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Undiagnosed OSA can double cardiovascular risk after surgery

Dr. Matthew T.V. Chan and colleagues stated, "General anesthetics, sedatives, and postoperative analgesics are potent respiratory depressants that relax the upper airway dilator muscles and impair ventilatory response to hypoxemia and hypercapnia."



Courtesy Dr. Matthew T.V. Chan

BY BIANCA NOGRADY

MDedge News

Unrecognized severe obstructive sleep apnea is a risk factor for cardiovascular complications after major noncardiac surgery, according to a study published in JAMA.

The findings indicate that perioperative mismanagement of obstructive sleep apnea can lead to serious medical consequences. "General anesthetics, sedatives, and postoperative analgesics are potent respiratory depressants that relax the upper airway dilator muscles and impair ventilatory response to hypoxemia and hypercapnia. Each of these events exacerbates [obstructive sleep apnea] and may predispose

patients to postoperative cardiovascular complications," said researchers who conducted the The Postoperative vascular complications in unrecognized Obstructive Sleep apnoea (POSA) study (NCT01494181).

They undertook a prospective observational cohort study involving 1,218 patients undergoing major noncardiac surgery, who were already considered at high risk of postoperative cardiovascular events – having, for example, a history of coronary artery disease, stroke, diabetes, or renal impairment. However, none had a prior diagnosis of obstructive sleep apnea.

Preoperative sleep monitoring revealed that two-thirds of the cohort had unrecognized and

OSA // continued on page 6

Smoking rates remain steady among the poor

BY ANDREW D. BOWSER

MDedge News

While an increasing number of U.S. citizens are saying no to cigarettes, current smoking rates are holding steady among people who face multiple forms of socioeconomic or health-related disadvantages, a recent study shows.

The odds of current smoking, versus never smoking, declined significantly during 2008-2017 for individuals with none of six disadvantages tied to cigarette use, including disability, unemployment, poverty, low education, psychological distress, and heavy alcohol intake, according to researchers.

Individuals with one or two of those disadvantages have also been cutting back, the data suggest. But, by contrast, odds of current versus never smoking did not significantly change for those with three or more disadvantages, according to Adam M. Leventhal, PhD, of the University of Southern California, Los Angeles, and coinvestigators.

"How this pattern can inform a cohesive policy agenda is unknown, but it is clear from these findings that the crux of the recently expanding tobacco-related health disparity problem in the

Smoking // continued on page 7

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Employed physicians now outnumber independents

BY ALICIA GALLEGOS
MDedge News

For the first time, employed physicians outnumber independent physicians, according to a

survey from the American Medical Association. The AMA's annual Physician Practice Benchmark Survey, which queried 3,500 doctors, showed that 47% of all physicians in 2018 were

employed, compared with 46% of doctors who were self-employed that year. The number of employed physicians has risen 6 percentage points since 2012, while the number of self-employed doctors has fallen by 7

percentage points over the same period, according to the study published May 6 on the AMA website. Younger physicians and women doctors were more likely to be employed than their counterparts. Nearly

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70% of physicians under age 40 years were employees in 2018, compared with 38% of physicians 55 years and older, the study found. About 35% of physicians worked either directly for a hospital or in a practice at least partly owned by a hospital in 2018, up from 29% in 2012.

More than half of physicians surveyed (54%) worked in physi-

cian-owned practices in 2018 either as an owner, employee, or contractor, a decrease from 60% in 2012. Male physicians were more likely to be practice owners than female physicians. Among female doctors, 58% were employees, compared with 34% who were practice owners, while 52% of men physicians were practice owners, compared with

42% who were employees.

Surgical subspecialists had the highest share of owners (65%) followed by obstetrician-gynecologists (54%) and internal medicine subspecialists (52%). Emergency physicians had the lowest share of owners (26%) and the highest share of independent contractors (27%). Family physicians, meanwhile, had the highest share of

employed physicians (57%).

A majority of doctors still work in small practices, the analysis found. In 2018, 57% of physicians worked in practices with 10 or fewer physicians versus 61% in 2012. However, fewer physicians work in solo practice. Between 2012 and 2018 the percentage of physicians in solo practice fell from 18% in 2012 to 15% in 2018.

The AMA's Physician Practice Benchmark Survey is a nationally representative survey of post-residency physicians who provide at least 20 hours of patient care per week, are not employed by the federal government, and practice in one of the 50 states or the District of Columbia. The 2018 survey was conducted in September 2018, and the final data included 3,500 physicians.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: Today

one hears of physician early retirement and burnout, and now data that reveal that most doctors are choosing employment



over ownership. With the hyperbolic expansion of administrative tasks related to government oversight, the institution of the electronic records, the ever-increasing cost of overhead, among many other pressures, it is not difficult to understand why physicians choose not to "own" a practice. If one transfers those headaches to someone else, the practice of medicine should be simplified. But as an employee, physicians are often judged more by their Press-Ganey score than how well they practice medicine. There is also a crowd of corporate clerks whose job it is to count things and tell you why you are not doing your job correctly or efficiently, while knowing nothing of what your job entails. In addition, most employment contracts contain a "termination without cause" clause that allows the employer to fire you without giving you a reason. I believe owning a practice may be less frightening.

untreated obstructive sleep apnea, including 11.2% with severe obstructive sleep apnea.

At 30 days after surgery, patients with obstructive sleep apnea had a 49% higher risk of the primary outcome of myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, or stroke, compared with those without obstructive sleep apnea.

However, this association was largely due to a significant 2.23-fold higher risk among patients with severe obstructive sleep apnea, while those with only moderate or mild sleep apnea did not show a significant increased risk of cardiovascular complications.

Patients in this study with severe obstructive sleep apnea had a 13-fold higher risk of cardiac death, 80% higher risk of myocardial injury, more than 6-fold higher risk of heart failure, and nearly 4-fold higher risk of atrial fibrillation.

Researchers also saw an association between obstructive sleep apnea and increased risk of infective outcomes, unplanned tracheal intubation, postoperative lung ventilation, and readmission to the ICU.

The majority of patients received nocturnal oximetry monitoring during their first 3 nights after surgery. This revealed that patients without obstructive sleep apnea had significant increases in oxygen desaturation index during their first night after surgery, while those with sleep apnea did not return to their baseline oxygen desaturation index until the third night after surgery.

“Despite a substantial decrease in ODI [oxygen desaturation index] with oxygen therapy in patients with OSA during the first 3 postoperative nights, supplemental oxygen did not modify the association between OSA and postoperative cardiovascular event,” wrote Matthew T.V. Chan, MD, of Chinese University of Hong Kong, Prince of Wales Hospital, and coauthors.

Given that the events were associated with longer durations of severe oxyhemoglobin desaturation, more aggressive interventions such as positive airway pressure or oral appliances may be required, they noted.

“However, high-level evidence demonstrating the effect of these measures on perioperative outcomes is lacking [and] further clinical trials are now required to test if additional monitoring or alternative interventions would reduce the risk,” they wrote.

The study was supported by the Health and Medical Research Fund (Hong Kong), National Healthcare Group–Khoo Teck Puat Hospital, University Health Network Foundation, University of Malaya, Malaysian Society of Anaesthesiologists, Auckland Medical Research Foundation, and ResMed. One author declared grants from private industry and a patent pending on an obstructive sleep apnea risk questionnaire used in the study.

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SOURCE: Chan MTV et al. JAMA. 2019;321(18):1788-98. doi: 10.1001/jama.2019.4783.

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

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VIEW ON THE NEWS

Wake-up call on OSA surgery risk

This study is large, prospective, and rigorous, and adds important new information to the puzzle of the impact of sleep apnea on postoperative risk, Dennis Auckley, MD, FCCP, and Stavros Memtsoudis, MD, wrote in an editorial accompanying this study. The study focused on predetermined clinically significant and measurable events, used standardized and objective sleep apnea testing, and attempted to control for many of the confounders that might have influenced outcomes.

The results suggest that obstructive sleep apnea should be recognized as a major perioperative risk factor, and it should receive the same attention and optimization efforts as comorbidities such as diabetes.

Dr. Auckley is from the division of pulmonary, critical care and sleep medicine at MetroHealth Medical Center, Case Western Reserve University, Cleveland, and Dr. Memtsoudis is clinical professor of anesthesiology at Cornell University, New York. These comments are adapted from an editorial (JAMA. 2019;321[18]:1775-6). Both declared board and executive positions with the Society of Anesthesia and Sleep Medicine. Dr. Auckley declared research funding from Medtronic, and Dr. Memtsoudis declared personal fees from Teikoku and Sandoz.

New guidance on TB screens for health care workers

BY BIANCA NOGRADY

MDedge News

U.S. health care personnel no longer need to undergo routine tuberculosis testing in the absence of known exposure, according to new screening guidelines from the National Tuberculosis Controllers Association and Centers for Disease Control and Prevention.

The revised guidelines on tuberculosis screening, testing, and treatment of U.S. health care personnel, published in *Morbidity and Mortality Weekly Report*, are the first update since 2005. The new recommendations reflect a reduction in concern about U.S. health care personnel's risk of occupational exposure to latent and active tuberculosis infection.

Lynn E. Sosa, MD, from the Connecticut Department of Public Health and National Tuberculosis Controllers Association, and coauthors wrote that rates of tuberculosis infection in the United States have declined by 73% since 1991, from 10.4/100,000 population in 1991 to 2.8/100,000 in 2017. This has been matched by similar declines among health care workers, which the authors said raised questions about the cost-effectiveness of

the previously recommended routine serial occupational testing.

"In addition, a recent retrospective cohort study of approximately 40,000 health care personnel at a tertiary U.S. medical center in a low TB-incidence state found an extremely low rate of TST conversion (0.3%) during 1998-2014, with a limited proportion attributable to occupational exposure," they wrote.



The new guidelines recommend health care personnel undergo baseline or preplacement tuberculosis testing with an interferon-gamma release assay (IGRA) or a tuberculin skin test (TST), as well as individual risk assessment and symptom evaluation.

The individual risk assessment considers whether the person has lived in a country with a high tuberculosis rate, whether they are immunosuppressed, or whether they have had close contact with someone with infectious tuberculosis.

This risk assessment can help decide how to interpret an initial positive test result, the authors said.

"For example, health care personnel with a positive test who are asymptomatic, unlikely to be infected with *M. [Mycobacterium] tuberculosis*, and at low risk for progression on the basis of their risk

assessment should have a second test (either an IGRA or a TST) as recommended in the 2017 TB diagnostic guidelines of the American Thoracic Society, Infectious Diseases Society of America, and CDC," they wrote. "In this example, the health

"In addition, a recent retrospective cohort study of approximately 40,000 health care personnel at a tertiary U.S. medical center in a low TB-incidence state found an extremely low rate of TST conversion (0.3%) during 1998-2014, with a limited proportion attributable to occupational exposure."

care personnel should be considered infected with *M. tuberculosis* only if both the first and second tests are positive."

After that baseline testing, personnel do not need to undergo routine serial testing except in the case of known exposure or ongoing transmission. The guideline authors suggested serial screening might be considered for health care workers whose work puts them at greater

risk – for example, pulmonologists or respiratory therapists – or for those working in settings in which transmission has happened in the past.

For personnel with latent tuberculosis infection, the guidelines recommend "encouragement of treatment" unless it is contraindicated, and annual symptom screening in those not undergoing treatment.

The guideline committee also advocated for annual tuberculosis education for all health care workers.

The new recommendations were based on a systematic review of 36 studies of tuberculosis screening and testing among health care personnel, 16 of which were performed in the United States.

The authors stressed that recommendations from the 2005 CDC guidelines – which do not pertain to health care personnel screening, testing, treatment and education – remain unchanged.

One author declared personal fees from the National Tuberculosis Controllers Association during the conduct of the study. Two others reported unrelated grants and personal fees from private industry. No other conflicts of interest were disclosed.

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SOURCE: Sosa LE et al. *MMWR*. 2019;68:439-43.

Economic disadvantages have cumulative impact on smoking risk // continued from page 1

United States is not tied to groups facing merely a single form of disadvantage," Dr. Leventhal and coauthors wrote in a report on the study in *JAMA Internal Medicine*.

The cross-sectional analysis by Dr. Leventhal and colleagues was based on National Health Interview Survey (NHIS) data from 2008 to 2017 including more than 278,000 respondents aged 25 years or older.

A snapshot of that 10-year period showed that current smoking prevalence was successively higher depending on the number of socioeconomic or health-related disadvantages.

The mean prevalence of current smoking over that entire time period was just 13.8% for people with zero of the six disadvantages, 21.4% for those with one disadvantage, and so on, up to 58.2% for those with all six disadvantages, according to data in the published report.

Encouragingly, overall smoking prevalence fell from 20.8% in 2008-2009 to 15.8% in 2016-2017, the researchers found. However, the decreasing trend was not apparent for individuals with many disadvantages.

The odds ratio for change of smoking per year was 0.951 (95% confidence interval, 0.944-0.958) for those with zero disadvantages, 0.96 (95% CI, 0.95-0.97) for one disadvantage, and

0.98 (95% CI, 0.97-0.99) for two, all representing significant annual reductions in current versus never smoking, investigators said. By contrast, no such significant changes were apparent for those with three, four, five, or six such disadvantages.

Tobacco control or regulatory policies that consider these disadvantages separately may be overlooking a "broader pattern" showing that the cumulative number of disadvantages correlates with the magnitude of disparity, wrote Dr. Leventhal and colleagues in their report.

"Successful prevention of smoking initiation and promotion of smoking cessation in multi-disadvantaged populations would substantially reduce the smoking-related public health burden in the United States," they concluded.

Dr. Leventhal and colleagues reported no conflicts related to their research, which was supported in part by a Tobacco Centers of Regulatory Science award from the National Cancer Institute and the Food and Drug Administration, among other sources.

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SOURCE: Leventhal AM. et al. *JAMA Intern Med*. 2019 Apr 22. doi: 10.1001/jamainternmed.2019.0192.



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Eosinophils key to glucocorticoid response in asthma

BY WILL PASS

MDedge News

Patients with mild asthma who rely solely on short-acting beta2-agonists (SABAs) to control their asthma symptoms remain at increased risk of exacerbations, according to investigators.

Two recent studies presented at the American Thoracic Society's international conference demonstrated the benefits of glucocorticoid therapy among patients with mild persistent or intermittent asthma while highlighting differential responses to steroids among patients with high versus low levels of eosinophils in sputum. Both studies were simultaneously published in the *New England Journal of Medicine*.

The first study, SIENA, led by Stephen C. Lazarus, MD of the University of California, San Francisco, and colleagues, involved 295 patients with mild, persistent asthma. Patients were classified as having either a high or low level of eosinophils in sputum, with a low level defined by two sputum samples consisting of less than 2% eosinophils. After a single-blind placebo run-in period of 6 weeks, patients were randomized to receive either mometasone (an inhaled glucocorticoid), tiotropium (a long-acting muscarinic antagonist [LAMA]), or placebo for 12 weeks each, with subsequent crossover through the two remaining treatments. The primary outcome was the response to each active agent, compared with placebo among low-eosinophil patients who had a differential response to a trial agent.

Out of 295 patients, 221 (75%) had low eosinophils and 74 (25%) had high eosinophils. In the low-eosinophil subgroup, 59% of patients had a differential response to a trial agent; among these, 57% responded better to mometasone, compared with 43% who responded better to placebo, and 60% responded better to tiotropium, compared with 40% who responded better to placebo.

Turning to secondary analyses, among patients with high eosinophil levels who had a differential response, 74% responded better to mometasone, compared with 26% who responded better to placebo, and 57% responded better to tiotropium, compared with 43% who responded better to placebo.

In an additional exploratory analysis, adults with low eosinophil levels had better responses to tiotropium than placebo (62% vs 38%).

The researchers stated that a key finding of the study is that three-quarters of the mild, persistent asthma population had low eosinophil levels, far fewer than expected and that the difference in their response to mometasone compared to tiotropium was not significant.

"Our results raise the question of whether treatment guidelines should be reevaluated for patients with mild, persistent asthma for whom evidence of type 2 inflammation is lacking," the investigators wrote. "The need for a change in treatment strategy is further highlighted by a growing body of literature suggesting that mild, persistent asthma can be managed safely without the daily use of inhaled glucocorticoids and by data showing that patients with a low eosinophil level may not have a favorable response to inhaled glucocorticoids" (*New Engl J Med*. 2019 May 19. doi: 10.1056/NEJMoa1814917).

The second study, Novel START, conducted by lead author Richard Beasley, DSc, of the Medical Research Institute of New Zealand, Wellington, and colleagues, compared the efficacy of two inhaled glucocorticoid regimens and albuterol alone for patients with mild persistent or intermittent asthma, measured by annualized exacerbation rate.

Initial randomization involved 675 patients, of whom 668 were included in the final analysis. Patients were randomized into three groups: albuterol as needed (100 mcg, two inhalations as needed for asthma symptoms), budesonide maintenance (200 mcg, one inhalation twice daily with as-needed albuterol), or budesonide/formoterol (budesonide 200 mcg and formoterol 6 mcg, one inhalation as needed). Along with annualized exacerbation rate, several secondary outcomes assessed symptoms, respiratory function, and number of severe exacerbations.

Data analysis showed that patients in the budesonide groups had similar rates of annualized exacerbation, both of which were significantly better than the exacerbation rate in the albuterol-only group; the absolute rate of exacerbations per patient per year was 0.175, 0.195, and 0.400 for budesonide maintenance, budesonide/formoterol, and albuterol only, respectively. Similarly, the median fraction of exhaled nitric oxide (FENO) was lower in the budesonide groups than in the albuterol-only group. Patients in the budesonide/formoterol group

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: In my city clinic, I see many patients with difficult-to-treat asthma. They are often young, poor, underinsured, and obese. The obstacles are many: co-pays are too high; patients' health literacy is low; medications are too often ineffective; and oral corticosteroids are continued indefinitely by other providers. Novel biologic agents can be unrealistic as a result of denied coverage and patient concerns about injectable medicines. New advances may help. Checking sputum eosinophil levels as an outpatient and targeting therapy in these patients may lead to improved outcomes from cost-effective strategies. Intermittent, as needed, combination ICS/LABA may be an effective, sensible, and affordable alternative for many with mild disease.



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had a 56% lower relative risk of severe pulmonary exacerbation than patients in the budesonide maintenance group and a 60% lower relative risk than the albuterol group. However, maintenance budesonide provided better symptom relief than budesonide/formoterol, "which suggests that for the patient for whom asthma symptoms rather than exacerbations are the most bothersome, maintenance treatment has value," the investigators wrote (*New Engl J Med*. 2019 May 19. doi: 10.1056/NEJMoa1901963).

"The findings of our trial are consistent with evidence regarding the treatment of moderate and severe asthma – that maintenance and reliever therapy" with inhaled glucocorticoid/formoterol "results in a lower risk of severe exacerbations than maintenance therapy with an

inhaled glucocorticoid–[long-acting beta agonist] and as-needed SABA," the investigators concluded.

SIENA was funded by National Heart, Lung, and Blood Institute, with medications provided by Boehringer Ingelheim, Merck, and Teva; the investigators reported relationships with Sanofi, Vectura, Circassia, DBV Technologies, and others. Novel START was funded by AstraZeneca and the Health Research Council of New Zealand; the investigators reported relationships with GlaxoSmithKline, Genentech, Theravance Biopharma, and others.

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SOURCES: Beasley R et al. *New Engl J Med*. 2019 May 19. doi: 10.1056/NEJMoa1901963; Lazarus SC et al. *New Engl J Med*. 2019 May 19. doi: 10.1056/NEJMoa1814917.

AFib on the rise in patients with COPD hospitalized for exacerbations

BY JEFF CRAVEN

FROM THE JOURNAL CHEST® ■ Atrial fibrillation is being seen with increasing frequency in patients admitted to U.S. hospitals for exacerbations of end-stage chronic obstructive pulmonary disease, based on a retrospective analysis of data from the U.S. Nationwide Inpatient Sample.

The prevalence of atrial fibrillation (AFib) among patients with end-stage chronic obstructive pulmonary disease (COPD) on home oxygen who were admitted with COPD exacerbations increased from 12.9% in 2003 to 21.3% in 2014, according to Xiaochun Xiao of the department of health statistics at Second Military Medical University in Shanghai and colleagues.

Additionally, “we found that comorbid [AFib] was associated with an increased risk of the need for mechanical ventilation, especially invasive mechanical ventilation. Moreover, comorbid [AFib] was associated with adverse clinical outcomes, including increased in-hospital death, acute respiratory failure, acute kidney injury, sepsis, and stroke,” the researchers wrote in the study published in the journal CHEST.

Patients included in the study were aged at least 18 years, were diagnosed with end-stage COPD and on home oxygen, and were hospitalized because of a COPD-related exacerbation. Based on

1,345,270 weighted hospital admissions of adults with end-stage COPD on home oxygen who met the inclusion criteria for the study, 18.2% (244,488 admissions) of patients had AFib, and the prevalence of AFib in COPD patients increased over time from 2003 (12.9%) to 2014 (21.3%; *P* less than .0001).

Patients with AFib, compared with patients without AFib, were older (75.5 years vs. 69.6 years; *P* less than .0001) and more likely to be male (50.7% vs. 59.1%; *P* less than .0001) and white (80.9% vs. 74.4%; *P* less than .0001). Patients with AFib also had higher stroke risk reflected in higher CHA₂DS₂-VASc scores (3.26 vs. 2.45; *P* less than .0001), and higher likelihood of in-hospital mortality and readmission reflected in Elixhauser scores greater than or equal to 4 (51.2% vs. 35.6%).

Larger hospitals in terms of number of beds, urban environment, and Medicare insurance status also were associated with a higher AFib prevalence.

AFib was associated with an increased cost of \$1,415 and an increased length of stay of 0.6 days after adjustment for potential confounders. AFib also predicted risk for several adverse events, including stroke (odds ratio, 1.80; in-hospital death, [OR, 1.54]), invasive mechanical ventilation (OR, 1.37), sepsis (OR, 1.23), noninvasive mechanical ventilation (OR, 1.14), acute kidney injury (OR,

1.09), and acute respiratory failure (OR, 1.09).

The researchers suggested that the reason for this increased Afib incidence may be an aging population, advancing AFib diagnostic approaches, increased AFib awareness improving AFib detection, an increase in the prevalence of AFib during the study period occurring as a result of reduced AFib-related mortality, and finally, increasing trends in risk factors may also be involved in the increased of AFib.

The researchers noted the database could have potentially overinflated AFib prevalence, as they could not differentiate index admissions and readmissions. The database also does not contain information about secondary diagnoses codes present on admission.

“Our findings should prompt further efforts to identify the reasons for increased [AFib] prevalence and provide better management strategies for end-stage COPD patients comorbid with [AFib],” the researchers concluded.

This study was funded by a grant from the Fourth Round of the Shanghai 3-Year Action Plan on Public Health Discipline and Talent Program. The authors reported no relevant conflict of interest.

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SOURCE: Xiao X et al. CHEST. 2019 Jan 23. doi: 10.1016/j.chest.2018.12.021.

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No raised risk of cardiovascular events for patients with COPD receiving aclidinium bromide

BY HEIDI SPLETE

MDedge News

Aclidinium bromide reduced exacerbations in adults with chronic obstructive pulmonary disease with no increased risk of major adverse cardiovascular events, compared with placebo, in a randomized trial of more than 3,000 patients.

Aclidinium, a long-acting muscarinic antagonist (LAMA), has been shown to reduce COPD exacerbation in the short term, but long-term effectiveness has not been examined, wrote Robert A. Wise, MD, FCCP, of Johns Hopkins University, Baltimore, and colleagues.

ASCENT-COPD is a multicenter, double-blind, randomized, placebo-controlled, parallel-group noninferiority study conducted at 522 sites in the United States and Canada. A paper on recent data from ASCENT-COPD, published in JAMA, supports early findings reported last year at the American Thoracic Society meeting.

The researchers randomized adults with COPD to a 400-mg dose of aclidinium bromide twice daily, or placebo. The average age of the patients was 67 years; 59% were men. The median exposure time to aclidinium or placebo was 365 days during the first year of treatment,



Dr. Robert A. Wise

and the median exposure overall was 495 days for aclidinium patients and 478 days for placebo patients.

Of the 2,537 patients who completed the study, 69 (3.9%) in the aclidinium group and 76 (4.2%) in the placebo group experienced a major adverse cardiovascular event (MACE, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke).

In addition, annual rates of moderate to severe COPD exacerbations were significantly lower in the aclidinium patients compared with

placebo patients (0.44 vs. 0.57, P less than .001).

In a secondary analysis with a definition of MACE expanded to include heart failure, arrhythmias, or

“No patient subgroup demonstrated a difference in efficacy except when analyzed by baseline COPD severity, in which the treatment benefit was observed only in

“Outcomes of this trial add data to the long-standing controversy over the safety of LAMAs in COPD” and support the need for additional research.

cerebrovascular disease, results remained similar between the groups; events occurred in 168 aclidinium patients (9.4%) and 160 placebo patients (8.9%). The rate of COPD exacerbations requiring hospitalization was significantly lower in aclidinium patients, compared with placebo patients (0.07 vs. 0.10, P = .006).

Overall, the most common treatment-emergent adverse events were similar in the aclidinium and placebo groups, respectively: pneumonia (6.1% vs. 5.8%), urinary tract infections (5.2% vs. 5.0%), and upper respiratory tract infections (4.8% vs. 5.6%). The most common serious adverse events (in at least 1% of patients) were pneumonia, atrial fibrillation, heart failure, and coronary artery disease. Dry mouth and urinary retention were rare, and occurred in less than 1% of patients in each group.

patients with FEV₁ [forced expiratory volume in 1 second] of 50% predicted or less,” the researchers noted. “This may be explained by the lower exacerbation rate seen in the placebo group in patients with moderate airway obstruction vs. severe or very severe obstruction,” they said.

“Outcomes of this trial add data to the long-standing controversy over the safety of LAMAs in COPD” and support the need for additional research, they said.

The study findings were limited by several factors including insufficient power to detect cause-specific mortality and the use of a LAMA with low risk of systemic effects, the researchers noted.

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SOURCE: Wise RA et al. JAMA. 2019. 321:1693-701.

Survey: Americans support regulation of vaping products

BY RICHARD FRANKI

MDedge News

Almost 70% of adults believe that the Food and Drug Administration should raise the legal age to purchase e-cigarettes and tobacco, according to a new survey by NORC at the University of Chicago, a nonpartisan research institution.

“Americans are particularly concerned about teens becoming newly addicted to e-cigarettes, and they support a range of actions the federal government could take to make vaping products less available, less addictive, and less appealing,” Caroline Pearson, senior vice president at NORC, said in a written statement.

The AmeriSpeak Spotlight on Health Poll, conducted Feb. 14-

18, 2019 (margin of error, plus or minus 4.12%), showed that 69% of adults strongly or somewhat support raising the age limit to purchase e-cigarettes and tobacco and 55% support restricting sales of flavored e-cigarettes, NORC reported. Almost 40% of the 1,004 respondents expressed support for a complete ban on e-cigarettes.

Despite FDA efforts under Commissioner Scott Gottlieb, MD, to raise awareness of teen vaping, only 21% of those surveyed correctly responded that e-cigarettes generally contain more nicotine than regular cigarettes. Dr. Gottlieb announced his resignation recently, “but he indicated that the Trump Administration will continue efforts to increase regulation of e-cigarettes,” NORC said.

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Public opinion on e-cigarette control



Raise the legal age to purchase tobacco and e-cigarettes

69%

Restrict sales of flavored e-cigarettes **55%**

Outlaw e-cigarettes entirely **39%**



Source: NORC at the University of Chicago

In a tight vote, FDA panel backs mannitol for treatment of cystic fibrosis

BY KARI OAKES

MDedge News

A Food and Drug Administration Advisory Committee voted that the benefit-risk profile of an inhaled treatment for cystic fibrosis merits approval of the drug – dry powder mannitol (DPM).

Mannitol is a naturally occurring sugar alcohol that is used as a low-calorie sweetener; it is generally recognized as safe when taken enterically. Inhaled DPM, marketed as Aridol, is currently approved as a bronchoprovocation agent. For the current indication, DPM is given as 10x40-mg capsules twice daily.

In a 9-7 vote, the FDA's Pulmonary-Allergy Drugs Advisory Committee (PADAC) decided that DPM's modest potential to improve pulmonary function in adults with cystic fibrosis (CF) outweighed a potential signal for increased exacerbations seen in clinical trials.

Chiesi USA is seeking approval of DPM for the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. It plans to market DPM as Bronchitol.

Some committee members who voted against approval, including PADAC chair David H. Au, MD, worried that DPM's ease of use might prompt patients and caregivers to substitute it for inhaled hypertonic saline, a medication that's more burdensome to use but has a longer track record for efficacy and safety. While hypertonic saline requires cumbersome equipment and cleaning regimens and takes 20-30 minutes to administer, DPM is administered over about 5 minutes via a series of capsules inserted into a small inhaler device.

"I was very impressed by conversations that we heard from the community that this will be viewed as a substitute drug [for hypertonic saline]," said Dr. Au, professor of medicine at the University of Washington, Seattle. "Before we make that leap of faith ... we have to better understand how it has to be used." He also acknowledged that making the call for DPM was "challenging."

Other committee members were reassured by the fact that DPM is approved for adult use in 35 countries; it's been in use since 2011 in Australia for adults and children.



Dr. John M. Kelso

Some members also noted an unmet need in CF therapies and placed confidence in those treating CF patients to find ways to use DPM safely and effectively. "I'm really counting on the cystic fibrosis clinicians who do this for a living to figure out where to use this in their armamentarium," said John M. Kelso, MD, an allergist at Scripps Clinic, San Diego.

In 2012, the initial new drug application submitted by Pharmaxis, which then held marketing rights to DPM, resulted in a "no" vote for

The FDA panel decided that mannitol's modest potential to improve pulmonary function in adults with cystic fibrosis outweighed a potential signal for increased exacerbations seen in clinical trials.

approval from PADAC, and eventual FDA denial of approval. The initial submission was supported by two phase 3 clinical trials, 301 and 302, that included pediatric patients. In the pediatric population, there was concern for increased hemoptysis with DPM, so the FDA advised the drug's marketers to consider seeking approval for an adult population only in its reapplication. The current submission followed a new double-blind, randomized, placebo-controlled trial, study 303, that included adults with CF aged 18 or over.

All three studies had similar designs, tracking change from baseline

in forced expiratory volume in 1 second (FEV₁) from baseline to the end of the 26-week study period. In addition to this primary endpoint, secondary endpoints included other pulmonary function measures, as well as the number of protocol-defined pulmonary exacerbations (PDPEs). Participants also reported quality of life and symptom measures on the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

In study 301, the dropout rate approached one in three participants with higher discontinuation in the intervention than the control arm, causing significant statistical problems in dealing with missing data. Thus, said the FDA's Robert Lim, MD, though this study had positive results for FEV₁, it was not "statistically robust."

The second study, 302, did not meet its primary endpoint, and there was "no support from secondary endpoints" for efficacy, said Dr. Lim, a clinical team leader in the FDA's Division of Pulmonary, Allergy, and Rheumatology Products.

The current submission was also supported by a new post hoc subgroup analysis of adults in studies 301 and 302. A total of 414 patients receiving DPM and 347 receiving placebo (DPM at a nontherapeutic level) were included in the integrated analysis of patients from all three studies. Studies 301 and 302 both had open-label extension arms, allowing more patients to be included in safety data.

The problems caused by the missing data from study 301 were addressed in the design of study 303 by encouraging patients who discontinued the study drug to continue data collection efforts for the study. Dropout rates were lower overall in study 303 and balanced between arms.

Over the 26-week duration of study 303, investigators saw a statistically significant improvement in FEV₁ of about 50 mL, according to the FDA's analysis. Post hoc analyses of studies 301 and 302 showed point estimate increases of approximately 80 mL, according to Dr. Lim.

In its presentations, Chiesi USA presented its integrated analysis of adult data from the three clinical trials. The analysis showed an increase in FEV₁ from baseline of 73 mL for the DPM group, compared with an increase of 7 mL for the control

group, using an intention-to-treat population (*P* less than .001). The committee heard evidence that in adults with CF, pulmonary function typically decreases by 1%-3% annually.

The PDPE rate was slightly higher in the DPM group than in the control group in studies 302 and 303, but the differences were not statistically significant. These findings have a backdrop of an overall low rate of PDPEs ranging from 0.221 to 0.995 per year, according to Chiesi presenter Scott Donaldson, MD, a pulmonologist who directs the adult cystic fibrosis center at the University of North Carolina at Chapel Hill.

When looking at the subgroup of United States study participants, the DPM integrated cohort included more patients with a history of

"This is not a drug for everybody; but absolutely, it's a drug for somebody. Ultimately we have to make that decision – I do think that we study populations, but we really take care of people."

prior pulmonary exacerbations. In the DPM group, 45% of U.S. participants had at least one exacerbation in the prior year, and 20% had two or more exacerbations, compared with 38% and 14%, respectively, in the control group. Chiesi argued that this imbalance was likely responsible for the increased exacerbation rate.

The sponsor and the FDA used different imputation methods to account for missing data from the earlier studies, complicating interpretation of the potential signal for increased exacerbations.

Quality of life data were similar between groups across the studies.

In the end, the view of the "yes" voters was encapsulated by James M. Tracy, DO, an allergist in private practice in Omaha, Neb. "This is not a drug for everybody; but absolutely, it's a drug for somebody. Ultimately we have to make that decision – I do think that we study populations, but we really take care of people."

The FDA usually follows the recommendations of its advisory panels.

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Circulating tumor cells predict NSCLC survival, but clinical role uncertain

BY WILL PASS

GENEVA – Circulating tumor cell (CTC) count is an independent predictor of both progression-free and overall survival in patients with advanced non-small cell lung cancer (NSCLC), according to data from 550 patients.

This is the largest CTC study to date and the first to compare test results from multiple centers, reported lead author Colin Lindsay, MD, PhD, of the University of Manchester (England) and colleagues. Among the centers, investigators found minimal variability in results guiding progression-free survival and no significant differences in results predicting overall survival. These findings suggest that CTC testing could be reproducible and reliable on a large scale, Dr. Lindsay said during a presentation at the European Lung Cancer Conference; he added that this conclusion addresses a previous concern about the process.

“A slight problem with the process



Dr. Colin Lindsay

is still that it is semi-automated,” Dr. Lindsay said at the meeting presented by the European Society for Medical Oncology. “The machine will harvest potential cells and stain potential cells, but the end step of the process is that a trained user in each laboratory will decide which cell is a CTC and which cell isn’t a CTC, and it’s that potential for user variability



Dr. Juergen Wolf

that was the basis of this study.”

The retrospective study involved 550 patients with NSCLC whose samples were processed at seven centers in multiple European countries, including 209 patients whose data were previously unpublished. The investigators looked for associations between CTC count and survival using Cox regression analysis and evaluated if CTCs could add value to prognostic clinicopathologic models based on c-indices and likelihood ratio statistics. CTC count was assessed as a continuous variable and, based on previous studies, using two categorical thresholds: at least 2 cells per 7.5 mL and at least 5 cells per 7.5 mL. In addition, the investigators looked for associations between NSCLC molecular subtypes and CTC levels.

The results showed that both cutoff levels were predictive of survival, with the higher threshold carrying a poorer prognosis. For progression-free survival, CTC counts of at least 2 cells per 7.5 mL carried a hazard ratio of 1.72, whereas the 5-cell threshold had a hazard ratio of 2.21 (P less than .001 for both). Similarly, overall survival hazard ratios for the lower and higher thresholds were 2.18 and 2.75, respectively (P less than .001 for both). When baseline CTC count was added to the analysis, predictive accuracy increased further, dropping P values 10-fold, down to .0001. C-index models had a more modest impact. Although minor heterogeneity was detected among centers for prediction of progression-free survival, overall survival data were broadly reliable. Dr. Lindsay noted that intercenter differences seemed to diminish with greater testing experi-

ence. No relationships were detected between molecular subtypes and CTC profiles.

“It’s always good to finish a talk with the white elephant in the room,” Dr. Lindsay said in his concluding remarks. “Is there room for CTCs in non-small cell lung cancer? I believe they have the potential to complement ctDNA work by offering a cellular context, but [CTCs] aren’t there yet for clinical roll-out.”

Invited discussant Juergen Wolf, MD, of the University Hospital Cologne (Germany) provided a similar conclusion, suggesting that CTCs have a clear place in research, but their clinical value is debatable. He noted that ctDNA, the most similar diagnostic and prognostic tool under development, has a pragmatic edge because ctDNA samples are more amenable to shipping and handling. Dr. Wolf noted that ctDNA also has been shown to have value for treatment planning, specifically for the EGFR T790M resistance mutation. This latter point tied into a larger issue described by Dr. Wolf, who suggested that in the current treatment landscape for NSCLC, predictive testing needs to be actionable.

“We cannot draw a consequence of a prognostic biomarker,” Dr. Wolf said. “In the era of personalized medicine, what we need is predictive markers, predictive of the outcome of specific therapies.”

The investigators disclosed financial relationships with AstraZeneca, Novartis, Pfizer, and others.

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SOURCE: Lindsay C et al. ELCC 2019, Abstract 210.



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Alirocumab reduces both type 1 and 2 MIs

BY BRUCE JANCIN

MDedge News

NEW ORLEANS – Lowering LDL cholesterol with alirocumab to levels below what's achievable with intensive statin therapy appears to be an important strategy for prevention of type 1 MI – and perhaps even more impressively, type 2 MI – following acute coronary syndrome, Harvey D. White, MD, reported at the annual meeting of the American College of Cardiology.

What's so important about the 23% reduction in risk of type 2 MI achieved with alirocumab (Praluent) relative to placebo documented in a prespecified secondary analysis from the ODYSSEY Outcomes trial?

"For type 2 MI, this is the first data indicating that a lipid-lowering therapy can attenuate risk," according to Dr. White, a cardiologist at Auckland (N.Z.) City Hospital.

The ODYSSEY Outcomes trial compared the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab to placebo in 18,924 patients with a recent acute coronary syndrome and an LDL cholesterol level of at least 70 mg/dL despite intensive statin therapy. At 4 months, the PCSK9 inhibitor plus statin therapy reduced participants'

mean LDL by 54%, from 93 to 48 mg/dL, while the LDL level actually drifted upward in the control group on placebo plus statin therapy. In the previously reported primary results of this landmark randomized clinical trial, alirocumab on top of background intensive statin therapy reduced the primary composite end-point of death attributable to coronary heart disease, ischemic stroke, MI, or unstable angina requiring hospitalization by 15%, compared with controls (N Engl J Med. 2018

Nov 29;379[22]:2097-107).

During a median 2.8 years of prospective follow-up, there were 1,860

"For type 2 MI, this is the first data indicating that a lipid-lowering therapy can attenuate risk."

new MIs in study participants. A blinded clinical events committee evaluated the myocardial infarctions

according to the Third Universal Definition and determined 66% were type 1 MIs, 21% were type 2, and 13% were type 4, with lesser numbers of types 3 and 5 MI.

Alirocumab reduced the risk of any MI by 15%, with a 6.8% incidence during follow-up, compared with 7.9% on placebo. The risk of type 1 MI, typically attributable to plaque rupture, was reduced by 13%, with an incidence of 4.9% with alirocumab and 5.6% with placebo.

Continued on following page

VIEW ON THE NEWS

Jason Lazar, MD, FCCP, comments: This study represents yet another important milestone in the broader incorporation of PCSK9 inhibitors for cardiovascular risk reduction.



While 2013 American Heart Association/American College of Cardiology guidelines focused on statin dose (high or intermediate intensity) rather than specific LDL targets, the 2018 revised guidelines re-emphasized LDL treatment goals as well as the adjunct use of non-statin agents to achieve treatment goals. Specifically, for patients with atherosclerotic cardiovascular disease and for those at very high risk, high-intensity statin therapy was recommended

to be used to obtain a 50% reduction in LDL cholesterol. The updated guidelines recommended the addition of ezetimide and PCSK9 inhibitors to statin therapy in patients not reaching treatment goals. While PCSK9 inhibitors are generally accepted to effectively lower LDL cholesterol markedly, their use has been limited by high cost and sparseness of data on clinical event reduction. Accordingly, more affordable pricing and the demonstration of clinical event reduction such as the ODYSSEY Trial will likely lead to expanded use of these agents. In addition, lowering of risk for both types 1 and 2 myocardial infarction, which are felt to result from plaque rupture and demand ischemia, respectively, suggest that lipid lowering in general may portend salutary pleiotropic effects that have been previously linked to statin therapy alone.

When to transition HF patients to alternative loop diuretic

BY ANDREW D. BOWSER

MDedge News

PHILADELPHIA – While many internists might think a switch to spironolactone would be warranted for a heart failure patient with inadequate response to oral furosemide (Lasix), transitioning to an alternative loop diuretic may be the preferable approach, a cardiologist said at the annual meeting of the American College of Physicians.

"Lasix is associated with very high variability in terms of absorption, so torsemide and bumetanide should be considered in patients who have a poor response," said Paul McKie, MD, MPH, a cardiologist and internist with Mayo Clinic, Rochester, Minn., in a session at the meeting.

When polled, only 22% of attendees at the session picked "transition to torsemide" as the best approach for restoring fluid balance with the lowest adverse potential in a 74-year-old woman with nonischemic cardiomyopathy on furosemide 80 mg twice daily who has been hospitalized for fluid overload three times in the year.

The majority of attendees (41%) said they would have added spironolactone. Dr. McKie disagreed with this approach. Instead, Dr. McKie said he would have transitioned this person to an

alternative loop diuretic.

"I think spironolactone is a great medication in heart failure with reduced ejection fraction, but the doses we typically use are generally suboptimal to achieve diuresis," he added.

The rationale for considering an alternative loop diuretic in this patient hinges on bioavailability, which is "highly variable" for oral furosemide, at 10%-100%, while by contrast, torsemide and bumetanide have a very consistent bioavailability of 80%-100%, according to Dr. McKie.

"For this reason, I think about using torsemide or bumetanide in patients who are not responding to oral Lasix," he said.

Dr. McKie described an algorithm that he and his colleagues use in clinic to intensify outpatient therapy for patients not achieving diuresis.

The first step is to ensure adherence and ask patients whether they are following sodium and fluid restriction: "I always ask about that first," he said. "I tell patients, 'You can out-eat and



Dr. Paul McKie

out-drink any diuretic regimen.'"

The next step is to double the dose of the loop diuretic and, sometimes, triple the dose if the double dose is not effective.

"If they're diuresing but it's just not adequate, then I'll move to twice-daily dosing," he said. "A practical tip is I tell patients to take their first dose as soon as they wake up and the second dose around 1:00 p.m. so that they're not urinating all night."

If twice-daily dosing doesn't help, then that's the point where an alternative loop diuretic would be warranted, according to Dr. McKie's algorithm.

"Then I add a thiazide like metolazone, but I only do that after I've increased the dose of the loop diuretic," he added.

If all else fails, then outpatient IV diuretics can be considered, according to the algorithmic approach.

Dr. McKie reported no relevant disclosures.

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Continued from previous page

The risk reduction conferred by the PCSK9 inhibitor was even more robust for type 2 MI, the type caused by an oxygen supply/demand imbalance most commonly attributable to coronary artery spasm, coronary embolism, arrhythmias, anemia, hypertension, or hypotension: a 23% relative risk reduction as reflected in a 1.3% incidence in the alirocumab group, compared with a 1.7% rate in controls.

In contrast, alirocumab had no impact on the incidence of type 4 MI, a category that includes peri-

1 MI, with a 10.2% rate as compared to 13.4% with placebo; that's a 31% relative risk reduction. Yet the PCSK9 inhibitor had no impact on the risk of death after a type 2 MI: 24.8% in the alirocumab group and 25.9% in controls.

Asked for his thoughts as to possible explanatory mechanistic path-

ways for the benefit of alirocumab in preventing type 2 MI, Dr. White noted that, in a Scottish study of the PCSK9 inhibitor evolocumab (Repatha), over the course of 72 months the drug appeared to reduce atherosclerotic progression and induce plaque stabilization and perhaps even regression.

"I think that's the probable mechanism. And we also know that statins improve endothelial function," he said.

He reported receiving research grant support and consultant fees from Sanofi and Regeneron, funders of the ODYSSEY Outcomes trial.

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Bruce Jancin/MDedge News

Dr. Harvey D. White

The beneficial effect of alirocumab on MI risk mostly involved a reduction in larger MIs – those with a biomarker peak greater than three times the upper limit of normal.

percutaneous coronary intervention MIs as well as those attributable to stent thrombosis or restenosis.

The beneficial effect of alirocumab on MI risk mostly involved a reduction in larger MIs – those with a biomarker peak greater than three times the upper limit of normal.

An emphatic difference was found in the risk of death following type 1 as opposed to type 2 MI. Patients who experienced a type 1 MI during the study had an 11.9% mortality rate during an average of 1.6 years of post-MI follow-up, as compared with a 25.4% rate during 1.3 years of follow-up after a type 2 MI.

Alirocumab significantly reduced the risk of mortality following a type

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High coronary artery calcium score points to CV risk

BY JIM KLING

A symptomatic patients with coronary artery calcium (CAC) scores of 1,000 or higher should be considered at higher risk for car-

diovascular disease and all-cause mortality than those with CAC scores of 400-999, based on data from a large retrospective study presented by Allison W. Peng at the annual meeting of the American College of Cardiology.

“Our data argues for consideration of CAC 1000 (or more) as a distinct group with CVD mortality greater than that of contemporary secondary prevention trials. ... We showed that those with CAC 1000

(or more) have both a higher area and density of calcification, a more dispersed pattern of calcification in their coronary artery tree (the majority with 4-vessel disease), with a

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markedly more diffuse distribution of extra-coronary calcification compared to the other CAC groups,” Ms. Peng and her colleagues wrote in the study, which was published online in the Journal of the American College of Cardiology.

Future guidelines should address these patients as a distinct risk

group that might gain the most benefit from targeted, aggressive preventive therapy, the researchers said.

Current guidelines identify individuals with CAC scores over 400 as the highest risk group. With a mean follow-up time of 12.3 years, the results from 66,636 asymptomatic individuals in the CAC consortium study, which included over 2,800

patients with CAC (Agatston) scores of 1,000 or more, indicate patients with CAC scores of 1000 or more have nearly a two-fold higher risk of CVD mortality compared to those with CAC scores of 400-999. While the mortality risk levels off slightly in those with scores exceeding 1,000, all-cause and cause-specific mortality risk still increases with no

apparent upper CAC threshold.

Patients with a CAC score of at least 1,000 were 66.3 years old, on average; 86.3% were male, 52.4% had 4-vessel CAC, and they had a larger total CAC area.

Compared with patients with CAC scores of 400-999, those with a CAC score of 1,000 or more had a greater risk of cardiovascular dis-

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ease (hazard ratio, 1.71; 95% confidence interval, 1.41-2.08), coronary heart disease (HR, 1.84; 95% CI, 1.43-2.36), cancer (HR, 1.36; 95% CI, 1.07-1.73), and all-cause mortality (HR, 1.51; 95% CI, 1.33-1.70).

Those with CAC scores of 400-999 had a 2.1, 3.6, 2.7, and 9.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause

mortality, respectively. But those with CAC scores of 1,000 or more had a 5.1, 8.0, 4.6, and 18.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively.

The leading cause of death was CVD; 36.5% in the CAC 400-999 group and 42.6% in the CAC 1,000 or more group. CHD mortality, as a

subset of CVD mortality, constituted 21.1% of deaths in the CAC 400-999 group and 27.1% of deaths in the CAC 1,000 or more group.

“Future randomized controlled trials of aggressive preventative therapies, for example PCSK9-inhibitors and anti-inflammatory drugs, in patients with CAC \geq 1,000, may prove helpful to evaluate the bene-

fits of such treatment in this unique group,” the authors wrote. They also urged updating current guidelines.

The study was funded by the National Institutes of Health. The authors have no relevant financial disclosures.

SOURCE: Peng AW et al. JACC 2019. doi: 10.1016/S0735-1097(19)31894-7.

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PCV13 vaccine reduces frequency of otitis media visits

BY HEIDI SPLETE

MDedge News

The mean number of office visits for otitis media in children younger than 5 years dropped

significantly after the introduction of the 13-valent pneumococcal conjugate vaccine, according to findings published in the International Journal of Pediatric Otorhinolaryngology.

Previous studies have shown that more than half of children with otitis media (OM) have serotypes included in the PCV7 vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F), wrote Xiaofeng Zhou, MD, of Pfizer, New

York, and colleagues.

To assess the impact of PCV13, with the additional serotypes 1, 3, 5, 6A, 7F, and 19A, the researchers analyzed data from the U.S. National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for three time periods: pre-PCV7 (1997-1999), after the introduction of PCV7 (2001-2009), and after the introduction of PCV13 (2011-2013).

Between the pre-PCV7 and PCV13 time periods, the researchers found significant reductions in the mean rates of OM visits of 48% and 41% among children younger than 2 years and younger than 5 years, respectively; reductions were 24% and 22%, respectively, when comparing PCV13 and PCV7.

For the PCV7 and PCV13 time periods, the mean number of OM visits per 100 children declined from 84 to 64 per 100 children younger than 2 years, from 41 to 34 per 100 children between ages 2 and 5 years, and from 59 to 46 per 100 children younger than 5 years.

The study findings were limited by several factors including the use of an ecologic study design, which was chosen to help reduce selection bias, but that did not show evidence of the field effectiveness of the PCV13 vaccine. Another limitation was the potential misclassification of patients with OM given clinician variability in diagnostic criteria, the researchers noted.

The investigators are employed by Pfizer, which funded the study.

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SOURCE: Zhou X et al. *Int J Pediatr Otorhinolaryngol.* 2019 Apr. 119:96-102.

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments:

In the present era of vaccination skepticism by non-medical parent groups, Dr. Zhou's study is welcome news. Acute otitis media and recurrent otitis media cause missed days from school for children and work for parents, potential hearing issues, and frequent antibiotic use that has risk of emergence of resistant bacterial strains. Parents, pediatricians, and pediatric subspecialists will be excited to get this information.

Combo respiratory pathogen tests miss pertussis

BY M. ALEXANDER OTTO

MDedge News

BALTIMORE – Comprehensive respiratory pathogen panels (RPN) cannot be relied on to detect pertussis, according to an investigation from the University of Michigan, Ann Arbor.

Respiratory pathogen panels are popular because they test for many things at once, but providers have to know their limits, said lead investigator Colleen Mayhew, MD, a pediatric emergency medicine fellow at the University of Michigan.

“Should [the Respiratory Viruses Pathogen Panel] be used to diagnosis pertussis? No,” she said at the Pediatric Academic Societies annual meeting. RPN was negative for confirmed pertussis 44% of the time in the study.

“In our cohort, [it] was no better than a coin flip for detecting pertussis,” she said. Also, even when it missed pertussis, it still detected other pathogens, which raises the risk that symptoms might be attributed to a different infection. “This has serious public health implications.”

“The bottom line is, if you are concerned about pertussis, it’s important to use a dedicated pertussis PCR [polymerase chain reaction]

assay, and to use comprehensive respiratory pathogen testing only if there are other, specific targets that will change your clinical management,” such as mycoplasma or the flu, Dr. Mayhew said.

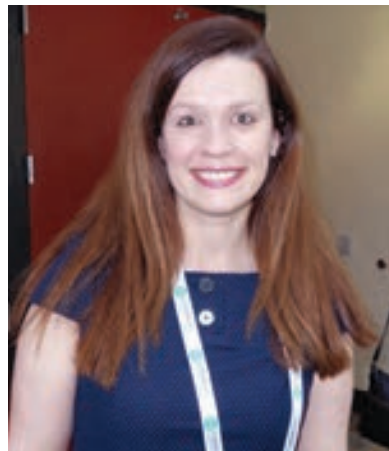
In the study, 102 nasopharyngeal swabs positive for pertussis on standalone PCR testing – the university uses an assay from Focus Diagnostics – were thawed and tested with RPN.

RPN was negative for pertussis on 45 swabs (44%). “These are the potential missed pertussis cases if RPN is used alone,” Dr. Mayhew said. RPN detected other pathogens, such as coronavirus, about half the time, whether or not it tested positive for pertussis. “Those additional pathogens might represent coinfection, but might also represent asymptomatic carriage.” It’s impossible to differentiate between the two, she noted.

In short, “neither positive testing for other respiratory pathogens, nor negative testing for pertussis by RPN, is reliable for excluding the diagnosis of pertussis. Dedicated pertussis PCR testing should be used for diagnosis,” she and her team concluded.

RPN also is a PCR test, but with a different, perhaps less robust, genetic target.

The 102 positive swabs were from patients



Dr. Colleen Mayhew

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Swabbing the nose to screen for infectious etiologies of respiratory infections such as pertussis, mycoplasma, respiratory syncytial virus, etc. is expensive but can be extremely helpful for specific populations at risk, such as immunocompromised patients, for example. I appreciate the information that using a panel to confirm pertussis may be inaccurate. Microbiology lab directors may block certain “extra tests” so we need more research on this topic to review sensitivity and specificity for different age groups tested.

aged 1 month to 73 years, so “it’s important for all of us to keep pertussis on our differential diagnose” no matter how old patients are, Dr. Mayhew said.

Freezing and thawing the swabs shouldn’t have degraded the genetic material, but it might have; that was one of the limits of the study.

The team hopes to run a quality improvement project to encourage the use of standalone pertussis PCR in Ann Arbor. It might save money, because the tests cost the university around \$400 each, instead of \$700 for RPN.

There was no industry funding. Dr. Mayhew didn’t report any disclosures.

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Role of mucin further delineated in CF pathogenesis

BY CALEB RANS

MDedge News

Mucin in children with cystic fibrosis precedes airway changes and infections, according to a cross-sectional cohort study.

It has been difficult for researchers to pinpoint the mechanisms that initiate lung disease in people with CF, because it is challenging to study young people with the disease and “CF animal models often fail to recapitulate aspects of human CF disease and yield disparate findings,” wrote Charles R. Esther Jr., MD, of the division of pediatric pulmonology at the University of North Carolina at Chapel Hill and his colleagues in Science Translational Medicine.

They studied 46 clinically stable young children (aged 3.3 years, plus or minus 1.7 years) with CF and 16 age-matched controls who did not have CF, but had respiratory symptoms (aged 3.2 years, plus or minus 2.0 years) using chest CT imaging and bronchoalveolar lavage fluid. BALF samples in CF patients were collected

over 62 study visits and subsequently cultured for detection and quantification of pathogens. The children with CF were enrolled in the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) program.

“We analyzed the relationships between airway mucus, inflammation,

“Elevated total mucin concentrations and inflammatory markers were observed in children with CF despite a low incidence of pathogens identified by culture or molecular microbiology.”

and bacterial culture/microbiome,” the researchers wrote. BALF total mucin levels were higher in CF samples versus non-CF controls. In addition, Dr. Esther and his colleagues found that these results were the same regardless of infection status and that increased densities of mucus flakes were also seen in samples from the CF patients.

“Elevated total mucin concentrations and inflammatory markers were observed in children with CF despite a low incidence of pathogens identified by culture or molecular microbiology. This muco-inflammatory state also characterized our CF population with the earliest lung disease in the setting of little or no pathogen infection,” they wrote.

Based on the findings, the investigators postulated that the airways of children with CF may show distinct defects in the clearance of recently created mucins, which could contribute to early CF lung disease.

A key limitation of the study was the prophylactic use of intermittent antibiotics. As a result, bacterial infection could have contributed to the development of early CF lung disease. “Agents designed to remove permanent mucus covering airway surfaces of young children with CF appear to be rational strategies to prevent bacterial infection and disease progression,” they concluded.

The study was supported by the National Heart, Lung, and Blood

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: We have known for a long time that even healthy cystic fibrosis infants have inflammation in their lungs. More basic science research in mucin clearance is needed.



Institute; the North Carolina Translational and Clinical Sciences Institute; the National Health and Medical Research Council; and the Cystic Fibrosis Foundation. Two coauthors reported financial affiliations with Parion Sciences.

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SOURCE: Esther CR et al. Sci Transl Med. 2019 Apr 3. doi: 10.1126/scitranslmed.aav3488.

Maternal immunization protects infants from RSV

BY BRUCE JANCIN

MDedge News

LJUBLJANA, SLOVENIA – Passive protection of infants from severe respiratory syncytial virus lower respiratory tract infection during the first 6 months of life has convincingly been achieved through maternal immunization using a novel nanoparticle vaccine in the landmark PREPARE trial.

“I think it’s important for everyone, especially people like myself who’ve been working on maternal immunization for about 20 years, to realize that this is a historic study,” Flor M. Munoz, MD, declared in reporting the study results at the annual meeting of the European Society for Paediatric Infectious Diseases.



Dr. Flor M. Munoz

“We have here for the first time a phase-3, global, randomized, placebo-controlled, observer-blinded clinical trial looking at an experimental vaccine in pregnant women for the protection of infants from a disease for which we really don’t have other potential solutions quite yet, and in a period of high vulnerability,” said Dr. Munoz, a pediatric infectious disease specialist at Baylor College of Medicine, Houston.

Indeed, respiratory syncytial virus (RSV) is the No. 2 cause of mortality worldwide during the first year of life. Moreover, most cases of severe RSV lower respiratory tract infection occur in otherwise healthy infants aged less than 5 months, when active immunization presents daunting challenges.

“While certainly mortality is uncommon in high-income countries, we do see significant hospitalization there due to severe RSV lower respiratory tract infection in the first year of life, sometimes more than other common diseases, like influenza,” she noted.

PREPARE included 4,636 women with low-risk pregnancies who were randomized 2:1 to a single intramuscular injection of the investigational RSV vaccine or placebo during gestational weeks 28-36, with efficacy assessed through the first 180 days of life. The study took place at 87 sites in 11 countries during 4 years worth of RSV seasons. Roughly half of participants were South African, one-quarter were in the United States, and the rest were drawn from nine other low-, middle-, or high-income countries in the Northern and Southern Hemispheres. The median gestational age at vaccination was 32 weeks.

The primary efficacy endpoint specified by the Food and Drug Administration – but not other regulatory agencies – was the placebo-subtracted rate of RSV lower respiratory tract infection as defined by RSV detected by reverse transcription polymerase chain reaction, along with at least one clinical manifestation of lower respiratory tract infection, oxygen saturation below 95%, and/or tachypnea. The risk of this outcome was reduced by 39% during the first 90 days of life and by 27% through 180 days in infants in the maternal immunization group, a difference which didn’t achieve statistical significance.

However, prespecified major secondary endpoints arguably of greater clinical relevance were consistently positive. Notably, maternal vaccination reduced infant hospitalization for RSV lower respiratory tract infection by 44% during the first 90 days of life, when levels of transplacentally transferred neutralizing antibodies against RSV A and B were highest, with events occurring in 57 of 2,765 evaluable infants in the active treatment arm and in 53 of 1,430 controls. Similarly, there was a 40% reduction through day 180. Moreover, rates of another key secondary endpoint – RSV lower respiratory tract infection plus severe hypoxemia with an oxygen saturation below 92% – were reduced by 48% and 42% through days 90 and 180, respectively. Thus, the vaccine’s protective effect was greatest against the most severe outcomes of RSV infection in infancy, according to Dr. Munoz.

No safety signals related to this immunization strategy were seen during 1 year of follow-up of infants and 6 months for the mothers. Side effects were essentially limited to mild, self-limited injection site reac-

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This is such an exciting trial! The risks of severe RSV infection, though, are often highest in extremely premature infants & premature infants with bronchopulmonary dysplasia (chronic lung disease of infancy) but in the trial, mothers got the placebo or the vaccine later in pregnancy. The vaccine would certainly help susceptible patient populations such as complex congenital heart disease infants born at term or close to term.



tions, with zero impact on pregnancy and delivery.

An intriguing finding in an exploratory analysis was that the vaccine appeared to have ancillary benefits beyond prevention of medically significant RSV disease in the young infants. For example, the rate of all lower respiratory tract infections with severe hypoxemia – with no requirement for demonstration of RSV infection – was reduced by 46% during the first 90 days of life in the immunized group. Similarly, the rate of all-cause lower respiratory tract infection resulting in hospitalization was reduced by 28%.

“This is actually quite interesting, because these are unexpected benefits in terms of all-cause effects,” the pediatrician commented, adding that she and her coinvestigators are delving into this phenomenon in order to gain better understanding.

Additional analyses of the recently completed PREPARE study are ongoing but already have yielded some important findings. For example, women immunized before 33 weeks’ gestation had significantly greater transplacental antibody transfer than those immunized later in pregnancy, with resultant markedly greater vaccine efficacy in their offspring as well: a placebo-subtracted 70% reduction in RSV lower respiratory tract infection with severe hypoxemia through 90 days, compared with a 44% reduction associated with immunization at gestational week 33 or later. And when the interval between immunization and delivery was at least 30 days, the risk of this endpoint was reduced by 65%; in contrast, there was no significant difference between vaccine and placebo groups when time from immunization to delivery was less than 30 days.

Also noteworthy was that maternal immunization afforded no infant protection in the United States. This unanticipated finding is still under investigation, although suspicion

centers around the fact that RSV seasons were generally milder there, and American women were vaccinated at a later gestational age, with a corresponding shorter interval to delivery.

The novel recombinant nanoparticle vaccine tested in PREPARE contains a nearly full-length RSV fusion protein produced in insect cells. The nanoparticles express both prefusion epitopes and epitopes common to pre- and postfusion conformations. Aluminum phosphate is employed as the adjuvant.

Novavax’s stock price has been kicked to the curb since the company earlier reported that a large phase 3 trial of the vaccine failed to meet its primary endpoint for prevention of RSV lower respiratory tract infection in older adults. Now the vaccine’s failure to meet its prespecified FDA-mandated primary endpoint in the maternal immunization study will doubtless spawn further financially dismissive headlines in the business press as well.

But pediatricians are famously advocates for children, and PREPARE received a warm welcome from the pediatric infectious disease community, regardless of investor response. Indeed, PREPARE was the only clinical trial deemed of sufficient import to be featured in the opening plenary session of ESPID 2019.

Ulrich Heininger, MD, professor of pediatrics at the University of Basel (Switzerland), who cochaired the session, jointly sponsored by ESPID and the Pediatric Infectious Diseases Society, declared, “These findings, I think, are a great step forward.”

Dr. Munoz reported receiving research grants from Janssen, the National Institutes of Health, the Centers for Disease Control and Prevention, and Novavax, which sponsored the PREPARE trial, assisted by an \$89 million grant from the Bill and Melinda Gates Foundation.

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Interaction of sleep and opioid use disorder is complex

BY KARI OAKES

MDedge News

MILWAUKEE – Individuals with chronic pain frequently have disrupted sleep and also may be at risk for opioid use disorder. However, even with advanced monitoring, it's not clear how sleep modulates pain and opioid cravings.

Sleep has an impact on positive and negative affect, but new research shows that the link between sleep and mood states that may contribute to opioid use disorder is not straightforward. At the scientific meeting of the American Pain Society, Patrick Finan, PhD, of Johns Hopkins University, Baltimore, discussed how sleep and mood affect cravings for opioids among those in treatment for opioid use disorder (OUD).

Affective function, mesolimbic system function, and pain modulation are all adversely affected by poor sleep, said Dr. Finan, who told attendees that one key question he and his colleagues were seeking to answer was whether those with OUD and chronic pain had more disturbed sleep than those with OUD alone. Also, the researchers wanted to know whether the ups and downs of sleep on a day-to-day basis were reflected in pain scores among those with OUD, as would be predicted by prevailing models.

Finally, two “proximal indicators” of relapse risk, affect, and heroin craving, might be affected by both sleep and pain, and Dr. Finan and collaborators sought to explore that association.

The work was part of a larger study looking at the natural history of OUD and OUD with comorbid chronic pain. To participate in this parent study, adults with OUD had to be seeking treatment or currently enrolled in methadone or buprenorphine maintenance treatment, and without current major depressive disorder. Also, patients could not have a history of significant mental illness, cognitive impairment, or a medical condition that would interfere with study participation. A total of 56 patients participated, and 20 of these individuals also had chronic pain.

Those with OUD and chronic pain qualified if they had pain (not related to opioid withdrawal) averaging above 3 on a 0-10 pain rating scale over the past week; additional criteria included pain for at least the

past 3 months, with 10 or more days per month of pain.

Pain ratings were captured via a smartphone app that prompted participants to enter a pain rating at three random times during each day. Each evening, patients also completed a sleep diary giving information about bedtime, sleep-onset latency, waking after sleep onset, and wake time for the preceding day.

A self-applied ambulatory electroencephalogram applied to the forehead was used for up to 7 con-

said, 58% of all patient-days had at least one momentary report of pain greater than zero. On average, participants recorded a pain score of 2.27.

Brief Pain Inventory scores at baseline showed a mean severity of 5, and a pain interference score of 5.07.

Participants with OUD and chronic pain did not differ across any EEG-recorded sleep measures, compared with those with OUD alone. However, subjective reports of sleep were actually better overall

those newly abstinent from cocaine, Dr. Finan said, adding that it's possible individuals with substance use disorder who are new to treatment simply feel better than they have in some time along many dimensions, with sleep being one such domain.

Pain on a given day didn't predict poor sleep on that night, except that sleep onset took slightly longer ($P = .01$), said Dr. Finan. He noted that “there was no substantive effect on other sleep continuity parameters.” Looking at how negative affect me-



MLADEN ZIVKOVIC/ISTOCK/GETTY IMAGES

secutive nights to capture sleep continuity estimates; the device has been validated against polysomnography data in other work. Participants were given incentives to use the device, and this “yielded strong adherence,” with an average of 5 nights of use per participant, Dr. Finan said.

Patients were an average age of about 49 years, and were 75% male. African American participants made up just over half of the cohort, and 43% were white. Participants were roughly evenly divided in the type of maintenance therapy they were taking. Overall, 39% of participants had a positive urine toxicology screen.

For patients with chronic pain, 45% of all momentary pain reports had a pain score over zero, with a mean of 32 days of pain. Looking at the data another way, Dr. Finan

for those with chronic pain than the objective EEG reports. The EEG recordings captured an average of 9.11 minutes more of waking after sleep onset (P less than .001). Also, total sleep time was 10.37 minutes shorter as recorded by the EEG than by self-report (P less than .001). Overall sleep efficiency was also worse by 5.96 minutes according to the EEG, compared with self-report (P less than .001).

“Sleep is objectively poor but subjectively ‘normal’ and variable in opioid use disorder patients,” Dr. Finan said. In aggregate, however, neither diary-based subjective nor EEG-based objective sleep measures differed between those with and without chronic pain in the research cohort. This phenomenon of sleep efficiency being self-reported as higher than objective measures capture sleep has also been seen in

diated craving for heroin, Dr. Finan and colleagues found that negative affect-related craving was significantly greater for those with chronic pain (P less than .001).

Unlike findings in patients without OUD, having disrupted sleep continuity was more associated with increased daily negative affect, rather than decreased positive affect. And this increased negative affect was associated with heroin cravings, said Dr. Finan. “In the past few years, we’ve seen quite a few studies that have found some abnormalities in the reward system in patients with chronic pain.” Whether poor sleep is a mediator of these abnormalities deserves further study.

The study was supported by the National Institutes of Health. Dr. Finan reported no outside sources of funding.

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Trial finds no link between CPAP and weight gain

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL CHEST®

Continuous positive airway pressure (CPAP) over several years did not lead to clinically concerning levels of weight gain among patients with obstructive sleep apnea and comorbid cardiovascular disease enrolled in a large international trial, findings from a large, multicenter trial show.

No differences in weight, body mass index, or other body measurements were found when comparing CPAP and control groups in a post hoc analysis of the Sleep Apnea Cardiovascular Endpoints (SAVE) trial, which included 2,483

adults enrolled at 89 centers in seven countries.

In a subanalysis, there was a small but statistically significant weight gain of less than 400 g in men who used CPAP at least 4 hours per night as compared to matched controls. However, there were no differences in BMI or neck and waist circumferences for these men, and no such changes were observed in women, according to the investigators, led by Qiong Ou, MD, of Guangdong (China) General Hospital and R. Doug McEvoy, MD, of the Adelaide Institute for Sleep Health at Flinders University, Adelaide, Australia.

“Such a small change in weight, even with good adherence over several years, is highly unlikely to have any serious clinical ramifications,” wrote the investigators of the study published in *Chest*.

“Taken together, these results indicate that long-term CPAP treatment is unlikely to exacerbate the problems of overweight and obesity that are common among patients with OSA,” they added.

In a previous meta-analysis of randomized trials, investigators con-

cluded that CPAP promoted significant increases in BMI and weight. However, the median study duration was only 3 months.

In contrast, the analysis of the SAVE trial included adults who had regular body measurements over a mean follow-up of nearly 4 years.

That long-term follow-up provided an “ideal opportunity” to assess whether CPAP treatment promotes weight gain in OSA patients over the course of several years, the authors of the SAVE trial analysis wrote.

For men in the SAVE trial, the difference in weight change for the CPAP group vs. the control group was just 0.07 kg (95% confidence interval, -0.40 to 0.54; $P = .773$) while in women, the difference for CPAP vs. controls was -0.14 kg (95% CI, -0.37 to 0.09; $P = .233$), the investigators reported.

Weight gain was significantly higher among men with good CPAP adherence, defined as use for at least 4 hours per night, investigators said, noting a mean difference of 0.38 kg (95% CI, 0.04-0.73; $P = .031$), though no other differences were found in body measurements for men, and no such associations were

found in women with good CPAP adherence.

It’s not exactly clear why this SAVE analysis would find no evidence of CPAP promoting weight gain over the long term, in contrast to the earlier meta-analysis of short-term studies finding a significant risk of weight gain.

However, it is possible that differences in study populations such as ethnicity, age, or comorbidities contributed to the differences, said investigators.

For example, results of regression analysis in the present study showed that, compared with recruitment in Australia, recruitment in China and India was significantly linked to weight loss, while recruitment in New Zealand was linked to weight gain.

Dr. Ou had no disclosures related to the study, while Dr. McEvoy reported disclosures related to Philips Respironics, ResMed, Fisher & Paykel, Air Liquide, and the National Health and Medical Research Council of Australia.

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SOURCE: Ou Q et al. *Chest*. 2019 Apr;155(4):720-9.



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Insomnia meds get boxed warning from FDA

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration will now require that certain medications prescribed for insomnia carry a boxed warning because of associated complex sleep behaviors.

These behaviors, including sleep walking, sleep driving, and engaging in other activities while not fully awake, are more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than they are with other prescription medicines used for sleep. Although these complex sleep behaviors are rare, they are potentially very dangerous. Boxed warnings are the FDA’s most prominent warning, but the agency will also require a contraindication – its strongest warning – to avoid use in patients who’ve previously experienced

these behaviors with any of these medications.

Complex sleep behaviors have been seen with these medications in patients with and without a history of them, at low doses, and even after one dose of the medication. They’ve also been observed with and without concomitant use of alcohol or other CNS depressants.

Health care professionals should advise patients about these risks, even though they are rare. Patients should contact health

care professionals if they either experience a complex sleep behavior while not fully awake on one of these medicines or have performed activities they don’t remember while taking the medicine.

More information about these risks and the safety warnings can be found in the FDA’s safety announcement. Other information is also available in a press announcement from the agency.

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Insomnia correlated with epilepsy seizure frequency

BY JAKE REMALY

MDedge News

PHILADELPHIA – Nearly a quarter of adults with epilepsy have moderate or severe insomnia, and insomnia symptoms are associated with depression, anxiety, worse seizure control, and poorer quality of life, according to a prospective analysis presented at the annual meeting of the American Academy of Neurology. Insomnia symptoms are not associated with epilepsy type, number of antiepileptic drugs (AEDs), or AED standardized dose, however.

“Given the potential benefits of sleep therapies on epilepsy outcomes, routine screening of insomnia symptoms is warranted,” said lead study author Thapanee Somboon, MD, a researcher at the sleep disorders center at Cleveland Clinic Neurological Institute and at Prasat Neurological Institute in Bangkok.

Insomnia is common and associated with depression in patients with epilepsy, but prior studies that looked at the relationship between insomnia and epilepsy-related characteristics yielded limited and conflicting results, according to Dr. Somboon.

To evaluate potential associations between insomnia and epilepsy, Dr. Somboon and colleagues conducted a prospective analysis of data from 270 patients with epilepsy who presented to the Cleveland Clinic Epi-



Dr. Thapanee Somboon

“Given the potential benefits of sleep therapies on epilepsy outcomes, routine screening of insomnia symptoms is warranted.”

lepsy Center for an initial evaluation between January and August 2018. The patients completed the Insomnia Severity Index (ISI). An ISI score of 8 or greater indicated clinical insomnia symptoms, and an ISI score of 15 or greater indicated moderate or severe insomnia symptoms.

The researchers used Spearman’s correlation and the Kruskal-Wallis test to evaluate associations among insomnia symptoms and AED standardized dose, monthly seizure frequency, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder Questionnaire (GAD-7), and Quality of Life in Epilepsy-10 (QOLIE10).

Among the 270 patients, the average age was 43.5 years, 58% were female, 74% had focal epilepsy, and 26% had one or more seizures per month. The population’s median ISI score was 7. Nearly half had an ISI score of 8 or greater, and 23% had an ISI score of 15 or greater.

“A positive correlation was found between ISI and PHQ-9 ($r = 0.64$, P less than .001), GAD-7 ($r = 0.68$, P less than .001), QOLIE ($r = 0.55$, P less than .001), and monthly seizure frequency ($r = 0.31$, P less than .001),” the researchers reported. Insomnia symptoms had a significantly stronger correlation with PHQ-9 and GAD-7 than with seizure frequency.

Dr. Somboon had no disclosures. A coinvestigator has received research support from Jazz Pharmaceuticals.

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SOURCE: Somboon T et al. AAN 2019, Abstract P3.6-026.

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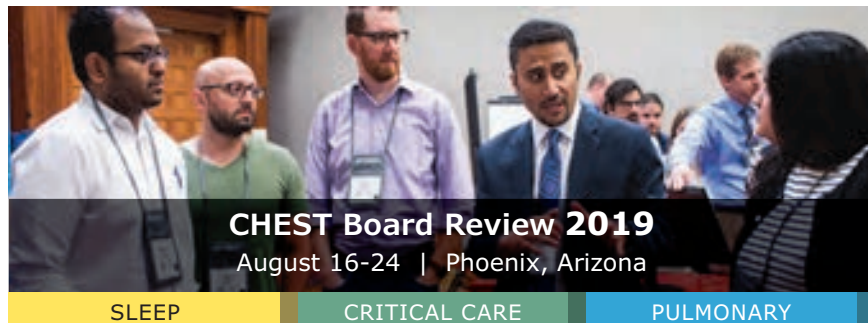
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Shared decision-making in action: Real data on biopsy risk and how to mitigate it

BY MATT ABOUDARA, MD,
FCCP

In a study highlighted in a recent issue of *CHEST Physician*, Hou and colleagues analyzed complications from biopsies of lung abnormalities seen on CT scans by conducting a large retrospective study with data gleaned from national databases of patients undergoing CT-guided biopsy, surgery, or bronchoscopy.¹ While it should not be interpreted as representative of a lung cancer screening population (for excellent comments by Drs. Rivera and Silvestri regarding the study, see: <https://tinyurl.com/y52ucb94>), it does raise two important questions when performing shared decision-making for low dose CT (LDCT) scanning: (1) What information should clinicians discuss with patients regarding various biopsy methods until more data are available? (2) How do we mitigate complications from biopsies?

While procedure-specific biopsy

risk may be generalizable, it may be institutionally specific, and knowledge of local skill and outcomes data can help guide discussions. With that said, some general information can inform decisions. The NAVIGATE study investigators recently published their 1-year follow-up results using a navigational bronchoscopy system (superDimension™). While inherent limitations to this study exist, it does provide some useful information as to procedure-related complications from a large sample of patients who approximate a lung cancer screening population. This group was composed of both academic and community centers and prospectively followed 1,215 patients for 1 year.² The average age of the population was 67.6 (± 11.3), and 80% were current or former smokers. The median nodule size was 2 cm. The diagnostic yield was 73% at 1 year follow-up (data will be re-analyzed at 2 years). The pneumothorax rate was 4%, with 3% requiring chest

tube. Hemorrhage occurred in 2.5% of all patients, with 1.5% having a common terminology criteria for adverse events (CTCAE) ≥ 2. Grade 4 respiratory failure occurred in 1 patient. There were no ENB procedure-related deaths. It should be noted that individuals performing these procedures were, by and large, high-volume and experienced users.

In comparison, the overall pooled sensitivity for CT scan-guided biopsy is 90% for pulmonary nodules and masses. The yield is lower, however, for smaller lesions (≤2.0) and ranges from 74% to 77%.³ The average pneumothorax rate is 20%, with 1% to 3% requiring chest tube placement. Risk factors for pneumothorax vary between studies, but, generally speaking, have been associated with nodules ≤ 2 cm, those within 2 cm of the pleura (but not abutting the pleura), and emphysema in the track of needle trajectory. Pulmonary hemorrhage occurs 30% of the time but is mild in most cases. Hemoptysis and severe hemorrhage occur at rates of 4% and <1%, respectively. Risk factors for development of pulmonary hemorrhage include small lesion size (< 2 cm) and lesions > 2 cm from the pleura.

When considering surgical lung biopsies and resection, recent data suggest every effort should be made to encourage smoking cessation in order to mitigate postoperative morbidity. In a retrospective study by Fukui and colleagues,⁴ respiratory morbidity (defined as hypoxia, pneumonia, atelectasis, and uncontrolled sputum production) was 22% in smokers vs 3.5% in never smokers. The rate of complications decreased as the time from smoking cessation to date of surgery increased.

The goal for each patient who is counseled should be to limit the number of procedures and achieve the greatest diagnostic confidence with the lowest complication rate. With these risks and diagnostic yield in mind, the decision to recommend a particular biopsy strategy (or no biopsy at all) should be based on current guideline recommendations: (1) patient co-morbidities and preferences; (2) size of index nodule or mass; (3) presence of pathologically enlarged mediastinal and/or hilar lymphadenopathy; (4) evidence of extrathoracic metastasis; and (5)

institutional expertise. Specifically speaking for the pulmonologist, this translates into identifying specific procedural “champions” who are dedicated to performing these procedures and are members of a multidisciplinary thoracic team. These individuals should have dedicated training in advanced diagnostic procedures to achieve the aforementioned goals.⁵ The same should hold true for transthoracic, CT-guided biopsies. Interventional pulmonology fellowships are structured to provide exposure to multidisciplinary nodule clinics and tumor boards, establishing quality improvement initiatives, as well as developing procedural expertise.⁶

It is apparent that shared decision-making can become complex. These details will likely be lost to a primary care provider simply due to time constraints and information overload. As such, pulmonologists should be at the forefront of lung cancer screening – in programmatic development, implementation, and providing education to providers directly involved with shared decision-making discussions.

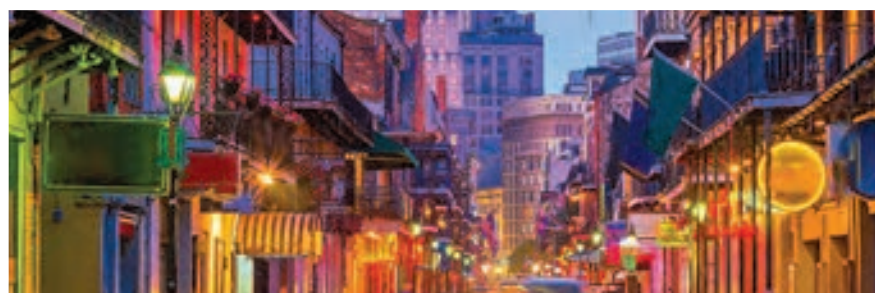
Dr. Aboudara is with the Division of Allergy, Pulmonary, and Critical Care; Vanderbilt University Medical Center; Nashville, Tennessee.

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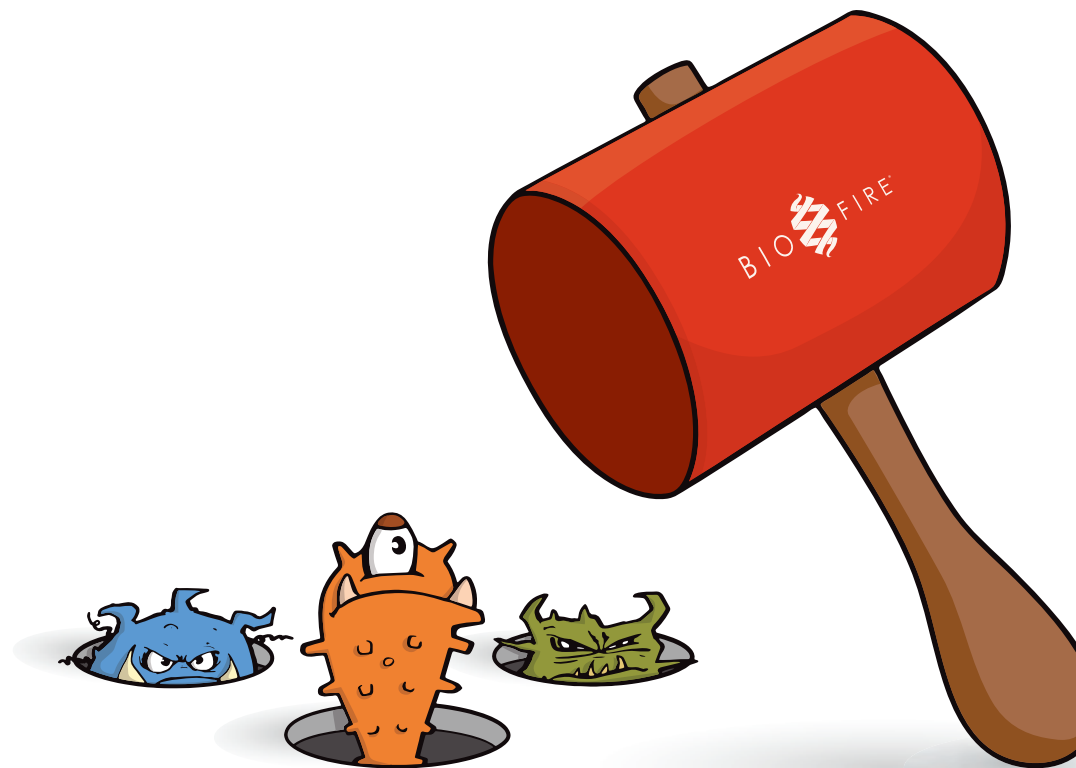
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Addressing current asthma management: What clinicians told us

A Medscape/CHEST Survey

BY MEGAN BROOKS

There are differences in how pulmonologists and other clinicians approach the diagnosis and management of patients with moderate to severe asthma, according to a survey conducted by Medscape in collaboration with CHEST, the American College of Chest Physicians. Despite some of these differences, those surveyed do predominantly favor similar treatment options, including inhaled corticosteroids and biologics. Biologics in particular are perceived as a promising therapeutic approach for moderate to severe asthma by clinicians overall, and many are also comfortable prescribing them.

Medscape and CHEST asked 763 clinicians about their views on moderate to severe asthma. Responses came from 100 pulmonologists; 102 allergists/immunologists; 102 critical care medicine physicians; 100 emergency medicine (EM) physicians; 104 pediatricians; 100 primary care physicians (PCPs); and 155 nurse practitioners (NPs), physician assistants (PAs), or registered nurses (RNs).

Inhaled steroids top treatment choice

Survey respondents ranked an inhaled corticosteroid with a long-acting bronchodilator as the favored medication for patients with moderate to severe asthma; 83% of allergists/immunologists feel this way, as do between 52% and 63% of the other clinicians, including pulmonologists.

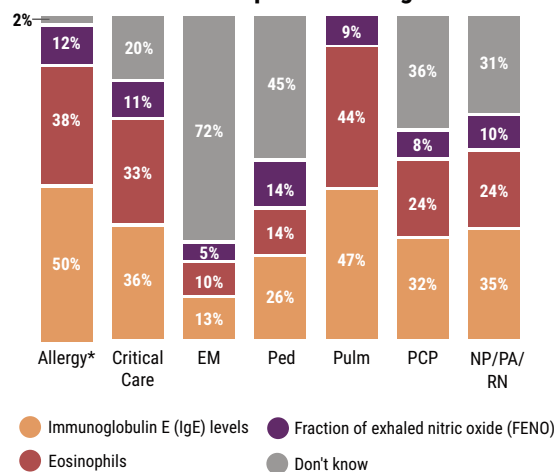
Inhaled corticosteroids alone are generally preferred by 23%-28% of clinicians surveyed, with the exception of allergists/immunologists (12%). EM physicians (19%) and pediatricians (16%) tend to more often favor an inhaled corticosteroid and leukotriene-modifying agent than do other clinicians, but notably, none of the allergists/immunologists felt this way.

Biologics are an important step forward

When it comes to biologic agents for moderate to severe asthma, it is allergists/immunologists (91%) who say they are most comfortable

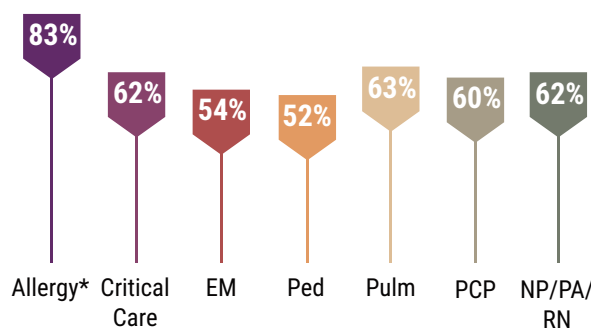
Medscape/CHEST Survey

Biomarkers for Moderate to Severe Asthma Considered Most Important Among Clinicians

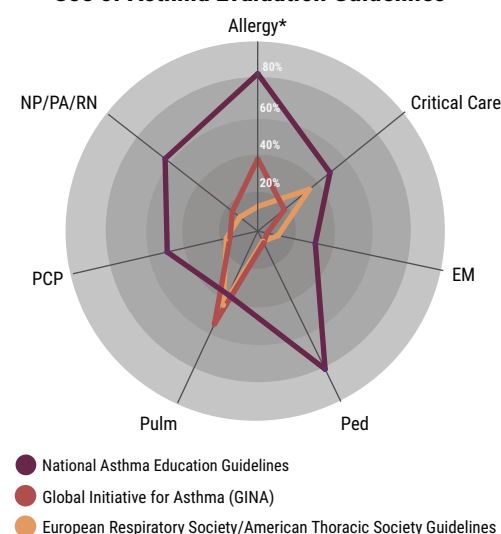


Inhaled Corticosteroid With Long-Acting Bronchodilator Favored as Treatment

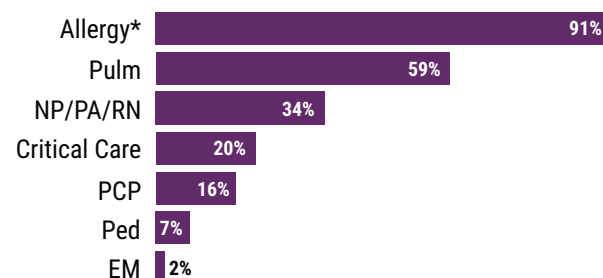
Percentage of Specialists Ranking This Medication As #1



Use of Asthma Evaluation Guidelines



Clinicians Comfortable With Prescribing Biologics



*Includes allergy and immunology

Source: Medscape/CHEST Survey of 763 clinicians; August 29 to October 11, 2018.

prescribing them. This percentage drops to 59% for pulmonologists, 34% for NP/PA/RNs, 20% for critical care medicine physicians, 16% for PCPs, 7% for pediatricians, and just 2% of EM physicians.

When it comes to biologic agents for moderate to severe asthma, it is allergists/immunologists (91%) who say they are most comfortable prescribing them. This percentage drops to 59% for pulmonologists, 34% for NP/PA/RNs, 20% for critical care medicine physicians, 16% for PCPs, 7% for pediatricians, and just 2% of EM physicians.

Aaron B. Holley, MD, FCCP, program director at the Pulmonary and Critical Care Medical Fellowship, Department of Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland, and a member of the Moderate to Severe Asthma Center of Excellence steering committee, noted that the latest

scientific papers, but remains difficult to operationalize in the clinic," said Holley.

He also noted that the new biologics all target one specific phenotype: eosinophilic asthma. "This phenotype makes up approximately 50% of all patients with asthma; however, the other 50% have no targeted

treatments available, and they don't necessarily respond well to conventional inhaler therapy," said Holley.

And for patients with severe, poorly responsive asthma, it's hard to say precisely what percentage is being treated inappropriately for their phenotype, versus what percentage is noncompliant, versus what percentage is due to socioeconomic status and behavioral health issues, he noted.

The solution? "There is no easy solution," said Holley. "More specialized, severe asthma clinics? Greater education on inhaler use and disease severity? Concomitant management of behavioral health complaints? All these are necessary, but they're also resource-intensive."

Still, in his view, the glass is half-full. "The biologics are an important step forward, and we're getting better at phenotyping. Compared with 5-10 years ago, we're in a much better place."

Preferred biomarkers

Familiarity with biomarkers for moderate or severe asthma is universal among pulmonologists. Only 2% of allergists/immunologists are not familiar with biomarkers, compared with nearly three quarters of EM physicians, 45% of pediatricians, 36% of PCPs, 31% of NP/PA/RNs, and 20% of critical care medicine physicians.

Immunoglobulin E (IgE) levels ranked as the most important biomarker for moderate or severe asthma, favored by 47% of pulmonologists and 50% of allergists/immunologists, followed by eosinophils, preferred by 44% of pulmonologists and 38% of allergists/immunolo-

gists. Between 26% and 36% of other clinicians rank IgE tops, except for EM physicians (13%). About one third of critical care medicine physicians and one quarter of PCPs and NP/PA/RNs think eosinophils are the most important biomarker, compared with only 14% of pediatricians and 10% of EM physicians.

Clinicians tend to see a lack of appropriate treatment as the greatest barrier for patients with moderate to severe asthma; 63% of pulmonologists feel this way, as do 60% of allergists/immunologists, 52% of PCPs, 50% of pediatricians, and 45% of NP/PA/RNs, compared with just 32% of EM and critical care medicine physicians.

Fraction of exhaled nitric oxide (FeNO) is least favored by all clinicians surveyed. Just 9% of pulmonologists, 12% of allergists/immunologists, and 5% of EM physicians like this biomarker. Pediatricians ranked FeNO the highest among those surveyed, but only at 14%.

Assessment tools and guidelines

One “interesting” finding is the difference between specialties in use of the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ), commented Holley. Most pulmonologists (57%) and allergists/immunologists (79%) favor ACTs for adults and children, whereas other clinicians seem to favor the ACQ.

Both the ACT and ACQ have decent literature to support their use, he noted. “I use the ACT, but personally, I don’t think it makes a difference which you use. I do think it’s important to get an objective score for their subjective symptoms to facilitate tracking over time, and to ensure that clinicians are speaking the same language. For example,

if someone else sees my patient for some reason, one look at the ACT score will summarize their disease control, as opposed to them having to pull it out of a running narrative history,” said Holley.

ACTs are also favored by 39% of NP/PA/RNs, 34% of pediatricians, 27% of PCPs, 16% of critical care medicine physicians, and just 6% of EM physicians. About one third of EM physicians and PCPs (34% each) favor the ACQ, as do 30% of NP/PA/RNs, 29% of pediatricians, 20% of pulmonologists, 17% of allergists/immunologists, and 8% of EM physicians.

Thirty-six percent of all clinicians said they don’t use any assessment

tool to gauge asthma control in patients with moderate to severe asthma, including 86% of EM physicians and 42% of PCPs – the specialties most apt to report no use.

As for guideline use, 83% of allergists/immunologists and 81% of pediatricians surveyed use the National Asthma Education and Prevention Program (NAEPP) guidelines. Pulmonologists tend to use these guidelines less often (37%), as they also rely on the Global Initiative for Asthma (GINA) (54%) and European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (43%).

About two thirds (62%) of NP/PA/RNs favor the NAEPP guidelines, as do 49% of PCPs and critical care medicine physicians and 31% of EM physicians. Sixty percent of EM physicians don’t use guidelines at all.

Chief culprits behind poor asthma control

Clinicians tend to see a lack of appropriate treatment as the greatest barrier for patients with moderate to severe asthma; 63% of pulmonologists feel this way, as do 60% of allergists/immunologists, 52% of PCPs, 50% of pediatricians, and 45% of NP/PA/RNs, compared with just 32% of EM and critical care medicine physicians. EM (67%) and critical care medicine (54%) physicians are also more apt to think that the patient not seeing a provider is the greatest barrier.

Overall, most clinicians surveyed

link poor asthma control to poor medication adherence and social or environmental risk irritants, such as smoking, secondhand smoke exposure, vaping, and pollutants.



‘We know from data that poor control is related to socioeconomic status and behavioral health.’

Dr. Holley

“No surprise here,” said Holley. “In my experience, medication adherence and environmental risks or irritants are big factors in patients with moderate to severe asthma who don’t respond to conventional, standard asthma treatment and continue to progress.”

“We know from data that poor control is related to socioeconomic status and behavioral health. We also know that proper inhaler use and compliance are a big problem. Does this account for most ‘progression’? That’s hard to say, I suppose, but certainly these are big factors,” Holley added.

Echoing Holley, Navitha Ramesh,

MD, clinical assistant professor of medicine at the Department of Clinical Sciences, Geisinger Commonwealth School of Medicine, Scranton, Pennsylvania, who is also a member of the Moderate to Severe Asthma Center of Excellence steering committee, said the biggest barriers to treatment, in her experience, are “poor health literacy, medication nonadherence, poor social support, and tobacco use.”

The survey was conducted August 29, 2018, to October 11, 2018. Pulmonologists were recruited from CHEST, and all other clinicians were recruited from Medscape members. Patients with moderate to severe asthma account for at least half of all patients with asthma seen by pulmonologists, allergists/immunologists, and critical care medicine physicians; this proportion falls to about 30% among pediatricians and PCPs. Of the clinicians surveyed, patients with moderate to severe asthma are overwhelmingly referred to pulmonologists. Among the reasons for referral are multiple emergency department visits, poor control, failure on first-line therapy, and confounding factors.

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Envisioning the future: The CHEST Environmental Scan

As a leader in education for pulmonary, critical care, and sleep medicine, staying ahead of trends in its professional fields and across educational delivery, in general, is critical to remaining relevant and to best serve the membership. The leadership of the American College of Chest Physicians (CHEST) developed a multifaceted program this year entitled, “CHEST Inspiration,” a series of programmatic initiatives aimed at stimulating and encouraging innovation within the association and recognizing individuals with great ideas that streamline current processes or disrupt ways of traditional thinking about everyday problems.

The CHEST Board of Regents recently completed one of the first components of the CHEST Inspiration program – the 2019 CHEST Environmental Scan. This article describes the development of the 2019 CHEST Environmental Scan and its fit with the other components of CHEST Inspiration program.

Environmental scanning is a formal process for tracking trends and occurrences in an organization’s internal and external environment that bear on its success—currently and in the future. The environmental scanning process examines both quantitative and qualitative factors and identifies a set of key environmental indicators believed to have the most important impact

on the organization’s work.

The 2019 CHEST Environmental Scan is a synthesis of work that took place in January 2019 at the CHEST Environmental Summit, a special joint session of the Board of Regents (BOR) and the CHEST Foundation Board of Trustees (BOT). In that session attendees attempted to free themselves from the usual

concentrated focus on the College and Foundation missions, goals, and strategies, recognizing that a possible (even likely) unintended conse-

quence of a narrow focus is losing sight of the outside world and the forces there that—like it or not—influence and could even disrupt the programs and strategies of CHEST and the CHEST Foundation.

To facilitate the process, CHEST engaged a market research and consulting agency with expertise in environmental scans and a client base of nonprofit organizations and associations. The consultant conducted secondary research organized around six drivers of change selected by CHEST leadership:

- Health Care
- Economy and Workforce
- Technology
- Education, Content Delivery, and Career Advancement
- Social, Political, Regulatory, and the Environment
- Philanthropy

The leadership had the opportunity to review the consultant’s research



findings prior to the Environmental Summit. Then, in the in-person BOT/BOR summit meeting, the consultant’s research findings were discussed and debated and were addressed with the following questions:

- How will this trend impact members? How will it change their work environment and what they need to know?
- How will this trend impact CHEST? What are the challenges and opportunities?
- What responses or actions should CHEST take?
- Does this insight require changes to our strategic plan?

The consultant synthesized the debates and discussions and prepared a draft document that shaped this year’s document.

The 2019 CHEST Environmental Scan, which will be updated periodically, will be used to:

- Inform members about external developments and put each in perspective
- Help leadership and staff determine future directions and program opportunities
- Keep the 5-year strategic plan fresh and relevant

The environmental scan will be explored in six monthly installments

in *CHEST Physician*, with each installment addressing one of the drivers of change. Most of the content is confirming rather than revolutionary in nature. Each installment will be accompanied by comments from one of four leading physician experts who will put the content into perspective.

The two other components of the CHEST Inspiration program are to engage a group of experts from outside the field of medicine and health care who are innovative and successful in their own professions. This focus group of professionals from outside of our association will be held in conjunction with the June Board of Regents meeting. An additional component to stimulate innovative thinking and celebrate great ideas will be a new competitive event at the annual meeting. Dubbed “CHEST FISH BOWL (Furthering Innovation and Science for Health),” this event will launch this month, with contestants submitting video applications that feature their great idea, and winners in select categories will be selected at CHEST 2019 in New Orleans. *CHEST Physician* will be your source for information about all the CHEST Inspiration programs through a new series of articles called “CHEST Inspiration: Pacing the Future.”

Are you up for the challenge? Dr. Salim Surani is!

Recently, the CHEST Foundation had the pleasure of sitting down with Salim Surani, MD, FCCP, to get his perspective on the NetWorks Challenge and its impact. Dr. Surani initially got involved with CHEST at the Board level and is now a leader within the Council of NetWorks. “My hope was that I could work within my NetWork to help them become more involved with CHEST and the CHEST Foundation. Through this involvement, I believe we can help shape changes in chest medicine practice dynamics. In the Practice Operations NetWork, we strive to educate physicians in practice to ensure they are up to date with government regulations and how to navigate changes in a positive way, ultimately with the goal of impacting our patients’ lives for the better.”

When asked about his involvement with CHEST and the Foundation, he said “It just

makes sense to be involved in an institution that is passionate about taking care of patients and clinicians. The CHEST Foundation has given tens of millions of dollars in funding for grants to help shape the future of education, the future of research, and the future of better patient care.”



Dr. Surani

that the biggest winner is the person who gives a gift. When you give something to the right cause, what you get in return is a tremendous amount

of satisfaction, and it is that satisfaction which drives you – which gives you a feeling of purpose. I want others to get involved and participate. If you feel passionate about something, put your money where your mouth is. This is why I will be matching any gift of \$500 or greater by 10% made to any NetWork during the NetWorks Challenge. This is an opportunity to multiply your donation before it goes to the CHEST Foundation so that grants and other awards can be larger in the coming years. The NetWorks Challenge helps fund our Diversity Travel Grants Program and provides additional travel grants to each participating NetWork.” Last year, Dr. Surani gave an additional \$2,365.17 through his challenge match. Are you up for the challenge this year?

Visit chestfoundation.org/donate today to help shape the future of our discipline!

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PULMONARY PERSPECTIVES®

Endobronchial valves for lung volume reduction: What can we offer patients with advanced emphysema?

BY CATHERINE L. OBERG, MD;
JASON A. BEATTIE, MD; AND
ERIK E. FOLCH, MD, MSC

The global burden of COPD is considerable. In the United States, it is the third most common cause of death and is associated with over \$50 billion in annual direct and indirect health-care expenditures (Guarascio AJ, et al. *Clinicoecon Outcomes Res.* 2013;5:235). For patients with severe emphysema with hyperinflation, dyspnea is often a quality of life (QOL)-limiting symptom (O'Donnell DE, et al. *Ann Am Thorac Soc.* 2017;14:S30). Few proven palliation options exist, particularly for patients with dyspnea refractory to smoking cessation, medical management with bronchodilators, and pulmonary rehabilitation. The recent Food and Drug Administration (FDA) approval of two endobronchial valves for lung volume reduction has established the increasing importance of bronchoscopy as a management tool in advanced COPD.

Why were these valves developed?

For decades, lung volume reduction has been investigated as a mechanical approach to counteract the physiologic effects of emphysematous hyperinflation. Its goal is to improve lung elastic recoil, respiratory muscle mechanical advantage and efficiency, and ventilation/

perfusion matching. The landmark National Emphysema Treatment Trial (NETT), published in 2001 and 2003, demonstrated that in a select patient population (upper lobe-predominant emphysema and low exercise capacity), lung volume reduction surgery (LVRS) lowers mortality and improves QOL and exercise tolerance (Fishman A, et al. *N Engl J Med.* 2003;348:2059). Despite the encouraging results in this study subpopulation, LVRS is performed infrequently (Decker MR, et al. *J Thorac Cardiovasc Surg.* 2014;148:2651). Concern about its morbidity and the specialized nature of the procedure has hindered widespread adoption. Subsequently, endobronchial techniques have been developed as an alternative to surgical lung volume reduction.

How does bronchoscopic lung volume reduction (BLVR) benefit patients with emphysema?

Valves used for ELVR are removable one-way flow devices placed by flexible bronchoscopy into select airways supplying emphysematous lung. The valves block air entry

but allow the exit of secretions and trapped air. This results in atelectasis of the targeted lobe and a decrease in lung volume.



Dr. Oberg



Dr. Beattie



Dr. Folch

Which endobronchial valves are available in the United States?

In 2018, two valves were approved by the FDA for bronchoscopic lung volume reduction (BLVR) – the Zephyr® EBV (Pulmonx) (Fig 1) and the Spiration® Valve System (Olympus) (IBV) (Fig 2). The Zephyr® EBV is a duckbill-shaped silicone valve mounted within a self-expanding nitinol (nickel titanium alloy) stent. It comes in three sizes for airways with a diameter 4 - 8.5 mm. The Spiration® IBV umbrella-shaped valve is composed of six nitinol struts surfaced with polyurethane. Its four sizes accommodate airway diameters 5 - 9 mm.

What's the evidence behind BLVR?

Zephyr® valves

The Endobronchial Valve for Emphysema Palliation Trial (VENT),

the largest valve trial thus far, randomized patients with severe heterogeneous emphysema to receive unilateral Zephyr® valve placement or standard medical care (Sciurba FC, et al. *N Engl J Med.* 2010;363:1233). Overall improvement in spirometry and dyspnea scores was modest in the valve group. Post-hoc analysis identified an important subgroup of patients with significant clinical benefit, those with a complete fissure. This finding gave guidance to further EBV studies on patients with severe emphysema and absent collateral ventilation (CV).

Identifying a complete fissure on imaging is now used as a surrogate for assessing CV and is an integral part of the initial profiling of patients for EBV therapy (Koster TD, et al. *Respiration.* 2016;92[3]:150).

In the STELVIO trial, 68 patients were randomized to Zephyr® EBV placement or standard medical care (Klooster K, et al. *N Engl J Med.* 2015;373:2325). Those with EBV placement had significantly improved lung function and exercise capacity. TRANSFORM, a multicenter trial evaluating Zephyr® EBV placement in heterogeneous emphysema, showed similar results (Kemp SV, et al. *Am J Respir Crit Care Med.* 2017;196:1535).

The IMPACT trial compared patients with homogenous emphysema without CV to standard medical therapy alone. It showed improve-

Continued on following page

Five traditional New Orleans dishes to try

What makes the traditional New Orleans food so special? The flair and broad history for these dishes unite the city and the love for all things tasty with its seafood, Creole, Cajun, and many other types of food options. We've picked five famous New Orleans dishes that you should try while you attend CHEST 2019.

Gumbo

As one of Louisiana's quintessential dishes, you can find gumbo in restaurants, at events, and homes all over the state. Claiming both French and West African roots, there's no one way to make gumbo, but it is usually served over rice and with a wide variety of other ingredients. With so many different recipes that each family and cook has perfected to be the "best," most cooks tend to guard their recipes closely.

Crawfish étouffée

The word étouffée (pronounced eh-too-fey) comes from the French word "to smother." This dish is a very thick stew full of crawfish (or shrimp) served over rice. It is also similar in some way to gumbo – same types of Creole seasonings, served over rice, and made with a roux – but it is often made with a "blonde" roux, which is lighter in color and gives an almost sweet flavor. It's a taste that's worth trying and claimed you won't forget.

Jambalaya

Another famous and traditional New Orleans dish is jambalaya. This is a rice dish that is a culinary staple of the city with a history from the time when colonial Spanish settlers tried reconstructing their native paella from locally sourced ingredients. It typically contains a mix of meat,

vegetables, spices, and rice, combined in a variety of ways.

Po-Boys

This classic French bread sandwich is stuffed and slathered with sauce. Filled with lettuce, tomato, and pickles, it's usually whatever filled with whatever meat you choose – roast beef, fried shrimp, oysters. This allows for many types of po-boy sandwiches. You tend to see very creative po-boys at the Oak Street Po-Boy Festival each year.

Beignets

These pastries are more than just a doughnut and are famous for being a doughnut without the hole. As the city's most popular sweet treat and staple, locals and visitors can enjoy beignets all year long, available 24-hours a day in New Orleans at more than one coffee hotspot.



Zephyr® valve

Continued from previous page

ment in FEV₁, QOL scores, and exercise tolerance in the EBV group. This study affirmed that the absence of CV, rather than the pattern of emphysema, correlates with the clinical benefit from EBV therapy (Valipour A, et al. *Am J Respir Crit Care Med*. 2016;194[9]:1073). Finally, LIBERATE, a multicenter study on the Zephyr® EBV, examined its placement in patients with heterogenous emphysema. This study demonstrated improvement in spirometry, QOL, and 6-minute walk test (6-MWT) distance (Criner GJ, et al. *Am J Respir Crit Care Med*. 2018;198:1151) over a longer period, 12 months, bolstering the findings of prior studies. These results prompted the Zephyr® valve's FDA approval.

Spiration® valves

Small trials have shown favorable results with the Spiration® IBV for BLVR, including a pilot multicenter cohort study of 30 patients with heterogeneous, upper-lobe emphysema who underwent valve placement (Wood DE, et al. *J Thorac Cardiovasc Surg*. 2007;133:65). In this trial, investigators found significant improvement in QOL scores, but no change in FEV₁ or other physiologic parameters.

The EMPROVE trial is a multicenter, prospective, randomized, controlled study assessing BLVR with the Spiration® IBV. Six- and twelve-month data from the trial were presented in 2018 at the American Thoracic Society Conference and at the European Respiratory Society International Conference.

Collateral ventilation

Identifying patients in whom there is no CV between lobes is critical to success with BLVR. Collateral ventilation allows air to bypass the valve occlusion distally, thereby negating the desired effect of valve placement, lobar atelectasis.

High-resolution computed tomography (HRCT) scanning combined with quantitative software can be used to assess emphysema distribution and fissure integrity. Additionally, a proprietary technology, the Chartis System®, can be employed intra-procedure to estimate CV by measuring airway flow, resistance, and pressure in targeted balloon-occluded segments. Absence of CV based on Chartis evaluation was an inclusion criterion in the aforementioned valve studies.

Which patients with emphysema should be referred for consideration of valve placement?

The following criteria should be used in selecting patients for referral for BLVR:

- FEV₁ 15% - 45% of predicted value at baseline
- Evidence of hyperinflation: TLC greater than or equal to 100% and RV greater than or equal to 175%
- Baseline postpulmonary rehabilitation 6-MWT distance of 100 - 500 meters
- Clinically stable on < 20 mg prednisone (or equivalent) daily
- Nonsmoking for at least 4 months
- Integrity of one or both major fissures at least 75%
- Ability to provide informed consent and to tolerate bronchoscopy

Complications

The most common complication after valve placement is pneumothorax – a double-edged sword in that it typically indicates the achievement of atelectasis. In published trials, the frequency of pneumothorax varies. Some studies document rates below 10%. Others report rates of nearly 30% (Gompelmann D, et al. *Respiration*. 2014;87:485). In landmark trials, death related to pneumothorax occurred rarely. Most severe pneumothoraces occur within the first 72 hours after valve placement. This has prompted many centers to observe postprocedure patients in hospital for



Spiration® valve

an extended period. Pneumonia and COPD exacerbations have also been reported after EBV placement. Therefore, in some trials, patients received prophylactic prednisolone and azithromycin. Other less common complications are hemoptysis, granulation tissue formation, and valve migration.

What's ahead for ELVR?

Overall, valve technology for BLVR is an exciting option in the management of patients with severe emphysema and is now a staple for any advanced emphysema program. Key areas of future interest include management of patients with partial

fissures, minimizing adverse procedural effects, and developing programs to optimize and streamline a multidisciplinary approach to timely and efficient referral, assessment, and intervention. As more patients with COPD undergo ELVR, one goal should be to create multi-institution prospective studies, as well as registries to delineate further the optimal use of endobronchial valves for lung volume reduction.

Zephyr® Endobronchial Valve (Pulmonx)

Spiration® Valve System (Olympus)



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CRITICAL CARE COMMENTARY

Not another burnout article

BY ROOZEHRA KHAN, DO, FCCP

Does this sound like your day?

You show up to work after a terrible night's sleep. Your back is tense, and you do some kind of walking/stretching combo as you walk through the doors. Your focus fades during the mind-numbing routine of the morning shift sign out. As the day moves forward, you begin to feel resentful as you sign orders, see patients, and address your ICU team needs. You know that's not right, that it's not in line with who you want to be, but the irritation doesn't go away.

Your lunchtime is filled with computer screens, notes, billing, and more billing. The previous feelings of irritation begin to boil into anger because more of your day is filled with bureaucratic demands and insurance reports rather than actually helping people. This isn't what you signed up for. Years and years of training so you could be a paper pusher? The thought leads to rage ... or sometimes apathy on days you give in to the inevitable.

You finish your shift with admissions, procedures, code blues, and an overwhelming and exhausting night shift sign out. You feel like a hamster in a wheel. You're going nowhere. What's the point of all of this? You find yourself questioning why you went into medicine anyways ... yeah, that's burnout.

I know what you're thinking. You keep hearing about this, and it's important to recognize, but then

you hear the same old solutions: be more positive, find balance, do some yoga, take this resilience module, be mindful (what on earth does this mean anyways?), get some more sleep. Basically, it's our problem. It's our burden. If all of these were easy to understand and implement, don't you think doctors and health-care providers would have done it already? I think you and I are a lot alike. These were my exact feelings. But stick with me on this one. I have a solution for you, albeit a little different. I'll show you a more "positive" spin on the DIY.

I burned out early. After fellowship, I didn't want to be a doctor anymore. I desperately sought to alter my career somehow. I looked into website development, something I had been good at in high school. I took a few refresher classes on my days off and started coding my own sites, but I had bills to pay. Big bills. Student loan bills. Luckily, my first job out of fellowship accepted many of my schedule demands, such as day shifts only, and after about a year, I recovered and remembered why I had loved medicine to begin with.

What is burnout?

Mind-body-soul exhaustion caused by excessive stress. Stress and burnout are closely related, but they're more like distant cousins. Stress can be (and is) a normal part of our jobs. I bet you think you're stressed, when you're probably burned out. Critical care doctors have the high-



Dr. Khan

est rate of burnout among all physician subspecialties at >55%, and it is even higher in pediatric critical care. (Sessler C. <https://www.mdedge.com/chestphysician/article/160951/society-news/turning-heat-icu-burnout>). The main difference between stress and burnout is hope. With stress, you still feel like things can get better and you can get it all under control. Burnout feels hopeless.

What are the three core symptoms of burnout?

- Irritability and impatience with patients (depersonalization)
- Cynicism and difficulty concentrating (emotional exhaustion)
- What's the point of all of this? Nothing I do matters or is appreciated (decreased self-efficacy)

We can talk about the symptoms of burnout all day, but what does that really look like? It looks like the day we described at the beginning. You know, the day that resonated with you and caused you to keep reading.

Why should we all be discussing this important topic?

Being burned out not only affects us on a soul level (achingly described above), but, more importantly, this can trickle down to our personal lives, family relationships, and how we care for our patients, with some studies showing that it affects our performance and, gulp, patient outcomes. That's scary (Moss M et al. *Crit Care Med*. 2016;44[7]:1414).

Causes of burnout

There are many causes of burnout, and several studies have identified risk factors. A lack of control, conflicts with colleagues and leadership, and performing menial tasks can add to the irritation of a workday. This doesn't even include the nature of our actual job as critical care doctors. We care for the sickest and are frequently involved in end-of-life care. Over time, the stress morphs into burnout. Female gender is also an independent risk factor for doctors (Pastores SM, et al. *Crit Care Med*. 2019;47[4]:550).

We've identified it. We've quantified it. But we're not fixing it. In fact, there are only a few studies that have incorporated a needs assessment of doctors, paired with appropriate environmental intervention. A study done with primary care doctors in New York City clinics found that surveying a doctor's "wish list" of interventions can help identify gaps in workflow, such as pairing one medical assistant with each attending (Linzer M, et al. *J Gen Intern Med*. 2015;30[8]:1105).

Without more data like these, we're hamsters in a wheel. Luckily, organizations like CHEST have joined together with others to create the Critical Care Societies Collaborative and have an annual summit to discuss research strategies.

Solutions

Even millennials are sick of the mindful "chore" list. Yoga pants, yoga mats, crystals, chakras, meditation, and the list goes on and on.



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What millennials want are work-life integrations that are easy; work-spaces that invite mindful behavior and daily rituals that excite and relax them. Co-working spaces like WeWork have designated self-care spaces.

Self-care is now essential, not an indulgence. I wasn't sure how to create this space in my ICU, so I started small, with things I could carry with myself. The key is to find small rituals with big meanings. What could this look like for you? I began doing breathwork. Frankly, the idea came to me from my Apple® watch. It just started giving me these reminders one day, and I decided to take it seriously. I found that my mind and muscles eased after only 1 minute of breathing in and out slowly. This elevated my mood and was the refresher I needed in the afternoons. My body ached less after procedures.

I also got a little woo-woo (stay with me now) and began carrying around crystal stones. You don't have to carry around crystals. Prayer

books, religious symbols, your child's toy car, anything can work if it has meaning for you, so when you see it or touch it during your day, you remember your big why. Why you're serving people. Why you're a doctor. I prefer the crystals over

Luckily, my first job out of fellowship accepted many of my schedule demands, such as day shifts only, and after about a year, I recovered and remembered why I had loved medicine to begin with.

jewelry because it's something unusual that I don't expect to be sitting in my pocket. It's always a nice gentle reminder of the love I have for my patients, my job, and humanity. When I put my hands in my pocket as I'm talking to yet another frustrated family member, my responses are more patient and more calm,

which leads to a more productive conversation.

Lastly, I started what I call a new Pavlov home routine. When I'm done with work, I light a candle and write out three things I'm grateful for. Retrain your brain. Retrain your triggers. What's your Pavlov's bell going to be? Many of us come home hungry and stressed. Food then becomes linked to stress. This is not good. Link it with something else. Light a candle, count to 3, then blow it out. Use your kids to incorporate something fun. Use a toy with "super powers" to "beam" the bad feelings away. Taking a few extra minutes to shift gears has created a much happier home for me.

There are things that we can't control. That's called circumstances. We can't control other people; we can't control the hospital system; we can't control our past. But the rest of everything we can control: our thoughts, feelings, and daily self-care rituals.

It reminds me of something my dad always said when I was a little

girl. When crossing the street, you always look twice, oftentimes thrice. Why be so careful? It's the pedestrian's right of way after all. "Well.." he replied, "If a car hits you, nothing much happens to them, but your entire life will be destroyed, forever."

Stop walking into traffic thinking everything will be okay. Take control of what you can.

Look, I get it. As health-care providers, we are an independent group. But just because you can do it alone, doesn't mean you have to.

Choose one thing. Whether it be something I mentioned or something that came to your mind as you read this. Then, drop me a line at my personal email at roozehra.khan.do@gmail.com. I will send you a reply to let you know I hear you and I'm in your corner.

Burnout happens.

But, so does joy, job satisfaction, and balance. Those things just take more effort.

Dr. Khan is Assistant Editor, Web and Multimedia, CHEST® journal.

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CHEST NETWORKS

Pulmonary medicine. Cardiovascular medicine and surgery. Chest infections. Interprofessional team.

Clinical Pulmonary Medicine Pulmonary embolism in pregnancy: A diagnostic conundrum

Pulmonary embolism (PE) is the 6th leading cause of maternal mortality in the United States. The clinical signs and symptoms of PE are usually nonspecific and often overlap with the normal physiologic changes of pregnancy. Due to low specificity and sensitivity of D-dimer test, pregnant patients with suspected PE often undergo CT pulmonary angiography (CTPA) and ventilation-perfusion scanning, both of which can cause radiation exposure to mother and fetus. To answer whether pregnancy-adapted YEARS



Dr. Adrish

algorithm (Van der Hulle T et al. *Lancet*. 2017;390[10091]:289) can be safely used to avoid diagnostic imaging, Artemis Study Investigators prospectively studied three criteria from YEARS algorithm in combination with a D-dimer level (Van der Pol et al. *N Engl J Med*. 2019;380[12]:1139). The three criteria included clinical signs of deep-vein thrombosis (DVT), hemoptysis, and PE as the most likely diagnosis. PE was considered ruled out when none of the three criteria were present and D-dimer was less than 1000 ng/mL or if one or more of the criteria were met and D-dimer was less than 500 ng/mL. Patients in whom D-dimer was greater than 1000 ng/mL or in those with D-dimer greater than 500 ng/mL and had one or more of the YEARS algorithm criteria present, PE could not be ruled out and underwent CTPA. A modification of the criteria was done only for patients

who had clinical signs of DVT at baseline. These patients underwent compression ultrasonography and, if a clot was found, CTPA was not performed, and patients were started on anticoagulation therapy. Those with negative DVT studies were subclassified based on D-di-

Due to low specificity and sensitivity of D-dimer test, pregnant patients with suspected PE often undergo CT pulmonary angiography and ventilation-perfusion scanning, both of which can cause radiation exposure to mother and fetus.

mer levels as the study population above. Patients in whom pulmonary embolism was not ruled out underwent CTPA. Of these 299 patients, 16 (5.4%) were confirmed to have PE at baseline. In the remaining 195 patients in whom PE was ruled out on the basis of study protocol, a 3-month follow-up diagnosed one patient (0.51%) with VTE. Using pregnancy-adapted YEARS algorithm, CTPA was avoided in 39% of the patients, of which 65% were in their first trimester when the radiation exposure can be most harmful to the fetus.

Muhammad Adrish, MD, FCCP
Steering Committee Member
Munish Luthra, MD, FCCP
Steering Committee Member

Cardiovascular Medicine and Surgery Physical examination of low cardiac output in the ICU

Rapid evaluation of shock requires identifying signs of tissue hypoperfusion and differentiating between cardiogenic, obstructive, hypovolemic, and vasodilatory etiologies. Cardiac abnormalities may also contribute to mixed shock states in a broad array of critically ill patients. Left ventricular dysfunction in inpatients correlates with physical exam, with a 2.0 positive likelihood ratio and 0.41 negative likelihood

ratio (Simel DL, Rennie D, eds. *The Rational Clinical Examination: Evidence-Based Clinical Diagnosis*. 2009). Accurate clinical assessment of cardiac output, however, is a fraught endeavor. In a recently published large series of patients with unplanned ICU admission, atrial fibrillation, systolic blood pressure (BP) < 90, altered consciousness, capillary refill time > 4.5 seconds at the sternum, or skin mottling over the knee predicted low cardiac output with specificity >90%. Of 280 patients with a cardiac index of < 2.2 L/min/m², less than half had any one of these findings (Hiemstra, et al. *Intensive Care Med*. 2019;45[2]:190).

Regarding determination of shock etiology, in a small series of patients with systolic blood pressure < 90 mm Hg, physical exam findings of relatively warm skin temperature and rapid capillary refill had 89% sensitivity for vasodilatory shock, and jugular venous pressure ≥8 had 82% sensitivity for cardiogenic etiologies (Vazquez, et al. *J Hosp Med*. 2010;5[8]:471). Thus, while physical exam findings may inform bedside shock assessment, their accuracy is limited. Critical care physicians should consider additional assessment techniques, such as echocardiography or invasive hemodynamic monitoring, if diagnostic uncertainty persists (Vincent, et al. *N Engl J Med*. 2013;369[18]:1726).

Benjamin Kenigsberg, MD
Steering Committee Member
Dr. David Bowton and Dr. Steven Hollenberg contributed to the article.



Dr. Kenigsberg

Chest Infections Lung infections in transplant recipients

The increase in lung transplantation over the years led to lung transplant recipients presenting to pulmonologists outside of specialized centers. One of the most common presentations is for infections. Infections account for more than 25% of all posttransplant deaths (Yusen, et al. *J Heart Lung*

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Transplant. 2014;33[10]:1009.

Multiple factors contribute to this increased infection risk, including donor lung colonization, disruption of local host defenses, constant contact with environmental pathogens, and heavy immunosuppression (Redmund KF, et al. *Proc Am Thorac Soc.* 2009;6[1]:94).

The onset of infectious manifestations, from the time of transplantation, is variable, depending on

Multiple factors contribute to this increased infection risk, including donor lung colonization, disruption of local host defenses, constant contact with environmental pathogens, and heavy immunosuppression.

the organism. Based on the time of onset, infections can be categorized into within the first month posttransplant, 1 to 6 months, and beyond 6 months, posttransplant. During the first month, because of allograft colonization, preexisting infections in the recipient, and surgical- and hospital-acquired nosocomial infections are more common. The first 6 months are where the patients are at the highest risk for opportunistic infections. As the immunosuppression is lowered after 6 months, the causative organisms tend to be more common pathogens (Green M. *Am J Transplant.* 2013;13[suppl 4]:3-8).

An early, aggressive, empiric antimicrobial therapy initiation

and proactive, invasive diagnostic approach with needed testing to identify the potential pathogen, is imperative in these patients. Early bronchoscopy with bronchoalveolar lavage remains the most sensitive test to identify pathogens. Therapy can then be tailored toward the identified pathogen.

As part of the Chest Infections NetWork, we would like to raise awareness of lung infections in unique subgroups, such as lung transplant recipients. Treating infections in such patients requires a high index of suspicion in the setting of an atypical presentation.

Raed Alalawi, MD, FCCP
Steering Committee Member



Dr. Alalawi

Interprofessional Team Extracorporeal membrane oxygenation (ECMO) in near fatal asthma

Near fatal asthma (NFA) is defined as acute severe asthma characterized by acute respiratory failure with hypercapnia and/or respiratory acidosis requiring ventilator support. NFA refractory to conventional medical management and ventilator therapy can lead to fatal outcomes. Near fatal asthma also carries substantial mortality if invasive ventilation is needed (Marquette CH, et al. *Am Rev Respir Dis.* 1992;146[1]:76). Use of sedatives can exacerbate bronchospasm, and positive pressure ventilation can exacerbate dynamic hyperinflation,

impairing hemodynamics, and gas exchange, and leading to barotrauma. This approach seems contrary to the goals of management. Outside of conventional therapies, such as IV steroids and inhaled beta-agonists, the data supporting other therapies such as IV beta-agonists, MgSO₄, methylxanthines, mucolytics, heliox, and volatile anesthetics are scant. In contrast, venovenous ECMO can provide adequate gas exchange and prevent lung injury induced by mechanical ventilation and may be an effective bridging strategy to avoid aggres-



Dr. Baeten

fully been described for obstructive airway disease (Langer T, et al. *Critical Care.* 2016;20[1]:150). Factors limiting this approach are the inva-



Dr. Luthra

sive nature of ECMO and the inherent risks of large cannula dislodgement; however, the safety of this has been demonstrated with ambulation of ECMO patients to receive phys-

ical therapy (Abrams D, et al. *Ann Cardiothorac Surg.* 2019;8[1]:44). Alternatively, extracorporeal carbon dioxide removal (ECCO₂R) systems utilize smaller catheters to satisfactorily remove CO₂ while oxygen

Performing “awake” ECMO has successfully been described for obstructive airway disease. Factors limiting this approach are the invasive nature of ECMO and the inherent risks of large cannula dislodgement; however, the safety of this has been demonstrated with ambulation of ECMO patients to receive physical therapy.

sive ventilation in refractory NFA (Hye Ju Yeo, et al. *Critical Care.* 2017;21[1]:297).

Use of early ECMO to permit spontaneous breathing while the circuit accomplishes required ventilation and oxygenation seems more ideal. Avoidance of mechanical ventilation not only prevents complications like barotrauma but also may reduce delirium, malnutrition, and neuromuscular dysfunction. Performing “awake” ECMO has success-

supplementation could be achieved via nasal cannula (Pisani L, et al. *Respiratory Care.* 2018;63[9]:1174). Incorporation of ECMO in select cases of NFA, especially ECCO₂R, should be considered as an early rather than rescue therapy for acute severe asthma refractory to conventional medical therapy.

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