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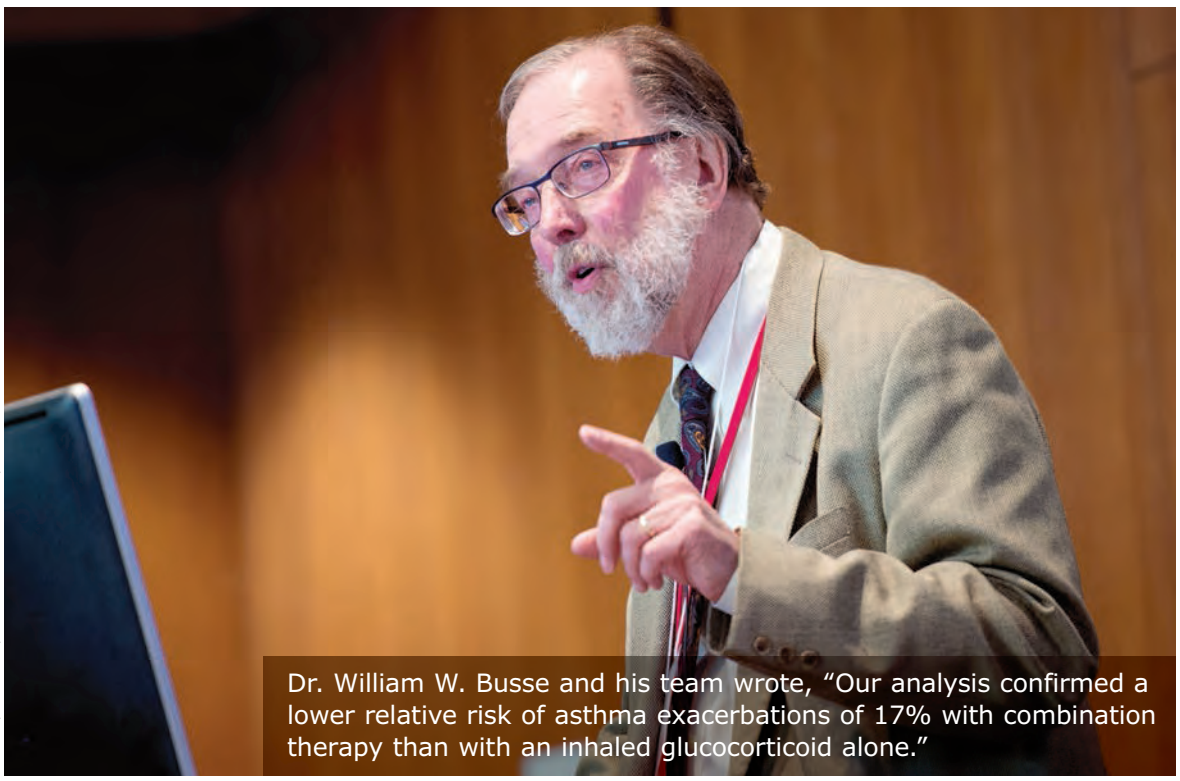

Courtesy University of Wisconsin Health System

Dr. William W. Busse and his team wrote, "Our analysis confirmed a lower relative risk of asthma exacerbations of 17% with combination therapy than with an inhaled glucocorticoid alone."

FDA walks back warning on LABA-containing asthma medications

BY MICHELE G. SULLIVAN
MDedge News

The combination a long-acting beta agonist (LABA) and an inhaled glucocorticoid decreases the risk of an asthma exacerbation by 17%, without increasing the risk of asthma-related intubation or death.

An independent analysis of four large, drug company–sponsored trials supports the Food and Drug Administration's recent decision to remove the black box warning on LABA/inhaled glucocorticoid products, wrote William W. Busse, MD, and his colleagues. The report was published in the New England Journal of Medicine.

"Our analysis confirmed a lower relative risk of asthma exacerbations of 17% with combination therapy than with an inhaled glucocorticoid alone. This finding corresponds to the lower relative rates of asthma exacerbations that were reported in the sponsored individual trials: by 21% in the GlaxoSmithKline trial [hazard ratio 0.79], by 16% in the AstraZeneca trial [HR. 0.84], and by 11% in the Merck trial [HR 0.89]," wrote Dr. Busse of the University of Wisconsin, Madison, and his coauthors.

The FDA based its December 2017 reversal on an initial review of the studies, which were reviewed by an independent committee and are now public. Dr. Busse led the expert analysis of

LABA // *continued on page 7*

Fluoroquinolones linked to fatal hypoglycemia, safety review finds

BY MICHELE G. SULLIVAN
MDedge News

Fluoroquinolones have caused at least 67 cases of life-threatening hypoglycemic coma, including 13 deaths and 9 permanent and disabling injuries, according to an internal safety review by the Food and Drug Administration. Most cases (44) were associated with levofloxacin.

The review also found new neuropsychiatric side effects associated with fluoroquinolones, including disturbances in attention, memory impairment, and delirium.

Considering these findings, the agency will strengthen warning labels on all fluoroquinolones, which already warn that the antibiotics may cause hypoglycemia and mental health issues, especially in older people, the FDA said in a press statement.

"Health care professionals should be aware of the potential risk of hypoglycemia, sometimes resulting in coma, occurring more frequently in the elderly and those with diabetes taking an oral hypoglycemic medicine or insulin," the statement said. "Alert patients of the symptoms

FLUOROQUINOLONE // *continued on page 13*

INSIDE HIGHLIGHT

CRITICAL CARE COMMENTARY

Balanced crystalloids vs saline for critically ill patients

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Medicare bundles didn't deliver expected cost savings

BY ANDREW D. BOWSER
MDedge News

Participation in Medicare's bundled payments initiative didn't significantly change payments per episode or care outcomes for the top five medical conditions selected under the program, a new analysis shows.

Payments for the common conditions (congestive heart failure, pneumonia, chronic obstructive pulmonary disease, sepsis, and acute myocardial infarction) remained around $24,000 per episode before and during participation in the Bundled Payments for Care Improvement (BPCI) initiative for the 125 participating hospitals evaluated in this study, conducted by Karen E. Joynt Maddox, MD, of Washington University, St. Louis, and her coauthors.

The finding contrasts with a pre-

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vious study showing that hospitals in BPCI successfully lowered overall Medicare payments for patients who underwent joint replacement.

"Bundling of services to encourage more efficient care has great face validity and enjoys bipartisan support," Dr. Joynt Maddox and her colleagues wrote. "For such bundling to work for medical conditions, however, more time, new care strategies and partnerships, or additional incentives may be required."

The Center for Medicare & Medicaid Innovation initiated the voluntary BPCI demonstration project in 2013. The program targets 48 conditions that account for about 70% of Medicare spending. Hospitals that achieve cost targets for a specific condition get to keep a portion of the savings, and they reimburse Medicare for part of the difference when costs are exceeded.

The present study focused on 2013-2015 Medicare claims for the five medical conditions that account for two-thirds of patients enrolled in medical bundles: congestive heart failure, pneumonia, chronic obstructive pulmonary disease, sepsis, and acute myocardial infarction.

Mean baseline payments per episode for those conditions were $24,280 before participation in the BPCI. After hospitals joined, their average payments per episode were $23,993 ($P$ = .41). For a set of matched control hospitals, payments were a mean of $23,901 at baseline and $23,503 in the corresponding follow-up period (P = .08).

That amounted to a $286 payment reduction for BPCI hospitals and a $398 reduction for controls, a difference of $112 ($P$ = .79), the study investigators reported.

Changes in length of stay, readmissions, emergency department use, and clinical complexity of cases from baseline to follow-up periods were not significantly different between BPCI and control hospitals. For example, 90-day mortality increases were seen in both groups, and the degree of increase was not statistically different between the groups. "Despite the importance of episode-based payment, there has been little research examining its efficacy or determining whether it has unintended consequences, such as hospitals' selecting patients with relatively less complex conditions to reduce costs and improve outcomes," Dr. Joynt Maddox and her colleagues cautioned.

It's unclear why the previous joint replacement study showed a successful reduction in costs under BPCI, while the new study did not. However, patients in the new analysis of the most common bundled conditions were older and had higher rates of poverty and disability.

"As a result of these complexities, patients admitted for medical conditions may have had post–acute care needs that were less amenable to intervention," Dr. Joynt Maddox said.

The investigators added that hospitals' lack of effective influence on post–acute care services may blunt their ability to achieve greater savings under BPCI. Better relationships with skilled nursing facilities, long-term care hospitals, home health agencies, and inpatient rehabilitation facilities could make a difference.

The Commonwealth Fund supported the study. One study author reported personal fees from the Department of Health & Human Services outside the submitted work, and another reported that he is an associate editor for the New England Journal of Medicine. No other disclosures were reported.

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SOURCE: Joynt Maddox KE et al. N Engl J Med. 2018 Jul 19;379(3):260-9.

New hypertension guidelines add 15.6 million diagnoses

BY ANDREW D. BOWSER

A new analysis estimates that adopting the 2017 American College of Cardiology/American Heart Association hypertension guidelines would add 15.6 million Americans to the ranks of the hypertensive patients, and half of those would be candidates for treatment.

Similar increases would occur in other countries, according to study authors, who analyzed two large datasets from the United States and China.

DR. KRUMHOLZ

That happened by resetting the definition of adult hypertension from the long-standing threshold of 140/90 mm Hg to a blood pressure at or above 130/80 mm Hg, meaning more than half of people aged 45-75 years in both countries would be classified as having hypertension, according to the researchers, led by Harlan M. Krumholz, MD, of the Center for Outcomes Research and Evaluation at Yale–New Haven (Conn.) Hospital and the section of cardiovascular medicine at Yale.

An additional 7.5 million Americans would be recommended for treatment under the new lower treatment thresholds, with a correspondingly large increase in the Chinese population, according to results published in the BMJ.

The guideline changes are "not firmly rooted in evidence" and could have health policy implications that include strain on public health programs, Dr. Krumholz and his colleagues wrote in their report on the study.

"The change occurs at a time when both countries have substantial numbers of people who are not aware of having hypertension, and who have hypertension that is not controlled, even according to the previous standards," they wrote.

The analysis by Dr. Krumholz and his colleagues was based on the two most recent cycles of the U.S. National Health and Nutrition Examination Survey (NHANES), representing 2013-2014 and 2015-2016 periods, as well as the China Health and Retirement Longitudinal Study (CHARLS) in 2011-2012.

Under the new ACC/AHA guidelines, they found, 70.1 million Americans aged 45-65 years would be classified as hypertensive, representing 63% of that age group. That's a 27% relative increase over the 55.3 million individuals, or 49.7%, with hypertension as defined in the JNC-8 guidelines. In addition, 15.6 million persons would be classified as eligible for treatment but not receiving it, up from 8.1 million under the JNC-8 guidance.

Previous estimates projected a far greater jump in new hypertension classifications, including one that used data from the National Health and Nutrition Examination Survey, antihypertensive clinical trials, and population-based cohort studies. That study estimated that 31 million people would newly carry the label (JAMA Cardiol. 2018 May 23. doi: 10.1001/jamacardio.2018.1240).

Dr. Krumholz noted that the ACC/AHA guideline changes were prompted by results from SPRINT. However, the improvements in outcomes seen in SPRINT, which included patients at high risk for cardiovascular events but without diabetes, have not been observed in individuals at low or intermediate risk, or in those with diabetes, they said.

"Expanding the pool of patients who merit treatment to include those at low risk could potentially render public health programs less efficient and viable," they wrote in a discussion of health policy implications.

Dr. Krumholz reported research agreements from Medtronic and from Johnson and Johnson (Janssen) through Yale University, and a grant from the Food and Drug Administration and Medtronic. He reported other disclosures related to UnitedHealth, the IBM Watson Health Life Sciences Board, Element Science, Aetna, and Hugo, a personal health information platform he founded. First author Rohan Khera, MD, reported support from the National Institutes of Health.

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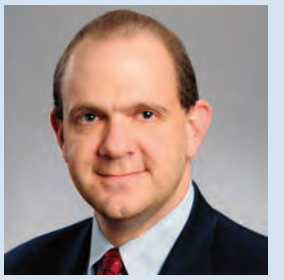
SOURCE: Khera R et al. BMJ. 2018 Jul 11;362:k2357.



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FDA expedited approvals can lack top-notch evidence

BY MICHELE G. SULLIVAN
MDedge News

About half of the drugs approved under the Food and Drug Administrations's Breakthrough Therapy designation have lacked the gold-standard evidence of a double-blind, randomized, placebo-controlled trial, according to a new JAMA report.

"This study of all FDA approvals granted Breakthrough Therapy designation from 2012 through 2017 suggests that pivotal trials supporting these approvals commonly lacked randomization, double-blinding, and control groups, used surrogate markers as primary end points, and enrolled small numbers of patients," wrote Jeremy Puthumana and his coauthors. "Furthermore, more than half were based on a single, pivotal trial."

The average premarket development time was about 5 years, but regulatory review of these agents took less than 7 months on average, the report found.

Mr. Puthumana, of Yale University, New Haven, Conn., and his coauthors, reviewed all 46 of the drugs and biologics approved by the FDA from 2012 to 2017 under the designation. The Breakthrough Therapy designation allows for the rapid review of drugs and biologics for serious or life-threatening conditions where there is preliminary evidence demonstrating a substantial improvement over existing therapies. The researchers identified all pivotal trials supporting approval, looking at randomization, blinding, comparator group, primary endpoint, and patient numbers.

Of these drugs, most (25) were oncologic agents; other indications were infectious disease (8), genetic or metabolic disorders (5), and other unspecified purposes (8). The median number of patients enrolled among all pivotal trials supporting an indication approval was 222.

Most of the approvals (27) were based on randomized trials, 21 (45.7%) were based on double-blind randomization, 25 (54.3%) employed an active or placebo comparator group, and 10 (21.7%) used a clinical primary endpoint.

Compared with drugs without accelerated approval, drugs with accelerated approval status were less likely to be examined in randomized or double-blinded trials (24 vs. 3 and 20 vs. 1, respectively), and were less likely to include a control group (32 vs. 3).

All drugs with Accelerated Approval status underwent at least one clinical safety or efficacy-focused postmarketing requirement, as did 64.3% of those without that status.

Mr. Puthumana reported having no financial disclosures.

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SOURCE: Puthumana J et al. JAMA. 2018;320(3):301-3.

VIEW ON THE NEWS

Some approvals are worth the risks

"The idea that doing something more quickly means it is not done as well has considerable face validity," Austin B. Frakt, PhD, wrote in an accompanying editorial. Nevertheless, at least one study suggests that expedited FDA approvals do confer substantial gains in quality of life. "However, drugs subject to less FDA scrutiny are more likely to exhibit safety problems, be withdrawn from the market, or carry black box warnings. ...Because expedited review programs are intended for drugs that treat serious conditions and address unmet medical needs, accepting greater risk may be reasonable and more consistent with patients' preferences," he said.

Dr. Frakt is director of the Partnered Evidence-Based Policy Resource Center at the Boston Veterans Affairs Healthcare System. His remarks are adapted from an accompanying editorial (JAMA. 2018;320[3]:225-6).

Independent analysis confirms industry trial findings

// *continued from page 1*

the studies, which the FDA required after it put the black box warning on the combination products.

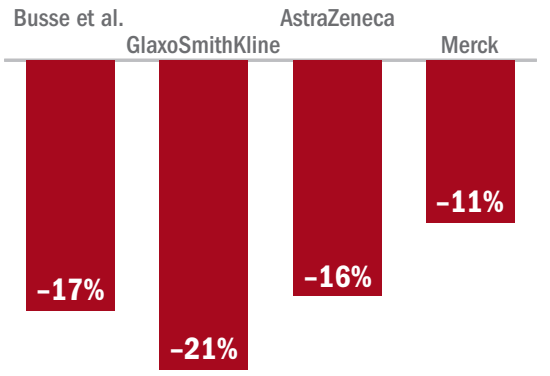
In 2010, the FDA advised that LABAs shouldn't be used as first-line therapy for asthma and required a black box warning on all LABA-containing products. Despite an FDA-conducted meta-analysis that found no increase in serious asthma-related incidents, the agency said there wasn't enough subgroup evidence to support the safety of LABAs when combined with an inhaled glucocorticoid.

"FDA stated that the small numbers of patients who were enrolled in these studies prevented a definitive conclusion regarding mitigation of serious asthma-related events with the addition of inhaled glucocorticoids," the investigators stated.

The agency required the four companies marketing a LABA for asthma to conduct prospective randomized trials comparing the safety of LABA/inhaled glucocorticoid to inhaled glucocorticoid alone. The trials by AstraZeneca, GlaxoSmithKline, Merck, and Novartis were identical. Three had complete, 26-week data; Novartis submitted partial data, as it withdrew its product from the American market in 2015. The committee reviewed all of the studies, which comprised a total of 36,010 teens and adults (aged 12-91 years). The primary endpoint was a composite of asthma-related intubation or death; secondary endpoints were a composite of hospitalization, intubation, or death, and individual assessments of each of those events.

Decreased risk of asthma exacerbation

LABA/inhaled glucocorticoid vs. glucocorticoid alone



MDedge News

Note: Busse et al. based on data for 36,010 teens and adults from the three studies shown plus a Novartis trial.

Source: N Engl J Med. 2018;78:2497-505

Among the four studies, there were three asthma-related intubations: two in the inhaled-glucocorticoid group and one in the combination-therapy group. There were also two asthma-related deaths, both in the combination group.

Serious asthma-related events occurred in 108 of the inhaled glucocorticoid group (0.60%) and in 119 of the combination-therapy group (0.66%), a nonsignificant difference.

However, the combination therapy did confer a significant 17% reduction in asthma exacerbations. Exacerbations occurred in 11.7% of the inhaled glucocorticoid group and in 9.8% of the combination therapy group (relative risk 0.83; *P* less than 0.001). All four trials showed a similarly decreased risk of exacerbation.

The committee looked at several subgroups, dividing the cohort by age, race/ethnicity/ obesity, and smoking history. The advantage associated with combination therapy remained significant in all these analyses.

"… Our data provide support for the treatment guidelines of both the Global Initiative for Asthma and the Expert Panel Report 3 of the National Asthma Education and Prevention Program, which recommend the use of a low-dose glucocorticoid (step 3) and a medium-dose glucocorticoid (step 4), plus a LABA, with the caution that LABAs should not be used as monotherapy in asthma; the convenience and safety of a combination inhaler is a likely plus," the committee wrote. "Finally, our combined analysis provides strong evidence to support the recent FDA decision to remove the boxed safety warning for combination therapy with a LABA plus an inhaled glucocorticoid for asthma treatment."

Dr. Busse disclosed financial relationships with a number of pharmaceutical companies, including Novartis, but noted that none of them were relevant to this work.

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SOURCE: Busse WW et al. N Engl J Med. 2018;78:2497-505.

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Project aims to identify and categorize pulmonary hypertension phenotypes

BY DOUG BRUNK
MDedge News

SAN DIEGO – A massive effort to better understand and treat patients with pulmonary hypertension and right heart dysfunction is underway.

The endeavor, funded by the National Heart, Lung, and Blood Institute and the Pulmonary Hypertension Association and known as Redefining Pulmonary Hypertension Through Pulmonary Vascular Disease Phenomics (PVDOMICS), began recruiting participants in 2017, with a goal of 1,500 by 2019. The aim is to perform comprehensive phenotyping and endophenotyping across the World Health Organization–classified pulmonary hypertension (PH) clinical groups 1 through 5 in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with pulmonary vascular disease.

At an international conference of the American Thoracic Society, one of the study's investigators, Robert P. Frantz, MD, discussed the role of echocardiography and MRI in the overall PVDOMICS program, which he characterized as a work in progress. "Imaging is critically important as we try to integrate severity of pulmonary vascular disease along with how well the ventricle functions as way to try and understand why some patients have a failing RV [right ventricle] at a given pulmonary resistance and others don't," said Dr. Frantz, who directs the Mayo Pulmonary Hypertension Clinic in Rochester, Minn. The goals are to be able to integrate cardiac morphology and function with contemporaneous hemodynamics, he said. This will allow for validation of noninvasive hemodynamics versus right heart catheterization across all the phenotypes.

"In addition, we'll have imaging parameters as predictors of hemodynamics at rest and with exercise, particularly in conditions like heart failure with preserved ejection fraction or concerns about left atrial stiffness," he said. "In these cases, our ability on the basis of echocardiography or MRI to guess what the wedge pressure is at rest or exercise, or to think about other more recently described phenotypes like left atrial stiffness in patients who have left atrial ablation procedures, will be enabled by looking at parameters such as left atrial strain."

Ultimately, he continued, a key goal of PVDOMICS is to be able to correlate the "-omics" with markers of RV compensation in an effort to understand what the determinants of RV compensation are across the varying types of pulmonary vascular disease.

To illustrate how this research might lead to new therapies, Dr. Frantz cited findings from researchers who set out to identify and characterize homogeneous phenotypes by a cluster analysis in scleroderma patients with pulmonary hypertension, who were identified from two prospective cohorts in the United States and France (PLoS ONE. 2018 May 15;13[5]:e0197112).

The researchers identified four different clusters of scleroderma patients: those with mild to moderate PH with no or minimal interstitial lung disease and low diffusing capacity for carbon monoxide; those with precapillary PH with severe ILD and worse survival; those with severe PH, who trended toward worse survival, and those similar to the first cluster but with higher DLCO.

Other parameters that can be analyzed include ventricular fractional area change, tricuspid annular plane systolic excursion, and RV free wall strain. "That strain of the right ventricle is one of the most important ways of looking at how the right ventricle works," Dr. Frantz said. "With this, we can integrate the concept of severity of RV dysfunction with severity of pulmonary vascular disease. This is where the rubber hits the road. It's going to be very complicated and time consuming, but I think critically important. Ultimately, we can make proteomic heat maps that track these correlates, and ultimately identify pathways that may be driving RV compensation in pulmonary vascular disease."

Dr. Frantz reported having no relevant financial disclosures.

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Alert highlights potential neuropsychiatric side effects

// *continued from page 1*

of hypoglycemia and carefully monitor blood glucose levels in these patients and discuss with them how to treat themselves if they have symptoms of hypoglycemia. Inform patients about the risk of psychiatric adverse reactions that can occur after just one dose. Stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, including psychiatric adverse reactions, or blood glucose disturbances and switch to a non–fluoroquinolone antibiotic if possible. Stop fluoroquinolone treatment immediately if a patient reports serious side effects involving the tendons, muscles, joints, or nerves, and switch to a non–fluoroquinolone antibiotic to complete the patient's treatment course."

The statement also warned not to prescribe fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections because the risks outweigh the benefits in these patients.

The FDA conducted the postmarketing review on all five of the fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin). The newest fluoroquinolone, delafloxacin, approved a year ago, was not included in the class review. However, the agency expects that similar adverse events will be associated with delafloxacin and labeling on that drug will include the new warnings.

The agency reviewed cases in the FDA Adverse Event Reporting System, and in published medical literature, during 1987-2017. Most of the incidents (56) were in the system; 11 additional cases were published. Levofloxacin caused most of the incidents (44), followed by ciprofloxacin (12), moxifloxacin (9), and ofloxacin (2). Four of the fluoroquinolones have a labeled drug interaction with sulfonylurea agents, which can cause hypoglycemia.

Some of those who died were getting the antibiotics for complicated infections, including urinary tract and upper respiratory tract infections, and postoperative antibiotic prophylaxis. Others had renal insufficiency – a risk factor for hypoglycemia.

Of the 54 patients who survived, 9 never fully recovered and had permanent disabilities. Four patients remained in a coma for at least 1 month, despite blood sugar normalization. Five experienced some type of neurologic injury.

The new label changes will also fortify the existing warning about mental health side effects, after the review found new reactions that are not listed in the current warning, including the new reports of disturbance in attention, memory impairment, and delirium.

The statement warned physicians not to prescribe fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

"In an effort to harmonize the psychiatric adverse reactions described in the drug labels across the class of fluoroquinolones, we are requiring that all fluoroquinolones include six psychiatric adverse reactions (disturbance in attention, memory impairment, delirium, nervousness, agitation, and disorientation) in the Central Nervous System Effects of the Warnings and Precautions section of the labels. Disturbance in attention, memory impairment, and delirium are new adverse reactions to be added to the labels of the entire class of fluoroquinolones. Nervousness, agitation, and disorientation had been previously listed in the fluoroquinolone drug labels and will now be added to the Warnings and Precautions section of each drug label to harmonize labels across the fluoroquinolone drug class."

The FDA has previously warned about other adverse events associated with fluoroquinolones in May 2016, restricting use for certain uncomplicated infections; July 2016, for disabling side effects; August 2013, for peripheral neuropathy; and July 2008, for tendinitis and tendon rupture.

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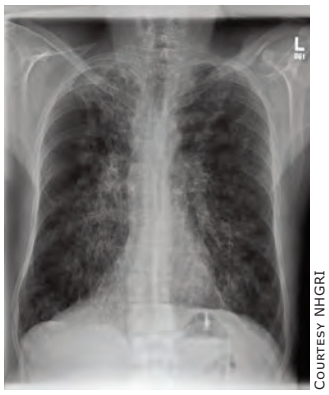
Delayed CF diagnosis portends worse prognosis

BY BIANCA NOGRADY
MDedge News

Older age at diagnosis, diabetes, and poorer lung function are all predictors of reduced survival among adults diagnosed with cystic fibrosis (CF), new research suggests.

A growing number of people with cystic fibrosis are diagnosed in adulthood, partly because of increased awareness among physicians of variations in disease presentation, more accessible genotyping, and easier diagnostic criteria.


COURTESY NHGRI

Adult-diagnosed cystic fibrosis patients generally have a milder form of the disease than that of those diagnosed in childhood; however, less is known about their prognosis and life expectancy.

Researchers reported the outcomes of a retrospective cohort study of 362 adults diagnosed with cystic fibrosis at age 18 years or older. The median age at diagnosis was 34.3 years, and 71% of patients presented with pulmonary and/or gastrointestinal symptoms. The study was published in Annals of the American Thoracic Society.

The patients were followed for a median of 7.7 years, during which time there were 15 lung transplants and 33 deaths without transplant. Overall, 10-year lung transplant–free survival was 87.7%, and 15-year survival was 86.1%.

Those who were diagnosed young and who had higher lung function had the best median survival times. For each 5-year increase in age at diagnosis, the risk of death or transplant increased by 24%, and for each 5% decrease in forced expiratory volume in 1 second (FEV_1), the risk was 35% higher.

Individuals who had diabetes at baseline had a more than fourfold higher risk of death or transplant than did those without diabetes.

"While newborn screening programs will reduce the rate of missed diagnoses in the future, clinicians still need to consider CF as a possible diagnosis if individuals are presenting with suspicious CF symptoms (e.g., GI or pulmonary symptoms) during adulthood, particularly if born prior to the introduction of newborn screening in their jurisdiction," wrote Sameer Desai, of the University of British Columbia, Vancouver, and his coauthors.

Commenting on the association with diabetes, the authors noted that this finding had some uncertainty but suggested the additional inflammatory burden could increase the risk of death in individuals with cystic fibrosis.

The authors highlighted that fewer than 5% of people with adult-diagnosed cystic fibrosis had two copies of the F508del mutation, which is associated with severe, early-onset disease. However, those who were homozygous for that mutation tended to be diagnosed at a younger adult age, had worse nutritional status and a lower FEV_1 percent predicted, compared with the overall adult-diagnosed population.

"This finding suggests potential delays in CF diagnosis for these people leading to worse outcomes," the authors wrote.

The researchers also identified 25 individuals who had a possible unconfirmed diagnosis based on the most recent cystic fibrosis diagnostic guidelines. These individuals were either asymptomatic or had unknown symptoms, had sweat chlorides at or below 60 mmol/L (where available), and either unknown or two non–cystic fibrosis–causing mutations. They were also more likely to be male, to be nonwhite, to have increased unknown mutations, and to be pancreatic sufficient, compared with individuals with a confirmed diagnosis.

The study looked at whether *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex increased the risk of transplant or death, but found these did not significantly predict survival.

"Adult CF clinicians can use this information to educate newly diagnosed adults with CF about their prognosis and to guide treatment decisions, specifically those at high-risk for a worse prognosis," the authors wrote.

The study was partly funded by the Rare Disease Foundation. Two authors declared support from Cystic Fibrosis Canada, but no other conflicts of interest were declared.

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SOURCE: Desai S et al. Ann Am Thorac Soc. 2018 Jun 26. doi: 10.1513/AnnalsATS.201801-037OC.

For smokers, the ends may not justify the ENDS

BY RICHARD FRANKI
MDedge News

Smokers who used e-cigarettes and other electronic nicotine delivery systems (ENDS) were less likely to quit than were those who did not use such products, according to a 2015 survey and a follow-up conducted a year later.

"Under 'real world' use and conditions [ENDS] may have suppressed or delayed quitting among some adult smokers," Scott R. Weaver, PhD, and his associates at Georgia State University, Atlanta, wrote in PLoS ONE. The original survey, conducted in August and September of 2015, involved 1,284 U.S. adult smokers from the GfK KnowledgePanel, of whom 858 completed the follow-up survey in September 2016.

Smokers who used ENDS at baseline were slightly more likely to attempt to quit (53.7%) than were those who did not (48.6%) but were much less likely to have quit (defined as no smoking for at least 30 days at the time of follow-up): 9.4% vs. 18.9%, for an adjusted odds ratio of 0.30. Those who used ENDS at any time during the study were much more likely than were non-ENDS users to make an attempt (58.5% vs. 44.4%), but they were, again, much less likely to succeed (7.7% vs. 22.2%; AOR, 0.25), the investigators reported.

The results were similar for the subset of respondents who smoked every day: ENDS users were more likely to attempt to quit but less likely to succeed. Odds ratios for quitting were 0.37 for those using ENDS at baseline and 0.36 for those who used ENDS at any time since the first survey, Dr. Weaver and his associates said.

"Use of current ENDS products in real world conditions [does] not seem to improve the chances of quitting for smokers, and, under the current landscape, may not be the disruptive technology that increases the population quit rate and reduces the harm of combustibles," they wrote.

The study was supported by the National Institute of Drug Abuse and the Food and Drug Administration's Center for Tobacco Products. One of the investigators has received funding in the form of grant funding from Pfizer and the National Institutes of Health and another has served as a paid consultant to the Centers for Disease Control and Prevention.

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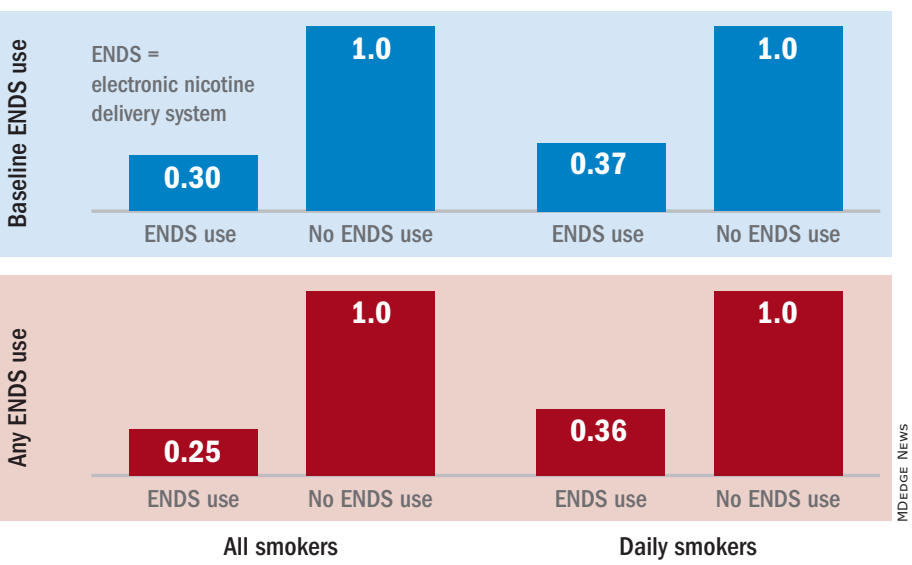
SOURCE: Weaver SR et al. PLoS ONE. 2018 Jul 9;13(7): e0198047. doi: 10.1371/journal.pone.0198047.

Odds ratios of not smoking for ≥30 days at follow-up



Note: 858 respondents to the original survey in 2015 completed the follow-up a year later.
Source: PLoS ONE. 2018 Jul 9:13(7): e0198047

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REM sleep disorder linked to synucleinopathies

BY M. ALEXANDER OTTO
MDedge News

LOS ANGELES – At least 70% of patients with idiopathic REM sleep behavior disorder will develop a neurodegenerative disease within about a decade, according to a years-long, multicenter investigation of 1,280 patients – the largest study of the issue to date.

REM sleep behavior disorder (RBD) has been known for years to increase the risk for synucleinopathies, namely Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. However, previous studies have mostly been conducted at single institutions, so the exact extent to which RBD increases the risk wasn't clear.

The new investigation lays the issue to rest. It nailed "down a precise and generalizable" estimate, according to lead investigator Ronald Postuma, MD, a movement disorder specialist at McGill University, Montreal. "What we found overall is that the risk is 6.3% per year; 50% of patients phenoconvert at 7.5 years, and at 12 years, we are up to 73%. This is quite striking. The bottom line is, if you have a patient with polysomnographic-proven RBD in front of you, you are talking to [someone] destined to develop a neurodegenerative disease in the next 10-12 years," he said.

These findings have important implications for the field. Now that it's known who's at risk, "we have a chance to do neuroprotective therapy. It's time to move forward and start preventing disease," Dr. Postuma said at the American Academy of Neurology annual meeting. He estimated that it would take only a few hundred patients to do a 2-year trial of neuroprotective therapy.

The 1,280 study subjects were selected from 24 sleep centers on four continents, all of them participants in the international RBD study group. The patients needed for a trial "are sitting right now" in the study group, "so maybe we can get on with this," he said.


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Dr. Ronald Postuma declared, "It's time to move forward and start preventing disease."

REM sleep – the dream state – normally paralyzes people, but something breaks down in RBD, and people act out their dreams, sometimes to disturbing effects. It occurs in about 1% of the population, usually in older people and in slightly more men than in women.

The risk of neurodegenerative disease in RBD increases even more if patients test positive at baseline for movement declines, cognitive issues, olfactory problems, constipation, color vision loss, erectile dysfunction, or abnormal dopamine transporter scans. Dr. Postuma and his team found no predictive value for somnolence, insomnia, urinary problems, depression, or anxiety. These negative findings were surprising, he said, because mood disorders and sleep troubles are known to increase the risk in the general population.

The subjects all had polysomnographic-proven RBD at baseline without neurodegenerative disease. Most of them were men and were about 70 years old, on average. Subjects were tested for synucleinopathies and risk variables annually. The mean disease-free follow-up was about 4 years but ranged out to 19 years. Risks were adjusted for age, sex, and study center.

Cognition deficits were the only thing that distinguished future dementia patients from those destined for movement disorders. "Everything [else] is really the same between who gets dementia and who gets Parkinsonism," Dr. Postuma said.

The study was funded by the Canadian Institute of Health Research and the Fonds de la Recherche Sante Quebec. Dr. Postuma disclosed consulting, speaking for, and receiving other fees from Biotie, Roche/Prothena, Teva Neurosciences, Novartis Canada, Theranexus, Jazz Pharmaceuticals, and GE HealthCare.

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SOURCE: Postuma R et al. AAN 2018, Plenary session.

Reduced waking theta activity found in depressed patients

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Disruption of slow-wave activity may potentially explain the positive influence that sleep deprivation may have on major depressive disorder, according to results of a study presented at the annual meeting of the Associated Professional Sleep Societies.

Jennifer Goldschmied, PhD, of the University of Pennsylvania, Philadelphia, reported preliminary results of a study of disruption of slow-wave activity (SWA) in 26 subjects – 12 healthy controls and 14 people diagnosed with major depressive disorder (MDD) – that found a significant decrease of about 20% in waking theta activity, as measured with EEG, in the MDD group. In the 3-night sleep study, conducted at the University of Michigan, Ann Arbor, an adaptation night was followed by baseline and SWA disruption nights with EEGs performed each night. After the baseline night, patients also had a morning and afternoon EEG.

Across the baseline day, patients with depression showed "no modulation of theta activity whatsoever," Dr. Goldschmied said. "And then we see, following slow-wave disruption, a significant decrease in theta activity," whereas healthy controls showed no change in waking theta following slow-wave disruption. "So what this means is that the presence of SWA may actually be facilitating the reduction of theta or sleep propensity during typical sleep in healthy individuals," she added. In MDD patients, the decline in theta power following slow-wave disruption was from about 5.4 to 4.3.

Dr. Goldschmied noted that this finding somewhat supports what is known as the synaptic homeostasis hypothesis that University of Wisconsin researchers Giulio Tononi, MD, PhD, and Chiara Cirelli, MD, PhD, reported (Brain Res Bull. 2003;62:143-50). This hypothesis holds that SWA is a marker of synaptic strength and promotes the downscaling of synaptic strength during sleep. No method for measuring synaptic strength in humans exists, Dr. Goldschmied added, but waking theta can be considered a proxy for net synaptic strength across the cortex.

Dr. Goldschmied noted other research that has found SWA disruption improves mood (Psychiatry Res. 2015;228:715-8; J Psychiatr Res. 2011;45:1019-26), but the study she reported on found no role of decreased theta activity in that change. "To go even further," she said, "we looked at the entire data set and found no relationship between the decrease in theta and any of the measures of sleep architecture – so there's really no way to predict this decrease in our sample of people with depression."

SWA plays a significant role in depression and merits more study, Dr. Goldschmied said. She noted that future research should examine the effects of SWA disruption in a larger sample, investigate theta findings with other proxy measures of synaptic strength such as brain-derived neurotrophic factor and transcranial magnetic stimulation, explore differences in SWA between sexes, and explore how SWA enhancement influences mood and theta activity.

Dr. Goldschmied reported having no financial relationships.

SOURCE: Goldschmied J et al. Sleep 2018, Abstract 0245.

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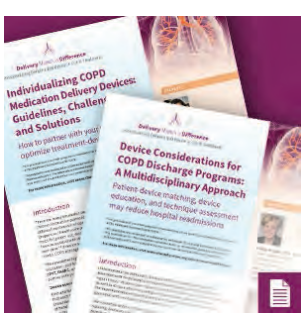

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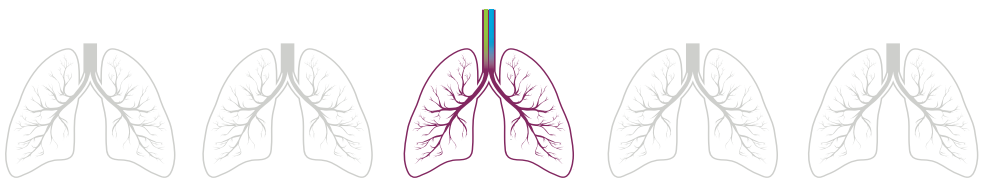

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Trial finds OSA associated with larger aortic diameter

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Individuals with moderate to severe obstructive sleep apnea were found to have slightly larger ascending aortic diameters and thus may be at a heightened risk of cardiovascular events, according to an analysis of a national, multisite research study presented at the annual meeting of the Associated Professional Sleep Societies.


DR. KWON

"Sleep apnea severity is associated with increased thoracic aortic size, particularly in women," Younghoon Kwon, MD, assistant professor of cardiovascular medicine at the University of Virginia Health System, Charlottesville, said in presenting the results. "However, obstructive sleep apnea severity was not associated aortic pulse-wave velocity or aortic distensibility."

The study evaluated a subgroup of 708 patients with no history of cardiovascular disease (CVD) from the Multi-Ethnic Study of Atherosclerosis (MESA).

Dr. Kwon noted that previous studies have shown that patients with thoracic aortopathy have a high rate of obstructive sleep apnea (OSA) (Am J Respir Crit Care Med. 2003;168:1528-31) and that those with OSA tend to have higher thoracic aortic size (J Am Coll Cardiol. 2008;52:885-6).

"There's also a degree of evidence suggesting that OSA is associated with high arterial stiffness, which is a marker of primary organ damage and a major cardiovascular risk that is predictive of cardiovascular disease," Dr. Kwon said (J Intl Med Res. 2011;39:228-38).

However, he also noted that some studies have found no relationship between OSA and aortic disease (Respiration. 2006;73:741-50). "The question can be raised as to whether sleep apnea may have implications" in thoracic aortic disease, he said.

Dr. Kwon's study evaluated three groups: patients with no OSA (apnea hypopnea index [AHI] less than 5, n = 87), mild OSA (AHI 5-15, n = 215), and severe OSA (AHI greater than 15, n = 406). All patients had polysomnography as part of an ancillary study. Cardiac MRI measured these three features of aortic function and physiology (unadjusted results):

- Diameter at the pulmonary artery bifurcation, which ranged from 3.13 cm in patients with no OSA to 3.37 cm in those with severe OSA (P = .0017).
- Pulse wave velocity, which averaged 8.07 m/s in the no-OSA group and 9.11 m/s in the severe group (P less than .0001).
- Distensibility, or aortic stiffness, which was 1.73% per mm Hg in the no-OSA group, 1.54% per mm Hg in the mild group, and 1.68% per mm Hg in the severe group (P = .0141).

"There was maybe some higher pulse wave velocity across the significant OSA group," Dr. Kwon said. "However, with aortic distensibility, there did not seem to be any significant trend."

In the adjusted analysis of aortic diameter, "there did appear to be a small but significant difference in the significant OSA group, compared with the reference group," Dr. Kwon said. He also noted that women with OSA typically had significantly larger aortic diameters than did non-OSA counterparts, whereas that trend was not as pronounced in men.

"Thoracic aorta size does seem to increase with OSA severity, but this has a sex-interaction component; it's more pronounced in women," Dr. Kwon said. He also noted a discrepancy in the results: "The functional properties of the aorta did not seem to bear a significant association with OSA severity."


monkeybusinessimages/Getty Images

In explaining why these results differed from previous studies, Dr. Kwon said that the study populations or their characteristics may be the cause or that MRI-based measures of aortic properties have not been extensively studied before.

"This is probably the first study to look at an unselected population, use a large sample size that was ethnically diverse, and use cardiac MRI technology," he said.

Limitations he noted were the study's cross-sectional nature and its small population of patients with enlarged thoracic aorta size, which left it underpowered to evaluate that population.

Dr. Kwon reported having no financial relationships.

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SOURCE: Kwon Y et al. SLEEP 2018, Abstract 0465.

Phase 3 trial: Tasimelteon effective for jet lag disorder

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Tasimelteon, a drug approved for non–24-hour sleep-wake disorder, has been shown to increase sleep times in travelers with jet lag, according to results from a phase 3 trial.

"Tasimelteon demonstrated an increase in total sleep time of 85 minutes versus placebo and also demonstrated improvement in next-day alertness versus placebo," Christos Polymeropoulos, MD, medical director of Vanda Pharmaceuticals, said in presenting results of the JET8 trial during the late-breaking abstracts session at the annual meeting of the Associated Professional Sleep Societies.

Tasimelteon, sold under the trade name Hetlioz, is a melatonin receptor agonist that is Food and Drug Administration–approved for non–24-hour sleep-wake disorder – but not for treatment of jet lag disorder (JLD). Dr. Polymeropoulos noted there is no FDA-approved treatment for JLD.

JET8 induced the circadian challenge equivalent to crossing eight time zones. The study involved 318 individuals randomized evenly to 20 mg tasimelteon or placebo 30 minutes before bedtime. The primary endpoint of the study was total sleep time in the first two-thirds of night measured by polysomnography.

Those on tasimelteon averaged 216.4 minutes of total sleep time in the first two-thirds of night versus 156.1 for those on placebo (P less than .0001), Dr. Polymeropoulos said. Full total sleep times were 315.8 minutes versus 230.3 minutes (P less than .0001), respectively.

"For total sleep time, the tasimelteon subjects gained about an hour and a half, as measured by PSG [polysomnography]," Dr. Polymeropoulos said.

Other key markers the trial measured were latency to persistent sleep and wakefulness after sleep onset. They measured 15 minutes less and 74.6 minutes less, respectively, in the tasimelteon arm.

Dr. Polymeropoulos also disclosed early results of a second trial of tasimelteon in JLD: the JET Study, a two-phase transatlantic travel study of 25 patients. The subjects were flown from four U.S. cities to London and then received tasimelteon or placebo for 3 nights.

The study was terminated before reaching its enrollment goal of 90 patients because of its complexity, Vanda said in a separate press release. Over 3 nights of study, the tasimelteon arm gained a total of about 130 minutes of sleep, Dr. Polymeropoulos said.

Vanda has said it plans to file a supplemental new drug application for tasimelteon for treatment of JLD in the second half of this year.

Dr. Polymeropoulos is an employee of Vanda Pharmaceuticals.

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SOURCE: Polymeropoulos C et al. SLEEP 2018, LBA 2.

New insights into sleep, pregnancy weight gain

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Pregnant women who are overweight and obese are like the general population in that the less they sleep, the more weight they gain, particularly in the first half of pregnancy. Prolonged daily total eating time was not associated with gestational weight gain in these women, particularly early in pregnancy, according to findings from a small study presented at the Associated Professional Sleep Societies annual meeting.

Those findings point to a need to further study the early gestational period to better understand the relationship between sleep, metabolic function, and pregnancy, said Rachel P. Kolko, PhD, a postdoctoral scholar at the Western Psychiatric Institute and Clinic of the University of Pittsburgh.


DR. KOLKO

"The association with total sleep time was found to be significant, such that if you had less sleep, you had higher amounts of weight gain; we did not find a significant relation with our eating window variable," Dr. Kolko said.

She reported on research involving 62 pregnant women, 53% of whom were overweight with a body mass index of 25-29.9 kg/m^2 and 47% of whom were obese with BMI greater than 30. Nearly half of the study population were nonwhite.

The research grew out of a need to identify potentially modifiable factors to curtail excessive gestational weight gain during pregnancy, she said. The study hypotheses were that both shorter total sleep time and longer total eating time would lead to higher gestational weight gain, but the study confirmed only the former as a contributing factor.

The women in the study were at 12-20 weeks of pregnancy. Gestational weight gain was calculated as the difference between self-reported pre-pregnancy weight and current weight. Total sleep time was based on the Pittsburgh Sleep Quality Index, and total eating time was calculated as the time difference between the day's first meal or snack of more than 50 calories and the last, as self-reported.

Average total sleep time was 7.8 hours, with total eating time spanning 10.8 hours. On average, study participants gained 9.7 pounds through the first half of pregnancy, Dr. Kolko said. She noted that the Institute of Medicine, now known as the National Academy of Medicine, recommends that women who are overweight gain 15-25 pounds during pregnancy and women who are obese gain 11-20 pounds (JAMA. 2017;317:2207-25).

Dr. Kolko reported having no financial relationships to disclose.

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New generation sequencing for NSCLC cuts costs

BY SUSAN LONDON
MDedge News

Comprehensive testing of newly diagnosed metastatic non–small cell lung cancer (NSCLC) with next-generation sequencing (NGS) for known lung cancer–related genomic alterations is cost-saving relative to single-gene testing strategies and often faster, a new study finds.

"We know now that genomic testing for all patients with advanced NSCLC is the standard of care to help detect oncogenic drivers, to inform treatment decisions," lead study author Nathan A. Pennell, MD, PhD, codirector of the Cleveland Clinic lung cancer program, said in a press briefing leading up to the ASCO annual meeting. But the optimal strategy for this testing is unclear.

He and his colleagues conducted a decision analytic modeling study among hypothetical insurance plans having 1 million enrollees. Outcomes were compared between NGS testing and three single-gene testing strategies.

Data indicated that, compared with exclusionary, sequential, or hot-spot panel testing approaches, NGS testing simultaneously for eight genomic alterations having Food and Drug Administration–approved or investigational targeted therapies could save up to $2.1 million among Medicare beneficiaries and up to $250,842 among patients covered by commercial insurance. The costs to payers decreased as the percentage of patients receiving NGS testing increased. Moreover, the wait time for results was similar or roughly half as long with NGS.

In the CMS population, NGS testing would save about $1.4 million compared with exclusionary testing, more than $1.5 million compared with sequential testing, and about $2.1 million compared with panel testing.

"Our results showed that there were substantial cost savings associated with upfront NGS testing compared to all other strategies," Dr. Pennell said. "In addition, NGS had a faster turnaround time than either sequential or exclusionary testing, which is critically important for sick lung cancer patients, to make sure they get their treatment as quickly as possible. Waiting a month or longer is simply no longer viable for patients because they get sick very quickly and these treatments work very well."

Of note, the model indicated that some patients undergoing initial single-gene testing strategies never had their genomic alterations detected because tissue for testing ran out and they were too sick to undergo another biopsy.

"The bottom line is, ultimately, using the best single test upfront results in the fastest turnaround time, the highest percentage of patients with targetable alterations identified, and overall the lowest cost to payers," he summarized.

A major challenge in this population is going back and retesting for known or new genomic alterations, agreed ASCO President Bruce E. Johnson, MD, FASCO. "At our upcoming meeting, we are going to hear about *RET*, which may end up as a target and may therefore need to be tested for."

Recently, oncologists have a new attractive option of billing for NGS panels rather than for single gene tests, he noted.

"This study really shows that by doing all the testing at the same time, you can both get results back more quickly as well as get information," said Dr. Johnson, professor of medicine at the Dana-Farber Cancer Institute and a leader of the Dana-Farber/Harvard Cancer Center Lung Cancer Program, Boston. "This study looked at an NGS panel of 8 genes, but most of the NGS panels contain somewhere between 50 and 400 genes, so you get a lot more information with this at a cost that's competitive or less. So this will be welcome news to people who are ordering these gene panels."

Study details

For NSCLC, there are currently approved treatments that target alterations in *EGFR, ALK, ROS1*, and *BRAF*, and investigational treat-

Continued on following page

Cell-free DNA assays successfully detect lung cancer

BY SUSAN LONDON
MDedge News

CHICAGO – A set of blood-based assays that search for abnormalities in cell-free DNA shows moderately good sensitivity for detecting lung cancer in its early stages, according to the first interim report from a substudy of the large, ongoing Circulating Cell-Free Genome Atlas (CCGA).


DR. OXNARD


DR. GRAHAM

"Lung cancer screening with low-dose CT is known to improve outcomes. And yet, CT-based lung cancer screening is not widely adopted," said lead study author Geoffrey R. Oxnard, MD, associate professor of medicine at Dana-Farber Cancer Institute and Harvard Medical School, Boston, in a press briefing at the annual meeting of the American Society of Clinical Oncology, where the study was reported. "Criticisms of low-dose CT include the risk of false positives and overdiagnosis. We proposed to investigate an untapped opportunity for cancer detection, which is using cell-free DNA."

Main substudy results among 164 patients with lung cancer and 923 comparable individuals without known cancer showed that, at a specificity of 98%, the three assays evaluated detected up to 51% of early-stage (stage I-IIIA) lung cancers and up to 91% of late-stage (stage IIIB-IV) lung cancers. And among the healthy participants with false-positive results for lung cancer, several were ultimately found to have cancers of other types.

"This first interim analysis of the CCGA study demonstrates that comprehensive sequencing of the plasma cell–free DNA can generate high-quality data across the entire genome, and it permits noninvasive cancer detection. The assays can detect lung cancer across stages, across histologies, across populations," Dr. Oxnard said.

"Together, these results support the promise of using cell-free, DNA-based assays to develop an early cancer detection test with high specificity. Further assay and clinical development is ongoing: There is a separate prospective trial enrolling, the STRIVE study, and there remain thousands of patients still on this CCGA study to be analyzed for further optimization and focusing of this assay toward an eventual cancer diagnostic."

The cohort studied was not a screening population, so the assays' performance cannot be compared with that of low-dose CT at this point, he said. But the hypothesis going forward is that the assays will have comparatively higher specificity, sparing some patients an unnecessary diagnostic work-up.

The population in which the final blood test might be used will depend on its diagnostic performance once the assays are fully refined and clinic ready, which will take some time, according to Dr. Oxnard. However, "2 years ago, this was a pipe dream. Two years ago, it was completely just a brainstorm that had no data to support it, and I didn't believe that this could be done. Today, we actually have data to show that this is really feasible to find early-stage cancer in the blood. So this is a huge step forward and actually means that this is going to be a reality."

"This is an important first step toward an easier way to detect lung cancer at earlier and hopefully more curable stages," agreed ASCO Expert David Graham, MD, who is also medical director at the Levine Cancer Institute in Charlotte, N.C. "If the promise of this report holds, we could easily see a day when a person could be screened for lung cancer and possibly other cancers simply by going into their regular doctor's office for a blood draw."

Study details

The CCGA study has enrolled more than 12,000 of its planned 15,000 participants (70% with cancer, 30% without) across 142 U.S. and Canadian sites.

The substudy reported had a development cohort (118 patients with lung cancer, 561 individuals without cancer) and a validation cohort (46 patients with lung cancer, 362 individuals without cancer), with the lung cancer and noncancer groups matched on age, race, and body mass index. "Having a comparable control cohort is very important in developing such a diagnostic for accurate analysis of the potential false-positive rate," Dr. Oxnard noted.

Three prototype assays were tested: A targeted sequencing assay entailing very deep sequencing across 507 genes for somatic mutations such as single-nucleotide variants and small insertions and/or deletions; a novel, whole-genome sequencing assay to detect somatic gene copy number changes; and a novel, whole-genome methylation sequencing assay to detect abnormal epigenetic changes.

Sequencing was also performed on DNA from white blood cells. "That's very important. The white blood cells are rich with mutations that can pollute the DNA and make you think that there is cancer present in the cell-free DNA," Dr. Oxnard explained. "You screen out this interference from the white blood cells and other biologic noise, and you are left with the final features: mutations, copy number variations, and methylation signatures that then go into the final assays being studied."

Results showed that when assay specificity was 98%, sensitivity for early-stage (stage I-IIIA) lung cancer ranged from 38% to 51%, and sensitivity for late-stage (stage IIIB-IV) lung cancer ranged from 87% to 91%.

Among five presumed cancer-free individuals having positive results on all three assays, two subsequently received a cancer diagnosis (one with stage III ovarian cancer, one with stage II endometrial cancer).

An additional 19 cancer types across all stages were tested in the CCGA substudy. Early results for breast, gastrointestinal, gynecologic, blood, and other cancers were also reported at the meeting (abstracts 536, 12021, and 12003).

Dr. Oxnard disclosed that he has a consulting or advisory role with AstraZeneca, Inivata, Boehringer Ingelheim, Takeda, Genentech/Roche, Novartis, Loxo Oncology, Ignyta, DropWorks, and GRAIL, and that he has patents, royalties, and/or other intellectual property with Chugai Pharmaceutical, Bio-Rad, Sysmex, and Guardant Health. The study was funded by GRAIL.

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SOURCE: Oxnard GR et al. ASCO 2018, Abstract LBA8501.

Continued from previous page

ments in clinical trials that target alterations in *MET, HER2, RET*, and *NTRK1*.

In the model Dr. Pennell and his colleagues developed, patients with newly diagnosed metastatic NSCLC received testing for programmed death ligand 1 (PD-L1) plus testing for the above known lung cancer–related genes using one of four strategies:

- NGS testing (testing of all eight genes plus *KRAS* simultaneously).
- Sequential testing (testing one gene at a time starting with *EGFR*).
- Exclusionary testing (testing for *KRAS* mutation, the most common genomic alteration, followed by sequential testing for changes in other genes only if *KRAS* was not mutated).
- Hot-spot panel testing (combined testing for *EGFR, ALK, ROS1*, and *BRAF*), followed by either single-gene or NGS testing for alterations in other genes.

Model results indicated that among 1 million hypothetical plan enrollees, 2,066 patients covered by the Centers for Medicare & Medicaid Services and 156 covered by U.S. commercial insurers would have newly diagnosed metastatic NSCLC and therefore be eligible for testing.

Estimated time to receive test results was 2 weeks for NGS testing and for panel testing, compared with 4.7 weeks for exclusionary testing and 4.8 weeks for sequential testing.

In the CMS population, NGS testing would save about $1.4 million compared with exclusionary testing, more than $1.5 million compared with sequential testing, and about $2.1 million compared with panel testing. In the commercial health plan cohort, NGS would save $3,809 compared with exclusionary testing, $127,402 compared with sequential testing, and $250,842 compared with panel testing.

Dr. Pennell disclosed that he has a consulting or advisory role with AstraZeneca, Lilly, and Regeneron, and that his institution receives research funding from Genentech, NewLink Genetics, Clovis Oncology, Astex Pharmaceuticals, Celgene, AstraZeneca, Pfizer, and Merck. The study received funding from Novartis.

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SOURCE: Pennell NA et al. ASCO Annual Meeting, Abstract 9031.

FDA approves minimally invasive endobronchial valve to treat severe emphysema

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved the Zephyr endobronchial valve system for those with severe emphysema who are experiencing difficulty breathing. The valve is the first minimally invasive device approved in the United States for treating such patients, according to Pulmonx, the device manufacturer.

The FDA previously granted the novel device expedited review, as patients who did not respond to drug treatment had only limited alternative options, including lung volume reduction and lung transplant, Tina Kiang, PhD, of the FDA's Center for Devices and Radiological Health, said in a press release. "This novel device is a less invasive treatment that expands the options available to patients," said Dr. Kiang, acting director of the center's Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices.

The device, which is the size of a pencil eraser, is designed to prevent air from entering the damaged parts of the lung but to allow trapped air and fluids to escape. It is placed into the damaged areas of the lung using a flexible bronchoscope.

The valve is contraindicated in patients with active lung infections; those allergic to nitinol, nickel, titanium, or silicone; and active smokers.

The approval is based on a multicenter study of 190 patients with severe emphysema. A total of 128 received Zephyr valves and medical management, while 62 received medical management only. The primary measure was the number of patients who achieved at least a 15% improvement in their pulmonary function score: At 1 year, 47.7% of the Zephyr valve patients had achieved such improvement versus 16.8% of the control group, according to the FDA.

Adverse events included death, pneumothorax, pneumonia, worsening of emphysema, coughing up blood, shortness of breath, and chest pain. The valve is contraindicated in patients with active lung infections; those allergic to nitinol, nickel, titanium, or silicone; and active smokers.

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Tools needed to triage ED sepsis patients for discharge

BY DOUG BRUNK
MDedge News

SAN DIEGO – More than 16% of emergency department sepsis patients are not admitted to the hospital, preliminary results from a large, retrospective cohort study found.

"Nothing is really known about this topic," lead study author Ithan D. Peltan, MD, said in an interview at an international conference of the American Thoracic Society. "In previous research, we've been focused on patients with sepsis who are admitted to the hospital. We have never thoroughly recognized that a fair number of patients who meet clinical criteria for sepsis in the emergency department are actually triaged to outpatient management. We don't really know anything about these patients. What are their clinical characteristics and what are the factors that are leading them to be discharged from the ED rather than be admitted to the hospital?"

To find out, he and his associates retrospectively reviewed the medical records of 12,002 adult ED patients who met criteria for sepsis at two tertiary hospitals and two community hospitals in Utah between July 2013 and December 2016. They excluded trauma patients, those who left the ED against medical advice, those who were discharged to hospice or who died in the ED, and eligible patients' repeat ED encounters. Patients transferred to another acute care facility were considered admitted, while transfers to nonacute care such as skilled nursing or psychiatric facilities were classified as discharges. Next, Dr. Peltan and his associates employed inverse probability weights using a propensity score for ED discharge based on age, sex, Charlson score, ED acuity score, initial ED vital signs, white blood cell count, lactate, sequential organ failure assessment (SOFA) score, busyness of the ED, and study hospital to compare 30-day mortality between patients admitted to the hospital versus those discharged from the ED.

Doug Brunk/MDedge News

Dr. Ithan D. Peltan

Of the 12,002 patients included in the analysis, 10,032 (83.6%) were admitted, while 1,970 (16.4%) were discharged. Compared with admitted patients, discharged patients were younger (a mean of 53 vs. 60 years, respectively; *P* less than .001); more likely to be female (65% vs. 55%; *P* less than .001); more likely to be nonwhite or Hispanic (21% vs 17%; *P* less than .001), and had fewer comorbidities and physiologic derangements. In addition, crude mortality at 30 days was lower in discharged versus admitted patients (1.0% vs. 6.2%, respectively; *P* less than .001). After the propensity-adjusted analysis, there was no significant difference in 30-day mortality for discharged versus admitted sepsis patients (adjusted odds ratio 1.0).

"We were worried that discharged ED sepsis patients were being mismanaged and weren't going to do well as similar patients who were admitted to the hospital," Dr. Peltan said. "This analysis is still a work in progress, but with that caveat, our findings so far suggest that physicians are making pretty good decisions overall."

The researchers also found that, among 89 ED physicians who cared for 20 or more eligible patients, some did not discharge any of their sepsis patients, while others discharged 39% of their sepsis patients. "That was surprising," Dr. Peltan said. "This could mean that some hospital sepsis admissions depend on physician practice style more than the patient's condition or treatment needs."

Researchers emphasized that they do not recommend routine outpatient management for individual sepsis patients. "Almost certainly, some of the discharged patients should have been admitted to the hospital." Dr. Peltan said. "I think there's still a lot of opportunity to understand who these patients are, understand why there is so much physician variation, and to develop tools to further optimize triage decisions."

The study was funded in part by the Intermountain Research and Medical Foundation in Salt Lake City. Dr. Peltan reported having no financial disclosures.

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SOURCE: Peltan ID et al. ATS 2018, Abstract A5994/702.

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Protocol helped identify inpatient children at VTE risk

BY DOUG BRUNK
MDedge News

SAN DIEGO – Following simple institutional care guidelines helped clinicians identify pediatric patients at moderate-to severe risk of venous thromboembolism (VTE), results from a single-center study showed.

"Hospital-acquired VTE is on the rise in the pediatric population," lead study author Emily Southard, MD, said at the biennial summit of the Thrombosis & Hemostasis Societies of North America. "This consists of a DVT [deep vein thrombosis] or [pulmonary embolism] 48 hours or more after admission, or any time at the site of a central venous catheter."

One published study found a 70% increased incidence in the pediatric population for 2001-2007 (Pediatrics. 2009;124[4]:1001-8). More than half of the children in that study (63%) had at least one coexisting complex medical condition.

Hospital-acquired VTE cases tend to harbor a number of complications, said Dr. Southard, who is a pediatric hematology/oncology fellow at Children's Hospital Colorado, Aurora. Risk factors in pediatric trauma patients include ICU admission (odds ratio, 6.25), transfusion of blood products (OR, 2.1), lower extremity fracture (OR, 1.8), and neurosurgery (OR, 2.13). She and her associates hypothesized that understanding the relative contributions of clinical, biological, and genetic risk factors for pediatric VTE would help appropriately risk stratify patients and allow better prophylactic approaches.

In 2012, Children's Hospital Colorado implemented a VTE risk assessment tool as part of a hospitalwide patient safety initiative. The assessment is triggered via an Epic Best Practice Advisory to complete in certain higher-risk patients, including ICU patients, hematology/oncology floor patients, any patients with a central-line catheter, and those who are over age 12 and obese.

Risk factors in pediatric trauma patients include ICU admission, blood transfusion, and lower extremity fracture.

Clinicians also assess for risk factors such as significant infection, recent surgery, and personal or family history of thrombophilia. Next, they classify each patient's risk of hospital-acquired VTE as high, moderate, or low risk.

In a pilot study, Dr. Southard and her associates set out to validate the accuracy of the institution's VTE risk assessment tool since it was implemented in 2012. She presented findings from 215 hospital-acquired VTE cases in patients younger than age 18, compared with age-matched inpatient controls. Data from patients under 6 months of age are available after October 2016, coinciding with a change in definition of pediatric hospital-acquired VTE.

Most hospital-acquired VTE patients (77.2%) ranged in age from 1 to 17 years. The number of patients admitted for a trauma diagnosis was similar between VTE cases and controls (7.4% vs. 7.9%, respectively). However, compared with controls, a significantly greater number of VTE cases were immobile (41.8% vs. 10.3%, respectively), required ICU admission (86.4% vs. 26.5%), had a central venous catheter (80.4% vs. 10.9%), had a positive blood culture (16.7% vs. 1.9%), required surgery or a medical procedure (57.7% vs. 36.7%), and had a longer procedure time (a mean of 151 vs. 133 minutes).

Dr. Southard had no financial disclosures.

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SOURCE: Southard E et al. THSNA 2018.

Respiratory distress common in ED ambulatory setting

BY MADHU RAJARAMAN
MDedge News

Respiratory illness was the most common pediatric emergency in ambulatory settings, followed by psychiatric and behavioral illness, seizures, and syncope, according to results published July 20 in Pediatrics.

Investigators conducted a retrospective observational study of data from the Indianapolis emergency medical services (EMS) system between Jan. 1, 2012, and Dec. 31, 2014. All patients younger than 18 years were eligible.

Of 38,841 pediatric EMS transports in the Indianapolis metropolitan area during the 3-year period, fewer than 1% (322) were verified as originating from an ambulatory practice, reported Matthew L. Yuknis, MD, and his coauthors at Indiana University, Indianapolis. Respiratory distress was the most common emergency (58%), followed by psychiatric and behavioral illness (6%), seizure (6%), and syncope (5%).

The most common interventions were use of supplemental oxygen (27%), albuterol (26%), and intravascular access (11%). The most common critical care interventions were administration of fluid bolus (2%), benzodiazepine (2%), or racemic or intramuscular epinephrine (1%). None required use of an artificial airway, cardiopulmonary resuscitation, intraosseous access, or bag mask ventilation, Dr. Yuknis and his colleagues said.

The average time from call to on-scene arrival was 6 minutes (ranging from less than 1 to 15 minutes). The average patient transport time was 13 minutes (ranging from less than 1 to 38 minutes). The average annual frequency of pediatric outpatient emergencies was 42 emergencies per 100,000 people under 18 years of age. Lower socioeconomic status was correlated with increased frequency of emergencies in ambulatory settings, the authors reported.

"These findings update and clarify existing literature with regard to the frequency of pediatric emergencies in the ambulatory setting, the conditions these patients present with, and the use of EMS data to define these events," the authors wrote. Additionally, the findings can be used to "inform future decisions regarding necessary equipment and procedures."

No relevant financial disclosures were reported. There was no external funding.

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SOURCE: Yuknis ML et al. Pediatrics. 2018. doi: 10.1542/peds.2017-3082.

Two-thirds of pediatric asthma exacerbations triggered by one or more respiratory viruses

BY JILL D. PIVOVAROV
MDedge News

NATA_ZHEKOVA/THINKSTOCK

Children with asthma who present to emergency departments for treatment are significantly more likely to test positive for one or more respiratory pathogens, reported Joanna Merckx, MD, of the Montreal Children's Hospital at the McGill University Health Centre, and her associates.

Nearly two-thirds of patients tested positive for one or more respiratory viruses in a study conducted by Dr. Merckx and her associates. "Given the documented safety of influenza immunization in children with asthma and its expected protective effect," such cases should be among those prioritized to receive influenza immunization.

Multicenter, prospective study

Dr. Merckx and her associates conducted an ancillary multicenter, prospective, ethics-approved cohort study to identify a possible connection between diagnosed respiratory pathogens, severity of illness, and the overall risk of ED treatment failure using data from the DOORWAY (Determinants of Oral Corticosteroid Responsiveness in Wheezing Asthmatic Youth) study.

Dr. Merckx and her colleagues sought to determine whether closely evaluating the effects of specific respiratory pathogens could be useful in further developing appropriate preventive treatments for children with asthma; improving efforts to diagnose pathogens at the time of ED treatment; and identifying patients at higher risk of treatment failure who could be candidates for more intensive treatment protocols.

Children aged 1-17 years presenting to one of five EDs in the Pediatric Emergency Research Canada network during 2011-2013 with moderate or severe asthma flares were considered for the study. All eligible DOORWAY study participants with a valid respiratory specimen were included in the study and received a standardized dose of oral and bronchodilator treatment with salbutamol; those with severe exacerbations also received ipratropium bromide (Atrovent).

Within 1 hour of study inclusion, patients were tested by way of nasopharyngeal aspirate or swab. Patients identified with coinfection presented with two or more pathogens. Failure of ED management was defined as patients admitted to the hospital for asthma; ED treatment lasting 8 or more hours after corticosteroid treatment; or returns to the ED within 72 hours after discharge that led to hospital admission or prolonged ED stay.

Study findings

Of 1,012 children enrolled in the study, 958 were assessed for worsening of asthma symptoms. Of the 958 respiratory specimens tested, 62% tested positive for one or more pathogens, 8.5% were found to have coinfection, of which respiratory syncytial virus (RSV) and coronavirus were the most frequent copathogens. Rhinovirus was the most prevalent pathogen, occurring in 29%, and of these, rhinovirus C was the most frequent species (18.2%), followed by RSV (17.9%); only two patients tested positive for *Mycoplasma pneumoniae*.

Children with a laboratory-confirmed pathogen were younger, had higher tobacco exposure, and were slightly more likely to present with fever (29% vs. 24%), compared with children without a laboratory-confirmed pathogen. Children with rhinovirus were less often febrile (16% vs 41%) and less frequently diagnosed with pneumonia (5% vs. 16%.) than those without a rhinovirus infection The proportion of children presenting with a severe exacerbation of asthma was 33%.

Overall, 17% of patients experienced treatment failure. Those with current respiratory infection were at increased risk of treatment failure, for a risk difference of 8% (95% confidence interval, 3.3%-13.1%). RSV, influenza, and parainfluenza virus (PIV) were associated with 21%, 38%, and 47% higher risks of treatment failure, respectively, noted Dr. Merckx and her associates. These resulted in absolute risks of 9%, 25%, and 34%, respectively, the authors reported in Pediatrics.

Coronavirus, adenovirus, enterovirus D68, and the presence of a coinfection, however, were not found to increase the risk of treatment failure, they noted.

Although rhinovirus may play a role in triggering reactions that require medical attention, such cases still appear to respond favorably to treatment, they said.

Confirmation of findings

A separate study cited by Dr. Merckx and her associates observed the same outcome for rhinovirus patients but more patients diagnosed with nonrhinovirus pathogens, especially human metapneumovirus (hMPV) and PIV, had moderate, rather than severe, symptoms and were much more likely to experience higher treatment failure, particularly those infected with RSV, influenza, and PIV.

"It appears reasonable to pursue strategies to improve immunization coverage for influenza and invest in efforts for the development of vaccines for RSV and rhinovirus," they said.

In cases in which respiratory pathogens were present (especially nonrhinovirus pathogens), greater treatment failure occurred, despite use of inhaler and corticosteroids. The researchers noted that severity of condition at time of treatment and patient response to treatment should be considered as two separate, distinct dimensions of viral infection impact in children with acute asthma. "The high prevalence of rhinovirus C in children presenting with asthma exacerbation, its presumed association with asthma-related hospitalization, and its peak in the fall," also should be considered as a leading cause for more potential severe disease.

Clinical implications

Dr. Merckx and her associates did point to several possibly significant implications with their findings. Intensifying treatment using inhaled anticholinergics or magnesium sulfate could block the vagally mediated reflex bronchoconstriction typically seen in cases of asthma exacerbation worsened by viral infection. Although these therapies currently only are used only in severe reactions, it may be useful to examine their efficacy in any cases triggered by RSV, influenza, and PIV because these have been associated with a poor treatment response.

While it still is necessary to clarify its mechanism of action, azithromycin's demonstrated benefit in preschoolers with severe reactions suggests it could be a possible alternative pathogen–nonspecific therapy to address antineutrophilic inflammation, they said.

Dr. Merckx had no relevant disclosures; two of her associates reported receiving grants, salary rewards, and/or unrestricted donations from various pharmaceutical companies or foundations.

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SOURCE: Merckx J et al. Pediatrics. 2018 Jun;142(1):e20174105.

Asthma prescriptions up

BY ANDREW D. BOWSER
MDedge News

Use of prescription medication overall decreased in children and adolescents over the past 15 years, but certain medication classes saw increases over that time period, according to a comprehensive analysis of cross-sectional, nationally representative survey data.

Reported use of any prescription medication in the past 30 days decreased from 25% during 1999-2002 to 22% during 2011-2014 ($P = .04$), according to the analysis based on data from 38,277 children and adolescents aged 0-19 years in the National Health and Nutrition Examination Survey (NHANES).

That decrease in part reflected less prescribing of antibiotics, antihistamines, and upper respiratory drugs, according to a report on the study in JAMA.

However, the study showed increases over time in prescribing of medications for asthma, ADHD, and contraception, according to Craig M. Hales, MD, of the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md., and his coinvestigators.

"Monitoring trends in use of prescription medications among children and adolescents provides insights on several important public health concerns, such as shifting disease burden, changes in access to health care and medicines, increases in the adoption of appropriate therapies, and decreases in use of inappropriate or ineffective treatments," Dr. Hales and his coauthors said.

Of note, antibiotic usage decreased significantly from 8% during 1999-2002 to 5% during 2011-2014, including decreases in amoxicillin, amoxicillin/clavulanate, and cephalosporins. Likewise, antihistamine use was down over time, from 4% to 2%, as was use of upper respiratory combination medications, which decreased from 2% to 0.5%.

Conversely, they found prevalence of ADHD medication usage increased significantly from 3% during 1999-2002 to 4% during 2011-2014, including significant increases for both amphetamines and centrally acting adrenergic agents.

Asthma medication also increased, from 4% to 6%, including significant increases in inhaled corticosteroids and montelukast. Taken together, these findings suggest an overall decrease in medication prescribing among children and adolescents, despite significantly increased prevalence of prescribing for certain drug classes, the investigators said.

They noted that the study had limitations. For example, NHANES does not include data on most over-the-counter medications, and for the drugs it does include, there are no data on dosages, frequency of use, or specific formulations, they said.

Dr. Hales and his coauthors had no conflicts of interest.

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SOURCE: Hales CM et al. JAMA. 2018;319(19):2009-20.

VIEW ON THE NEWS

Implications uncertain for practice

"Some of these trends likely signal potential improvements in the care of children, others may suggest little progress has been made, and yet others are difficult to interpret with certainty," Gary L. Freed, MD, wrote.

One finding that seems clear in the data, according to Dr. Freed, is a decrease in antibiotic use among children and adolescents, from 8% to 5% from the 1999-2002 to 2011-2014 time period. That likely reflects the success of efforts to decrease overuse of these agents in community settings.

On the other hand, the decreased use of antihistamines documented in this study may reflect the success of efforts to reduce overuse, or the fact that several prescription medications became approved for OTC use over the course of the study. NHANES does not include OTC drug data in its survey.

Dr. Freed is a pediatrician with the Child Health Evaluation and Research Center, University of Michigan, Ann Arbor. These comments are derived from his editorial accompanying the study by Hales et al. (JAMA. 2018;319[19]:1988-9). Dr. Freed had no conflicts of interest.

Implantable monitor best at detecting subclinical AF

BY BRUCE JANCIN
MDedge News

ORLANDO – An insertable continuous ECG monitor detected previously unidentified atrial fibrillation that would otherwise have gone unnoted with other intermittent ambulatory monitoring strategies, in a secondary analysis from the REVEAL AF study.

"If you really want to look for atrial fibrillation because your concern is that the patient has a high-risk profile, and if you saw it you would anticoagulate it and maybe prophylactically use rate control, nothing beats the implanted monitor," James A. Reiffel, MD, said at the annual meeting of the American College of Cardiology.

He was principal investigator for REVEAL AF, a multicenter prospective single-center study in which 385 patients without previously known atrial fibrillation (AF) received an insertable cardiac monitor and were followed for 30 months. Of note, this was a population at high risk for AF and for stroke as well, as demonstrated by the requirement that they either had to have a CHADS2 score of 3 or more, or a score of 2 plus either known coronary artery disease, renal impairment, chronic obstructive pulmonary disease, or sleep apnea.

As previously reported (JAMA Cardiol. 2017 Oct 1;2[10]:1120-7), the primary outcome – an AF episode lasting for at least 6 minutes – occurred during the first 18 months of the study in 29% of participants. By 30 months, it was 40%. At ACC 2018, Dr. Reiffel presented a new analysis looking at how the insertable cardiac monitor (ICM) would have stacked up against other device-based strategies aimed at detecting silent AF, including a 30-day implantable memory loop, daily transtelephonic ECG monitoring, and one-time or periodic 24- or 48-hour Holter monitoring.

Dr. Reiffel and his coinvestigators conducted modeling studies harnessing the REVEAL AF continuous monitoring data. They looked at how many of the real-world patients found to have AF in the study would have been identified had they instead undergone a one-time recording period lasting 1, 2, 7, 14, or 30 days beginning at the time they would have received their ICM. They also looked at the yield of repeated monitoring strategies, including monthly or quarterly 24- or 48-hour Holter monitoring sessions. They repeated the various simulated monitoring strategies 10,000 times each in order to beef up the sample size and stability of the results.

It was no contest, according to Dr. Reiffel, professor of clinical medicine at Columbia University in New York.

That's because the median time to AF detection in REVEAL AF was 123 days. Thus, any monitoring strategy of 30 days duration or less was doomed to be of comparatively low yield. Indeed, the 12-month AF incidence rate as detected by ICM in REVEAL AF was 27.1%, compared with 1.1%-13.5% for the various modeled monitoring strategies.

Among patients who met the primary endpoint in REVEAL AF, 10.2% had one or more AF episodes lasting 24 hours or more. So a significant proportion of the asymptomatic episodes of AF were not brief.

The take-home lesson of this analysis is straightforward, he said. "While the incidence of screen-detected atrial fibrillation is dependent upon the population screened, it is also strongly dependent upon the duration and intensity of monitoring."

Session cochair Jeanne E. Poole, MD, observed that, while the new REVEAL AF analysis is informative, it leaves unanswered the big questions regarding the clinical importance of these silent episodes of subclinical device-detected AF. That is, are these episodes associated with significantly increased stroke risk, and if so are they just another nonmodifiable risk marker, or are they a risk factor that can be dampened via oral anticoagulation, like symptomatic AF? said Dr. Poole, professor of medicine and director of the clinical cardiac electrophysiology program at the University of Washington, Seattle.

"My own belief is that they are both a risk marker and a risk factor that contributes to stroke," Dr. Reiffel replied.

He noted that there are two major ongoing clinical trials evaluating the impact of oral anticoagulation in patients with ICM-detected AF. The 3,400-patient German multicenter Non–vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH–AFNET 6) trial is testing whether oral anticoagulation with edoxaban (Savaysa) is superior to aspirin or no antithrombotic therapy for prevention of stroke or cardiovascular death. And the 4,000-patient Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESIA) trial is randomizing patients to apixaban (Eliquis) or aspirin.

"We'll know within the next 3-4 years whether patients with high-risk profiles for atrial fibrillation but no clinically manifest atrial fibrillation should in fact be detected and should in fact be anticoagulated if atrial fibrillation is detected. Putting on my 'Carnac The Magnificent' hat [made famous by Johnny Carson on the 'Tonight Show'], I predict the answer to both of those questions is likely to be yes," the cardiologist added.

"There's no major surgical technique involved in putting [the ICM] in," he said.

The REVEAL AF study was sponsored by Medtronic. Dr. Reiffel reported serving as a consultant to the company.

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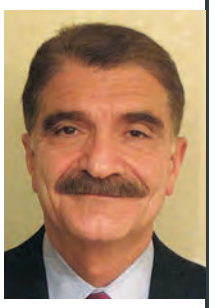
SOURCE: Reiffel JA et al. ACC 2018, Abstract 900-08.

VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: Technically speaking, the implantable Cardiac Monitor (ICM) is a continuous Holter monitor used for the detection of silent episodes of atrial fibrillation. Although subcutaneous implantation is quite quick and easy, the device is expensive. As mentioned by the chair of the session during this paper presentation at the ACC and the author's response, the clinical significance of silent AF episodes detected by ICM device, and by extension, the need for oral anticoagulation, awaits further studies currently underway.

DOACs' safety affirmed in real-world setting

BY ANDREW D. BOWSER
MDedge News

Direct oral anticoagulants (DOACs) were associated with decreased bleeding risk versus warfarin in a recent retrospective analysis of primary care databases.

Apixaban (Eliquis) was associated with decreased risk of major bleeding events versus warfarin both in patients with atrial fibrillation (AF) and those prescribed anticoagulants for other causes, according to study results.

Rivaroxaban (Xarelto) was associated with a decrease in risk of intracranial bleeding, compared with warfarin in patients without AF, as was dabigatran (Pradaxa), reported Yana Vinogradova, a research statistician in the division of primary care at the University of Nottingham (England) and her coauthors.

An increased risk of all-cause mortality was seen with both rivaroxaban and low-dose apixaban, possibly because more patients died of age-related causes while on these direct oral anticoagulants, they reported.

"This large observational study, based on a general population in a primary care setting, provides reassurance about the safety of DOACs as an alternative to warfarin across all new incident users," Ms. Vinogradova and her colleagues said in the BMJ.

Evidence establishing the noninferiority of DOACs to warfarin comes mostly from controlled trials in AF leaving "residual concerns" about the safety of these newer agents in real-world settings, where a broader range of patients may receive them.

They conducted an analysis based on patient data from two U.K. primary care databases representative of the national population, according to the researchers. A total of 196,061 patients were represented in the study, including 103,270 (53%) with AF and 92,791 (47%) who received anticoagulants for other reasons.

A total of 67% of patients received warfarin, though its use declined from 98% in 2011, the beginning of the study period, to 23% in 2016, the end of the study period. Over that same time period, use of rivaroxaban rose from 1% to 42%, and use of apixaban rose from 0% to 31%, while dabigatran use peaked in 2013 at 10%, dropping to 3% by 2016.

For patients with AF, apixaban was linked to a lower major bleeding risk, both versus warfarin (adjusted hazard ratio, 0.66; 95% confidence interval, 0.54-0.79) and versus rivaroxaban, the published data show. Apixaban was associated with a lower risk of intracranial bleed versus warfarin in patients with AF (aHR, 0.40; 95% CI, 0.25-0.64) as was dabigatran (aHR, 0.45; 95% CI, 0.26-0.77).

For patients without AF, apixaban was again associated with a lower risk of major bleeding versus warfarin and versus rivaroxaban, while rivaroxaban was associated with lower intracranial bleeding risk versus warfarin, and apixaban with lower risks for gastrointestinal bleeds.

"Our study has shown that the risk of major bleeding is lower in patients taking apixaban regardless of the reason for prescribing," they wrote. The study was supported by a grant from the National Institute for Health Research. The investigators had no relevant disclosures.

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SOURCE: Vinogradova Y et al. BMJ. 2018;362:K2505.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP comments: This retrospective analysis of primary care databases in a large patient population of over 196,000 in the U.K. is a comparison of the use, safety, and risks of three DOACs vs warfarin. All three agents had a better risk profile with apixaban having the more favorable results. One notable exception was a higher all-cause mortality with rivaroxaban and lower-dose apixaban, compared with warfarin. The findings of this study are of value to the physicians caring for elderly and patients with a higher risk profile for cardiovascular events.

CHEST 2018 postgrad courses – incredible learning opportunities

BY DAVID A. SCHULMAN, MD, FCCP
CHEST 2018 Program Chair

CHEST® Annual Meeting 2018

One of the great educational opportunities that comes with each annual CHEST meeting is the slate of postgraduate courses that kicks the meeting off. I have always found them to be in-depth, clinically relevant reviews on specific aspects of pulmonary, critical care, and sleep medicine, as delivered by the best educators and clinical experts CHEST has to offer. And, this year is no exception.

We have a total of 11 courses offered this go around, including four dedicated full-day sessions on subjects as wide-ranging as lung and pleural ultrasonography, state-of-the-art practices in the diagnosis and management of interstitial lung diseases, and a year-in-review of the best of the pulmonary literature. The American Association for Bronchology and Interventional Pulmonology will hold its annual 1-day meeting at this time, as well.

If you prefer our half-day courses, we have seven: morning sessions focus on pulmonary hypertension, asthma, and sleep medicine, while our afternoon courses cover updates in lung cancer, critical care medicine, use of noninvasive ventilation, and our always-popular InPHOCUS case-based hands-on simulation course for pulmonary vascular disease.

It has been a little while since I attended my first CHEST meeting as a pulmonary and critical care medicine fellow, but I vividly remember thinking how incredibly valuable these courses were, how engaging and welcoming the faculty was, and how much knowledge CHEST was able to cram into a single day. Those opinions have not changed over the last 2 decades. While we think we've got some pretty cool stuff going on throughout the San Antonio meeting, I hope you won't miss the chance to sign up for these incredible learning opportunities.

Looking forward to seeing you all in Texas!

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This month in the journal *CHEST*®

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

GIANTS IN CHEST MEDICINE
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By Dr. Mitchell Drumm

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EVIDENCE-BASED MEDICINE
Chronic Cough Related to Acute Viral Bronchiolitis in Children: CHEST Expert Panel Report
By Dr. A. B. Chang, et al, and the CHEST Expert Cough Panel

News from the Board – June 2018

BY JACK BUCKLEY, MD, FCCP
Regent-at-Large

The Board of Regents met at CHEST headquarters in June to review our work and progress with the 2018-2022 Strategic Plan. As President of CHEST, Dr. John Studdard leads these meetings and shared the great progress toward our goals.

• A theme emphasized by John and CHEST EVP and CEO Steve Welch is the importance of nurturing healthy relationships with other organizations. Whether these are sister societies, like ATS and SCCM, industry partners, or international organizations, CHEST's mission is furthered when we collaborate on important issues. Keep an eye out for upcoming collaborative projects on everything from position statements and clinical guidelines on medical topics, to educational materials for our patients and joint conferences with our international partners; we anticipate holding more than 20 international events over the next year, including programs in Dubai, China, Bangkok, India, Helsinki, and Athens.

DR. BUCKLEY

• The finance committee, led by Dr. Jan Mauer, reported that CHEST is on track to meet its budget for the year. In addition, greater revenue from our publishing enterprises is anticipated for next year, which will help enable enhanced offerings at CHEST courses, live-learning events, and other programs. Thanks to all of our members for making *CHEST*® journal and *CHEST*® *Physician* the top two most widely read publications in the field of Pulmonary Medicine.

• CHEST's new Governance Committee will be reviewing nominations for President and members of the Boards of Regents and Trustees, with a goal to ensure our leaders reflect our membership and bring a wide variety of skills to match organizational needs.

• Planning continues for CHEST's annual meeting October 6-10, 2018, in San Antonio, Texas. Under the leadership of the Scientific Program Chair, Dr. David Schulman, this year's theme is Learn by Doing and will offer more than ever before hands-on learning activities as requested by so many of our members. We look forward to seeing you in San Antonio.

• On a related note, there was a lengthy discussion regarding abstract and case report acceptance. CHEST is very fortunate to receive hundreds of excellent submissions for its annual meeting each year. There are always some proposals that are not accepted for presentation but likely could be with a little polishing. The Board agreed to develop a plan to mentor these submitters to help them get their content accepted for the meeting;

this will roll out for submissions to CHEST 2019.

• CHEST's Board of Regents continues to pursue its own development. Max Reed, Vice President of Leadership and Strategic Initiatives at Lake Forest Graduate School of Management, was invited to the meeting to help the board better understand unconscious bias and learn the steps to strengthen the goals of being an inclusive organization. This most worthwhile half-day educational session will help CHEST achieve one of the most important goals of its strategic plan.

Editor's Note

One of the missions of *CHEST® Physician* is to keep you—our members, colleagues, and friends—apprised of ongoing actions of your CHEST Board of Regents. Thanks to Dr. Buckley for penning this column. We plan to run quarterly updates from the Board, and hope to have regular updates from the CHEST Foundation's Board of Trustees, as well! If there are additional items that you'd like to see related to the function of the College or the Foundation, please let us know at pgoorsky@chestnet.org.

David A. Schulman, MD, FCCP

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

Restaurants galore at CHEST 2018

San Antonio is known for its sports teams, the River Walk, and, of course, the Alamo, but one thing that doesn't get the recognition it deserves is the food. San Antonio offers a variety of must-try food items that you simply can't find anywhere else. Ready to get your grub on? Here are just a few picks to try out while visiting the Alamo City.

Bella on the River

A 13-minute walk from the Convention Center along the River Walk will land you at this San Antonio hotspot. Bella on the River is known for its "Texas Style Italian food," which means bigger, flavor-packed portions with an Italian twist. From antipasto to paella, you're sure to find something on the menu to feast on. Be sure to take a look at their extensive wine list, as well.

Cookhouse

Who says you can't get a little taste of New Orleans while in Texas? The Cookhouse is serving up cajun favorites just a 6-minute drive from the Convention Center. Known for its New Orleans barbequed shrimp, fried boudin balls, and Po' Boys, it'll be hard to pick which one to feast on for dinner.

El Mirador

Just a 4-minute Uber from the Convention Center, you'll find El Mirador, known for its deliciously authentic Mexican food. El Mirador has been serving up chicharrones, fresh breakfast tacos, and other savory dishes to the San Antonio community since 1968. Be sure to grab a seat on their outdoor patio, and take a look at the nearby shops and bars while enjoying your delicious meal.

La Fonda on Main

Take a trip to the Alta Vista neighborhood post-CHEST and visit the oldest Mexican restaurant in San Antonio, open since 1932. La Fonda on Main is known for its lively atmosphere and its traditional Tex-Mex food options. Be sure to take your dinner outside, and sit along their tree-lined patio. As this is one of San Antonio's most recommended restaurants, we suggest making reservations.

Restaurant Gwendolyn

Tired out from the latest in medical advancements and tech? Kick it old school and grab a seat at Restaurant Gwendolyn along the River Walk and feast on local, seasonal, and handmade food from around the San Antonio area. This restaurant's mission is to serve food entirely old school, which means using what they had and creating food like it was prepared prior to the industrial revolution in 1850. If you like surprises, you're in luck, as the menu constantly changes based on what is available at that time!

Keep in mind, these are just some of the San Antonio restaurants serving up delicious dishes. If you find other restaurants we should add to our list, tag us on social media (@accpchest) with your picks!

Clinician educator opportunities at CHEST 2018

BY MATTHEW MILES, MD, MEd, FCCP
Vice-Chair, CHEST Training and Transitions Committee

Are you a clinician educator? Chances are, the answer is yes! Teaching is integral to the practice of chest medicine, whether the audience is medical students, residents, fellows, nurse practitioners, physician assistants, nurses, respiratory therapists, or patients. If you are interested in further developing this essential skill, CHEST 2018 has you covered! This year at the annual meeting, you will find more than 25 hours of content focused on enhancing your teaching.

If most of your teaching is in an academic setting, be sure to make time for the CHEST/APCCMPD Symposium on Sunday afternoon. Here you will learn from experienced program directors and faculty how to implement state-of-the art faculty development methods. You will also have the opportunity to discuss your own experience giving feedback to learners, as best practices are discussed and shared. And the Sunday content doesn't stop there; we also have sessions on ICU burnout – an important factor for all of us – and the use of new mobile technologies to enhance your teaching.

DR. MILES

Monday's sessions will cover teaching in several different settings. First up, a session covering several techniques you can use to teach one-on-one or in a small group setting – perfect for enhancing your teaching during rounds!

Next, learn practical tips to increase the impact of your teaching in a large group lecture or a small group session. The afternoon opens with the latest innovations in Pulmonary and Critical Care fellowship training, to keep you abreast of the newest opportunities for your learners, and a session at the end of the day reviews advances in the teaching of point-of-care ultrasound.

Finally, don't miss the 3:15 symposium on tips to get your CHEST Foundation Grant funded – this session will be pure gold for increasing your proposal's chance for success!

Educators will also be interested in the Tuesday sessions on implicit bias. Although educators always have clear and defined curriculum that we teach to our learners, we can all recognize when a "hidden curriculum" exists. This hidden curriculum can influence our learning and working environment in positive or negative ways. Learning more about our implicit biases can help tilt the balance in the right direction!

Above and beyond the didactics, CHEST 2018 will offer many opportunities for clinician educators beyond what I've described here. While you are planning your personal meeting schedule, be sure to make time for networking with other clinician educators from around the globe. As is the case with so many other skills, we are better teachers together!

Looking forward to seeing you at CHEST 2018!

For more on CHEST 2018—**chestmeeting.chestnet.org**

CHEST® Annual Meeting 2018

CHEST NETWORKS

Ebola virus, social media, opioid crisis, gender in pulmonary disease

Disaster Response

Ebola virus outbreak preparedness

The 2014-2016 Ebola virus disease (EVD) outbreak in West Africa highlighted the global reach of emerging infectious diseases and shattered a sense of complacency in an increasingly interconnected world. Consequently, a subsequent outbreak of EVD in the Democratic Republic of the Congo (DRC) in early May 2018 triggered a swift response. International agencies and workers benefited from increased experience with the disease, new investigational vaccines, including the rVSV-ZEBOV vaccine, and novel therapies, including ZMapp, favipiravir, and remdesivir (GS-5734).


DR. MAVES


DR. MADAR

However, are health-care providers and facilities outside of outbreak areas truly more prepared to handle high-risk pathogens today than they were in 2014? The answer, at least in the United States, seems to be "yes," due to a regional concentration of funding and resources.

The US Department of Health and Human Services (HHS) has identified treatment centers for Ebola and other special pathogens nationwide.[1] The National Ebola Training and Education Center (NETEC) trains health systems' staff to implement disease management plans.[2] The Centers for Disease Control and Prevention (CDC) has prepared recommendations for public health planners.[3]

In nonreferral centers, providers should always obtain a travel history, remain cognizant of emerging diseases,[4] and optimize supportive care. Early collaboration with public health authorities and appropriate infection control precautions are necessary for rapid confirmation of a suspected high-risk pathogen and for ensuring patient and staff safety. Most centers will not need to care for a patient with EVD for an extended period, but the ability to recognize, contain, and refer is essential for good outcomes.

Ryan Maves, MD, FCCP
Cristian Madar, MD, FCCP
Steering Committee Members

References

1. www.hhs.gov/about/news/2016/06/14/hhs-selects-regional-ebola-treatment-center-southwestern-us.html. Accessed July 18, 2018.
2. www.netec.org. Accessed July 18, 2018.
3. www.cdc.gov/vhf/ebola/public-health-planners. Accessed July 18, 2018.
4. www.cdc.gov/travel/notices. Accessed July 18, 2018.

Practice Operations

Current impact of social media on health care

In an age of connectivity, social media websites pose many challenges. Not immune to this are the physicians and their health-care practices, particularly in regards to their online presence to their patients.

Many of these sites publish user-submitted patient appreciation or complaints. These postings are generally viewable to the public and often not moderated or restricted in content. With value-based care at the front lines, these posts may be detrimental to the success of the practice. Public postings exist regardless of providers' awareness or management of them.

There is limited training on social media presence, handling negative reviews, addressing patient-specific posts online, or mediating conflicts. This includes legal issues related to licensing, privacy, litigation, and fraud. Compliance to ethical requirements and protecting patient privacy online still remains crucial in the heavily regulated health-care industry.

The burden of social media remains a widely unacknowledged impediment to growing physicians' practice. While several organizations have published guidelines to help ensure success and to better inform physicians, these are not widely practiced or well known.

However, significant potential benefits to social media include marketing opportunities, education, and connection with patients. Social media has been key for support group networks amongst patients. Similar to professionals in other fields, it is recommended that providers separate their public and private social media accounts or use alternate names.


DR. SISK


DR. ANJUM

For more information about social media and answers to many legal questions, attend the Practice Operations NetWork Featured Lecture at the CHEST Annual Meeting on Monday, October 8, at 1:30 PM.

Megan Sisk, DO
Fellow-in-Training Member
Humayun Anjum, MD, FCCP
Steering Committee Member

Transplant

Implications of the opioid crisis on organ donation for lung transplantation

The opioid epidemic in the United States claims a substantial number of lives annually, with overdose-related deaths increasing five times between 2000 and 2016.[1]

In the midst of this national crisis, perhaps one solace is an increase in organ donation for thoracic transplantation. In fact, data show that patients dying of overdose have the highest donation rates,[2] and a staggering 10 times increase in the proportion of eligible donors dying of overdose has been witnessed over this period (1.2% of donors in 2000, 13.7% in 2016),[3] with a parallel increase in transplants performed.[4]

Despite this, transplant program organ utilization in overdose deaths falls well short of expected, in part due to disease transmission concerns, supported by the observation that these donors are two to five times more likely designated as "Public Health Service (PHS)-Increased-Risk" Criteria for transmission of transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV.[2,5] In lung transplantation, additional concerns over donor quality often exist, including aspiration, edema, or other opioid-induced injuries.

Although a disturbing premise, as the health-care community and lawmakers attempt to curtail the opioid epidemic, it is important to recognize opportunities for improvement in organ utilization, which offers potential to help many patients with cardiopulmonary disease. In addition to community-wide organ donation campaigns, this may stem from dissemination of knowledge of the low infectious risks in PHS-increased-risk donors,[5] as well as analyses showing similar survival among recipients of allografts from overdose-death donors compared with donors from other causes.[3]


DR. KUMAR


DR. KAPNADAK

Use of HCV-positive organs, particularly in the modern era of infectious testing and therapies, offers additional potential,[6] as does fine-tuning technologies such as ex-vivo lung perfusion, which may enhance organ quality making lungs suitable for transplant.

Anupam Kumar, MD
Fellow-in-Training Member
Siddhartha G. Kapnadak, MD
Steering Committee Member

References

1. Rudd RA, et al. MMWR Morb Mortal Wkly Rep. 2016;Dec 30;65(5051):1445.
2. Goldberg DS, et al. Am J Transplant. 2016 Oct; 16(10): 2836.
3. Mehra MR, et al. N Engl J Med. 2018 May 17;378(20):1943.
4. Durand CM, et al. Ann Intern Med. 2018 May 15;168(10):702.
5. Sibulesky L, et al. Clin Transplant. 2015 Sep;29(9):724.
6. Abdelbasit A, et al. Am J Respir Crit Care Med. 2018 Jun 1;197(11):1492.

Women's Health

Sex and gender in pulmonary disease

On September 18-19, 2017, the National Heart, Lung, and Blood Institute convened a workshop of investigators with the National Institutes of Health, the Office of Research on Women's Health, and the Office of Rare Diseases Research to discuss the role of sex and gender in pulmonary disease. The findings of this workshop, published online ahead of print (Han MK, et al. *Am J Respir Crit Care Med*. 2018 May 10. doi: 10.1164/rccm.201801-0168WS. [Epub ahead of print]), outline important future directions for research in pulmonary medicine.

DR. DESAI

The group identified several areas in which there are substantial sex-specific differences in clinical presentation and treatment outcomes in pulmonary diseases, including tobacco cessation, circadian rhythms and sleep-disordered breathing, COPD, asthma, cystic fibrosis, and interstitial lung disease.

In addition to defining the terms sex and gender, the committee called for standardization of the reporting of sex as a variable in animal and cellular models. Given the observed relationship between sex hormones and the development of lung disease, a collaboration across disciplines, including endocrinology, would be useful to understand this relationship at a basic and clinical science level.

Furthermore, in the era of big data research, sex and gender should be included as co-variates when possible to better clarify the contributions of these variables in pulmonary disease.

The workshop also highlighted the need to educate clinicians about these differences. Just as trainees are taught that women can present with atypical symptoms for a heart attack, so should they be taught about the differences in management of chronic lung disease and tobacco dependence between men and women.

Nikita Desai, MD
Fellow-in-Training Member

New opportunity for CHEST Foundation

In June 2018, the CHEST Foundation was approved to participate as a National Organization in the 2018 Combined Federal Campaign (CFC).

The CFC is the only authorized solicitation of employees in the federal workplace on behalf of charitable organizations. As an approved organization, we will be listed on the 2018 CFC Charity List and receive our own code to promote to donors. Receiving this approval to participate in the CFC is a wonderful honor for the CHEST Foundation, and we are excited to share our news with you!

CHEST Foundation President, Lisa K. Moores, MD, FCCP, shares her insight and value about this new opportunity to engage and support the foundation's mission of clinical research, community service, and patient education.

"As a long-time federal employee, I am extremely excited that I can now show my support of the CHEST Foundation through employee giving during the annual CFC campaign," Dr. Moores said. "This will also allow me to share the story of the CHEST Foundation with colleagues. When they choose who they want to give to for their work place giving, they can support the CHEST Foundation, as well. This is a great opportunity for the CHEST Foundation, as I know each year during the CFC campaign (September -January), it is highly encouraged and promoted to employees. This increased exposure is very exciting and will hopefully allow us to strengthen the philanthropic work we do with the Foundation."

Stay tuned for more information as we kick off the Combined Federal Campaign in September 2018!

CRITICAL CARE COMMENTARY

Balanced crystalloids vs saline for critically ill patients

BY MATTHEW W. SEMLER, MD, MSc

If you work in an ICU, chances are good that you frequently order IV fluids (IVF). Between resuscitation, maintenance, and medication carriers, nearly all ICU patients receive IVF. Historically, much of this IVF has been 0.9% sodium chloride ("saline" or "normal saline"). Providers in the United States alone administer more than 200 million liters of saline each year (Myburgh JA, et al. *N Engl J Med.* 2013;369[13]:1243). New evidence, however, suggests that treating your ICU patients with so-called "balanced crystalloids," rather than saline, may improve patient outcomes.

For over a century, clinicians ordering IV isotonic crystalloids have had two basic options: saline or balanced crystalloids (BC). Saline contains water and 154 mmol/L of sodium chloride (around 50% more chloride than human extracellular fluid). In contrast, BCs, like lactated Ringer's (LR), Hartman's solution, and others, contain an amount of chloride resembling human plasma (Table 1). BC substitute an organic anion such as bicarbonate, lactate, acetate, or gluconate, in place of chloride, resulting in lower chloride level and a more neutral pH.

Over the last 2 decades, evidence has slowly accumulated that the different compositions of saline and BC might translate into differences in patient physiology and outcomes. Research in the operating room and ICU found that saline administration caused hyperchloremia and metabolic acidosis. Studies of healthy volunteers found that saline decreased blood flow to the kidney (Chowdhury AH, et al. *Ann Surg.* 2012;256[1]:18). Animal sepsis models suggested that saline might cause inflammation, low blood pressure, and kidney injury (Zhou F, et al. *Crit Care Med*. 2014;42[4]:e270). Large observational studies among ICU patients found saline to be associated with increased risk of kidney injury, dialysis, or death (Raghunathan K, et al. *Crit Care Med.* 2014 Jul;42[7]:1585). These preliminary studies set the stage for a large randomized clinical trial comparing clinical outcomes between BC and saline among acutely ill adults.

Between June 2015 and April 2017, our research group conducted the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) (Semler MW, et al. *N Engl J Med.* 2018;378[9]:819). SMART was a pragmatic trial in which 15,802 adults in five ICUs were assigned to receive either saline (0.9% sodium chloride) or BC (LR or another branded BC [PlasmaLyte A]). The goal was to determine whether using BC rather than saline would decrease the rates of death, new dialysis, or renal dysfunction lasting through hospital discharge. Patients in the BC group received primarily BC (44% LR and 56% another branded BC [PlasmaLyte A]), whereas

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patients in the saline group received primarily saline. The rate of death, new dialysis, or renal dysfunction lasting through hospital discharge was lower in the BC group (14.3%) than the saline group (15.4%) (OR: 0.90; 95% CI, 0.82-0.99; *P*=.04). The difference between groups was primarily in death and new dialysis, not changes in creatinine. For every 100 patients admitted to an ICU, using BC rather than saline would spare one patient from experiencing death, dialysis, or renal dysfunction lasting to hospital discharge (number needed to treat). The benefits of BC appeared to be greater among patients who received larger volumes of IVF and patients with sepsis. In fact, among patients with sepsis, mortality was significantly lower with BC (25.2%) than with saline (29.4%) (*P*=.02).

Another trial was conducted in parallel. Saline against LR or another branded BC (PlasmaLyte) in the ED (SALT-ED) compared BC with saline among 13,347 non-critically ill adults treated with IVF in the ED (Self WH, et al. *N Engl J Med*. 2018;378[9]:829). Like the SMART trial, the SALT-ED trial found a 1% absolute reduction in the risk of death, new dialysis, or renal dysfunction lasting to hospital discharge favoring BC.

The SMART and SALT-ED trials have important limitations. They were conducted at a single academic center, and treating clinicians were not blinded to the assigned fluid. The key outcome was a composite of death, new dialysis, and renal dysfunction lasting to hospital discharge – and the trials were not powered to show differences in each of the individual components of the composite.

Despite these limitations, we now have data from two trials enrolling nearly 30,000 acutely ill patients suggesting that BC may result in better clinical outcomes than saline for acutely ill adults. For clinicians who were already using primarily BC solutions, these results will reinforce their current practice. For clinicians whose default IVF has been saline, these new findings raise challenging questions. Prior to these trials, the ICU in which I practice had always used primarily saline. Some of the questions we faced in considering how to apply the results of the SMART and SALT-ED trials to our practice included:

1. Recent data suggest BC may produce better clinical outcomes than saline for acutely ill adults. Are there any data that saline may produce better clinical outcomes than BC? Currently, there are not.

2. Cost is an important consideration in critical care, are BC more expensive than saline? The cost to produce saline and BC is similar. At our hospital, the costs for a 1L bag of saline, LR, and another branded BC (PlasmaLyte A) are exactly the same.

Table 1. Composition of common IV isotonic crystalloid solutions

	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Lactate	Gluconate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111		1–2		275–295
0.9% saline	154				154				308
Lactated Ringer's	130	4.0	2.7		109		28		273
PlasmaLyte A®	140	5.0		3.0	98	27		23	294

MDedge News

Note: All values are in mEq/L except calculated osmolarity, which is in mOsm/L. 0.9% saline is "Sodium Chloride Injection, USP"; lactated Ringer's is "lactated Ringer's Injection, USP"; and PlasmaLyte A® is "Multiple Electrolyte Injection, Type 1, USP"; all from Baxter Healthcare Corporation in Deerfield, IL, USA.

Source: Dr. Semler

These data challenge ICU providers primarily using saline to evaluate the available data, their current IVF prescribing practices, and the logistical barriers to change, to determine whether there are legitimate reasons to continue using saline, or whether the time has come to make BC the first-line fluid therapy for acutely ill adults.

3. Is there a specific population for whom BC might have important adverse effects? Because some BC are hypotonic, the safety of administration of BC to patients with elevated intracranial pressure (eg, traumatic brain injury) is unknown.

4. Are there practical considerations to using BC in the ICU? Compatibility with medications can pose a challenge. For example, the calcium in LR may be incompatible with ceftriaxone infusion. Although BC are compatible with many of the medication infusions used in the ICU for which testing has been performed, less data on compatibility exist for BC than for saline.

5. Are BC as readily available as saline? The three companies that make the majority of IVF used in the United States produce both saline and BC. Recent damage to production facilities has contributed to shortages in the supply of all of them. Over the long term, however, saline and BC are similar in their availability to hospital pharmacies.

After discussing each of these considerations with our ICU physicians and nurses, consultants, and pharmacists, our ICU collectively decided to switch from using primarily saline to BC. This involved (1) our pharmacy team stocking the medication dispensing cabinets in the ICU with 90% LR and 10% saline; and (2) making BC rather than saline the default in order sets within our electronic order entry system. Based on the results of the SMART trial, making the change from saline to BC might be expected to prevent around 100 deaths in our ICU each year.

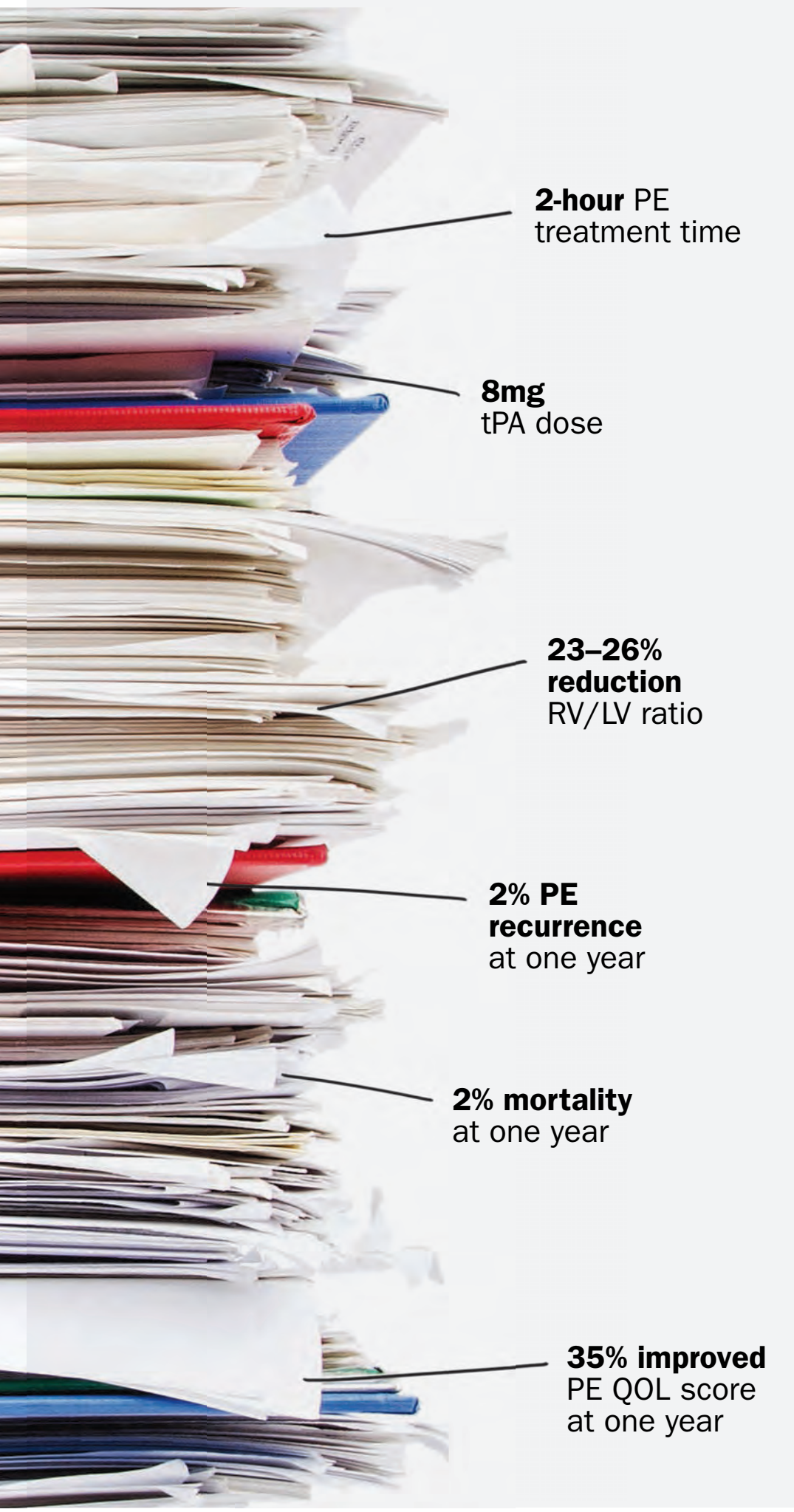
Many questions regarding the effect of IV crystalloid solutions on clinical outcomes for critically ill adults remain unanswered. The mechanism by which BC may produce better clinical outcomes than saline is uncertain. Whether acetate-containing BC (eg, PlasmaLyte) produced better outcomes than non-acetate-containing BC (eg, LR) is unknown. The safety and efficacy of BC for specific subgroups of patients (eg, those with hyperkalemia) requires further study. Two ongoing trials comparing BC to saline among critically ill adults are expected to finish in 2021 and may provide additional insights into the best approach to IVF management for critically ill adults. An ongoing pilot trial comparing LR to other branded BC (Plasmalyte/Normosol) may inform the choice between BC.

In summary, IVF administration is ubiquitous in critical care. For decades, much of that fluid has been saline. BC are similar to saline in availability and cost. Two large trials now demonstrate better patient outcomes with BC compared with saline. These data challenge ICU providers, pharmacies, and hospital systems primarily using saline to evaluate the available data, their current IVF prescribing practices, and the logistical barriers to change, to determine whether there are legitimate reasons to continue using saline, or whether the time has come to make BC the first-line fluid therapy for acutely ill adults.

Editor's Comment

For a very long time, normal saline has been the go-to crystalloid in most ICUs around the globe. In the recent past, evidence started mounting about the potential downside of this solution. The recent SMART trial, the largest to date, indicates that we could prevent adverse renal outcomes by choosing balanced crystalloids over normal saline. These results were even more marked in patients who received a large amount of crystalloids and in patients with sepsis. Dr. Matthew Semler presents solid arguments to consider in changing our practice and adopting a "balanced approach" to fluid resuscitation. We certainly should not only worry about the amount of fluids infused but also about the type of solution we give our patients. Hopefully, we will soon learn if the different balanced solutions also lead to outcome differences.

Angel Coz, MD, FCCP – Section Editor



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

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