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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Earlier lactate draw benefits patients with severe sepsis

BY ANDREW D. BOWSER

MDedge News

FROM THE JOURNAL CHEST[®] • For patients identified as having severe sepsis, delays in lactate measurement were associated with delayed treatment and progressive mortality increases, findings of a retrospective study show.

Those patients had a longer time to administration of IV fluids (IVF) and antibiotics, senior author Matthew M. Churpek, MD, of the department of medicine, University of Chicago, and a team of researchers reported in the journal *CHEST**.

In previous studies, delayed antibiotics in patients with sepsis has been associated with

increased mortality, wrote co-author Xuan Han, MD, and coauthors. "Systematic early lactate measurements when a patient presents with sepsis may thus be useful in prompting earlier, potentially life-saving interventions," they noted.

The retrospective study comprised 5,762 adults admitted to the University of Chicago from November 2008 to January 2016. These patients met criteria for severe sepsis, as outlined in the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1), a quality measure introduced by the Centers for Medicare & Medicaid Services in 2015. SEP-1 identifies patients who meet two of four systemic inflam-

LACTATE // continued on page 4

CT lung cancer screening remains underutilized

BY SUSAN LONDON

MDedge News

ost heavy smokers in the United States who are eligible for low-dose CT screening for lung cancer do not receive it, according to a cross-sectional study reported at the annual meeting of the American Society of Clinical Oncology.

Results of the National Lung Screening Trial reported in 2011 showed a 20% reduction in lung cancer mortality with targeted low-dose CT (LDCT) screening, noted lead study author Danh C. Pham, MD, of the James Graham Brown Cancer Center at the University of Louisville (Ky.).

Since 2013, the U.S. Preventive Services Task Force has recommended this screening for people aged 55-80 years who are current or former heavy smokers, defined as having smoked at least 30 pack-years, he added. "More importantly, in 2015, the Centers for Medicare & Medicaid Services expanded Medicare coverage for LDCT for lung cancer screening," he said.

However, results of the new study showed LUNG CANCER // continued on page 7



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New Medscape-CHEST Moderate to Severe Asthma Center of Excellence

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Delays in lactate measurement led to delays in treatment // continued from page 1

matory response syndrome (SIRS) criteria, display at least one new organ dysfunction, and have documentation of suspicion of infection. Those patients meeting all of these criteria within a 6-hour period are identified as having "severe sepsis." The SEP-1 mandates interventions

including lactate draws and antibiotics for patients identified as having severe sepsis via clinical and laboratory evaluation, the authors noted. The investigators assumed that "given prior work suggesting lactate clearance as a goal of sepsis management, it is likely that patients with

elevated values would likely receive more aggressive resuscitation."

The Chicago study focused on the timing of lactate measurements, the timing of the initiation of treatment, and the impact of these two factors on mortality risk among these patients.

They found that 60% of these

patients identified as having severe sepsis had serum lactate measurements drawn within the time window specified in SEP-1. But timelines varied significantly by setting, at just 32% in patients who first met the criteria on the wards, compared with 55% in the ICU, and





A large number of patients become newly septic on the wards and have higher mortality than those in the ED.

DR. HAN

79% in the emergency department.

In-hospital mortality among the sample was highest in patients with delayed lactate measurements, at 29%, compared with 27% for those with lactates taken within the specified time window, and 23% for sepsis patients who had no lactate draw (*P* less than .01), the researchers reported.

Those patients with higher initial lactate levels and a delay in measurement were at greater risk of death. Among patients with initial lactate levels greater than 2.0 mmol/L was an increased odds of death by 2% for each hour of delay, while no such increase was noted in patients with initial lactates lower than that threshold.

The increased odds of death in patients with higher initial lactates was significant (odds ratio, 1.02; 95% confidence interval, 1.0003-1.05; P = .04); however, the association was no longer significant when adjusted for time to IVF and antibiotics (P = .51). Based on that observation, the difference in mortality may be due to earlier interventions among patients treated in the specified time frame. Overall, the sooner the lactate measurement was drawn, the sooner treatment was initiated. "Patients with lactates drawn within the SEP-1 window received both

Among patients with initial lactate levels greater than 2.0 mmol/L was an increased odds of death by 2% for each hour of delay.

IV antibiotics and fluids sooner than their counterparts who had lactates drawn outside of the window," the investigators explained. The timing of treatment initiation reflects the difference between the early and delayed groups: median 2.0 h to receiving antibiotics and 1.3 h to IVF bolus for those whose lactates were measured within the SEP-1 window vs. 3.9 h to antibiotics and 4.8 h to IVF bolus for whose lactate draw was done later, respectively.

These findings complement prior studies suggesting the benefit of interventions in patients with lactate levels above 2.0 mmol/L, and, conversely, highlight the fact that many patients who meet the severe sepsis criteria nevertheless have normal lactates.

In addition, the investigators noted, "Sepsis bundles have often focused on ED patients, but our study demonstrates that a large number of patients become newly septic on the wards and have higher mortality than those who initially meet criteria in the ED. This is an important population of patients in which to effectively and quickly identify and treat sepsis."

They reported disclosures related to Philips Healthcare, Laerdal Medical, and Quant HC, among other entities.

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SOURCE: Han X et al. Chest. 2018 May 24. doi: 10.1016/j. chest.2018.03.025.



Flu vaccine still not mandatory in many hospitals

BY ANDREW D. BOWSER

MDedge News

early two-thirds of hospitals had mandatory influenza vaccination in place in 2017, up from just one-third in 2013, according to survey responses submitted by infection preventionists working at Veterans Affairs (VA) and non-VA hospitals.

However, that substantial increase was driven almost entirely by the non-VA hospitals: Fewer than 5% of VA hospitals in 2017 had mandatory requirements for health care personnel who provided care for veterans, according to M. Todd Greene, PhD, MPH, with the Patient Safety Enhancement Program at the Veterans Affairs Ann Arbor Healthcare System/University of Michigan and his coauthors.

Despite recommendations to vaccinate health care personnel against

mandatory influenza vaccination requirements, the 2017 survey showed a significant increase to 61.4% (*P* less than .001), Dr. Greene and his colleagues wrote in their report.

By contrast, the proportion of VA hospitals with such requirements increased only slightly, from 1.3% in 2013 to just 4.1% in 2017 (P = .29), the report showed.

Penalties for not complying with the policy were not universal in hospitals with mandates, they added. Only 74% said they had such penalties, and 13% allowed health care personnel to decline influenza vaccination without a specified reason.

After the survey responses were received, the VA issued a directive stating that all health care personnel should receive annual influenza vaccination and should wear masks during influenza season, Dr. Greene noted.

That directive is in line with rec-



influenza, there are several challenges and barriers to implementing the practice, the authors wrote in JAMA Network Open.

"Mandating influenza vaccination remains a controversial topic, with uncertainty of the effectiveness of health care personnel influenza vaccination in reducing patient morbidity and mortality, different conclusions regarding the grading of the evidence, and numerous legal and ethical precedents to be carefully considered," they wrote.

Their study was based on 1,062 responses to a panel survey of infection preventionists conducted every 4 years. The survey asked providers about practices used in their hospitals to prevent health care–associated infections.

Compared with 2013, when only 37.1% of non-VA hospitals had

ommendations from the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices, which have stated that all health care personnel should receive influenza vaccination each year.

In addition, the U.S. Department of Health & Human Services has set a goal of 90% of health care personnel to be vaccinated by 2020, Dr. Green and his coauthors noted

Mandating influenza vaccination is just one proven successful strategy for increasing coverage at hospitals, according to the study authors. Other approaches include influenza education, incentives, free and easy access to vaccination, and annual campaigns directed at health care personnel, as well as written policies describing the vaccination goal.

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Continued from previous page

"Regardless of whether an organization has an official mandate for vaccinations, establishing a written policy that states the organizational commitment to increasing vaccination rates is among the recommended strategies for improving vaccination coverage among health care personnel," they wrote.

Dr. Greene and his coauthors reported receiving grants from the Blue Cross Blue Shield of Michigan Foundation and the U.S. Department of Veterans Affairs Patient Safety Center of Inquiry during the conduct of the study. One study coauthor reported personal fees from Jvion and from Doximity outside the submitted work.

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SOURCE: Greene MT et al. JAMA Network Open. 2018;1(2):e180143.

VIEW ON THE NEWS

Knowledge gaps remain on vaccination benefit

This study suggests a significant increase in use of mandatory influenza vaccination policies during 2013-2017, driven mainly by increases at non-Veterans Affairs (VA) hospitals and little change at VA facilities. However, there are some caveats to the findings that should be considered, Hilary M. Babcock, MD, MPH, wrote in an editorial referencing the study.

The sample for the 2013 and 2017 surveys included different facilities and different size facilities, so direct comparisons cannot be made, according to Dr. Babcock.

Moreover, the survey questions were worded somewhat differently in the two surveys, and it does not appear that "mandate" was defined by the study authors, she said in her editorial.

The VA recently issued a directive that all health care personnel should receive influenza vaccination and wear masks during influenza season. This new directive provides an "excellent opportunity" to address knowledge gaps regard-

ing the effects of influenza vaccination of health care personnel on patient outcomes, according to Dr. Babcock.

"While the assumption that decreasing the risk of influenza in health care personnel will result in decreased risk of influenza in patients cared for by those health care personnel is common sense, for acute care settings, it is still largely an assumption," Dr. Babcock wrote. "Hopefully, the Veterans Health Administration will combine this initiative with thoughtful, planned, patient outcome assessments to help define the anticipated benefit of these efforts."

Dr. Babcock is with Washington University and the BJC HealthCare Infection Prevention & Epidemiology Consortium, both in St. Louis. These comments are derived from her editorial in JAMA Network Open (2018;1[2]:e180144). Dr. Babcock reported no conflict of interest disclosures related to her editorial.

Stigma smoking may deter patients from lung cancer screening // continued from page 1

that nationally only 1.9% of more than 7.6 million eligible current and former smokers underwent LDCT screening in 2016. By region, the South had one of the lowest rates, despite having the most accredited screening sites and the greatest number of eligible patients.

The findings are stark when juxtaposed with rates of screening for some other cancers, Dr. Pham maintained. For example, 65% of women aged 40 years or older underwent mammography for breast cancer screening in 2015.

"This ultimately begs the question as to the root of the disparity," he said. "Are physicians not referring enough? Or perhaps, are eligible patients not wanting screening, even if they know a test is available? Unfortunately, controversy still exists among providers about costs and benefits of screening, while patients at risk for lung cancer also perhaps lack adequate awareness of the benefits of screening."

It is also possible that the stigma attached to smoking, a modifiable risk factor, and thus to lung cancer screening may be a deterrent, Dr. Pham speculated. Specifically, patients may perceive screening-detected lung cancer as confirmation of a poor lifestyle choice.

"Regardless of the reason, this ultimately is a call to action on everyone's part to increase this much-needed screening, whether that's through creating awareness or conducting additional research, to urgently increase screening for the No. 1 cancer killer in America, as it

has been now documented that effective screening can prevent nearly 12,000 premature lung cancer deaths per year," he concluded.

Oncologists in the lung cancer field "would certainly like to be put out of business by an effective screening program," commented ASCO President Bruce E. Johnson, MD, FASCO.

These new findings should be considered in light of the fact that the study period came only about a year after the change in reimbursement for LDCT, he noted. "So this is not a measure of the steady-state situation, but rather when this was first implemented."

Nonetheless, it is "very disappointing" how little LDCT screening is being used, added Dr. Johnson, who is also a professor of medicine at the Dana-Farber Cancer Institute in Boston, and a leader of the center's lung cancer program. "It should be saving 12,000 lives a year, and with this number, it's about 250 lives. As correctly stated, there is a certain stigma whereby people who smoke feel as if they deserve it or that it's sort of a self-punishment."

Policy changes

Policy change would likely help increase uptake of LDCT lung cancer screening, according to Dr. Pham. "I think the most radical thing we could suggest based on our study so far would potentially be making lung cancer screening a national quality health measure, just the way that CMS made [mammograms for] breast cancer and colonoscopies [for

colorectal cancer] national areas of improvement in 2008," he elaborated.

"I agree that that could be an effective strategy, particularly since physicians are increasingly being required [to follow] our quality measures to optimize the reimbursement," commented Richard L. Schilsky, MD, FACP, FASCO, chief medical officer of ASCO and press briefing moder-

ator.



DR. PHAM

"Keep in mind that, generally speaking, screening of healthy or high-risk individuals for cancer is typically performed by primary care physicians, not by oncologists,"

he further noted. "So one of the things that we also need to do is to be sure that primary care physicians are well aware of the screening data and the importance of referring the appropriate patients for screening, and are aware of screening centers available in their communities."

Dr. Johnson said that the society has been active in that area. "ASCO is working with the American College of Physicians and some of the other primary care groups to try to get the message out about the screening," as well as to educate them about the large potential impact of screening and treatment. "There are 15 million cancer survivors in the United States, and for the people who fit those criteria for

smoking, [we need] to make certain they are getting screened."

Study details

For the study, Dr. Pham and his colleagues used data from the American College of Radiology's Lung Cancer Screening Registry, collecting total number of LDCTs performed in 2016 from all 1,796 accredited radiographic screening sites. They also used data from the 2015 National Health Interview Survey to estimate eligible smokers who could be screened based on the USPSTF recommendations.

Overall, 1.9% of 7,612,975 eligible current and former heavy smokers underwent LDCT, he reported. By census region, the rate was highest in the Northeast (3.5%) and lowest in the West (1.0%).

Notably, only 1.6% of eligible heavy smokers in the South underwent LDCT, even though that region had, by far, the most accredited screening sites (663) and the most eligible patients (3,072,095). The rate was highest in the Northeast, at 3.5%, even though that region had the second-lowest number of accredited screening sites (404) and the fewest eligible patients (1,152,141).

Dr. Pham disclosed no relevant conflicts of interest. The study received grant funding from the Bristol-Myers Squibb Foundation.

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SOURCE: Pham DC et al. ASCO 2018, Abstract 6504.

Vaccine nonmedical exemptions creating metro 'hotspots' across the United States

BY RICHARD FRANKI

MDedge News

ecent increases in nonmedical exemptions (NMEs) to vaccination have created metropolitan "hotspots" with large numbers of unvaccinated children, according to a report published June 12 in PLoS Medicine.

Since 2009, NMEs based on philosophical beliefs have increased in 12 of the 18 states that currently allow them, although rates seem to have plateaued in some states since 2014. As a result of those increases, there were, during the 2016-2017 school year, 15 metro areas with kindergarten NME populations over 400, reported Jacqueline K. Olive, and her associates at Baylor College of Medicine. Their report was based on data from state health departments and the Centers for Disease Control and Prevention

Leading the way was Maricopa County, Ariz., home of Phoenix and 2,947 unvaccinated kindergartners, which was more than triple the number in county/city No.

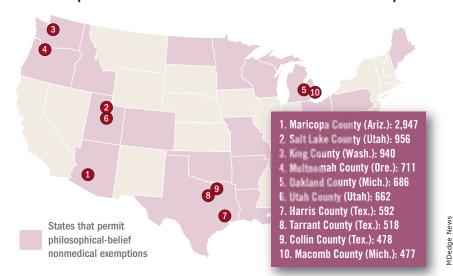
2, Salt Lake County/Salt Lake City (NME total, 956). Close behind in third was King County, Wash. (Seattle), at 940, followed by Multnomah County, Ore. (Portland) at 711 and Oakland County, Mich. (Troy), at 686, the investigators said.

Other hotspots not indicated on the map are: Wayne County, Mich. (Detroit); Allegheny County, Pa. (Pittsburgh); Travis County, Tex. (Austin); Jackson County, Mo. (Kansas City); and Spokane County, Wash. (Spokane).

In addition to the large-population hotspots, there are also a number of mainly rural counties with smaller populations but high NME rates.

Eight of the 10 highest such rates can be found in Idaho, and at the top of that list is Camas County, which had an NME rate of 27% in 2016-2017, the researchers reported.

Analysis of the relationship between NMEs and MMR vaccination showed that "states with more NME students exhibited lower MMR vacMetro 'hotspots' with over 400 nonmedical vaccine exemptions



Notes: Based on 2016-2017 data from state health departments and the Centers for Disease Control and Prevention. Data for Texas are from 2015-2016.

Source: PLoS Med. 2018 Jun 12:15(6):e1002578

cination rates. In contrast, states that have banned NMEs - Mississippi, California, and West Virginia - exhibit the highest MMR vaccine uptake and lowest incidence of vaccine preventable diseases," the investigators wrote.

Ms. Olive and her associates said

that there was no specific funding for the study and that no conflicts of interest existed.

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SOURCE: Olive JK et al. PLoS Med. 2018 Jun 12;15(6):e1002578. doi: 10.1371/journal.pmed.1002578.

E-cigarette flavorings foster cardiovascular dysfunction

BY HEIDI SPLETE

MDedge News

lavorings used in e-cigarettes have a negative impact on endothelial cells that may play a role in cardiovascular toxicity.

Flavored tobacco products are popular among current smokers, including youth, and the flavorings have been deemed ingestible, but their impact on heart health has not been studied, wrote Jennifer Fetterman, PhD, of Boston University, and her colleagues. The report was published in Arteriosclerosis, Thrombosis, and Vascular Biol-

The researchers studied nine types of flavorings

hearm ...

To characterize the decompounds, the researchers also acquire mercially available endothelial cells and exposed them to nine flavorings: eugenol (clove), vanillin (vanilla), cinnamaldehyde (cinnamon), menthol (mint), 2,5-dimethylpyrazine (strawberry), diace tyl (butter), isoamyl acetate (banana), eucalyptol

used in alternative tobacco products to assess their impact on cardiovascular health.

The first part of the study comprised a population of nine nonsmokers, six nonmenthol cigarette smokers, and six menthol cigarette smokers without cardiovascular disease. The researchers isolated venous endothelial cells from each participant.

Overall, cells from both nonmenthol and menthol cigarette smokers had significantly lower nitric oxide production compared with nonsmokers (P = .003 and P = .012, respectively). In addition, the flavoring compounds menthol and eugenol impaired nitric oxide production in the cells of healthy individuals.

"Increased inflammation and a loss of nitric oxide are some of the first changes to occur leading up to cardiovascular disease and events like heart attacks and stroke, so they are considered early predictors of heart disease," Dr. Fetterman said in a statement, adding that the "findings suggest

(mint), and acetylpyridine (burnt).

All nine flavorings induced cell death at the highest concentration tested, ranging from 10 to 100 mmol/L).

The study findings were limited by several factors, primarily a lack of data on how heating the flavorings in the in vitro part of the study might have affected toxicity in the body, the researchers

"Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an e-cigarette," they said.

However, data support the need for regulation and limits on the level of flavorings used in e-cigarettes and other tobacco products, they empha-

"These findings suggest that flavoring compounds induce endothelial cell dysfunction in human cells similarly to the abnormal function in active cigarette smokers," the researchers noted.

The study was funded by the National Heart, Lung, and Blood Institute; Food and Drug Administration Center for Tobacco Products; and the American Heart Association. The researchers had no financial conflicts to disclose.

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SOURCE: Fetterman J et al. Arterioscler Thromb Vasc Biol. 2018. doi: 10.1161/ATVBAHA.118.311156.



Hospital-acquired conditions drop 8% since 2014

BY MICHELE G. SULLIVAN MDedge News

rom 2014 to 2016, the rate of potentially deadly hospital-acquired conditions in the United States dropped by 8% – a change that translated into 350,000 fewer such conditions, 8,000 fewer inpatient deaths, and a national savings of almost \$3 billion.

The preliminary new baseline rate for hospital-acquired conditions (HACs) is 90 per 1,000 discharges – down from 98 per 1,000 discharges at the end of 2014, according to the Agency for Healthcare Research and Quality's new report, "AHRQ National Scorecard on Hospital-Acquired Conditions – Updated Baseline Rates and Preliminary Results 2014-2016."

The largest improvements occurred in ventilator-associated pneumonias (down 32% from 2014), central line–associated bloodstream infections (down 31%), postoperative venous thromboembolism (21%), and adverse drug events (15%). A new category, *C.difficile* in-

fections, also showed a large decline over 2014 (11%).

These numbers build on earlier successes associated with a national goal set by the Centers for Medicare & Medicaid Services to reduce HACs by 20% by 2019. They should be hailed as proof that attention to prevention strategies can save lives and money, said Seema Verma, CMS administrator.

"Today's results show that this is a tremendous accomplishment by America's hospitals in delivering high-quality, affordable healthcare," Ms. Verma said in a press statement. "CMS is committed to moving the healthcare system to one that improves quality and fosters innovation while reducing administrative burden and lowering costs. This work could not be accomplished without the concerted effort of our many hospital, patient, provider, private, and federal partners – all working together to ensure the best possible care by protecting patients from harm and making care safer."

The numbers continue to go in



Hospitalacquired
conditions

Reduction in HACs from 2014 to 2016

-32%

Ventilator-associated pneumonias

-31%

Central line-associated bloodstream infections

-21%

Postop venous thromboembolisms

Source: Agency for Healthcare Research and Quality

the right direction, the report noted. Data reported in late 2016 found a 17% decline in HACs from 2010 to 2014. This equated to 2.1 million HACs, 87,000 fewer deaths, and a savings of \$19.9 billion.

Much work remains to be done to achieve the stated 2019 goal, the report noted, but the rewards are great. Reaching the 20% reduction goal would secure a total decrease in the HAC rate from 98 to 78 per 1,000 discharges. This would result in 1.78 million fewer HAC in the years 2015-2019. That decrease would ultimately save 53,000 lives and \$19.1 billion over 5 years.

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Systemic changes needed for bronchoscope disinfection

BY JEFF CRAVEN

MDedge News

FROM THE JOURNAL CHEST® Current guidelines for disinfecting bronchoscopes may not be adequate to prevent transmission of infection, as researchers found all reprocessed bronchoscopes they observed had residual contamination and over half showed microbial growth, according to results from a recent study in CHEST.

"Evidence-based, bronchoscope-specific reprocessing and maintenance guidelines are needed, along with quality management programs to ensure that these complex processes are carried out effectively," Cori L. Ofstead, MSPH, president and CEO of Ofstead & Associates, and her colleagues wrote in their study. "Shifting toward using sterilized or single-use bronchoscopes could reduce the risk of infection transmission among vulnera-

MATOWAL INSTITUTE OF ALL BROWNIN INFECTIOUS DISEASES

ble pulmonary patient populations."

The researchers inspected 24 reprocessed bronchoscopes used clinically (9 pediatric, 9 therapeutic, 6 endobronchial ultrasound) at three U.S. tertiary care centers in 2017 and compared them with two bronchoscopes that had not been used. Of the bronchoscopes observed, all had residual contamination after manual cleaning and high-level disinfection (HLD). Manually cleaned bronchoscopes had microbial growth in 11 of 20 (55%) samples, while 14 of 24 (58%) of HLD samples contained microbial growth. Upon inspection, the researchers said they discovered "oily residue; dried fluid spots; brown, red, and white residue; scratches; insertion tube buckling; and damaged distal ends," while internal inspections yielded "fluid, discoloration, scratches, filamentous debris, and dented channels."

Ms. Ofstead and colleagues noted that, while the first site exceeded national guidelines, sites B and C contained technicians who did not wear personal protective equipment and the sites did not follow national or manufacturer use guidelines, such as passing bronchoscopes "through a window to a clean room for automated cleaning and HLD with peracetic acid in automated endoscope reprocessor," flushing the bronchoscopes with alcohol, drying them with medical-grade forced air pressure, and storing them in a dedicated clean and dry area. Site A had microbial growth in 20% and 50% of manually cleaned and HLD bronchoscopes, respectively; site B had microbial growth in 100% and 75% of manually cleaned and HLD

bronchoscopes, respectively; and site C had microbial growth in 83% and 50% of manually cleaned and HLD bronchoscopes, respectively. Among the microbial species identified were "environmental bacteria and normal flora" such as *Bacillus spp* and *Staphylococcus epidermidis*, molds such as *Lecanicillium lecanii* and *Verticillium dahliae*, and pathogens such as *Stenotrophomonas maltophilia* and *Escherichia coli/Shigella spp*.

"The clinical implications for patients are unknown as the study did not involve assessing patients or reviewing medical records," Ms. Ofstead and her colleagues wrote. "However, the results are worrisome as patients undergoing bronchoscopy are commonly at high risk for infection due to transplant status, critical illness, or immune suppression due to malignancy or chronic disease."

Ms. Ofstead and three authors are employees of Ofstead & Associates, which received research funding and speaking honoraria from 3M, Advanced Sterilization Products (Johnson & Johnson), Ambu, Auris Health, Boston Scientific, Cogentix, ConvergAscent, Healthmark Industries, Invendo Medical, Medivators, Nanosonics, and STERIS. Dr. Ferguson has received fees from NeuWave Medical and PPD, research grants and personal fees from OncoCyte, and research grants from Concordia and PneumRx. Dr. Sonetti reported no relevant financial disclosures.

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SOURCE: Ofstead CL et al. Chest. 2018 May 30. doi: 10.1016/j.chest.2018.04.045.

Identifying insomnia in patients with mental disorders

BY BIANCA NOGRADY

MDedge News

he Insomnia Severity Index might be the most effective screening tool at identifying insomnia among outpatients with mental disorders, according to a study published in Sleep Medicine.

The cross-sectional study compared six self-administered sleep measures – the Pittsburgh Sleep Quality Index, Insomnia Severity Index (ISI), Epworth Sleepiness Scale, Flinders Fatigue Scale, Functional Outcomes of Sleep Questionnaire, and Dysfunctional Beliefs and Attitudes About Sleep Scale – in 400 psychiatric outpatients

Of those, the Insomnia Severity Index was the most accurate way to discriminate between cases of insomnia and noncases according to both the DSM-5 and ICD-10 criteria. In fact, the Insomnia Severity Index was the only scale that was able to discriminate both with good accuracy.

The area under the curve for the ISI was 0.88 for the ICD definition, and 0.82 for the DSM-5 criteria. Researchers found that the best sensitivity and specificity for the ISI was achieved using cutoff scores of less than or equal to 14 for ICD-10 insomnia and less than or equal to 11 for DSM-5 insomnia.

A cutoff of 14 or above for the ISI

the ISI at detecting insomnia cases, according to the DSM-5 criteria, in people with either bipolar affective or anxiety disorders.

The Flinders Fatigue Scale, Functional Outcomes of Sleep Questionnaire, and Dysfunctional Beliefs and Attitudes About Sleep Scale all

'Identifying a self-report sleep measure that can detect clinically significant insomnia ... not only provides the clinicians with the ease of administration but also helps them in detecting and treating psychiatric patients whose conditions may be aggravated by the presence of comorbid insomnia.'

yielded a sensitivity of 81.3%, specificity of 80.9%, positive predictive value of 66.7%, and negative predictive value of 90.2%.

The Pittsburgh Sleep Quality Index was found to have good accuracy in discriminating between cases and noncases using the ICD-10 criteria, but had only fair accuracy for the DSM-5 criteria. However, it was slightly better than

showed fair accuracy for the ICD-10 criteria but low accuracy for the DSM-5 criteria, while the Epworth Sleepiness Scale had low accuracy for the ICD-10 criteria and was nondiscriminatory for the DSM-5 criteria.

The scales were all self-administered, were designed to take 15 minutes or fewer to complete, and were chosen because they covered the six

key aspects of sleep, including sleep quality, daytime sleepiness, sleep-related quality of life, and sleep-disruptive cognitions.

The investigators cited one limitation that might limit the generalizability of their findings: Only outpatients with psychiatric disorders were recruited for the study. Nevertheless, the findings have clinical implications, they wrote. "Identifying a self-report sleep measure that can detect clinically significant insomnia ... not only provides the clinicians with the ease of administration but also helps them in detecting and treating psychiatric patients whose conditions may be aggravated by the presence of comorbid insomnia," wrote Lee Seng Esmond Seow, BA, and his colleagues at the Institute of Mental Health in Singapore.

The study was supported by the Singapore Ministry of Health's National Medical Research Council. No conflicts of interest were declared.

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SOURCE: Seow LSE et al. Sleep Med. 2018 Jan;41:86-93.



Impact of marijuana on sleep not well understood

BY RICHARD MARK KIRKNER MDedge News

BALTIMORE – Although the national trend of legalization of marijuana for medical and recreational uses has accelerated, physicians should be cautious about prescribing medical marijuana to treat sleep disorders, a sleep specialist told attendees at the annual meeting of the Associated Professional Sleep Societies.

"Increased legalization of medical marijuana may cause reduction in perception of the risk of potential harm," said Ashima Sahni, MD, of Northwestern University, Chicago.

She noted the long-term implications of marijuana use have been documented, including decreased cognition, lack of motivation, and psychotic effects. Marijuana also appears to affect sleep, although most studies were done in the 1970s and showed mixed results, she said.

"Overall the consensus is that the short-term use of medical marijuana causes an increase in slow-wave sleep [SWS], a decrease in sleep onset latency, a decrease in wake after sleep onset [WASO] and a decrease in REM sleep," Dr. Sahni said. But chronic use decreases SWS and results in inconsistencies in REM sleep patterns and sleep fragmentation. These changes lead to a self-perpetuating negative cycle that causes chronic users to progressively increase their intake, furthering sleep disruption, she noted. Marijuana withdrawal also can

cause significant disturbances in sleep patterns, including reduced total sleep time and SWS, increased WASO, increased REM sleep associated with strange dreams, and increased limb movements during drocannabinol [THC] cannabinoid, which acts on the nonselective CB1 and CB2 agonists," she said. THC is the euphoria-inducing compound in marijuana. While the mechanism of action of dronabinol is similar to



sleep, Dr. Sahni said. "The effects can be seen as early as 24 hours after discontinuation and can last as long as 6 weeks," she said. In addition, poor sleep quality prior to a withdrawal attempt has been linked to relapse (Am J Psychiatry. 2004;161:1967-77).

The use of medical marijuana in the management of sleep disorders is fraught with controversy, Dr. Sahni said. She reviewed studies investigating the use of dronabinol for obstructive sleep apnea (OSA). "This is not medical marijuana," Dr. Sahni said. "It's a synthetic tetrahymarijuana, the pharmacokinetics may differ. Dronabinol has been approved by the Food and Drug Administration for cancer-related nausea and appetite stimulation in AIDS patients. She referred to a proof-of-concept study of 17 patients with OSA in which dronabinol reduced the apnea-hypopnea index (AHI) with no degradation of sleep architecture or serious adverse events (Front Psychiatry. 2013 Jan 22;4:1-5). Dr. Sahni also noted a randomized, placebo-controlled trial of 73 patients that reported an average reduction in AHI of 12.9 (Sleep.

2018 Jan 1;41[1] doi: 10.1093/sleep/zsx184). But she pointed out that the American Academy of Sleep Medicine does not recommend medical cannabis or its synthetic extracts for treatment of OSA (J Clin Sleep Med. 2018 Apr 15;14:679-81).

Insomnia, on the other hand, represents the most common use of medical marijuana for sleep. "Studies have shown mixed results because of differences in the ratios of THC to CBD [corticobasal degeneration] in the forms of marijuana examined," she said. "In the short term, subjective sleepiness is reported to be better, but then the self-perpetuating negative cycle initiates with chronic long-term use."

In treatment of nightmares and posttraumatic stress syndrome, Dr. Sahni cited studies that found "good effects" of medical marijuana use (CNS Neurosci Ther. 2009;15:84-8; J Clin Psychopharmacol. 2014 Oct;34:559-64). For REM behavior disorder, medical marijuana was found to be beneficial in four patients with Parkinson disease (J Clin Pharm Ther. 2014 Oct;39:564-6). In poorly treated restless leg syndrome, medical marijuana was reported to be beneficial (Sleep Med. 2017 Aug;36:182-3).

"It should be noted that these were very small studies and therefore more research is needed before we change our medical practices toward various sleep disorders," Dr. Sahni said.

Dr. Sahni and her coauthors reported having no financial relationships to disclose.

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Poor sleep tied to suicidal behaviors in college students

BY GINA L. HENDERSON

MDedge News

poor sleep is associated with increased suicidal behaviors in college students – even when controlling for depression, a study of 1,700 students shows.

"Findings suggest that some specific sleep components – shorter sleep duration, more frequent bad dreams, feeling too cold while sleeping, and greater sleep medication use – are particularly associated with increased suicidal behaviors in college students," reported Stephen P. Becker, PhD, of the Cincinnati Children's Hospital Center, and his associates.

The researchers recruited students from two universities. Most of the students were female (65%), white (82%), and in their first year of college (63%). The participants' sleep was assessed using the nine-item Pittsburgh

Sleep Quality Index (PSQI), their depressive symptoms were assessed using the Depressive Anxiety Stress Scales-21, and their suicidal behavior was assessed using the Suicidal Behaviors Questionnaire-Revised (SBQ-R), which is a four-item, self-report measure.

About two-thirds of the students (64%) were found to have sleep problems (total PSQI score greater than 5), and 24% were found to have suicide risk (total SBQ-R score of at least 7). Of the students who were found to have suicide risk, 83% also had sleep problems.

Using regression analysis, Dr. Becker and his associates found that the odds of being classified with suicide risk were 6.5 times greater for students with depression and 2.7 times greater for those with sleep problems.

"We found that the four-fifths of college students who were classified with suicide risk were also classified with poor sleep (conversely, almost one-third of the participants classified with sleep problems were also classified with suicide risk). Furthermore, poor sleep remained significantly with increased suicide risk after controlling for sex and depression," the investigators wrote.

In addition, the association between depression and suicidal behaviors/risk was reduced when sleep was adjusted for, suggesting that sleep may mediate the link between depression and suicide

The results add to the literature suggesting that sleep would be an "important component to include in screening and intervention efforts to prevent suicidal ideation and attempts on college campuses," the researchers wrote.

Dr. Becker and the other investigators had no conflicts to disclose.

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SOURCE: Becker SP et al. J Psychiatr Res. 2018 Apr;99:123-8.

CBT-I bests acupuncture for treating insomnia

BY SUSAN LONDON

MDedge News

ancer survivors who have trouble sleeping saw improvements with both cognitive-behavioral therapy designed specifically for insomnia (CBT-I) and acupuncture, according to results from the randomized, controlled CHOICE trial. But the former is more efficacious.

"Insomnia can have deleterious effects on quality of life and function, and occurs in up to 60% of cancer survivors," lead study author Jun J. Mao, MD, chief of integrative medicine service at Memorial Sloan Kettering Cancer Center, New York, said in a press briefing held in advance of the annual meeting of the American Society of Clinical Oncology.

"CBT-I is a highly effective therapy and can be considered the gold standard of treatment," he noted. However, this modality may be limited by poor adherence and non-response. Moreover, it is highly specialized and not currently available in many cancer centers or communities.

Functional imaging studies have shown that acupuncture can regulate brain regions involving cognition and emotion that are essential to sleep regulation, and clinical research has shown that it can improve pain- and hot flash-related sleep disturbances, according to Dr. Mao.

Main results of the CHOICE (Choosing Options for Insomnia in Cancer Effectively) trial showed that patients in both the CBT-I and acupuncture groups reduced their Insomnia Severity Index scores by more than one-half at the end of the 8-weeks treatment period, but the reduction was a statistically significant 2.6 points greater with CBT-I. Benefit of each treatment was still evident after 12 weeks.

Response rate was higher with CBT-I than with acupuncture only among patients having mild insomnia at baseline, and the two treatments yielded similar improvements in mental and physical quality of life.

"Among cancer patients with insomnia, we found that both acupuncture and CBT-I produced clinically meaningful and durable benefit, but overall, CBT-I is more effective in reducing insomnia severity," Dr. Mao concluded. "Our hope is that by doing this type of research, we can help patients and clinicians pick the right kind of

treatment and help them to manage their sleep. Our next step is to really examine for what type of patient treatment would be beneficial, and how to deliver this type of effective treatment to the broader community of cancer patients."

Insomnia among cancer survivors is both prevalent and problematic, agreed ASCO President Bruce E. Johnson, MD, FASCO.

"The most common way we treat this is pharmacologically, with sleeping pills," he noted. "This trial shows that two different methods using something other than medications can help people with sleep, and not only do they help people with sleep, but they improve their quality of life, said Dr. Johnson, who is also a professor of medicine at the Dana-Farber Cancer Institute in Boston, and a leader of the center's lung cancer program.

The CHOICE trial did not have any restrictions on cancer type or stage; more than a half-dozen types were represented among the 160 patients enrolled, with breast cancer (31%) and prostate cancer (23%) accounting for the largest shares. The majority of patients were white (70%) and had moderate to severe insomnia (79%).

Patients were randomized to receive either acupuncture sessions (10 sessions, with points selected to treat insomnia plus comorbid symptoms such as fatigue and anxiety) or CBT-I (7 sessions), each over the course of 8 weeks.

Main results showed that, at the end of treatment, the reduction in Insomnia Severity Index was 8.3 points with acupuncture and 10.9 points with CBT-I (P = .0007), Dr. Mao reported. Benefit of each treatment was sustained after 12 weeks.

In stratified analysis, the rate of response (defined as a greater than 8-point reduction) was higher with CBT-I than with acupuncture among patients with mild insomnia (Insomnia Severity Index of 8-14) (85% vs. 18%; P less than .0001), but not among patients with moderate or severe insomnia (Insomnia Severity Index of 15 or higher) (75% vs. 66%; P = .26).

Dr. Mao disclosed no relevant conflicts of interest. The study received funding from the Patient-Centered Outcomes Research Institute.

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SOURCE: Mao JJ et al. ASCO 2018, Abstract 10001.

Black women more likely to have poor sleep quality

BY RICHARD MARK KIRKNER

MDedge News

BALTIMORE – Analysis of data from a national multicenter study of women's health has found that middle-aged black women were at higher risk for sleep problems than their white counterparts, according to a presentation at the annual meeting of the Associated Sleep Societies.

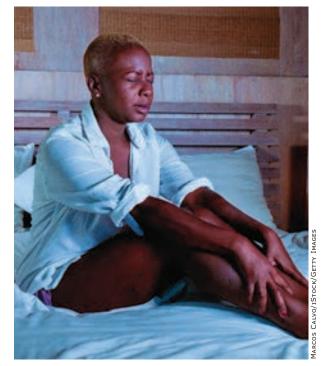
"Race is emerging as a significant moderator in the relationship between sleep and health outcomes," said Marissa Bowman, a doctoral student at the University of Pittsburgh. The study was based on 10- to 15-year follow-up data from the SWAN (Study of Women's Health Across the Nation) sleep research. The researchers evaluated sleep in 265 midlife women, 45% of whom were black.

She noted that black women in the study were more likely to have poor sleep quality as assessed by Pittsburgh Sleep Quality Index, shorter sleep duration as assessed by polysomnography, longer periods of wakefulness after sleep onset, shorter sleep efficiency, and apnea-hypopnea index greater than 15. The study evaluated six factors of sleep quality: regularity, satisfaction, alertness, timing, efficiency, and duration.

At baseline, the study assessed sleep health using both actigraphy and a daily diary, along with

body mass index, waist circumference (WC), and waist-to-hip ratio (WHpR), then collected data on the anthropometric factors 10-15 years later.

Cross-sectional and prospective analyses found that sleep health was correlated with lower BMI



but was not significantly associated with WC or WHpR. A prospective analysis found no overall significant correlation between sleep health and any of the three factors. But in a separate analysis of the study group by race, all three anthropometric factors had a stronger link to sleep health in black women than in those of European descent, respectively, with beta coefficients of –0.14 vs. 0.1 for BMI, –0.17 and 0.1 for WC and –0.17 and 0.07 for WHpR.

"We need to explain this association and conceptualize how sleep health might be more strongly related with weight in African Americans," Ms. Bowman said. "One possibility might be that sleep health reflects a health disparity. We can see how race is related to other health disparities, and this might be one of them."

During questions, Ms. Bowman acknowledged that SWAN did not have data on what kind of access to health care the black women in the study had. "That might be a possible reason they're not getting their sleep treated; they're not getting other health factors treated," she said.

Ms. Bowman and her coauthors reported no financial relationships. The study was funded by the National Institute on Aging, National Institutes of Health, and the National Institutes of Health Office of Research on Women's Health.

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OSA with hypoxemia raises metabolic syndrome risk

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – An 8-year cohort study has found that patients with obstructive sleep apnea who are prone to worsening of hypoxemia at night have a heightened risk of developing metabolic syndrome, an investigator reported at the annual meeting of the Associated Professional Sleep Societies.

"Considering that we have a very high prevalence of moderate to severe obstructive sleep apnea (OSA) in the general population, this is a very important finding because it indicates that we need some clinical options of treating OSA in those that have metabolic syndrome to decrease the risk of morbidity and mortality and cardiac events in these patients," said Camila Hirotsu, PhD, of the Federal University of São Paulo.

Dr. Hirotsu presented 8-year follow-up results of the EPISONO cohort, an observational prospective study conducted in Brazil, the goal of which was to evaluate how OSA can impact the risk of developing metabolic syndrome (MetS) in the general population. MetS is defined as a cluster of three or more cardiovascular metabolic components: low HDL levels, high glucose and triglycerides, hypertension, and abdominal obesity. Dr. Hirotsu said that 50%-60% of MetS patients have OSA (PLoS One. 2010;5:e12065).

The study enrolled 1,074 patients at baseline, closing enrollment in 2008, and obtained follow-up on 712, evaluated from July 2015 to April 2016. After exclusions, the study evaluated 476 patients who were free of MetS at baseline. Of



those 476, 44% went on to develop MetS.

Median age of patients who developed MetS was 40.8 years vs. 36.1 for those who did not. Patients who developed MetS also had a high-

er body mass index, but were not obese: 26.9 kg/m² vs. 23.8 kg/m². Patients were evaluated by completing questionnaires, undergoing full polysomnography, and having clinical assessments.

Patients with moderate to severe OSA were found to have an odds ratio of 2.47 (P = .016) of developing incident MetS, Dr. Hirotsu said. Rates of moderate to severe OSA were 21.3% for the group that devel-



oped MetS versus 9% for the non-MetS group, said Dr. Hirotsu.

The study determined that the following sleep changes were associated with incident MetS: apnea-hypopnea index (AHI) (OR, 1.16); 3% oxygen desaturation index (ODI) (OR, 1.24); and time with oxygen saturation by pulse oximeter (SpO2) less than 90% (OR, 1.42).

Patients with moderate to severe OSA were found to have an odds ratio of 2.47 of developing incident metabolic syndrome.

Rates of moderate to severe OSA were 21.3% for the group that developed MetS vs. 9% for the non-MetS group.

"Moderate to severe OSA at baseline and worsening of nocturnal hyperemia from baseline to follow-up are really independent risk factors to increase the incidence of MetS in the general population," Dr. Hirotsu explained.

A secondary aim of the study was to evaluate the impact of MetS on the risk of developing OSA in the general population. "It seems that MetS is not really an independent risk factor for OSA."

Dr. Hirotsu reported having no conflicts of interest.

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Waning vaccine immunity linked to pertussis uptick

BY BIANCA NOGRADY

MDedge News

he resurgence of whooping cough in the United States could be the result of waning

pertussis immunity combined with incomplete historical coverage, researchers said.

Researchers reported in Science Translational Medicine on a study that used different models of transmission to explore what might be the cause of the steady increase in pertussis infections since the mid-1970s. "We considered whether pertussis vaccines failed to confer immunity in some recipients whether vaccine-induced immunity waned with time; and whether vaccines may have induced some, but imperfect, protection against the disease," they wrote.

The three modes of vaccine failure modeled in the study were primary vaccine failure in a fraction of the population; waning of vaccine-induced protection over time; and failure in the degree of protection offered by the vaccine, perhaps caused by antigenic evolution in the pertussis bacteria

Using 16 years' worth of detailed, age-stratified incidence data from Massachusetts, researchers found that the model which assumed a gradual waning in protection was

Individuals who either did not get vaccinated as children or who did not gain immunity from vaccination were growing to adulthood without ever being exposed to natural infection.

the best fit for the observed patterns of pertussis incidence across the population.

This model suggested significant variability in how the level of protection changes over time, with a 10% risk of vaccine protection waning to zero within 10 years of completing routine vaccination and a 55% chance that the vaccine would confer lifelong protection.

"Crucially, we find that the vaccine is effective at reducing pathogen circulation but not so effective that eradication of this highly contagious bacterium should be possible without targeted booster campaigns," wrote Dr. Matthieu Domenech de Cellès, PhD, of the Institut Pasteur at the University of Versailles (France) and his coauthors.

The model also considered the possibility that the whole-cell and acellular pertussis vaccines might show differences in immunity, which had been suggested as one explanation for the resurgence of the disease. However, the authors found little evidence of a marked epidemiological switch from the whole-cell to acellular vaccines, although their results did suggest the acellular vaccine has a moderately reduced efficacy.

"Our results suggest that the train of events leading to the resurgence of pertussis was set in motion well

Continued on following page



Cash, not e-cigarettes, helped patients stop smoking

BY RANDY DOTINGA

MDedge News

new study finds it pays to pay people to stop lighting up: Smokers were more likely to quit if they had an opportunity to gain rewards worth \$600 than if they simply received free cessation aids or free e-cigarettes.

The wide majority of the more than 6,000 smokers in the randomized study didn't quit despite offers of various incentives. All the same, "programs that offered financial incentives tripled the rates of smoking cessation, reduced employers' costs per successful quit, as compared with programs that offered cessation aids alone, and yielded total costs that compared favorably with the costs of employing smokers," the study authors wrote.

The study, led by Scott D. Halpern, MD, PhD, of the University of Pennsylvania, was published online May 23 in the New England Journal of Medicine.

The researchers reached out to employees and spouses at 54 companies that use wellness programs provided by the Vitality Institute, which supports research into health promotion. The institute provided grant support for the study.

Just over 6,000 employees and spouses who smoked were assigned to five groups. One group received usual care. The others received interventions: free smoking-cessation aids (nicotine replacement therapy, bupropion, or varenicline); free e-cigarettes; up to \$600 worth of an unidentified "reward incentive" plus free cessation aids; and up to \$600 via a redeemable deposit, plus free cessation aids.

Participants could get the entire

'Programs that offered financial incentives tripled the rates of smoking cessation, reduced employers' costs per successful quit, as compared with programs that offered cessation aids alone, and yielded total costs that compared favorably with the costs of employing smokers.'

tion. However, the researchers noted there wasn't a significant difference in the quit rates between the usualat 1, care, free cessation—aid, and free e-cigarette groups.

"The observation of greater e-cigarette use in the free e-cigarette group than in the free cessation aids group, coupled with the absence of benefit of free e-cigarettes versus no intervention, supports the conclusion that offering free e-cigarettes does not promote smoking cessa-

In the reward incentive and \$600 redeemable-deposit groups, 2% and

2.9% of participants quit over a sustained period, respectively. Cessation rates in the \$600 deposit group were superior to the free cessation aid group (P less than .001) and the free e-cigarette group (P = .008). Cessation rates in the incentive group were superior to those in the free cessation—aid group (P = .006).

"Average costs per participant assigned to each intervention were lowest in the usual-care group (\$0.82) and highest in the redeemable-deposit group (\$100.96)," the researchers reported. "The overall cost of each program per participant who was abstinent for 6 months was lower in the rewards and redeemable-deposit groups than in the free e-cigarettes or free cessation aids groups."

The study received grant support from the Vitality Institute. Most of the study authors reported no relevant disclosures. One author reported serving on the scientific advisory board of VAL Health, and another reported various grants and personal fees.

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SOURCE: Halpern SD et al. N Engl J Med. 2018 May 23. doi: 10.1056/NE-JMsa1715757.

reward incentive or the full \$600 redeemable deposit only if they showed signs of sustained smoking cessation via blood or urine test at 1, 3, and 6 months.

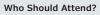
The median age in the groups ranged from 43 to 45 years, and most were not college graduates. Just over half were women, and roughly 90% said they wanted to quit smoking.

Overall, 20% of the 6,006 participants logged onto the trial website, a sign that they were "engaged." The number was highest in the free e-cigarette and reward groups (21%-23%) and lowest in the usual-care group (16%).

The researchers focused on how many participants abstained from smoking – as confirmed by blood or urine test – for 6 months past the target quit date. The test data confirmed that just 1.3% of the total participants, 80 people, sustained cessation over 6 months.

Only 0.1% of the usual-care group sustained smoking cessation, and the number wasn't much higher (0.5%) in the free cessation—aids group.

One percent of those in the free e-cigarette group sustained cessa-



tion," they cautioned.

Intensive care providers, pulmonary and critical care physicians, advanced practice providers (NPs and PAs), ECMO specialists (RN, RT), cardiothoracic surgeons, trauma surgeons, cardiologists, and any provider who cares for patients with severe respiratory or cardiac failure are encouraged to attend.



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Continued from previous page

before the shift to the DTaP vaccine," Dr. Domenech de Cellès and his associates said.

The model also pointed to big shifts in the age-specific immunological profile caused by introduction of vaccination, which led to a reduction in transmission and also a reduction in natural infections both in vaccinated and unvaccinated individuals.

This meant individuals who either did not get vaccinated as children or who did not gain immunity from vaccination were growing to adulthood without ever being exposed to natural infection.

"Concurrently, older cohorts, with

their long-lived immunity derived from natural infections experienced during the prevaccine period, were gradually dying out," the authors said. "The resulting rise in the number of susceptible adults sets the stage for the pertussis resurgence, especially among adults."

Two authors were supported by the National Institutes of Health and by Models of Infectious Disease Agent Study–National Institute of General Medical Sciences. No conflicts of interest were declared.

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SOURCE: Domenech de Cellès M et al. Sci Transl Med. 2018 Mar 28;10:eaaj1748.

Methotrexate-induced pulmonary fibrosis risk examined in 10-year study

BY SARA FREEMAN

MDedge News

LIVERPOOL, ENGLAND – A 10-year follow-up of patients with inflammatory arthritis has shown that methotrexate does not appear to increase the risk of pulmonary fibrosis.

"It's a really important message that methotrexate does not cause chronic pulmonary fibrosis and it should not be stopped because of pulmonary fibrosis," Julie Dawson, MD, said in an interview at the British Society for Rheumatology annual conference. "It's the rheumatoid arthritis. It's not the methotrexate."

Dr. Dawson, of St. Helens and Knowsley Teaching Hospitals NHS Trust, St. Helens, England, added that the current findings were consistent with her team's prior research looking at earlier time periods. There was also no correlation between the duration or dose of methotrexate used and the development of the lung disease, she said.

If patients are not doing well on methotrexate, then perhaps adjusting therapy or changing to another drug would of course be the next step, but if patients are well controlled then "stopping it is the worst thing to do" for their arthritis, she said.

"This is of great clinical interest, and we can be reassured now about this, I think. This is really good, long-term data," said Devesh Mewar, MD, of Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, who was not involved in the research.

"We know that methotrexate is associated with a pneumonitis reaction, but there is no high-quality evidence that methotrexate is associated with a chronic pulmonary fibrosis" Dr. Dawson said, explaining the rationale for the current study she presented during a poster session. Previous studies considered data for up to 5 years, she added, so the aim of the current study, therefore, was to look at the longer-term effect of methotrexate use on the incidence of pulmonary fibrosis.

Data on 129 patients who had started treatment with methotrexate from 2004 to 2007 were analyzed, of whom 63 (49%) had stayed on methotrexate for 10 or more years. Most (82%) had been given methotrexate to treat rheumatoid arthritis, with other indications including inflammatory arthritis (5.4%) and



Dr. Julie Dawson

psoriatic arthritis (4.7%).

"Practice was different 10 years ago, so just 56% of patients commenced methotrexate within the first year of the diagnosis of rheumatoid arthritis," Dr. Dawson reported.

Only four cases of symptomatic pulmonary fibrosis were seen, all in the RA patients, and three of these were in patients who had started methotrexate over 1 year after their diagnosis. The incidence of 3.8% seen in the study matches the expected incidence of pulmonary fibrosis in RA and was actually "at the lower end of the expected incidence," Dr. Dawson said. Previous studies have suggested an incidence rate of RA-associated interstitial lung disease of about 3%-7%.

All of the pulmonary fibrosis cases had occurred in men and 75% were seropositive for rheumatoid factor. The mean duration of RA at the time of onset of pulmonary fibrosis was 7.8 years, and the usual interstitial pattern of fibrosis was seen. The 125 patients without pulmonary fibrosis had taken methotrexate for a mean of 8 years at a mean final weekly dose of 16.3 mg, compared with a mean of 6 years at a mean dose of 18.1 mg per week in the 4 patients with pulmonary fibrosis.

One of the next steps is to look at cases where methotrexate has been stopped and the effects of that on pulmonary fibrosis and disease activity. In Dr. Dawson's experience, stopping methotrexate just affects the management of the arthritis and had no difference to the progression of pulmonary fibrosis.

If patients start to experience any lung symptoms while continuing methotrexate, such as shortness of breath, then they would need to be assessed and undergo lung function tests to monitor their condition. Treating the fibrosis using an antifibrotic drug, such as pirfenidone, is something that might be possible in the future, but this needs investigation in inflammatory arthritis as the drug is currently licensed for use only in idiopathic cases.

This is something the British Rheumatoid Interstitial Lung network plans to investigate in a place-bo-controlled study of RA patients with fibrotic lung disease. "We're looking to see if antifibrotic agents are going to slow the disease as it does in idiopathic pulmonary fibrosis, which is obviously quite exciting when it's such a hard condition to treat," said Dr. Dawson, who will be one of the study's investigators.

Dr. Dawson had no conflicts of interest to disclose. Dr. Mewar was not involved in the study and had nothing to disclose.

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SOURCE: Dawson J et al. Rheumatology. 2018;57(Suppl. 3):key075.470.

VIEW ON THE NEWS

Study generates hypotheses but leaves incidence unknown

The subject of this retrospective study is of great interest. The authors point out that pulmonary fibrosis (as opposed to acute allergic reaction, which is extremely rare) is also extremely uncommon in patients using methotrexate over the long haul. Over 10 years, their data point to a 3.1% incidence of symptomatic pulmonary fibrosis.

The issue here is its generalizability. There were 63 patients who used methotrexate for 10 years or more and 88 who used it for 5 years or more, according to the poster. This must represent a highly selected population. For example, what percent of the total RA/psoriatic arthritis/"inflammatory arthritis" population do these patients represent; i.e., what is the denominator here? The authors stated that the 63 patients who stayed on methotrexate for 10 or more years represent 49% of the 129 patients on methotrexate overall in the study. This is a highly unusual datum, as most of the literature indicates that only 40% or less of patients stay on methotrexate for even 5 years. And this completely ignores the issue of adherence over this long a period; these patients must represent a truly minuscule percentage of the total if they actually stayed on

methotrexate with even moderate adherence for 10 years.

Importantly, the authors point out that they had only four cases of symptomatic pulmonary fibrosis. Once more, this points to the highly selective group of patients seen, as this study does not examine patients with asymptomatic pulmonary fibrosis, including

those with fibrosis on high-resolution CT of the lungs or chest film or evidence of abnormalities on pulmonary function tests, but who do not have sufficient symptoms ascribed to methotrexate to bring them to medical attention.

This is a nice hypothesis-generating study, but the actual incidence of methotrexate-induced lung fibrosis remains completely unknown. I heartily applaud their intention to start a prospective study to answer this interesting question.

Daniel E. Furst, MD, is professor of rheumatology at the University of Washington, Seattle, who also is affiliated with the University of California, Los Angeles, and the University of Florence (Italy). He was not involved with the study.



Aclidinium bromide for COPD: No impact on CV events

BY DOUG BRUNK

MDedge News

SAN DIEGO – The use of aclidinium bromide 400 mcg b.i.d. did not increase the risk of major adverse

cardiac events or mortality in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) with significant cardiovascular risk factors, compared with placebo.

Those are two key findings from the ASCENT COPD trial presented by Robert A. Wise, MD, FCCP, at an international conference of the American Thoracic Society. "Cardiovascular risk factors and

comorbidities are prevalent in patients with COPD, and about 30% of COPD patients die of cardiovascular disease," said Dr. Wise, who serves as director of research for the division of pulmonary and critical care medicine at the Johns Hopkins University School of Medicine, Baltimore. "However, patients who have cardiovascular disease are often excluded from, or not enrolled in, COPD clinical trials. Moreover,



DR. WISE

there has been controversy as to whether or not treatment with a long-acting muscarinic antagonist is associated with an increased risk of cardiovascular events. That's been seen in

randomized trials, meta-analyses, as well as in observational studies."

Aclidinium bromide 400 mcg

b.i.d., administered by the Pressair inhaler, is approved as a maintenance treatment for patients with COPD. However, during the registration studies, there were not an adequate number of cardiovascular events in order to ascertain clearly whether or not the drug was associated with increased risk, Dr. Wise said. Therefore, he and his associates in the ASCENT COPD study set out to assess the long-term cardiovascular safety profile of aclidinium 400 mcg b.i.d. in patients with moderate to very severe COPD at risk of major adverse cardiovascular events (MACE) for up to 3 years (Chronic Obstr Pulm Dis. 2018;5[1]:5-15). For the randomized, placebocontrolled, parallel-group study, patients received treatment with aclidinium bromide or a placebo inhaler of similar appearance. The study was designed to be terminated when at least 122 patients experienced an adjudicated MACE. The primary safety endpoint was time to first MACE during follow-up of up to 3 years, while the primary efficacy endpoint was the rate of moderate to severe exacerbations per patient per year during the first year of treatment.

To be included in the study, patients had to be at least 40 years of age with moderate to very severe stable COPD, have a smoking history of at least 10 pack-years, and have at least one of the following significant risk factors: cerebrovascular disease;

Continued on following page



Phase 2a trial: Investigational drug delivered significant bronchodilation in two-week study

BY DOUG BRUNK

MDedge News

SAN DIEGO – The investigational agent AZD8871 at once-daily doses of 100 mcg and 600 mcg led to statistically significant, clinically relevant, and dose-ordered differences in trough forced expiratory volume (FEV $_1$) at 2 weeks, compared with placebo, results from a phase 2a trial showed.

AZD8871 is a long-acting, bifunctional bronchodilator that combines a muscarinic antagonist and a beta₂ adrenoceptor agonist. "There are some interesting avenues that you can explore with such a molecule," one of the study authors, Dave Singh, MD, said at an international conference of the American Thoracic Society. "First, theoretically, as a single molecule you will be able to deposit both the active ingredients to the same site in the lung. On a more practical note, if you want to add something else to a dual bronchodilator, which is essentially what AZD8871 is, this provides a platform. Perhaps that's the most interesting use of this type of approach."

Single doses of AZD8871 (400 mcg and 1,800 mcg) administered in chronic obstructive pulmonary disease (COPD) patients demonstrated sustained bronchodilation over 36 hours. In a study presented at the 2017 meeting of the European Respiratory Society, Dr. Singh and his associates found that AZD8871 1,800 mcg showed greater bronchodilation than both indacaterol and tiotropium for peak and trough FEV₁.

For the current study, researchers at one site in the United Kingdom and one site in Germany conducted a phase 2 randomized, double-blind, placebo-controlled trial of AZD8871 in 42 patients aged 40-80 years with moderate to severe reversible COPD. Patients were randomized to receive repeated once-daily doses of AZD8871 100 mcg, 600 mcg, or placebo via a dry powder inhaler device for 14 days. Between-treatment washout periods were 28-35 days. "We keep the patients inhouse on day 1 and day 14 of each treatment peri-



Dr. Dave Singh discussed phase 2a trial results for AZD8871, an investigational agent.

od, and we measure lung function over 24 hours," said Dr. Singh, professor of clinical pharmacology and respiratory medicine at the University of Manchester (England). "Patients were allowed to continue any preexisting steroid therapy, but at the end of screening they had to withdraw any long-acting bronchodilator therapy."

The primary efficacy endpoint was change from baseline trough FEV₁ on day 15. Secondary endpoints included change from baseline in peak FEV₁, total score of breathlessness, cough, sputum scale questionnaire, and rescue medication use.

At baseline, the mean age of the 42 patients was 64 years, and 67% were male. Their mean FEV_1 was about 58% predicted, and their FEV_1 absolute reversibility was a mean of 379 mL, "which is rather high," he said.

Of the 42 randomized patients, 31 completed all three treatments. Both doses of AZD8871 had a positive, dose-dependent effect on FEV₁, compared with placebo, and both doses demonstrated an onset of action within 15 minutes. On day 15, least square

mean change from baseline differences in trough FEV₁ for AZD8871 100 mcg and 600 mcg versus placebo were 161 mL and 260 mL, respectively.

A similar association was observed with peak FEV₁, which between baseline and day 14 increased by 380 mL at the 100-mcg dose and by 420 mL at the 600-mcg dose, compared with placebo. Sustained bronchodilation was observed over 24 hours on both day 1 and day 14.

Statistically significant COPD symptom improvements, measured by breathlessness, cough and sputum scale (BCSS), were observed for AZD8871 600 mcg on day 8 (P = .002) and day 14 (P less than .001), compared with placebo.

In addition, substantial symptomatic improvements were observed for AZD8871 600 mcg on day 14 versus placebo (least square mean of –1.16). Similar results were observed for individual domains of the BCSS. "When you separate out the different components of the scale, most of this is driven by the change in breathlessness," he said. "We were surprised that we could capture this in such a small number of patients."

On days 1-8 and days 9-14, the researchers observed a statistically significant improvement in change from baseline rescue medication use for AZD8871 600 mcg (P less than 0.001) and 100 mcg (P = .029 and P = .012, respectively), compared with placebo.

The most common adverse events for patients in all three treatment groups were headache (21.4%) and worsening of COPD-related symptoms (14.3%). No dose dependence was observed with any adverse event, including serious adverse events and/or those leading to discontinuation.

AstraZeneca, the developer of AZD8871, sponsored the study. Dr. Singh reported being a consultant to and receiving research support from AstraZeneca and numerous other pharmaceutical companies.

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SOURCE: Singh D. et al. ATS 2018, Abstract 7708.

Continued from previous page

coronary artery disease; peripheral vascular disease, or history of claudication; or at least two atherothrombotic risk factors (male at least 65 years of age, female at least 70 years of age; waist circumference of at least 40 inches among males or at least 38 inches among females; an estimated glomerular filtration rate of less than 60 mL/min and microalbuminuria; dyslipidemia; or hypertension).

The researchers randomized 1,791 patients to the aclidinium group and 1,798 to the placebo group. Their mean age was 67 years, and about 60% of patients had an exacerbation in the preceding year. Nearly two-thirds of patients (63%) were receiving concomitant long-acting beta, ago-

nists (LABA) or LABA/inhaled corticosteroid therapy. In addition, 44% of patients entered the study with a history of a prior cardiovascular event plus at least two atherothrombotic risk factors, 52% reported at least two

in patients with moderate to very severe COPD with significant cardiovascular risk factors, compared with placebo (hazard ratio 0.89; P = .469); noninferiority was concluded as the upper bound of the 95% con-

The ASCENT COPD study set out to assess the long-term cardiovascular safety profile of aclidinium 400 mcg b.i.d. in patients with moderate to very severe COPD at risk of major adverse cardiovascular events, or MACE, for up to 3 years.

atherothrombotic risk factors without any prior cardiovascular events, and 4% had a history of a prior cardiovascular event only.

Dr. Wise reported that aclidinium did not increase the risk of MACE

fidence interval was less than 1.8). In terms of all-cause mortality, aclidinium did not increase the risk of death, compared with placebo (HR, 0.99; P = .929).

During the first year of treatment,

Dr. Wise and his associates also observed a 22% reduction in COPD exacerbation rate for aclidinium vs. placebo groups (HR, 0.44 vs. 0.57, respectively; P less than .001), and a 35% reduction in the rate of COPD exacerbations leading to hospitalizations (HR, 0.07 vs. 0.10; P = .006). "The reduction in exacerbation risk was similar, whether or not patients had an exacerbation in the past year," Dr. Wise said. He reported being a consultant to, and receiving research support from, AstraZeneca, Boehringer Ingelheim, ContraFect, and GlaxoSmithKline.

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SOURCE: Wise R. et al. ATS 2018, Abstract 7711.

Custom-made 3-D stents created for anatomically complex airway stenosis

'Conventional devices

are either not suited or

may result in a significant

complication rate,

including poor clinical

tolerance, migration, or

granulation tissue reaction

due to lack of congruence.'

BY DOUG BRUNK

MDedge News

SAN DIEGO – Customized airway stents made from 3-dimensional imaging software provided compelling outcomes in patients with nonmalignant, anatomically complex, and symptomatic stenosis for whom conventional stents were not suitable or failed, results from a small study demonstrated.

"Anatomically complex airway stenosis remains a challenging situation," lead study author Nicolas Guibert, MD, said at an international conference of the American Thoracic Society. "Conventional devices are either not suited or may result in a significant complication rate, including poor clinical tolerance, migration, or granulation tissue reaction due to lack of congruence."

Dr. Guibert, a pulmonologist at Toulouse (France) University Hospital, and his associates hypothesized



A virtual 3-D stent and corresponding mold was designed for each patient.

that patient-specific, fully customized 3-D stents created by computer-assisted design has the potential for improving tolerance and decreasing

the complication rate. In a feasibility study, they recruited 10 patients with nonmalignant, anatomically complex, and symptomatic stenosis for whom conventional stents were not suitable or failed. After computer-assisted segmentation of the

airways from a CT scan and virtual relief of the stenosis, a virtual 3-D stent and corresponding mold was designed for each patient, a process that takes 3-4 weeks, including sterilization. Numerical data were then entered into a 3-D computer numeric control machine to produce the Ertacetal mold, from which the silicon stent is made. The researchers placed the stents under general anesthesia through rigid bronchoscopy and collected data on complication rate, dyspnea as defined by the New York Heart Association classification, quality of life as defined by the VQ11 measure, and respiratory function at day 7 and at 3, 6, and 12 months. Congruence of the stent was assessed preoperatively via bronchoscopy and at 1 week via CT scan.

Dr. Guibert reported results from several patients. Of these, three had posttransplant complex airway stenoses involving the bronchus intermedius. Each improved after placement of the customized stents. For example, one patient with vanishing bronchus intermedius syndrome experienced improvements in NYHA dyspnea score from 3 to 1, the VQ11 score from 22 to 11/55, and forced

expiratory volume in 1 second (FEV₁) from 70% to 107%. The stent was removed after 3 months. Meanwhile, a patient with localized malacia and stenosis of the right main bronchus experienced improvements in NYHA dyspnea score from

3 to 1, VQ11 score from 27 to 15/55, and FEV₁ from 70% to 102%. That person's stent is still in place with no complications. Another patient with localized malacia and stenosis of the bronchus intermedius experienced improvements in FEV₁ from 84% to 100%. That person's device was removed after 3 months, with no residual stenosis.

A fourth patient underwent stent placement for localized malacia (cartilage ring rupture). That person experienced improvements in NYHA dyspnea score from 3 to 1, VQ11 from 23 to 15/55, and FEV₁ from 66% to 92%, and peak flow from 49% to 82%. The device is still in place with no complications. A fifth patient received stent placement for extensive tracheobronchomalacia, but it had imperfect congruence and was removed after 3 months because it caused intense cough.

One patient with posttracheotomy stenosis experienced improvements in NYHA dyspnea score from 3 to 0, VQ11 from 29 to 12/55, and peak

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: As discussed in

the article, significant symptoms related to anatomic airway abnormalities affect the daily lives of some patients in a major



way. Unfortunately, for a large proportion of them airway interventions yield variable results and often ones that wane with time. Efforts to improve the options available for these patients are very much welcomed - since for many of them there is often little to offer. Another aspect in the care of these patients reflected by this work recognizes that a given modality for one patient may not be optimal for another, and the personalization of a given intervention may be equally as important.

flow from 45% to 81%. That person's device is still in place, Dr. Guibert said. Two other patients treated for posttracheotomy experienced stent migration (conventional stents also migrated in these two cases), despite good bronchoscopic congruence after placement.

Dr. Guibert reported having no financial disclosures.

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Women still underrepresented in cardiovascular trials

BY ANDREW D. BOWSER

MDedge News

Women remain underrepresented in studies of heart failure, coronary artery disease, and acute coronary syndrome, a recent study authored by Food and Drug Administration researchers has revealed.

Representation was favorable in trials of drugs treating hypertension, atrial fibrillation, and pulmonary arterial hypertension, authors of the study wrote in the Journal of the American College of Cardiology.

However, representation of women fell below an acceptable participation-to-prevalence ratio in

several critical categories of heart disease, according to researchers, including lead author Pamela E. Scott, PhD, of the FDA's Office of Women's Health.

To quantify the participation of women in clinical trials, Dr. Scott and coinvestigators reviewed publicly available FDA reviews from 2005 to 2015 supporting the approval of 36 drugs. They used a metric called the participation-to-prevalence ratio (PPR) to compare representation of women in a study relative to the representation of women in the disease population being studied. The range of PPR of 0.8-1.2 represented similar representation of women in the study and disease population.

A PPR of less than 0.8 was found for coronary artery disease trials, at 0.6; acute coronary syndrome/

myocardial infarction trials, also at 0.6; and heart failure trials, at 0.5-0.6. Participation of women in drug trials varied widely – from a low of 22% to a high of 81% – with a mean of 46%, they found.

The PPR was within the desirable range for hypertension, at 0.9, and atrial fibrillation trials, at 0.8-1.1, while participation for pulmonary arterial hypertension trials was above the desirable range, at 1.4, according to the report.

Dr. Scott and coauthors reported that they had no relationships relevant to their study.

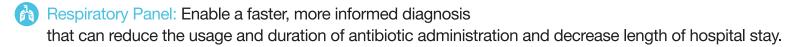
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SOURCE: Scott PE et al. J Am Coll Cardiol. 2018 May 18;71:1960-9.

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Reversal agent for apixaban, rivaroxaban approved

BY CATHERINE HACKETT

MDedge News

ndexanet alfa, the first agent shown to reverse the anticoagulant effects of rivaroxaban and apixaban, has been approved by the Food and Drug Administration, according to a May 3 statement from Portola Pharmaceuticals.

It is approved for use in patients treated with these factor Xa inhibitors when reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding, according to the company.

Andexanet alfa (Andexxa, Portola) received both U.S. Orphan Drug and FDA Breakthrough Therapy designations and was approved under the Food and Drug Administration's Accelerated Approval pathway.

"Today's approval represents a significant step forward in patient care and one that the medical community has been eagerly anticipating," said Stuart J. Connolly, MD, professor of medicine and an electrophysiologist at McMaster University in Hamilton, Ont., who is chair of the ANNEXA-4 executive committee. "Andexxa's rapid reversal of the anticoagulating effects of rivaroxaban and apixaban will help clinicians treat life-threatening bleeds, where every minute counts," he added in the statement.

The approval was supported by two phase 3 trials in the ANNEXA series, which showed acceptable change from baseline in anti-Factor Xa activity in healthy volunteers. But the strongest data came from interim results from ANNEXA-4, a single-arm cohort study with 227 patients who were receiving a factor Xa inhibitor and were experiencing an acute major bleeding

Clinicians administered andexanet alfa as a bolus followed by a 2-hour continuous infusion, with hemostatic efficacy assessed 12



'Andexxa ... will help clinicians treat life-threatening bleeds, where every minute counts.'

DR. CONNOLLY

hours after the start of treatment. The results showed that factor Xa inhibition fell by a median 90% for rivaroxaban and 93% for apixaban.

Andexanet alfa is a factor Xa "decoy" molecule that acts by latching onto the inhibitor molecules and thereby preventing them from interacting with actual factor Xa, but andexanet also has a short half-life

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The use of newer oral anticoagulants has facilitated the care of many patients in need of anticoagulants, but the lack of a reversal agent, unlike warfarin, has led to major difficulties in cases where emergency surgical interventions are re-

quired. This report is welcome news for the medical community caring for these patients.



and hence the effect quickly reduces once treatment stops, Dr. Connelly reported at the American College of Cardiology annual meeting in March when presenting AN-

He noted at the time the results placed and examet in the same ballpark for efficacy and safety as idarucizumab (Praxbind) approved in 2015 for reversing the anticoagulant dabigatran (Pradaxa).

"The expansion of available reversal agents for people prescribed newer oral anticoagulant therapies is crucial," Randy Fenninger, CEO of the National Blood Clot Alliance. said in the Portola statement. "The availability now of a reversal agent specific to rivaroxaban and apixaban expands choice and enables patients and providers to consider these treatment options with greater confidence."

The prescribing information

for andexanet states that treated patients should be monitored for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. Further, anticoagulant therapy should be resumed as soon as medically appropriate following andexanet treatment to reduce thromboembolic risk.

The most common adverse reactions, occurring in at least 5% of patients, were urinary tract infections and pneumonia.

Portola intends to bring Andexxa to limited markets in early June; a broader commercial launch is anticipated in early 2019.

The FDA is requiring a postmarketing clinical trial that randomizes patients to either and exanet or usual care. The study is scheduled to begin in 2019 and report outcomes in

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Nebivolol most effective beta-blocker for hypertension

BY BRUCE JANCIN

MDedge News

ORLANDO – The use of nebivolol as part of a multidrug regimen to treat hypertension was associated with a significantly lower cardiovascular event risk than was combination antihypertensive therapy featuring either metoprolol or atenolol in a large observational study, Brent M. Egan, MD, reported at the annual meeting of the American College of Cardiology.

This retrospective study used health insurance claims data within the massive PharMetrics national U.S. database for 2007-2014 in order to identify 16,787 patients who started on nebivolol as part of a multidrug regimen for hypertension. They were aggressively propensity score-matched on the basis of demographics, clinical characteristics, and duration of follow-up to 16,787 hypertensive individuals on either metoprolol succinate or metoprolol tartrate as part of combination therapy, and to another 16,787 patients who started on atenolol for the

Patients averaged 53 years of age in all three groups. Importantly, this was a primary prevention study: None of the participants had a baseline history of any cardiovascular event.

The primary outcome was hospitalization for acute MI, stroke, heart failure, or angina during a mean 600 days of follow-up. In a Cox proportional hazards regression analysis, the risk of the com-

Since nebivolol is a vasodilatory betablocker and atenolol and metoprolol are not, the investigators hypothesized that this distinction could result in differences in cardiovascular event rates.

posite outcome was 1.33-fold greater with atenolol and 1.91-fold greater with metoprolol than in the group on nebivolol for their hypertension.

The risk of hospitalization for MI was 1.47-fold greater in the atenolol group and 2.19-fold greater with metoprolol than in patients on nebivolol. Hospitalization for angina was 2.18 times more likely in the atenolol group and 3.39 times more likely in the metoprolol group than in patients on nebivolol. However, there was no between-group

difference between the three beta-blockers in terms of stroke or heart failure rates, according to Dr. Egan of the University of South Carolina, Greenville.

He explained that the impetus for this study was that, even though beta-blockers are universally recognized as a cornerstone of secondary cardiovascular prevention, there are much fewer outcome data to support their use in primary prevention. Since nebivolol is a vasodilatory beta-blocker and atenolol and metoprolol are not, Dr. Egan and his coinvestigators hypothesized that this distinction could result in differences in cardiovascular event rates.

One audience member commented, "this study gives a nice hypothesis-generating rationale for doing a large randomized outcomes trial." Dr. Egan concurred.

His study was supported by Allergan. He reported receiving research grants from Boehringer Ingelheim and serving as a consultant to Medtronic.

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SOURCE: Egan BM et al. ACC 18, Abstract 1324M-



Biomarkers elevated in children with LRTIs

BY DOUG BRUNK

MDedge News

TORONTO – While C-reactive protein, procalcitonin, and proadrenomedullin are associated with development of severe clinical outcomes in children with lower respiratory tract infections (LRTI), proadrenomedullin is most strongly associated with disease severity, preliminary results from a prospective cohort study showed.

"Despite the fact that pneumonia guidelines call the site of care decision the most important decision in the management of pediatric pneumonia, no validated risk stratification tools exist for pediatric lower respiratory tract infections," lead study author Todd A. Florin, MD, said at the annual Pediatric Academic Societies meeting. "Biomarkers offer an objective means of classifying disease severity and clinical outcomes."

Three frequently studied blood biomarkers in adults with LRTI by risk stratification are C-reactive protein (CRP), procalcitonin (PCT), and midregional proadrenomedullin (proADM). CRP is secreted by hepatocytes stimulated by interleukin (IL)-6, IL-1 beta, and tumor necrosis factor (TNF) alpha in response to inflammation and infection. "Elevation of CRP and the failure of CRP to fall over the course of treatment has been shown to be associated with adverse outcomes and severity scores, but not mortality in adults

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This review excellently

summarizes a pivotal study by Cincinnati Children's Hospital. Proadrenomedullin appears to be the best biomarker found by these re-



searchers to predict disease severity and included a robust number of study subjects screened but a smaller group (478 out of 1,142 enrolled) in their ER over a period of 5 years. A multicenter study is an important next step.

with lower respiratory tract infections," said Dr. Florin, a pediatric emergency physician at Cincinnati Children's Hospital.

PCT and CPT link to LRTIs

PCT is a precursor of calcitonin secreted by the thyroid, lung, and intestine in response to bacterial infections. It also has been shown to be associated with adverse outcomes and mortality in adults, with results generally suggesting that it is a stronger predictor of severity than CRP.

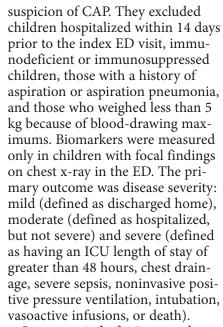
"There is limited data on the association of CRP or PCT with severe outcomes in children with LRTIs," Dr. Florin noted. "One recent U.S. study of 532 children did demonstrate an association of elevated PCT with ICU admission, chest drainage, and hospital length of stay in children with CAP [community-acquired pneumonia]."

ProADM, meanwhile, is a vasodilatory peptide with antimicrobial and anti-inflammatory functions synthesized during severe infections. It has a half-life of several hours and has been shown to be associated with disease severity in adults with LRTI. Recent studies have shown that it has improved prognostication over WBC, CRP, and PCT. "

Dr. Florin said, "Although all three of these markers demonstrate promise in predicting severe outcomes in adults with LRTIs, very few studies have examined their association with disease severity in pediatric disease. Therefore, the aim of the current analysis was to determine the association between blood biomarkers and disease severity in children who present to the ED with lower respiratory tract infections."

The CARPE DIEM study

In a study known as Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM), he and his associates performed a prospective cohort analysis of children with suspected CAP who were admitted to the Cincinnati Children's Hospital ED between July 2012 and December 2017. They limited the analysis to children aged 3 months to 18 years with signs and symptoms of an LRTI, and all eligible patients were required to have a chest radiograph ordered for



Over a period of 4.5 years, the researchers enrolled 1,142 patients. Of these, 478 had focal findings on chest x-ray and blood obtained. The median age of these 478 children was 4.4 years, 52% were male, and 82% had all three biomarkers performed. Specifically, 456 had CRP and PCT performed, while 358 had proADM performed. "Not every child had every marker performed due to challenges in obtaining sufficient blood for all three biomarkers in some children," Dr. Florin explained.

Preliminary data that Dr. Florin presented at PAS found that the median CRP, PCT, and proADM did not differ by gender, race, ethnicity, or insurance status. "In addition, there were not significant differences in the distribution of disease severity by biomarker performed, with approximately 27% of patients being classified as mild, 66% as moderate, and 7% as severe," he said.

The median CRP was 2.4 ng/ mL in those with mild disease, 2.5 ng/mL in those with moderate disease, and 6.25 ng/mL in those with severe disease, with the dif'I do not anticipate that any single biomarker will be the magic bullet for predicting disease severity in pediatric CAP. It will likely be a combination of clinical factors and several biomarkers that will achieve optimal prognostic ability. That said, our results suggest that similar to adult studies, proADM appears to have the strongest association with severe disease.'

DR. TODD A. FLORIN

ference between the two subclasses of nonsevere disease and moderate disease and severe disease reaching statistical significance (P = .002). The median PCT was 0.16 ng/mL in those with mild disease, 0.26 ng/mL in those with moderate disease, and 0.49 ng/mL in those with severe disease, with the difference between the two subclasses of nonsevere disease and moderate disease and severe disease reaching statistical significance (P = .047). Meanwhile, the median proADM

was 0.53 ng/mL in those with mild disease, 0.59 ng/mL in those with moderate disease, and 0.81 ng/mL in those with severe disease, with the difference between the two subclasses of nonsevere disease and moderate disease and severe disease also reaching statistical significance (*P* less than .0001).

Conclusions

Dr. Florin concluded saying that he is "cautiously optimistic" about the study results. "As is the case in many biomarker studies, I do not anticipate that any single biomarker will be the magic bullet for predicting disease severity in pediatric CAP," Dr. Florin said. "It will likely be a combination of clinical factors and several biomarkers that will achieve optimal prognostic ability. That said, our results suggest that, similar to adult studies, proADM appears to have the strongest association with severe disease, compared with CRP and PCT. Combinations of biomarkers did not perform better than proADM alone."

The study received funding support from the Gerber Foundation, the National Institute of Allergy and Infectious Diseases, and Cincinnati Children's Hospital Medical Center. Dr. Florin reported having no financial disclosures.

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Simple tool improves inpatient influenza vaccination

BY DOUG BRUNK

MDedge News

TORONTO – Implementation of a simple screening tool improved the influenza vaccination status of hospitalized children, results from a single-center study showed.

"When we looked at the immunization status of children in New York City, we found that one of the vaccines most commonly missed was influenza vaccine, especially from 2011 through 2014," one of the study authors, Anmol Goyal, MD, of SUNY Downstate Medical Center, Brooklyn, N.Y., said in an interview at the Pediatric Academic Societies meeting.

"Given this year's epidemic of influenza and the increasing deaths, we decided to look back on interventions we had done in the past to see if any can be reimplemented to help improve the vaccination status for these children," he said. "The national goal is 80%, but if we look at the recent trend, even though we have been able to improve vaccination status, it is still below the national goal." For example, he said, according to New York Department



Dr. Anmol Goyal said "one of the vaccines most commonly missed was influenza vaccine."

of Health data, the 2012-2013 influenza vaccination rates in New York City were 65% among children 6 months to 5 years old, 47% among those 5-8 years old, and 31% among those 9-18 years old, which were well below the national goal.

In an effort to improve influenza vaccine access, lead author Stephan Kohlhoff, MD, a pediatric infectious disease specialist at the medical center, and his associates, implemented a simple vaccine screening tool to use in the inpatient setting as an opportunity to improve vaccination rates among children in New York City. It consisted of nursing staff assessing the patient's influenza immunization status on admission and conducting source verification using the citywide immunization registry, or with vaccine cards brought by parents or guardians during admission. Influenza vaccine was administered as a standing order before discharge, unless refused by the parents or guardians. The study population comprised 602 patients between the ages of 6 months and 21 years who were admitted to the inpatient unit during 2 months of the influenza season (November and December) from 2011 to 2013.

Dr. Goyal, a second-year pediatric resident at the medical center, reported that the influenza vaccination status on admission was positive in only 31% of children in 2011, 30% in 2012, and 34% in 2013. The vaccine screening tool was implemented in 64% of admitted children in 2012 and 70% in 2013. Following implementation, the researchers observed a 5% increase in immunization rates in 2012 and an 11% increase in 2013, with an overall increase of 8% over 2 years (*P* less than .001). He was quick to point out that the influenza rate could have been improved by an additional 22% had 77% of patients not refused vaccination.

The researchers reported having no financial disclosures.

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Respiratory allergies linked to autism spectrum disorder

BY MADHU RAJARAMAN

MDedge News

The prevalence of respiratory and other allergies is greater in U.S. children with autism spectrum disorder (ASD) than in U.S. children without the disorder, according to findings published in JAMA Network Open.

An analysis of data from the National Health Interview Survey found that the weighted prevalence of respiratory, skin, and food allergies was, 18.73%, 16.81%, and11.25%, respectively, in children with ASD, compared with 12.08%, 9.84%, and 4.25%, respectively, in children without ASD (*P* less than .001).

Survey data were collected between 1997 and 2016, and included patients aged 3-17 years. Allergic conditions were defined by the respondent, usually a parent, answering in the affirmative that the child had any kind of respiratory, food, digestive, or skin allergy in the past 12 months. ASD was defined based on an affirmative response to a question asking whether the child received an ASD diagnosis from a health professional, wrote Guifeng Xu, MD, of the department of epidemiology at the University of Iowa, Iowa City, and her coauthors.

Of the 199,520 children included in the study, 24,555 had respiratory allergy, 8,734 had food allergy, and 19,399 had skin allergy. An ASD diagnosis was reported in 1,868 children. The weighted prevalence was 12.15% for respiratory allergy (95% confidence interval, 11.92%-12.38%), 4.31% for food allergy (95% CI, 4.20%-4.43%), and 9.91% for skin allergy (95% CI, 9.72%-10.10%), the authors said.

Overall, children with ASD were more likely to have a respiratory, food or skin allergy (*P* less than .001).

Respiratory allergy and skin allergy also were significantly associated with ASD, but to a lesser degree, with an odds ratio of 1.53 (95% CI, 1.32-1.78; *P* less than .001) for respiratory allergy and 1.80 (95% CI, 1.55-2.09; *P* less than .001) for skin allergy, Dr. Xu and her colleagues reported.

The findings suggest a "possible presence of shared mechanisms (e.g., immunologic dysfunction) among these allergic conditions in relation to ASD," though the underlying mechanisms still need to be identified, the authors wrote.

"Large prospective cohort studies starting from birth or early life are needed to confirm our findings," the authors concluded.

No conflicts of interest were reported.

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SOURCE: Xu G et al. JAMA Network Open. 2018 Jun 8. doi: 10.1001/jama-networkopen.2018.0279.









CHEST 2018 has a new date OCTOBER 6-10

This year's Learn by Doing-focused program is built by expert faculty, and includes cutting-edge educational sessions and hands-on opportunities designed with the goal of learning through active participation.

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FDA approves epinephrine autoinjector for infants

BY IAN LACY

MDedge News

he AUVI-Q 0.1 mg, an epinephrine autoinjector (EAI) for infants and toddlers weighing 16.5-33 pounds, was available by prescription beginning May 1, 2018, according to a press release from Kaléo, a privately-held pharmaceutical company.

"Anaphylactic reactions can be frightening and serious, and when experienced by the very young, some of whom can't communicate about what's happening, these episodes can be particularly alarming,"

It features a shorter, retractable needle and a lower dose of epinephrine than other EAIs have, which makes it ideal for young children.

Vivian Hernandez-Trujillo, MD, a pediatric allergist and fellow of the American Academy of Allergy, Asthma, and Immunology, said in a statement. "Now, caregivers can have the AUVI-Q 0.1 mg in hand to respond to an allergic emergency and safely administer epinephrine to infants and toddlers."

The device was granted Priority Review by the FDA because of its potential to significantly improve treatment of a serious condition and was approved Nov. 20, 2017. The injection is indicated to treat life-threatening allergic reactions, including anaphylaxis, in infants and toddlers. It features a shorter, retractable needle and a lower dose of epinephrine than other EAIs have, which makes it ideal for young children. This EAI also features a voice instruction system that provides caregivers step-by-step instructions on how to administer treatment. The epinephrine autoinjector also comes with two autoinjectors, plus an

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: AUVI-Q is a sleek device and is now supplied in 0.1-mg, 0.15-mg, and 0.3-mg dosing sizes. This is extremely exciting for treating older infants and toddlers.

additional trainer for patients and caregivers to practice so they are prepared in an emergency situation.

The approval comes at a time when a higher percentage of chil-

dren are being admitted to the hospital for food-related anaphylaxis: a 130% increase among children aged 0-4 years and a 196% increase in children aged 5-17 years.

The epinephrine autoinjector has

been available for \$0 out of pocket for commercially insured patients using the AUVI-Q AffordAbility Program and Direct Delivery Service since May 1, 2018.

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Simple bedside tool effectively detected sepsis in the ED

BY DOUG BRUNK

MDedge News

SAN DIEGO – The product of pulse pressure and heart rate was more accurate in identifying the presence

of culture-positive sepsis, compared with the quick Sequential Organ Failure Assessment prompt, a small, single-center study showed.

"We know a lot about the pathophysiology of sepsis, but we don't have great ways of identifying septic patients at an early stage," lead study author David Lynch, MD, said in an interview at an international conference of the American Thoracic Society. He noted that screening tools such as the quick Sequential Organ Failure Assessment and Systemic Inflammatory Response Syndrome criteria have a sensitivity of about 70% in detecting sepsis. "Over the last 10-15



years we've been able to find ways of improving outcomes in patients whom we confirm are septic with early antibiotics and fluids," said Dr. Lynch, a second-year resident in the division of pulmonary and critical care medicine within the department of medicine at the University of North Carolina at Chapel Hill. "We know that in sepsis systemic vascular resistance is

decreased and cardiac output is increased. We tried to come up with a way of estimating cardiac output at the bedside by multiplying heart rate with pulse pressure, with the pulse pressure being the surrogate for stroke volume, which you can measure easily."

In a cross-sectional, observational study, Dr. Lynch, senior author Thomas Bice, MD, and their associates reviewed the records of 116 patients who were admitted directly to the University of North Carolina's medical ICU (MICU) from the UNC ED between Jan. 5, 2016, and June 30, 2017. The primary outcome of interest was culture-positive sepsis, and the primary exposure was the product of pulse pressure and heart rate. Patients were determined

to be positive for sepsis if an infection was suspected (such as if blood cultures were drawn and antibiotics were started), the admitting physician suspected sepsis, and cultures were subsequently positive.

The average age of all patients was 53 years, 51% were female, the mortality rate was 12%, and the median length of stay was 4 days. A total of 25 of the 116 patients (22%) were positive for sepsis. The researchers observed that the pulse pressure multiplied by the heart rate was significantly higher in the culture-pos-



"We were surprised by how high the sensitivity was. The question is, will this translate to a larger cohort?" said Dr. David Lynch.

itive sepsis group, compared with controls (6,710 vs. 3,741, respectively; *P* less than .001).

Dr. Lynch and his associates found that, as a continuous variable, pulse pressure multiplied by the heart rate accurately classified 90% of sepsis cases (area under the receiver operator curve, 0.96; P less than .001). When use of 5,000 as a cutoff, pulse pressure multiplied by the heart rate had a sensitivity of 100% and a specificity of 89% in detecting culture-positive sepsis. "We were surprised by how high the sensitivity was," Dr. Lynch said. "The question is, will this translate to a larger cohort? And, would this be transferable to all patients in the ED, as opposed to the sicker patients who are going to the MICU?"

He and his associates plan to confirm the study's results in a broader population of patients. "We don't yet understand at what point in time this would be most applicable," he added. "We looked at the first set of vitals when they came into the ED. We'd like to know if that applies to the second, third, and fourth set of vitals, and whether it would be most useful to have an average of those."

The study was supported in part by a grant from the National Institutes of Health. Dr. Lynch reported having no financial disclosures.

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Sepsis-associated coagulopathy ups mortality risk

BY ANDREW D. BOWSER MDedge News

atients with sepsis-associated coagulopathy appear to be at heightened risk of death, according to results of a large retrospective cohort study.

The risk of death in the study increased with the severity of the sepsis-associated coagulopathy, which was defined using international normalized ratio (INR) and platelet counts

Those findings suggest that the severity of coagulation abnormalities might be used to quantify mortality risk, according to investigator Patrick G. Lyons, MD, of the division of pulmonary and critical care medicine, Washington University, St. Louis, and his coinvestigators.

"Future trials of sepsis therapies targeting the coagulation cascade should take into account the presence or absence of sepsis-associated coagulopathy, as well as the severity of sepsis-associated coagulopathy, when formulating potential trial designs," the investigators wrote in the journal Critical Care Medicine.

Their retrospective cohort study included 6,148 consecutive patients with sepsis or septic shock hospitalized at a 1,300-bed urban aca-

demic medical center between 2010 and 2015. Of that group, 26% had sepsis-associated coagulopathy, defined as having both an INR of 1.2 or higher and a platelet count less than 150,000/mcL. Sepsis-associated coagulopathy was classified as mild for 4%, moderate for 16%, and severe for 6% of the cohort.

Hospital mortality was 25.4% for patients with no sepsis-associated coagulopathy, the research team found, increasing progressively from 27.0% for mild, 40.7% for moderate, and 56.1% for patients in the most severe category of sepsis-associated coagulopathy (*P* less than .001).

Hospital and ICU days also increased progressively according to the severity of coagulopathy, they wrote

Both presence and severity of sepsis-associated coagulopathy remained independently associated with hospital mortality even after adjustments were made for patient characteristics, hospitalization variables, and interactions between sepsis-associated coagulopathy and cancer, investigators said. Odds ratios ranged from 1.33 to 2.14 for presence of sepsis-associated coagulopathy, and from 1.18 to 1.51 for severity, they reported in the journal.

"This could have important impli-

VIEW ON THE NEWS

Jennifer Cox, MD, FCCP, comments: Lyons et al. used predefined cutoff values for INR and platelets to define the presence and graded severity (mild, moderate, and severe) of sepsis associated coagulopathy. In this study, we have further evidence that sepsis-associated coagulopathy has implications on mortality. As mentioned in the article, human activated protein C was removed from the market after subsequent trials found no mortality



benefit. Given it's mechanism of action and the low volume of patients with moderate to severe sepsis-associated coagulopathy in the trial, a potential benefit may have been missed. Here is where this retrospective cohort study gives me hope. Platelet count and INR are routine labs that are ordered on virtually every patient coming to the ICU. If the increase in mortality seen using these common variables to predict and stratify sepsis-associated coagulopathy hold up with further research, this could prove to be a simple yet effective tool to identify the cohort of patients that should be studied in future trials of new/novel sepsis drugs aimed at the coagulation cascade. Maybe it could re-open the debate on human activated protein C.

cations for comparing the outcomes of patients with sepsis from different hospitals, especially with increasing requirements for public reporting of such data through systems such as the Severe Sepsis/Septic Shock Early Management Bundle-1 and New York State's Rory's Regulations," the investigators wrote.

Reported disclosures for the study

included institutional funding from Asahi Kasei Pharma America by one coauthor, and support from Barnes-Jewish Hospital Foundation by another. No other potential conflicts of interest were reported.

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SOURCE: Lyons PG et al. Crit Care Med. 2018 May;46(5):736-42.

In-hospital mortality predictors eyed in pneumonia patients

BY DOUG BRUNK

MDedge News

SAN DIEGO – About one in four intubated or mechanically ventilated (MV) patients with gram-negative pneumonia die during hospitalization, results from a large retrospective cohort study found.

In a poster abstract presented at an international conference of the American Thoracic Society, researchers led by Thomas P. Lodise Jr., PharmD, noted that ventilator-associated pneumonia is one



of the most common hospital-acquired infections in intensive care units and affected an estimated 9%-27% of all intubated patients.

In an effort to describe mortality rates and associated risk factors for intubated and MV patients diagnosed with gram-negative pneumonia, Dr. Lodise of the Albany (N.Y.) College of Pharmacy and Health Sciences and his associates conducted a retrospective cohort study of data from the Healthcare Cost and Utilization Project (HCUP) National Readmission Database (NRD). HCUP is the largest source of hospital care data in the United States, accounting for 49.3% of the total U.S. resident population and 49.1% of U.S. hospitalizations. The researchers included patients at least 18 years of age who were hospitalized with a primary or secondary diagnosis of gram-negative pneumonia between Feb. 1, 2013, and Nov. 30, 2013. They excluded index hospitalizations with a primary or secondary diagnosis of viral pneumonia, fungal pneumonia, atypical organisms, gram-positive bacterial pneumonia, or pneumonia occurring secondary to an infectious disease. They examined mortality rates descriptively and modeled them via adjusted multivariate logistic regression to evaluate the impact of baseline characteristics and comorbidities.

A total of 32,683 patients met all study criteria. Of these, 2,323 (7.1%) had a primary diagnosis

and 30,360 (92.9%) had a secondary diagnosis for gram-negative pneumonia. Their mean age was 64 years, and 61.1% were male. In all, 7,928 patients (24.3%) died during hospitalization. Multivariate analysis revealed that patients with concomitant sepsis had the highest risk of mortality (odds ratio, 2.60), followed by patients aged 65 years and older (OR, 1.88) and those with any prior hospitalization within 30 days (OR, 1.34). Comorbidities upon admission with highest risk of mortality included cancer (OR, 2.45), liver disease (OR, 1.91), AIDS/ HIV (OR, 1.59), renal disease (OR, 1.33), and congestive heart failure (OR, 1.15). Diabetes was found to have a decreased risk of mortality, with an OR of 0.80. "However, a majority of patients with diabetes had no complications; thus, these patients may be representative of a less severe patient population," the authors noted.

They acknowledged certain limitations of the study, including the potential for coding errors. They also pointed out the HCUP NRD does not contain treatment-specific information, drugs administered or treatment patterns during hospitalization, the number of days patients spent in the ICU, or the number of days on ventilation. Bayer Healthcare Pharmaceuticals funded the study. Dr. Lodise reported having no financial disclosures.

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Could Right to Try law undermine drug safety?

BY GREGORY TWACHTMAN

MDedge News

he Food and Drug Administration is generally achieving the balance between ensuring safety and providing access to investigational drugs through compassionate-use programs, according to results from a new analysis that found that most of these drugs are available within 6 months of an application to the FDA.

But that balance may be undermined by the recently enacted Right to Try Act, Jeremy Puthumana, of Yale University, New Haven, Conn., and his colleagues reported in an article published on JAMA Network Open. They said the new law encourages sponsors to make investigational drugs available earlier in the clinical development period, potentially jeopardizing safety.

"These findings suggest the FDA and the pharmaceutical industry have established a balance between

investigational new drug access and protection of patients from therapies without established safety, which may be compromised by policy makers seeking to speed access to investigational medicines through the Right to Try Act by removing the requirements for FDA oversight and approval of expanded access requests," the researchers wrote.

The cross-sectional study examined all expanded-access programs registered with ClinicalTrials. gov through Aug. 1, 2017. Of 92 expanded-access programs for investigational drugs, 69.6% were initiated within 6 months following (43.5%) or preceding (26.1%) submission of a new drug application. Ninety of the 92 drugs ultimately went on to receive FDA approval.

Of the most common uses of the 92 drugs registered in expanded-access programs between September 1996 and June 2017, half were used for the treatment of cancer; 16 drugs were used to treat metabolic, endocrine, and genetic diseas-

es; and 14 drugs were used for the treatment of infectious diseases. But there were no significant differences in the timing of program initiation by therapeutic characteristics, the researchers found.

President Trump signed the Right To Try Act of 2017 (S. 204) into law on May 30, 2018, despite opposition from physician and patient groups who expressed concerns that the law will remove FDA safeguards.

The study was funded by a grant from the National Institutes of Health. The researchers reported research support from the Laura and John Arnold Foundation, Johnson and Johnson, Medtronic, the Blue Cross-Blue Shield Association, the FDA, and other federal agencies.

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SOURCE: Puthumana J et al. JAMA Network Open. 2018 Jun 15. doi: 10.1001/jamanetworkopen.2018.0283.

Reducing liability by improving doc-nurse teams

BY ALICIA GALLEGOS

MDedge News

physicians and nurses not only make for a smoother work environment, they also may reduce medical errors and lower the risk of lawsuits.

A recent study of closed claims by national medical malpractice insurer The Doctors Company found that poor physician oversight is a key contributor to lawsuits against nurses. Investigators analyzed 67 nurse practitioner (NP) claims from January 2011 to December 2016 and compared them with 1,358 claims against primary care physicians during the same time period.

Diagnostic and medication errors were the most common allegations against NPs, the study found, a trend that matched the most frequent allegations against primary care (internal medicine and family medicine) doctors. Top administrative factors that prompted lawsuits against nurses included inadequate physician supervision, failure to adhere to scope of practice, and absence of or deviation from written protocols.

The findings illustrate the importance of effective collaboration between physicians and NPs, said Darrell Ranum, vice president for patient safety and risk management for The Doctors Company. Below, legal experts share six ways to strengthen the physician-nurse relationship and at the same time, reduce liability:

1. Foster open dialogue. Culti-

vating a comfortable environment where nurses and physicians feel at ease sharing concerns and problems is a key step, says Louise B. Andrew, MD, JD, a physician and attorney



DR. ANDREW



MS. BALESTRA

who specializes in litigation stress management. A common scenario is a nurse who notices an abnormal vital sign but fails to mention it to the supervising physician because they feel they can handle it themselves or because they believe the doctor is too busy or too tired to be bothered, she said. The patient's condition then worsens, resulting in a poor outcome that could have been avoided with better communication among providers. Delayed/ wrong diagnosis accounted for 41% of claims against primary care physicians and 48% of claims against NPs in The Doctors Company study.

"Nurses must not be afraid to ask doctors why they are doing something, and to inquire further if they see something they don't understand," Dr. Andrew said in an interview. Doctors, on the other hand, have an obligation, no matter how stressed or hurried they may be, not to send signals – bodily or otherwise

- that they are not to be approached. That is a recipe for disaster."

Set the tone early by exemplifying positive and clear communication, practicing good listening, and remaining empathetic, yet firm when making your needs known, Dr. Andrew advised.

2. Stick to the scope. When hiring an NP, make sure their scope of practice is clearly understood by all parties and respect their limitations, said Melanie L. Balestra, a Newport Beach, Calif., attorney and nurse practitioner who represents health providers.

Start by knowing your state's scope of practice law for nurse practitioners. In 23 states and the District of Columbia, NPs have full authority to practice independently and can evaluate, diagnose, and manage treatment. In 15 states, NPs have reduced practice authority that requires a regulated collaboration agreement with a physician. In 12 states, NPs have restricted practice authority that requires supervision, delegation, or team management by a doctor.

Nurses practitioners must refrain from overstepping their authority, but physicians also must be careful not to ask too much of their NPs, experts stress. Ms. Balestra notes there is frequent confusion among doctors and NPs over how and whether scope of practice can be expanded as needed.

"This happens all the time,"
Ms. Balestra said. "I get at least
two questions on this every week
[from nurses] asking, 'Can I do
this? Can I do that?'"

The answer depends on the circumstances, the nurse's training, and the type of practice being broadened, Ms. Balestra said. For example, an NP in cardiology care may be allowed to perform more procedures in that field after internal training, but an NP who is trained in the care of adults can see pediatric patients only by going back to school.

"Know who you're hiring, where their expertise lies, and where they feel comfortable," she emphasized.

3. Preplan reviews. Early in the doctor-NP relationship, discuss and decide what type of medical cases warrant physician review, Mr. Ranum said. This includes agreeing on the type of patient conditions that will require a physician review and determining the types and percentage of medical records the doctor will evaluate, he said.

"The numbers should be higher at the beginning of the relationship until the physician gains an understanding of the NP's experience and competence," Mr. Ranum said. "Setting expectations will open the door to more frequent and more effective communication."

NPs, meanwhile, should feel confident in requesting the physician's assistance when a patient's presentation is complex or a patient has returned with the same complaints, he added.

4. Convene regularly. Schedule regular meetings to catch up and discuss patient cases – not just when something goes awry, said Ms. Balestra. During weekly or monthly meetings, physicians, NPs, and oth-

Continued on following page



2018 Education Calendar



Live Learning Courses

Courses held at the CHEST Innovation, Simulation, and Training Center in Glenview, Illinois.

Bronchoscopy and Pleural Procedures for Pulmonary and Critical Care Medicine Fellows July 20

Mechanical Ventilation: Advanced Critical Care Management July 26-28

Cardiopulmonary Exercise Testing (CPET)

August 10-12

Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers August 24-26

Difficult Airway Management September 7-9

Ultrasonography: Essentials in Critical Care

September 13-15 November 29-December 1 Comprehensive Bronchoscopy With Endobronchial Ultrasound September 20-22

Comprehensive Pleural Procedures November 3-4

Critical Care Ultrasound: Integra-

Into Clinical Practice November 9-11

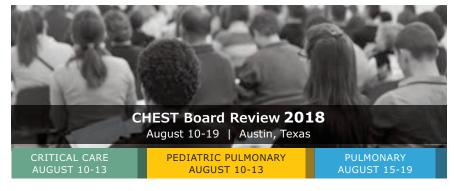
Advanced Critical Care Board Review Exam Course

December 7-8

Extracorporeal Support for Respiratory and Cardiac Failure in Adults

December 7-9

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Calendar subject to change. For most current course list and more information, visit livelearning.chestnet.org.

Continued from previous page

er team members can converse in a more relaxed atmosphere and share any concerns or ideas for improvements.

"Have a meeting, whether by phone or in person, just to see how things are going," she said. "That way, the NP may be able to take some things off the plate for the physician and the physician can see how [he or she] can assist the NP."

"It is often helpful to debrief on patients who were seen during that day and who represent complex conditions," he said. "Physicians may see opportunities to improve care following the NP's assessment and diagnosis."

5. Consider noncompliant policy. Create a noncompliant patient policy and work together to address uncooperative patients. Noncompliant patients are a top lawsuit risk, Ms. Balestra said. A noncompliant patient for instance, may provide conflicting information to different health professionals or attempt to blame providers for adverse events, she said.

"Your noncompliant patient is your easiest patient for a lawsuit because they're not following [instructions] and then something happens, and they say, 'It's your fault, you didn't treat me right."

Physician and NPs should be on the same page about noncompliant patients, including taking time to discuss when and how to terminate them from the practice if necessary, she said. Consistent documentation about patients by both physician and NPs is also critical, experts emphasize. Insufficient or lack of documentation led to patient injuries in 17% of cases against primary care doctors and in 19% of cases against NPs in The Doctors Company study.

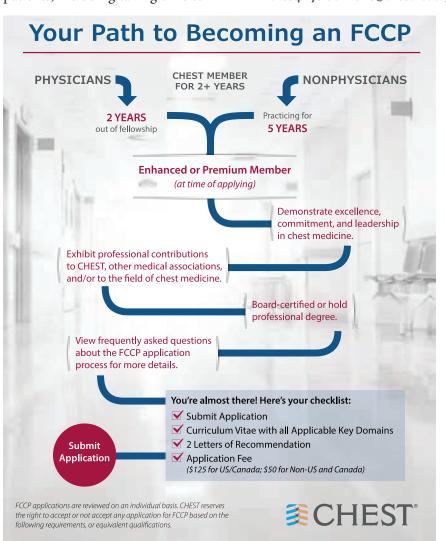
6. Keep patients out of it. When disagreements or grievances occur, discuss the problem in private and ensure all staff members do the same, Dr. Andrew said. Refrain from letting anger or annoyance with another team member carry into patient care or worse, trigger a negative comment about a staff member in front of a patient, she said.

"All it takes is for something to go wrong and a patient or family who has heard such sentiments is tuned into the fact there may be some culpability," she said. "This is probably a key factor in many a claimant's decision to seek redress for a bad outcome."

Instead, address problems or differences as soon as possible and work toward a resolution. It may help to create a conflict resolution policy that outlines behavioral expectations from all team members.

"We have to put our egos aside," Ms. Balestra said. "The ultimate goal is the best care of the patient."

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FROM THE EVP/CEO

CHEST heading into a very active fiscal year

BY STEPHEN J. WELCH,

CHEST Executive Vice President & CEO

s we wrap up CHEST's fiscal year 2017-18 (our fiscal year runs July 1 – June 30), it has been an incredibly positive and productive year, on all fronts. We have educated more learners than ever before, expanded



MR. WELCH

our educational offerings, increased our collaboration with other organizations, grown our CHEST Foundation activities, and are in excellent financial shape to continue our commitment to clinical chest medicine education.

As we prepare for fiscal year 2018-19, I want to highlight some of the

key programs, events, and projects we will be undertaking that will support our strategic plan (http://www.chestnet.org/About/Overview/Strategic-Plan) and achieve our mission to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

Our organization goals are primarily focused on (but are not limited to) the following broad achievements:

- a Increasing the number of learners that CHEST engages (and increasing their engagement with our content) and assessing the results of our educational interactions
- b. Keeping our journal *CHEST*^e among the top Pulmonary, Critical Care, and Sleep peer reviewed journals in the world
- c. Expanding domestic and global access to CHEST guidelines and other relevant clinical content.
- d. Continuing to offer a positive and inclusive culture and work environment at CHEST, for our volunteers, world-class faculty, members, and staff
- e. Meeting or exceeding our budget, reserve policy, and grant funding targets to ensure delivery of our mission-based educational efforts and programs

Because our mission as a 501(c)3 not-forprofit is education, I'll start with those key programs that are driving our budget for FY2018-19 and will also cover publishing and membership.

Education – Clinical

- Increased global activity due to global partnerships with several key international educational providers
 - ◆ Holding April 2019 CHEST World Congress in Bangkok
 - Planning June 2019 Board Review conference in Athens, Greece
 - ◆ 21 total international courses planned
- Increased Live Learning courses, simulation, and hands-on skills training
 - 21 courses planned (including 3 new courses)

- Holding two fellows courses at CHEST HQ (up to 80 fellows)
- Annual Meeting includes 11 postgraduate programs and 24 simulation courses (including more cadaver courses)
 - * Includes more fellows courses (up to 240 fellows)
- Board Courses include two half-day simulation courses; more sponsorship/exhibits, games, and virtual patient tours (VPTs)
- Continuing to build Board Review on-demand and e-learning content packages for those who cannot attend live events
- Launching inaugural e-Learning program with Elsevier

Education - Patient

- Developing multiple CHEST Foundation disease awareness campaigns and patient education resources
 - New patient education guides
 - Increased visual content (infographics, graphically based materials)
 - Increased use of multimedia and video content
- Increased funding for clinical research grants, community service programs and lung health events, and fund raising through cause marketing (ie, Feldman Family Poker Night, NYC events, and other local fund raising events)
- Expanding awareness of and access to our patient education materials
 - Institutions, large group practices
 - ◆ International reach
 - Digital distribution via social media and online campaigns

Education – Industry

- Projecting seven new live clinical immersion
- Two new proposed PREP courses with CTS
- Expansion of educational games, VPTs, and e-learning
- Expanded CHEST Analytics product lines
 - ◆ View Points (3 focus groups, 4-5 KOL panels, 4 pulse surveys)
 - Deep Dives (3 advanced analytics projects, 5 premium research projects, 2 ethnography studies, and 4-6 Clinical Perspectives)
 - Data Lab (looking to launch beta partner)
 - ◆ Booth IQ (increasing capacity for booth flow and booth intel reports)

Publications, Guidelines and Digital Content

- CHEST[®] Journal
 - •Elsevier partnership remains strong; leveraging key data and Elsevier offerings, will be announcing the next Editor in Chief
- CHEST Physician
 - New content and delivery mechanisms
 - * Supplements
 - * Electronic features
- CHEST SEEK
 - ◆ Publish Volume 28 (Critical Care)
 - Continue development of SEEK online library

- Guidelines
 - Completions: Antithrombotic therapy, cough, ILD diagnosis, hypersensitivity pneumonitis, lung cancer, and PAH
 - Updates: Antithrombotic therapy, lung cancer, cough, neuromuscular weakness, EBUS needle sampling, and blood transfusions in critical care setting (doing more in critical care)
 - Piloting use of DoctorEvidence methodology services and platform for "living guidelines"

Membership

- Focusing on adding value to CHEST membership for key segments
- Bundling e-learning packages with membership
- Exploring international group/society memberships and group practice/institutional memberships
- Working to attract advanced practice providers
- Performing member market research, including member satisfaction, net promoter scores, and other key metrics

Supporting Divisions (Finance, Marketing, IT, Capital Expenses)

- Have more visibility (booth presence) at more meetings (AACN, AARC (new), ALAT, APSR, ATS, CTS, ERS, SCCM, and more)
- Develop and execute comprehensive marketing and branding strategies for all business units
 - Clinical Education (CHEST annual meeting, Board Reviews, all int'l meetings and live learning, simulation)
 - Industry Education (PREP, CHEST Analytics)
 - ◆ Patient Education
 - Foundation Fundraising
 - Publishing and Content Strategy
 - Membership
- Support new IT platforms and bolster security (HR, Finance, Board Effect, Tableau, CHEST Analytics, LMS, CMS, NetForum AMS), as well as marketing and social interaction tools (HubSpot)
- Maintain Capital Budget for building, infrastructure, technology, etc

All in all, CHEST has a very active fiscal year planned, with a number of new educational programs and e-learning opportunities showcasing CHEST's unique brand of innovative clinical education. We look forward to connecting with you and impacting health-care delivery and patient outcomes.

It is an honor and a privilege to be able to lead this organization, and all of this news is directly attributable to our dedicated volunteer leadership, faculty, content expertise, staff, and valuable time that you all contribute to make this organization great. Thank you for your ongoing support of CHEST.

Mentors creating mentors

BY LAUREN HUGHES

CHEST Marketing Specialist

pon wrapping up a successful 2018 NetWorks Challenge Giving campaign – supporting travel grants to CHEST 2018 for early career and diverse clinicians, CHEST Foundation staff sat down with one of our champions, Demondes Haynes, MD, FCCP. Our conversation focused heavily on the role of mentorship in the development of early career clinicians and his own experience as both a mentor and mentee.

Dr. Haynes has had several mentors over the course of his career, but one stands out to him in particular: Doug Campbell, MD, FCCP. Dr. Campbell is a pulmonary and critical care physician who was the division chief at the University of Mississippi Medical Center in Jackson

"When I was finishing my chief residency, the entire pulmonary division imploded. All of the faculty left, except one or two professors, and all those who were going to become fellows here started looking for other places to go. I was actively looking as well... planning to leave my home state, which was not my initial plan. Dr. Campbell came in about that time and promised me that if I gave him some time, we could rebuild the division. He told me if I stayed for my fellowship, I could really help rebuild it. From that day forward, he was my mentor. I stayed for my fellowship under Dr. Campbell.

He delivered on all of those promises. He taught pulmonary medicine extremely well. Not only was he a great clinician, but he built up the faculty – started a telemedicine program for the ICU and brought in a diverse set of faculty who had all trained at other institutions. He really helped build and strengthen the program. I was very happy I chose to stay and learn under his leadership."

Doug Campbell not only had an impact on Dr. Haynes' professional life, but also his personal life.

"When I agreed to stay for my fellowship, he sent a beautiful handwritten note to my mother, thanking her for raising me to be respectful. She was amazed." Dr. Haynes mother passed 10 years ago. The night before the funeral at the visitation,

ECHEST FOUNDATION

Dr. Campbell brought the card his mother sent back – an exchange that Dr. Haynes never knew took place. "It really meant the world to me, not only had he mentored me in my academic career, but he made those personal touches. Those moments are very special to me."

Dr. Haynes is now mentoring residents and feels it is even more rewarding being a mentor.

"You actually get to invest in others, and when you invest in others, the best comes out in them. Sometimes, in this mentoring role, you're helping people uncover what their qualities are. Sometimes they don't even know what they are capable of until you push them just a little bit. That's been so rewarding. I have been blessed, my mentors have invested so much in me, and I am able to pay it forward and give back."

Dr. Haynes chose to honor Dr. Campbell through giving during the

NetWorks Challenge Giving Month. "The NetWork Challenge is great because part of our mission as an organization is philanthropy. We are an education organization,

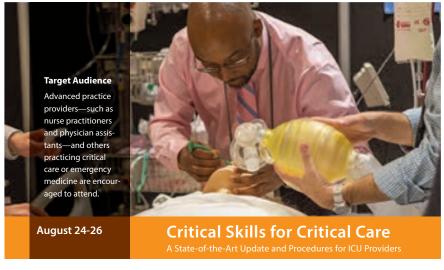
and, in medicine in general, we should support philanthropy. We talk a lot about empathy for our patients... and giving back is just a small part of that. There is a scripture

that says, 'To whom much is given, much is required.' I truly believe that. I believe that it should just be an ingrained part of our calling as physicians."

Your generosity funds young clinicians' learning opportunities that will change the future of patient outcomes and lung diseases. Thank you for making these opportunities possible.

Your continued support will advance the next generation of mentees launching their careers (with the proper hands-on training). You can be a Champion for Lung Health and DONATE today through a new gift to the CHEST Foundation by going to chestfoundation.org/donate or calling 224/521-9527.

Again, thank you for all you do to improve patient outcomes. You are the lung health champions who patients and families count on to positively impact lung health.





Join an expert panel of nurse practitioners, physician assistants, and physicians for this state-of-the-art update in critical care medicine for the whole team, featuring intensive, hands-on, and simulation-based experience in high-yield ultrasound, mechanical ventilation, and airway management procedure skills.

Attend to:

- Study the latest evidence in critical care medicine from a team-based perspective.
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- Participate in concise, evidence-based reviews, case-based discussions, audience response, and expert debates in areas of clinical controversy.

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CHEST Innovation, Simulation, and Training Center

This month in the journal CHEST® Editor's Picks

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

GIANTS IN CHEST MEDICINE

Arthur S. Slutsky, MD, MASc, BASc

By Dr. Eliot A. Phillipson

ORIGINAL RESEARCH

A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging: The MESA Lung Study By Dr. C. P. Aaron, et al.

The Effect of Alcohol Consumption on the Risk of ARDS: A Systematic Review and Meta-analysis

By Dr. E. Simou, et al.



The Relationship Between COPD and Frailty: A Systematic Review and Meta-analysis of Observational Studies
By Dr. A. Marengoni, et al.

Explore Ultrasound Corner

BY KRISTIN CROWE

CHEST Marketing and Communications Specialist

he use of ultrasound is often overlooked when it could very well aid in the diagnosis of a critical illness in a shorter amount of time, while eliminating potential risks that come with many of the usually administered tests.

In 2013, Seth Koenig, MD, FCCP, of Hofstra School of Medicine in New Hyde Park, New York, noticed the need to educate providers about the use of ultrasound in the ICU. Dr. Koenig approached Richard Irwin, MD, Master FCCP, and Editor in Chief of the journal *CHEST**, with an idea for a new section in the journal. So began "Ultrasound Corner," an online, video-based series in the journal that provides readers with real cases where ultrasound has played a large role in diagnostic patient care.

Each month, the journal receives two to four submissions from chest medicine clinicians who want to share their critical care ultrasound patient stories. One to two stories are selected and published monthly with real video images that are explained in the manuscript and in a narration done by Dr. Koenig.

"This creates a section where clinicians worldwide can share their experiences so that others may incorporate different methods of diagnosis into their practice," said Dr. Koenig. "This method of learning challenges the readers to interpret images and integrate the results into a patient management plan."

Dr. Koenig recommends that clinicians who have experienced benefit using ultrasound in critical care



situations submit their cases so that viewers can learn from each other. Visit https://mc.manuscriptcentral. com/chest, log in to your account, and click "Start a New Submission" under the "Author" section.

Dr. Koenig encourages the journal readership to explore Ultrasound Corner (https://journal.chestnet.org/ ultrasound) every month in CHEST to learn of different courses of diagnosis and treatment being used to strengthen patient diagnostic and management plans in new, evolving ways.



Launching the Moderate to Severe Asthma Center of Excellence

he American College of Chest Physicians (CHEST) announces a new partnership with Medscape focused on supporting physicians in addressing the challenges of diagnosing and treating moderate to severe asthma. The Moderate to Severe Asthma Center of Excellence (https://www.medscape.com/resource/moderate-severe-asthma) will provide news, expert commentary, and insights on challenging cases to physicians specializing in chest medicine, allergy, primary care, pediatrics, and emergency medicine.

Medscape is a leading source of clinical news, health information, and point-of-care tools for physicians and health-care professionals. This new Center of Excellence available on Medscape. com will explore the diagnostic, therapeutic, and



prevention strategies associated with moderate to severe asthma, including the latest research and breakthroughs. Topics will include challenges in classifying and diagnosing disease; risks, benefits, and barriers to treatment; and impact on patients' quality of life.

"We look forward to working with Medscape on the Center of Excellence to ensure that all physicians treating patients with asthma have access to the latest information and research on managing this pervasive and challenging disease," said John Studdard, MD, FCCP, President, American College of Chest Physicians.

"The Moderate to Severe Asthma Center of Excellence with CHEST provides a new, accessible channel for information, practical insights, and commentary to the thousands of physicians and health-care professionals who visit Medscape daily," said Jo-Ann Strangis, Senior Vice President, Editorial for Medscape. "We are privileged to be working with CHEST and look forward to the Center of Excellence making a meaningful difference in patient care."

Don't miss Dr. Aaron Holley's video on "Diagnosing Severe Asthma: 'Not as Easy as It Sounds" (https://goo.gl/4v1VHY).

Visit the Moderate to Severe Asthma Center of Excellence: https://goo.gl/6L5u9t.

Family fun in San Antonio during CHEST 2018

Planning on bringing your family with you to CHEST 2018 in San Antonio? Well, we've got you covered on ways to have some family fun when you're not immersed in learning at the convention center. Here are a few activities you can take part in:

San Antonio Missions National Historical Park

There are four San Antonio Missions you can visit: San José, Espada, Concepción, and San Juan. Explore the missions on your own, or join a park ranger or volunteer for a free, 45- to 60- minute guided tour of your chosen mission. While Mission San José is the most popular tour with ranger-led tours between 10:00 AM and 3:00 PM, make sure to stop at the visitor center or information center of the other missions you want to tour to check available tour times.

World's Largest Cowboy Boots Just outside Saks Fifth Avenue at North Star Mall, you can take a selfie next to the World's Largest Cowboy Boots. These 35-foot tall and 30-foot



The Boots



long boots shouldn't be too hard to spot. Originally the boots were built by Bob "Daddy-O" Wade in Washington, DC, in 1979 and moved to San Antonio just 1 year later.

Cool Off at a Waterpark

While October weather in San Antonio may be slightly cooler than in the summer, it still averages in the mid-80 degrees Fahrenheit, so you'll want to cool off at the pool or a waterpark. Take some downtime with the family and head to one of the several waterparks in the area, including Schlitterbahn, Splashtown San Antonio, and Aquatica at SeaWorld.

The Alamo Trolley

Need a captivating-yet-low impact activity? Ride the Alamo Trolley. This "hop-on, hop-off" trolley allows you to explore San Antonio at your own pace. With 10 stops around town, this entirely narrated tour includes The Alamo, Hemisfair Park, River Walk, the Mission Trail, and more.

Clyde and Seamore's Sea Lion High If you go to SeaWorld San Antonio,

show called "Clyde and Seamore's Sea Lion High." The sea lions perform tricks and interact with the audience as Clyde and Seamore go back to school in search of their diplomas.



Natural Bridge Cavern

Natural Bridge Caverns

Explore the Natural Bridge Caverns, the largest caverns in Texas. This family-owned and family-operated attraction offers guided and adventure tours, an outdoor maze, mining for gems and fossils, and more! When you're done, you can visit the Shops of Discovery Village where you'll find treats, a general store, and souvenirs to take home.

Brackenridge Park

Spend the day at one of San Antonio's most popular parks, Brackenridge Park. Hike or bike along one of the nature trails, have a picnic, play with your kids at the Kiddie Park, or find the Japanese Tea Garden. Want to add something a little more exciting to your day? The San Antonio Zoo is also on the grounds, where there are lots of animals, experiences, and events.



Aquatica at SeaWorld San Antonio

CHEST NETWORKS

Transcutaneous CO₂ monitoring, updated ILD patient education coming

Airways Disorders

Quadrupling the inhaled glucocorticoid dose in those with deteriorating asthma control: Zone 2 asthma

Asthma exacerbations account for most asthma-associated health-care costs and are a key outcome for successful asthma management programs.

Inhaled corticosteroid (ICS) forms the cornerstone of asthma maintenance therapy.

Previously published data show that:

 Most therapeutic benefit of budesonide was achieved at dose range of 400-1000 μg/ day (Masoli et al. Eur Respir J. 2004;23:552).

- Doubling ICS dose was ineffective in preventing acute asthma exacerbations (*Harrison et al. Lancet. 2004;363:271. FitzGerald et al. Thorax. 2004;59: 550*).
- Increasing ICS dose was unlikely to reduce systemic glucocorticoid use or hospitalization for asthma exacerbations(*Kew et al. Cochrane Database Syst Rev.* 2016;6:CD007524).

A recent open-label pragmatic study, published in the *New England Journal of Medicine*, included 1,922 adolescents and adults with asthma. The authors observed a small reduction in severe asthma exacerbations (Hazard ratio 0.81 for time to first severe exacerbation) by quadrupling the dose of





DR. RAMESH

DR. ANAND

ICS during periods of worsening asthma control (*McKeever et al. N Engl J Med. 2018;378:902*).

This study does create opportunities for cost-benefit by decreasing health-care utilization, decrease in systemic steroid exposure in some patients, and increase in patient awareness of asthma control allowing self-man-

agement. Although statistically significant, the treatment effect was small, with 45% of subjects in the 'quadrupling dose' arm still experiencing severe exacerbations. Intervention arm also experienced increased rate of adverse effects.

Additional studies are needed before this strategy can be broadly applied. In the same issue of NEJM, quintupling the dose of ICS in children was not associated with decrease in exacerbations (*Jackson et al. N Engl J Med. 2018;378:891*).

The fact that nearly half of asthmatics who quadrupled ICS dose had exacerbations is disconcerting. This highlights an urgent need to understand treatment-responsive

Continued on following page

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Yale school of medicine

THE SECTION OF PULMONARY,
CRITICAL CARE & SLEEP MEDICINE,
YALE SCHOOL OF MEDICINE,
IS SEEKING OUTSTANDING INDIVIDUALS
FOR THE FOLLOWING POSITION

Ambulatory Clinician

Section of Pulmonary, Critical Care and Sleep Medicine at Yale School of Medicine (Yale PCCSM), is seeking applicants to practice in our Ambulatory Pulmonary program (Winchester Chest Clinic) and satellite practices. The successful candidate is expected to see the majority of their patients in the general comprehensive pulmonary practice but may also work in our sub-specialty practices as well dependent on interest. All candidates are expected to have outstanding skills in the clinical and educational arena and will have the opportunity to take an active role teaching and mentoring fellows and residents. Successful applicants are expected to make a significant contribution to the clinical, educational, and research missions of the section. Minimum requirements include: board eligibility or certification in pulmonary diseases and critical care medicine.

Review of applications will begin immediately, and will continue until the position is filled.

Yale University is an affirmative action/equal opportunity employer. Yale values diversity in its faculty, students, and staff and especially welcomes applications from women, persons with disabilities, protected veterans and members of minority groups.

For more information please contact Dr. Jonathan Siner, Clinical Chief, Yale PCCSM e-mail, **jonathan.siner@yale.edu** or phone 203-737-4523

For more information on Yale PCCSM

Website https://medicine.yale.edu/intmed/pulmonary/

Facebook https://www.facebook.com/yalepccsm/

Twitter @YalePCCSI

YouTube https://www.youtube.com/channel/UC12y2CWB9774zxNZwy1TmbA/videos

Yale school of medicine

THE SECTION OF PULMONARY, CRITICAL CARE & SLEEP MEDICINE, YALE SCHOOL OF MEDICINE, IS SEEKING OUTSTANDING INDIVIDUALS FOR THE FOLLOWING POSITIONS:

Associate Clinic Director

Section of Pulmonary, Critical Care and Sleep Medicine, Yale School of Medicine (Yale PCCSM), is seeking candidates for Associate Director of our rapidly growing Ambulatory Pulmonary program (Winchester Chest Clinic). This academic position will be filled at a rank of: Instructor, Assistant Professor, or Associate Professor commensurate with qualifications. The successful candidate is expected to assist the Clinic director with the day to day management of the Winchester Chest Clinic, as well as develop initiatives to improve and optimize patient care and experience in the clinic. The candidate is expected to see patients in the Comprehensive Pulmonary Program but may also work in our subspecialty practices as well dependent on interest. All candidates are expected to have outstanding skills in the clinical and educational arena, will take an active role teaching and mentoring fellows and residents and other opportunities for career development in the thriving academic environment of Yale PCCSM. Successful applicants are expected to make a significant contribution to the clinical, educational, and research missions of the section. Minimum requirements include: board eligibility or certification in pulmonary diseases and critical care medicine. Experience in pulmonary ambulatory care, medical education and management is encouraged.

All applications materials should be submitted electronically to: http://apply.interfolio.com/41048

Review of applications will begin immediately, and will continue until the position is filled.

Yale University is an affirmative action/equal opportunity employer. Yale values diversity in its faculty, students, and staff and especially welcomes applications from women, persons with disabilities, protected veterans and members of minority groups.

For more information on Yale PCCSM

Website https://medicine.yale.edu/intmed/pulmonary/

Facebook https://www.facebook.com/yalepccsm/

Twitter @YalePCCSM

YouTube https://www.youtube.com/channel/UC12y2CWB9774zxNZwy1TmbA/videos

Continued from previous page

phenotypes, mechanisms of steroid sensitivity, and modalities to improve them, if we are to reduce asthma morbidity in the community.

Navitha Ramesh, MD Steering Committee Member Mahesh Padukudru Anand, MBBS, FCCP

Steering Committee Member

Clinical Research

Informed consent: Do we need to change our practice?

Informed consent is the keystone of clinical research and helps respect



DR. 1147

and protect the rights of the participants/ subjects. While the informed consent process has been standardized, some challenges still remain, such as pieces of information

that should be disclosed, how to disclose information and document understanding of participants,

and how detailed that disclosure should be (Grady, *N Engl J Med.* 2015;372:855). Digital technology can and has been used to improve the process of obtaining informed consent.

Substituting long and complex written forms with electronic consent (e-consent), however, has issues. Few people read through online agreements before clicking "agree," which may lead to participants consenting without a clear understanding of what they are consenting to.

On the other hand, it is also possible to use e-consent to improve comprehension by including videos and graphics. Interactive quizzes can assess the understanding of the participants, embedded links to audios or videos can further enhance the grasp of information. With e-consents, queries from participants can be answered via phone call or email. When e-consent is obtained remotely, the identity can be confirmed by electronic signatures, username, password, or biometrics.

E-consent has advantages, can be done remotely, no paper is needed, etc. It has potential disadvantages like being costly, videos can add time to the process, and multicenter international trials can be difficult (Grady, et al. *N Engl J Med*, 2017; 376:e43). Studying e-consents to identify gaps in communication between the researcher and the participant in the digitalized world may help improve the process and allow research to proceed with better understanding of the risks and benefits of involvement in clinical research.

Mohsin Ijaz, MD, FCCP Steering Committee Member

Critical Care

Fluid resuscitation in ICU patients with sepsis

Appropriate fluid resuscitation is a major goal in sepsis management. Debate remains regarding fluid choice and the impact on acute kidney injury (AKI), renal replacement therapy (RRT), and mortality. Normal saline solution (NS) may be associated with hyperchloremic metabolic acidosis, AKI, and death, but study results have been inconsistent.

A large before-after study revealed that balanced crystalloids (BC) were associated with lower rates of AKI and RRT but did

2018

not impact mortality (Yunos et al. *JAMA*. 2012;308:1566). A meta-analysis specifically examining



DR. DISSELKAMP

patients with sepsis failed to find a significant difference in RRT or mortality, although this conclusion was of low certainty (Rochwerg, et al., *Intensive Care Med.*

2015;41:1561).

Earlier this year, a large RCT comparing NS vs BC demonstrated a reduction in major adverse kidney events using BC. Independent rates of new RRT, mortality, and persistent renal dysfunction were not significant, but when combined as a composite outcome, the difference was significant. A 30-day mortality reduction was significant in patients with sepsis (25.2% BC vs 29.4% NS) and in patients with large infusions of NS (Semler et al., *N Engl J Med.* 2018;378:829).

Given these results, a move toward a "balanced approach" to fluid resuscitation seems prudent and may be the next step toward im-



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- Capture new ideas on how to optimize the multidisciplinary conference approach to outstanding lung cancer care.
- Interpret multimodality images in the care of patients with lung cancer, and utilize newer tumor markers for oncologic planning.
- Optimize your interdisciplinary skills with regards to lung cancer diagnosis, therapy, and patient care.

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proving outcomes in sepsis. These results are likely related to the large infusions of fluid in patients with sepsis or to the inflammatory effects of the disease. Finally, the applicability of these outcomes to the overall critically ill population is still open to debate.

Margaret Disselkamp, MD Steering Committee Member

Home-Based Mechanical Ventilation and Neuromuscular Disease

Transcutaneous carbon dioxide monitoring: New era for home ventilation

A primary objective of noninvasive home ventilation is normalization



DR. ACKRIVO

of arterial blood gas tensions, night and day. Pulse oximetry has long enabled estimation of arterial oxygen saturation (SpO₂) in outpatient offices and overnight at home; however,

until recently, measurement of the partial pressure of carbon dioxide (PCO₂) has been limited to invasive arterial blood gas testing (PaCO₂) or end-tidal CO₂ (PetCO₂) measurements.

Assessment of PetCO₂ has been limited by challenges in accessing true end-tidal exhaled gas under a face mask during noninvasive ventilation, particularly for patients with parenchymal lung diseases such as COPD.

Thanks to recent technological advances, transcutaneous measurement of carbon dioxide (PtcCO₂) is emerging as the method of choice for assessing the adequacy of noninvasive ventilation. PtcCO₂ monitoring is a standard assessment for

pediatric patients in the sleep lab, and it is increasingly being utilized in adults to complement diagnostic and treatment purposes.

The transcutaneous CO₂ sensors work by heating underlying skin to approximately 43° C, increasing blood flow through the underlying dermal capillary bed. Within 2 to 5 minutes, the "arteriolized" capillary PtcCO₂ approximates PaCO₂.

Commercially available devices for measuring PtcCO₂ reliably estimate PaCO₂ in patients undergoing noninvasive ventilation to within 5 mm Hg (95% CI) (Storre et al. Respir Med. 2010;105:143).

 ${
m PtcCO}_2$ measurement has limitations. Measured ${
m PtcCO}_2$ can drift upward (i.e., technical drift) during continuous monitoring; however, currently available devices adequately adjust for this phenomenon. Arterialization may be limited by thickened skin, edema, or hypoperfusion.

Currently, U.S. insurance companies do not accept PtcCO₂ for documentation of hypercapnia, and the cost of measuring PtcCO₂ is not reimbursed. Nevertheless, Ptc-CO₂ technology promises a new era for home mechanical ventilation guided by accurate and practical assessment of PCO2, in particular for chronic respiratory failure syndromes. In this setting, home PtcCO₂ monitoring potentially can be utilized in place of in-laboratory sleep studies for assessment of nocturnal hypoventilation and optimizing home mechanical ventilation.

> Jason Ackrivo, MD Steering Committee Member

Interstitial and Diffuse Lung Disease

Electronic patient education

The management of patients with an interstitial lung disease (ILD) is challenging. A provider must

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examine the fine details about current and prior medication history, explore various occupational and environmental exposures, perform a thorough physical examination



DR. KERSHAW

that includes a careful dermatologic and rheumatologic review, and peruse the objective data, such as the high-resolution CT scan of the chest and pulmonary function tests.

Then, the pulmonologist and the patient (plus often multiple family members) discuss diagnostic possibilities, any future testing for confirmation, and prognostic implications. Understandably, the patient may leave the office bewildered, overwhelmed, and in search of clarification.

Bewilderment may lead to the internet. In 2001, 4.5% of all internet searches were determined to be health-care-related (Eysenbach et al. *AMIA Annu Symp Proc.* 2003;225).

It is reasonable to presume the percentage is higher today. Just

as with any nonmedical website, the choices for digital health-care information are sometimes not contemporaneous and vary in quality. By exploring the most common "hits" on popular search engines when searching for idiopathic pulmonary fibrosis, a 2016 study found that not only is information presented at a high reading level – 12th grade – but often outdated or simply wrong (Fisher, et al. *Am J Respir Crit Care Med.* 2016;194[2)]:218).

Adding to a patient's possible confusion is that websites expected to be the most helpful, foundation or advocacy websites, were more likely to suggest disproven and even harmful therapies years after those conclusions were published.

CHEST and the Interstitial and Diffuse Lung Disease NetWork are committed to patient education both in and out of the clinical setting.

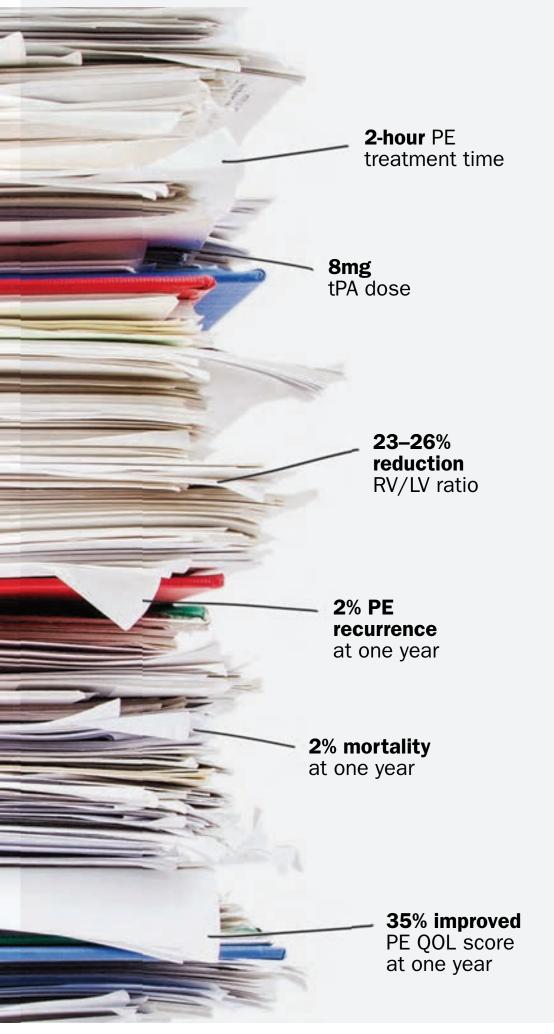
An ongoing redesign of ILD patient education on the CHEST Foundation website is nearing completion and will ensure patients have the most accurate and understandable information available.

Corey Kershaw, MD Steering Committee Member



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

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