convince our patients to avoid the online milieu entirely, our role as health-care providers is to help our patients process and appropriately weigh the information that they receive, potentially partnering with our national societies to help curate such information."

Dr. Schulman's approach to the potential of patient misinformation is to initiate almost all discussions with patients with the question "Have you read or seen anything about this condition?" He said, "It is rare for patients to answer negatively. And listening to them speak about their understanding of their disease provides me with invaluable information about how the remainder of our visit should be spent. Do we need to correct misunderstandings? Are there gaps in the explanation that I can fill? Can we move directly into a conversation about treatment options? Can I provide you with some additional resources that might help to further your knowledge about the condition?"

Generational factors will play a big role in health-care demand and delivery. Health-care companies are already building lower cost delivery models to capture the millennial market.<sup>4</sup> Cost-saving digital tools and virtual contacts are currently most commonly used by younger patients.<sup>5</sup> Physicians need to understand and be a part of this trend, Dr. Schulman argued. "We should embrace telemedicine and mobile applications to collect data from the patients in their day-to-day lives. While insurance coverage of telemedicine is far from universal at the moment, and the reliability of mobile applications is highly variable, we know that a growing number of our patients are already relying on their digital devices to manage their health. In much the same way that we will need to help patients evaluate online information, we should work with our national societies to support the creation of tools that will allow us to collect data in the home environment in a more robust and reliable fashion."

The proportion of the US population over the age of 65 is increasing yearly.<sup>6</sup> Six out of 10 Americans live with a chronic illness, such

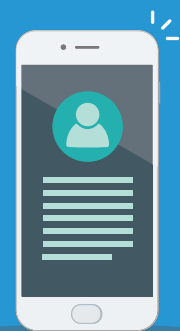
as heart disease or diabetes. These and other chronic diseases are the leading drivers of the \$3.3 billion annual health-care costs.<sup>7</sup> Cost containment for these older patients and those with chronic illness will involve a focus on quality and outcomes data, a drive to deliver treatment in lower cost outpatient settings, and an acceleration of the adoption of value-based models currently underway.<sup>8</sup>

Taken together, these trends will mean a growing digital interface between physician and patient, a more active consumer-patient, and the availability of a vast array of new tools to access and manage health-care data.

*Continued on page 42*

*CHEST Inspiration is a collection of programmatic initiatives developed by the American College of Chest Physicians leadership and aimed at stimulating and encouraging innovation within the association. One of the components of CHEST Inspiration is the Environmental Scan, a series of articles focusing on the internal and external environmental factors that bear on success currently and in the future. See "Envisioning the Future: the CHEST Environmental Scan," CHEST Physician, June 2019, p. 44, for an introduction to the series.*

**37%** of millennials  
vs. **9%** of baby  
boomers rely on  
digital devices to  
manage health care



Option A...\$  
Option B...\$\$  
Option C...\$\$\$

**78%**  
of consumers  
interested in 'menu'  
of care options by  
multiple providers



**57%** of  
millennials  
vs. **82%** of  
baby boomers  
have a primary  
care provider



**51%** increase in outpatient  
facilities over 2005 to 2016

**54%**  
of consumers  
would try  
health care  
app for  
treatment



## A distinguished 14-year editorship

In 1968, Richard S. Irwin, MD, Master FCCP, graduated from Tufts University School of Medicine. After completing medical residency training at the Tufts-New England Medical Center and pulmonary training at Columbia Presbyterian Medical Center, he has been practicing in pulmonary and critical care medicine for the last 50 years.

It was in 1979 that he became a CHEST member; in 2003-2004, he served as President of CHEST; and he has been actively involved as a CHEST leader throughout his career, serving on every major CHEST committee. But Dr.



Dr. Richard S. Irwin

Irwin's most beloved position has been as Editor in Chief of the journal *CHEST*, a journey that began in 2005 – a position that he has filled for 14 years and that which he has recently stepped down from in June 2019. What better description of those 14 years at the helm of one of the

most recognized and respected journals in chest medicine than to hear it straight from the Editor in Chief himself. In the June 2019 issue of the journal *CHEST*, Dr. Irwin shares his thoughts in this Commentary: "On Being the Editor in Chief of the journal *CHEST*: 14 Memorable Years." Don't miss it! <https://journal.chestnet.org>.

Continued from page 35

- Delivery of procedures and services will trend from physicians to other members of the health-care team and to lower cost, outpatient settings.<sup>9</sup>
- Health-care systems will ramp up investment in products and services that improve outcomes and cost effectiveness.<sup>10</sup>
- Increased regulatory requirements and new payment models mean an ever-growing utilization of information technology by providers to fulfill data imperatives.<sup>11</sup>
- Physicians will have an increased need for tools that prioritize costs and outcomes data at the point of care.<sup>12</sup>
- Integration of data from new technologies will touch every aspect of health-care delivery with the objective of improving outcomes and, in turn, reducing costs.<sup>13</sup>
- Changing consumer attitudes toward delivery of care will be based on a growing familiarity of patients with a digital or virtual interface with providers, facility with health-care apps, and preference for a menu of options for health-care delivery.<sup>14</sup>

Dr. Schulman concluded, "We can no more expect our patients to ignore the full panoply of medical information on the internet and digital tools on their mobile devices than we can tell the tide not to

come in. The die is cast; this is the world within which we must ply our trade. By identifying best practices and sharing our successes, we can come through this revolution better for the experience."

1. <https://www.modernhealthcare.com/article/20181220/NEWS/181229992/number-of-outpatient-facilities-surges-as-industry-values-more>
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  3. <https://www.accenture.com/us-en/insights/health/digital-health-primary-care>
  4. PcW Health Research Institute: Top health industry issues of 2019
  5. <https://www.accenture.com/us-en/insights/health/digital-health-primary-care>
  6. <https://www.census.gov/newsroom/press-releases/2017/cb17-100.html>
  7. <https://www.cdc.gov/chronicdisease/index.htm>
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  9. PcW Health Research Institute Top health industry issues of 2019: The New Health Economy comes of age
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  13. <https://www2.deloitte.com/insights/us/en/industry/health-care/volume-to-value-based-care.html>
  14. <https://www.accenture.com/us-en/insights/health/digital-health-primary-care>
- Note: Background research performed by Avenue M Group.

## SLEEP STRATEGIES

# Restless legs syndrome: Update on evaluation and treatment

BY MARK J. BUCHFUHRER, MD, FCCP, FAASM

Restless legs syndrome (RLS) is a very common disease affecting about 10% of Caucasian adults with about one third of them having RLS symptoms severe enough to require treatment.

Although many patients still go undiagnosed or misdiagnosed, the diagnosis is easily established with the five diagnostic criteria that are simplified by the acronym URGES:

1. *Urge* to move the legs associated with unpleasant leg sensations.
2. *Rest* induces symptoms.
3. *Gets* better with activity.
4. *Evening* and nighttime worsening.
5. *Solely* not accounted by another medical or behavioral condition.

The diagnosis is based completely upon the history. However, supplemental tests can be helpful to rule out underlying conditions that increase the risk of RLS. Routine lab tests, such as serum creatinine (to rule out renal disease), TSH (to rule out thyroid disease), and a CBC/feritin/iron with transferrin saturation (to rule out low iron stores) should be ordered if not done recently.

A polysomnographic sleep study should not be ordered unless there is a strong suspicion that sleep apnea is present. Even very frequent PLM (periodic limb movements) are not that helpful in confirming the diagnosis of RLS since they are nonspecific and often occurring with drug treatment (SSRIs, SNRIs) and many medical conditions such as sleep apnea, narcolepsy, and REM behavior disorder.

The paradigm for treating RLS has been presented in the consensus article published in 2013 (Silber MH, et al. *Mayo Clin Proc.* 2013 Sep;88[9]:977). Since 2013, there has been a gradual shift of that paradigm that recommended starting an approved dopamine agonist (pramipexole, ropinirole, or rotigotine) or an alpha-2-delta ligand (gabapentin enacarbil, gabapentin, or pregabalin) as first-line treatment. Although dopamine agonists provide excellent relief of RLS symptoms initially, with time, they tend to markedly worsen RLS. This process is called RLS augmentation and has become one of the

most common causes of refractory RLS and difficult-to-treat patients.

RLS augmentation typically onsets a few months to several years after starting a short-acting dopamine



Dr. Buchfuhrer

agonist (DA) like pramipexole or ropinirole. It presents with symptoms occurring a few hours earlier than prior to starting the medication, symptoms becoming more intense with less

rest time needed to trigger RLS symptoms, drugs becoming less effective both in effectiveness and duration of action, and spread of symptoms to other body parts (arms, trunk, and even head). The majority of physicians mistake this worsening of RLS for the natural progression of the disease and, thus, increase the dose of the DA, which provides temporary improvement. Further increases become progressively necessary until the patient is receiving very large doses, often exceeding 10 times the FDA maximum recommended doses. Eventually, further dose increments provide minimal additional benefit, leaving patients with severe, around the clock RLS symptoms causing extreme misery. To be more aware of augmentation, physicians should consider augmentation may be occurring whenever a patient who has been receiving a regimen of stable dopamine agonist treatment for at least 6 months requests more medication.

The incidence of augmentation for patients taking short-acting DA drugs is about 7% to 8% per year so that by 10 years, the vast majority of these patients with RLS are experiencing augmentation. Since it has been over 13 years since pramipexole and ropinirole have been approved for treating RLS, currently, over 75% of patients referred to national RLS experts are referred due to augmentation (although the actual referral diagnosis is often "refractory RLS"). Despite the concerns about augmentation, the short-acting DA drugs are by far the most commonly prescribed medications

for initial treatment of RLS.

To help educate doctors about RLS augmentation, a consensus article was published in 2016 promoting guidelines for the prevention and treatment of RLS augmentation (Garcia-Borreguero D, et al. *Sleep Med.* 2016;21:1-11). Since augmentation occurs only with dopaminergic drugs (with the exception of tramadol), considering the use of nondopaminergic drugs for first-line therapy of RLS would dramatically decrease the occurrence of augmentation. This is a clear shift in the paradigm of choosing equally amongst the approved RLS drugs.

Unless contraindicated, the alpha-2-delta drugs should be the first consideration for treating new RLS patients. These drugs can be as effective as the DA drugs but cannot cause augmentation and, also, do not cause impulse control disorders, which occur with the use of DAs. Furthermore, they reduce insomnia and anxiety that are both associated with RLS. The use of these drugs may be limited by their side effects, which include CNS depressive effects (sedation, dizziness, decreased balance or cognition) or depression.

When the alpha-2-delta ligands can't be used due to lack of efficacy,

side effects, or cost, the DA drugs may then be appropriate. The rotigotine patch has the lowest incidence of augmentation, especially at the approved doses of up to 3 mg. If the rotigotine patch cannot be used (most often due to skin side effects or cost), then the short-acting DA drugs may be employed. Augmentation may be prevented or significantly delayed by starting these drugs at their lowest dose (.125 mg for pramipexole and .25 mg for ropinirole) and increasing the dose as little as possible, definitely not exceeding the approved RLS limits of .5 mg for pramipexole and 4 mg for ropinirole. My personal suggestion is not to exceed .25 mg for pramipexole and 1 mg for ropinirole, as augmentation is dose-related but may occur at even the lowest doses. When patients need and request increased treatment for their RLS, rather than increasing the dose of the DA, instead, consider adding other medications, such as the alpha-2-delta ligands or even low dose opioids.

Managing augmentation is typically a very challenging problem for both the physician and patient; this is described in detail in the augmentation article referenced previously. Decreasing, or better yet eliminating, the short-acting DA is the preferred

method for treating augmentation. However, upon elimination of the DA, there is a short period of 1 to 4 weeks (average of 10-12 days) when the RLS symptoms get dramatically worse. Patients typically experience extremely severe RLS symptoms around the clock and may not be able to sleep at all until the RLS calms down. Most often, only low dose opioid treatment will enable them to get through this transition. The augmentation article (with its algorithm) may help physicians manage augmentation, but patients with severe augmentation may need referral to an RLS specialist who is experienced in this area and who is comfortable managing the disease with opioids.

Low iron levels are often associated with RLS, cause RLS symptoms to worsen, and increase the risk of augmentation (Allen RP, et al, and the International Restless Legs Syndrome Study Group. *Sleep Med.* 2018;41:27). We typically suggest that patients with ferritin levels under 100 mcg/L should get supplemental iron. However, oral iron absorption is very limited when the patient's ferritin is above 50 mcg/L and, most patients may require IV iron to improve their RLS symptoms. There are several IV iron preparations but only iron dextrose, iron carboxy-

maltose, and ferumoxytol are effective. When the ferritin level is increased to over 200 mcg/L, RLS symptoms may be dramatically improved.

With the currently available treatment options, most patients should have their RLS symptoms well controlled without developing augmentation.

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