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Pirfenidone and nintedanib are among the newest agents in IPF. Multiple clinical trials are aimed at expanding treatment options.

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IPF pipeline crowded with new drug candidates

BY RICHARD MARK KIRKNER

MDedge News

With the emergence of pirfenidone and nintedanib over the past decade or so, pulmonologists now have at their disposal two breakthrough antifibrotic agents for the treatment of idiopathic pulmonary fibrosis (IPF).

But these two drugs have a number of shortcomings that a host of investigative agents are aiming to address. For one, while pirfenidone and nintedanib have been shown to slow disease progression and improve symptoms, they don't stop or reverse the disease. Also, a large number of patients with IPF don't tolerate these drugs well. And, their high cost is a barrier for many patients.

"There are no curative therapies that improve lung function or improve symptoms, so there remains a very large unmet need in terms of therapies or interventions that have better efficacy, better long-term tolerability, and that improve symptoms and quality of life for our patients with IPF disease," said Joyce Lee, MD, associate professor of medicine-pulmonary at the University of Colorado at Denver, Aurora, and senior medical adviser for research and health care quality for the Pulmonary Fibrosis Foundation.

The National Institutes of Health estimates that more than 30,000 new cases of IPF are diagnosed in the United States annually, and

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Short-, long-acting bronchodilators may be similar for COPD exacerbations

BY JIM KLING

MDedge News

AT CHEST 2023 ■ HONOLULU – Among patients hospitalized with chronic obstructive pulmonary disease (COPD) exacerbations, treatment with a combination of long-acting bronchodilators was similar in safety and efficacy to a short-acting combination of albuterol and ipratropium. The 2023 Gold Report on prevention, management, and diagnosis of COPD recommended switching to long-acting bronchodilators despite a lack of clinical evidence showing safety in patients hospitalized for COPD exacerbation, according to Rajiv Dhand, MD, who presented the new study (2023. doi: 10.1016/j.chest.2023.07.3179) at the annual meeting of the American College of Chest Physicians (CHEST).

"We established that it was safe and that it was comparably effective, but you could give 30% lower doses. Patients don't have to be woken up to get the medication, and there's a better chance that all the doses will be administered to these patients. So I think that it provides convenience with similar efficacy and safety," said Dr. Dhand, a pulmonologist

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INSIDE HIGHLIGHT



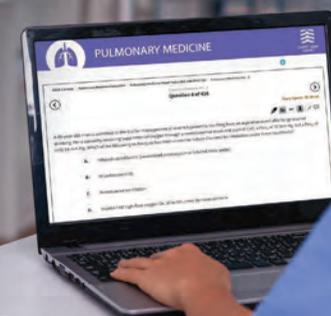
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as many as 3 million people have the disease worldwide. The 5-year survival rate is less than 40% after diagnosis. Bloomberg News reported that more than 80 pharmaceutical companies are working on IPF treatments. iHealthcareAnalyst estimates the global market for IPF will reach \$10.1 billion by 2029 thanks to rapidly increasing prevalence and incidence with age, premium-priced drugs, and rapid approval of new treatments.

The perils of phase 3 studies

A search on ClinicalTrials.gov turned up 89 investigative IPF treatments in human trials. However, the search for alternatives can be perilous. “In the field, we have gotten used to promising phase 2 studies that failed in the phase 3 stage of development,” Dr. Lee said. “I don’t hold my breath these days just in terms of trying to predict whether or not the efficacy will be present in the phase 3 clinical trial.”

Three notable phase 3 flops include the ISABELA 1 and 2 trials of the autotaxin-inhibitor ziritaxestat, which failed to meet their primary endpoint and were halted early (JAMA. 2023;329:1567-78). The phase 3 ZEPHYRUS-1 trial failed to show any benefit of pamrevlumab to improve percent predicted force vital capacity (ppFVC) at week 48, causing discontinuation of a second phase 3 trial. The phase 3 STARScape-OLE study of intravenous recombinant human pentraxin-2 was terminated earlier this year when the sponsor, Hoffmann-LaRoche, decided it was unable to meet its primary objective (NCT04594707).

In the meantime, these six other phase 3 programs in IPF are still in the field:

Anlotinib. A phase 2 and 3 trial in China is evaluating 1-year outcomes of once-daily oral anlotinib for treatment of IPF/progressive fibrosis-interstitial lung disease (PF-ILDs) (NCT05828953). Anlotinib is a tyrosine kinase inhibitor (TKI) that targets four factors: vascular endothelial growth factor receptor (VEGR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR), and c-kit. It’s approved in China as a third-line therapy for non-small cell lung cancer (NSCLC).

BI 101550. Enrollment in the FIBRONEER-IPF trial commenced last fall (NCT05321069), with

completion scheduled for late next year. BI 101550 is an oral phosphodiesterase 4B (PDE4B) inhibitor. FIBRONEER-ILD is a separate phase 3 trial in fibrosing idiopathic lung disease (NCT05321082). In both trials, the primary endpoint is the absolute change from baseline in FVC at week 52.



Dr. Lee

BMS-986278. Results of a phase 2 trial showed that twice-daily treatment with oral BMS-986278 60 mg over 26 weeks reduced the rate of decline in ppFVC by 69% vs. placebo. The phase 3 ALOFT trial has been approved but hasn’t yet started recruiting patients (NCT06003426).

BMS-986278 is a lysophosphatidic acid receptor 1 (LPA1) antagonist.

Lansoprazole. Commonly used to treat and prevent gastrointestinal problems like stomach ulcers and esophagitis, this oral proton pump inhibitor (PPI) is the focus of a trial in the United Kingdom evaluating if PPIs can slow the progression of IPF (NCT04965298).

N-acetylcysteine (NAC). The PRECISIONS trial is evaluating the effect of NAC plus standard-of-care treatment in IPF patients who have the TOLLIP rs3750910 TT genotype (NCT04300920). Participants receive 600 mg NAC orally or matched placebo three times daily for 24 months. Trial completion is scheduled for 2025.

Treprostinil. Already approved to treat pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease, inhaled Treprostinil is the subject of the TETON 1 and 2 trials evaluating its impact on ppFVC after 52 weeks of treatment (NCT04708782, NCT05255991).

Phase 2 candidates

The primary endpoint in most of the phase 2 trials is change in ppFVC capacity from baseline to week 24. The following investigative therapies are in phase 2 trials:

Bexotegast (PLN-74809) is an oral, small-molecule, dual-selective inhibitor of alpha_v/beta₆ and alpha_v/beta₁ (NCT04396756).

BBT-877, described as a potent autotaxin (ATX) inhibitor, demonstrated its ability to inhibit lysophosphatidic acid (LPA) production by as much as 90% (NCT05483907).

CC-90001 is an oral, once-daily c-Jun N-terminal kinases inhibitor. JNKs have been implicated in the underlying mechanisms of fibrosis,

IPF TRIALS continued on following page

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Nintedanib dose reductions in IPF may do no harm

BY NEIL OSTERWEIL

AT CHEST 2023 ■ HONOLULU – There's new evidence to support a practice many pulmonologists have been doing empirically anyway: reducing the dose of antifibrotic medication nintedanib (Ofev) for patients with idiopathic pulmonary fibrosis (IPF) who can't tolerate the full 150-mg twice-daily dose.

An analysis of data from a large administrative claims database showed there were no significant differences in all-cause mortality or hospitalization rates between patients with IPF treated at the 150-mg twice-daily dose and at a reduced twice-daily dose of 100 mg nintedanib (CHEST. 2023 Oct. doi: 10.1016/j.chest.2023.07.1996). Although the results need to be confirmed, they suggest patients with IPF can still fare just as well with a reduced-dose nintedanib regimen, ideally with fewer side effects, reported Andrew Limper, MD, of the Mayo Clinic in Rochester, Minn. "This is not definitive proof, I'm not making more out of this than it is, but we all put people on 100 mg

twice daily because their guts don't tolerate it; they live in the bathroom and they don't want to live that way," said Dr. Limper in an oral abstract session at the annual meeting of the American College of Chest Physicians (CHEST) 2023. Dr. Limper noted the data were preliminary.

Nintedanib is approved in the United States for the treatment of IPF, chronic fibrosing interstitial lung diseases (ILD) with a progressive phenotype, and systemic sclerosis-associated ILD. For IPF, the standard dose established in randomized clinical trials is 150 mg twice daily.

However, nintedanib is associated with side effects, including hepatic and other gastrointestinal toxicities, arterial thromboembolic events, and proteinuria within the nephrotic range. As a result, clinicians often reduce the dose to 100 mg twice daily, but there is a lack of data to indicate whether it's safe to do so or if efficacy will be compromised. To see whether dose reductions might result in poorer outcomes for patients with IPF, Dr. Limper and colleagues analyzed data from the OptumLabs

Data Warehouse, a large administrative claims database, to compare outcomes for patients treated with IPF at either the 150-mg or 100-mg twice-daily doses. They used propensity-score matching to account for differences among individuals according to age, sex, race/ethnicity, residence, insurance type, additional medication use, oxygen use, smoking status, health care use, and comorbidities. The final cohort included 346 patients in each dosing group. There was no difference between the dosing groups for the primary outcome of all-cause mortality at 18 months, with a nonsignificant hazard ratio of 0.65 ($P = .313$), and no significant difference over 24 months in risk of hospitalization, with a hazard ratio of 0.98 ($P = .899$). "This is not randomized controlled data; I doubt that [nintedanib maker Boehringer Ingelheim] is ever going to do a 150- vs 100-milligram head-to-head trial, but it does give us some ground to start to look at this," Dr. Limper said.

The study was supported by a grant from Three Lakes Foundation. Dr. Limper and Dr. Baqir have disclosed no relevant financial relationships. ■

IPF DRUGS *continued from previous page*

including epithelial cell death, inflammation and polarization of profibrotic macrophages, fibroblast activation, and collagen production (NCT03142191).

C21 targets the underlying fibrosis in IPF by stimulating the protective arm of the renin-angiotensin system. It also has an upstream effect by promoting alveolar repair by which it can reduce fibrosis formation, stabilize disease, and increase lung capacity (NCT04533022).

CSL312 (garadacimab) is a humanized anti-FXIIa monoclonal antibody administered intravenously (NCT05130970).

Cudetaxestat is a noncompetitive autotaxin inhibitor (NCT05373914).

Bersiposocin/DWN12088, an inhibitor of prolyl-tRNA synthetase 1 (PARS1), is suspected to control the pathologic accumulation of collagen containing high amounts of proline in fibrotic diseases (NCT05389215).

ENV-101, a small-molecule inhibitor of the Hedgehog (Hh) signaling pathway, which plays a key role in IPF. This agent was originally developed to target Hh-driven cancers (NCT04968574).

GKT137831 (setanaxib) inhibits nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) isoforms (NCT03865927).

HZN-825 is a lysophosphatidic acid receptor 1 (LPAR1) antagonist (NCT05032066).

Ifetroban, a potent and selective thromboxane-prostanoid receptor

(TP α) antagonist, exhibits a high affinity for TP α on platelets, vascular and airway smooth muscle, and fibroblasts, and lacks agonistic activity (NCT05571059).

INS018_055 is a small-molecule, oral antifibrotic candidate notable for being the first entirely AI-generated drug to enter phase 2 trials. Trial enrollment started in October (NCT05975983, NCT05983920).

Jaktinib dihydrochloride monohydrate is an oral JAK1, JAK2, and JAK3 inhibitor (NCT04312594).

Leramistat is an anti-tumor necrosis factor (TNF) agent (NCT05951296).

LTP001, an oral, selectively deuterated form of pirfenidone designed to retain the antifibrotic and anti-inflammatory activity of pirfenidone with a differentiated pharmacokinetic profile (NCT05497284, NCT05321420).

ME-015 (suplatast tosilate) aims to stabilize ion channels in the neuronal endings in the lungs that mediate IPF-related cough (NCT05983471).

Nalbuphine, a small-molecule, dual-mechanism treatment for chronic cough in IPF, acts as both a mu opioid receptor antagonist and a kappa opioid receptor agonist (NCT05964335). The CANAL trial, complete last year, is evaluating an extended-release formulation (NCT04030026).

NP-120 (ifenprodil), a small-molecule N-methyl-D-aspartate (NMDA) receptor antagonist,

specifically targets the NMDA-type subunit 2B (GluN2B) (NCT04318704).

Orvepitant, a selective antagonist for the NK $_1$ receptor, is being evaluated to treat IPF-related cough (NCT05815089).

RXC007 (zelasudil), a Rho-associated coiled-coil-containing protein kinase 2 (ROCK2) selective inhibitor, was granted FDA orphan drug designation in August 2023 (NCT05570058).

Saracatinib is a selective Src kinase inhibitor originally developed for oncological indications (NCT04598919).

SHR-1906, an intravenous treatment, inhibits binding of a target protein to a variety of cytokines and growth factors, affects downstream signaling pathways, and reduces cell proliferation and migration (NCT05722964).

TTI-101, an oral, small-molecule inhibitor of signal transducer and activator of transcription (STAT3), which has been found to accumulate in the lungs of IPF patients (NCT05671835).

VAY736 (lanalumab) is a BAFF-R inhibitor (NCT03287414).

Vixarelimab is a human monoclonal oncostatin M receptor beta antibody (NCT05785624).

Some investigative programs, however, didn't make it out of phase 2. The trial evaluating inhaled GB0139, a selective functional antagonist of G-protein-coupled receptor 84, which plays a key role in fibrosis, failed to meet its primary

endpoint (NCT03832946). Likewise, oral GLPG1205 failed to show a significant difference in FVC decline vs. placebo (NCT03725852). The program to develop SAR156597, also known as romilkimab, was halted (NCT02345070). ND-L02-s0201n, an siRNA oligonucleotide drug designed to inhibit heat shock protein 47 (HSP47), which regulates collagen synthesis and secretion that causes fibrosis, didn't show the expected efficacy (NCT03538301).

Phase 1 trials

No fewer than 27 phase 1 trials are evaluating investigative treatments for IPF, many in the early phase or not yet recruiting. According to GlobalData, phase 1 drugs for IPF have a 66% chance of moving onto phase 2. Among the advanced phase 1 trials, the list of those that have gained corporate backing can be found on the CHEST PHYSICIAN website at <https://tinyurl.com/mr827jyx>.

"While we have therapies that we're able to give patients, we need to do more and we need to do better," Dr. Lee said. "We're all hopeful the next phase 3 clinical trial will be something that will help change the treatment paradigm for our patients. We're very patient, and hopefully those that are interested in improving this treatment landscape will continue to persist."

Dr. Lee disclosed financial relationships with Boehringer Ingelheim, Pliant Therapeutics, Blade Therapeutics, United Therapeutics, Eleven P15, and Avalyn Pharma. ■

and professor of medicine at the University of Tennessee, Knoxville.

The researchers randomized 60 patients to receive nebulized albuterol (2.5 mg) and ipratropium (0.5 mg) every 6 hours (short-acting group) or nebulized formoterol (20 mcg) every 12 hours and revefenacin (175 mcg) every 24 hours (long-acting group). The mean age was 63.2 years, 58.3% were male, and 65% were current smokers. The median decrease between day 1 and day 3 in the Modified Borg Dyspnea score was 4.0 in the long-acting group ($P < .001$), and 2.0 in the short-acting group; the latter was not statistically significant ($P = .134$). Both groups had a decrease in supplemental oxygen requirement, with no difference between the groups, and no difference in the number of respiratory visits for rescue therapy. Respiratory therapists welcomed the evidence. “As a respiratory therapist, I feel we should move away from giving good short-acting [therapies]. The new guidelines state we should move away from them, but I think physicians in general have not gone that way. The way that we’re working, giving short-acting every 4 hours – I don’t see that it’s a benefit to our patients,” said Sharon Armstead, who attended the session and was asked to comment on the study. She is a respiratory therapist at Ascension Health and an instructor at Concordia University, Austin, Tex. Ms. Armstead has asthma, and has first-hand experience as a patient when respiratory therapists are unable to attend to the patient every 4 hours. She suggested that continued use of short-acting therapies may be due to inertia. “It’s easier [for a physician] to click a button on [a computer screen] than to actually slow down and write the order. If we need a rescue, then we’ll call for a rescue,” Ms. Armstead said.

She anticipates long-acting therapies will ultimately lead to better outcomes because they will increase the time respiratory therapists can spend with patients. “That’s what we really want to do. We want to spend time with our patients and stay there and watch our patients. But if you’re just telling us to [administer a therapy] every 4 hours, it’s not really giving the patient what they need.”

Specifically, there were concerns about cardiovascular safety, but the researchers found no between-group differences. Asked for comment, session co-moderator Brittany Duchene, MD, said: “From a practical perspective, it’s challenging to get those drugs placed

on an outpatient basis. They are very expensive, and they’re newer [drugs], but I think overall it’s good to give less.” Dr. Duchene is a pulmonary critical care physician at Northeastern Vermont Regional Hospital, St. Johnsbury. A concern raised by one audience member is

that some patients are used to frequent treatment and may be anxious with less frequent therapy. “I think we just need some reeducation that this is like a long-acting medicine. It also decreases the burden on our respiratory therapists, which is very good,” said Dr. Duchene.

The study was funded by Mylan/Theravance Biopharma. Dr. Dhand has received research support from Theravance, Mylan, and Viatrix. He has received honoraria from Teva and UpToDate. Ms. Armstead and Dr. Duchene have no relevant financial disclosures. ■

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High phosphate tied to increased AECOPD mortality

BY WALTER ALEXANDER

MDedge News

An investigation into associations between serum phosphate levels and in-hospital mortality

risk among patients with acute exacerbations of chronic obstructive pulmonary disease found significantly higher in-hospital mortality among AECOPD patients with high serum phosphate levels. The finding,

according to Li et al. in a HELIYON article (2023 Sep 6. doi: 10.1016/j.heliyon.2023.e19748), suggests that hyperphosphatemia may be a high-risk factor for AECOPD-related in-hospital mortality.

Phosphorus is key to several physiological processes, among them energy metabolism, bone mineralization, membrane transport, and intracellular signaling. Li et al. pointed

AECOPD continued on following page

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out that, in patients with multiple diseases, hyperphosphatemia is associated with increased mortality. In the development of COPD specifically, acute exacerbations have been shown in recent studies to be an important adverse event conferring heightened mortality risk. However, AECOPD mortality rates remain high, making

identification of potential factors, Li et al. stated, crucial for improving outcomes in high-risk patients. The electronic Intensive Care Unit Collaborative Research Database (eICU-CRD) holds data associated with over 200,000 patient stays, providing a large sample size for research studies. To determine the relationship between serum phosphate and

in-hospital mortality in AECOPD patients, investigators analyzed data from a total of 1,199 AECOPD patients (mean age, 68 years; ~55% female) enrolled in eICU-CRD and divided them into three groups according to serum phosphate level tertiles: lowest tertile (serum phosphate ≤ 3.0 mg/dL, $n = 445$), median tertile (serum phosphate > 3.0 mg/dL

and ≤ 4.0 mg/dL, $n = 378$), and highest tertile (serum phosphate > 4.0 mg/dL, $n = 376$). The Li et al. study's primary outcome was all-cause in-hospital mortality, defined as survival to hospital discharge. Secondary outcomes included length of stay in the ICU, LOS in the hospital, and all-cause ICU mortality. The analysis of patient characteristics

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showed patients in the highest tertile of serum phosphate had significantly higher body mass index (BMI) ($P < .001$), lower temperature ($P < .001$), lower heart rate ($P < .001$), lower mean arterial blood pressure ($P = .011$), higher creatinine ($P < .001$), higher potassium ($P < .001$), higher sequential organ failure assessment ($P < .001$), higher acute physiology and

chronic health evaluation (APACHE IV) ($P < .001$), and higher ICU mortality ($P < .001$). Patients with higher serum phosphate levels were more likely to receive renal replacement therapy ($P < .001$) and vasoactive drugs ($P = .003$) than those with lower serum phosphate. Differences were also observed for age ($P = .021$), calcium level ($P = .023$), sodium level

($P = .039$), hypertension ($P = .014$), coronary artery disease ($P = .004$), diabetes ($P = .017$), and chronic kidney disease ($P < .001$). No significant differences were observed for gender, respiration rate, SpO_2 , white blood cell count, hemoglobin, platelets, cirrhosis, stroke, ventilation, LOS in ICU and in hospital ($P > .05$). A univariate logistic regression

analysis performed to determine the relationship between serum phosphate level and risk of in-hospital mortality revealed that higher serum phosphate level correlated with increased in-hospital mortality (odds ratio, 1.30; 95% confidence interval, 1.16-1.46; $P < .001$). Li et al. posited several mechanisms may explain increased mortality at higher serum phosphate levels in AECOPD: Increased serum phosphate induces vascular calcification and endothelial dysfunction, leading to organ dysfunction; hyperphosphatemia causes oxidative stress, cell apoptosis, and inflammation, which are all involved in the pathogenesis of AECOPD, and a higher phosphate diet exacerbates aging and lung emphysema phenotypes; and restriction of phosphate intake and absorption relieves these phenotypes and alveolar destruction, possibly contributing to AECOPD development. Li et al. stated: "Reducing serum phosphate levels may be a therapeutic strategy to improve prognosis of AECOPD patients."

"This large retrospective analysis on eICU database in the U.S. revealed elevated serum phosphate levels with increased in-hospital mortality among patients experiencing acute exacerbation of COPD," Dharani Narendra, MD, assistant professor of medicine at Baylor College of Medicine, Houston, said. "This association, previously observed in various chronic conditions including COPD, particularly in men, is now noted to apply to both genders, irrespective of chronic kidney disease. The study also hints at potential mechanisms for elevated phosphate levels, such as inflammation, oxidative stress, and cell apoptosis in AECOPD, as well as a high-phosphate diet. It remains imperative to ascertain whether treating hyperphosphatemia or implementing dietary phosphate restrictions can reduce mortality or prevent AECOPD episodes. These demand additional clinical trials to establish a definitive cause-and-effect relationship and to guide potential treatment and prevention strategies."

Study limitations include that smoking, exacerbation frequency, severity, PH, Pao_2 , $Paco_2$, and lactate, were not included, owing to more than 20% missing values. This work was supported by the National Natural Science Foundation of China, Scientific Research Fund of Hunan Provincial Education Department, Hunan Provincial Natural Science Foundation, and Special fund for rehabilitation medicine of the National Clinical Research Center for Geriatric Disorders Clinical Research Fund. The authors declare no competing interests. ■

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Pediatric sleep-disordered breathing linked to multilevel risk factors

BY WALTER ALEXANDER

MDedge News

In the first study evaluating pediatric sleep-disordered breathing from indoor environment and neighborhood perspectives, multilevel risk factors were associated with SDB-related symptoms. Beyond known associations with environmental tobacco smoke (ETS), a novel association with SDB symptoms was observed for exposure to mice, cockroaches, and rats.

Although it is well known that pediatric SDB affects low-socioeconomic status (SES) children disproportionately, the roles of multilevel risk factor drivers including individual health, household SES, indoor exposures to environmental tobacco smoke, pests, and neighborhood characteristics have not been well studied, Gueye-Ndiaye et al. wrote in *CHEST Pulmonary* (2023 Sep 5. doi: 10.1016/j.chpulm.2023.100019). Pediatric SDB, a known risk factor for many health, neurobehavioral, and functional outcomes, includes habitual snoring and obstructive sleep apnea and may contribute to health disparities. Adenotonsillar hypertrophy and obesity are the most commonly recognized risk factors for SDB in generally healthy school-aged children. A role for other risk factors, however, is suggested by the fact that Black children have a fourfold increased risk for obstructive sleep apnea (OSA), compared with White children, unexplained by obesity, and have decreased response to treatment of OSA with adenotonsillectomy, compared with White children. Several studies point to neighborhood disadvantages as factors in heightened SDB prevalence or severity, Gueye-Ndiaye et al. stated.

The authors performed cross-sectional analyses on data recorded from 303 children (aged 6-12 years) enrolled in the Environmental Assessment of Sleep Youth (EASY) study from 2018 to 2022. Among them, 39% were Hispanic, Latino, Latina, or Spanish origin; 30% were Black or African American; 22% were

White, and 11% were other. Maternal education attainment of a high school diploma or less was reported in 27%, and 65% of the sample lived in disadvantaged neighborhoods. Twenty-eight percent of children met criteria for objective SDB (Apnea-Hypopnea Index/Oxygen Desaturation Index ≥ 5 /hr). Exposure docu-



Dr. Coates

mentation was informed by caregiver reports, assays of measured settled dust from the child's bedroom, and neighborhood-level census data from which the Childhood Opportunity Index characterizing neighborhood disadvantage (ND) was derived.

The study primary outcome was the SDB-related symptom burden assessed by the OSA-18 questionnaire total score. Compared with children with no adverse indoor exposures to ETS and pests, children with such exposures had an approximately 4- to 12-point increase in total OSA-18 scores, and the increase among those with exposure to both ETS and pests was about 20 points (approximately a 1.3-standard deviation increase), Gueye-Ndiaye et al. reported.

In models adjusted for age, sex, minority race, and ethnicity, low maternal education was associated with a 7.55 (95% confidence interval, 3.44-11.66; $P < .01$) increased OSA-18 score. In models adjusted for sociodemographics including maternal education, history of asthma and allergic rhinitis were associated with a 13.63 (95% CI, 9.44-17.82; $P < .01$) and a 6.95 (95% CI, 2.62-11.29; $P < .02$) increased OSA-18 score, respectively. The authors noted that prior Canadian studies have shown OSA to be three times as likely in children with mothers reporting less than a high school education than in children with university-educated mothers.

Speculating on the drivers of this association, they noted that the poor air quality due to tobacco smoke and allergen exposures to rodents, mold, and cockroaches are known contributors to asthma symptoms. Despite the differing pathogenesis of OSA and asthma, they suggest overlapping risk factors. Irritants and allergens may

exacerbate SDB by stimulating immune responses manifested as adenotonsillar hypertrophy and by amplifying nasopharyngeal inflammation, adversely affecting upper airway patency. While ETS was not common in the sample, it was associated strongly with SDB. Gueye-Ndiaye et al. also showed associations between pest exposure, bedroom dust, and SDB symptoms. The findings, they concluded, support the importance of household- and bedroom-environmental conditions and sleep health.

OSA-18 scores were also elevated by about 7-14 points with allergic rhinitis and asthma, respectively. The findings, Gueye-Ndiaye et al. stated, underscore that asthma-prevention strategies can be leveraged to address SDB disparities. No amplification of pest exposure effects, however, was found for asthma or allergic rhinitis.

"This is an incredibly important study, one that adds to our understanding of the risk factors that contribute to pediatric sleep health disparities," said assistant professor of pediatrics Anne C. Coates, MD, FCCP, Tufts University, Boston. "We have previously understood risk factors for sleep-disordered breathing like adenotonsillar hypertrophy, but this adds other elements like environmental tobacco smoke, pests, and home and neighborhood factors," she told this news organization. "One of the most important takeaways is that, beyond the importance of accurate diagnosis, there is the importance of advocating for our patients to ensure that they have the healthiest homes and neighborhoods. We need to inspire our colleagues to be advocates – for example – for pest mitigation, for antismoking policies, for every policy preventing the factors that contribute to the burden of disease."

Dr. Coates is coauthor of "Advocacy and Health Equity: The Role of the Pediatric Pulmonologist," currently in press (*Clinics in Chest Medicine*), and a member of the *CHEST PHYSICIAN* Editorial Board.

The authors noted that a study limitation was that the sample was from one geographic area (Boston). Neither the authors nor Dr. Coates listed any conflicts. ■

Sentinel central events prevalent during DISE for OSA

BY HEIDI SPLETE

Nearly half of patients undergoing drug-induced sleep endoscopy (DISE) experienced a sentinel central event after an average of 6 minutes in a study of 103 individuals with obstructive sleep apnea (OSA).

DISE has become the top choice for surgical selection in patients with OSA, but it has a variable effect on surgical outcomes, Julianna G. Rodin, MD, of the University of

Pennsylvania, Philadelphia, and colleagues explained.

The University of Pennsylvania sleep surgery team developed a comprehensive DISE platform that includes simultaneous collection of respiratory airflow and effort measurements, airway collapsibility, and videoendoscopy.

"This home sleep study-style setup has allowed us to better characterize the upper airway during DISE, and even helped our team diagnose a patient with Cheyne-Stokes

breathing/central sleep apnea," Dr. Rodin said in an interview.

"With it, we also began to notice relatively frequent central and/or mixed sleep-disordered breathing events during DISE after propofol dosing initiation," she said.

In a study presented at the American Academy of Otolaryngology-Head and Neck Surgery annual meeting, researchers measured the frequency and timing of sentinel central and/or mixed events (SCent) in adults undergoing DISE to assess

the prevalence and impact on DISE. The researchers assessed differences in VOTE (velum, oropharynx, tongue base, and epiglottis) classification in sentinel central events, compared with obstructive events. VOTE scores were calculated using a grade 0 for no obstruction, 1 for partial obstruction, and 2 for total obstruction.

The study population included 103 adults with OSA who underwent DISE with propofol sedation

DISE continued on page 14

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Patient transplanted with modified pig heart doing well

BY STEVE STILES

The second patient to be transplanted with a genetically modified pig heart at the University of Maryland Medical Center (UMMC), Baltimore, is said to be stable and doing well after the Sept. 22 operation. The organ passed an early test by avoiding hyperacute rejection.

Physicians for the patient, a 58-year-old former lab tech repeatedly turned down for standard allograft transplantation, say they are making good use of lessons from last year's case of David Bennett, who survived in hospital with difficulty for 2 months after receiving the first such heart at the center in January 2022.

Mr. Bennett's clinical course had been promising at first but grew turbulent with repeated bouts of infection followed by adjustments to his aggressive immunosuppressant regimen and other complications. It was also learned weeks after the xenotransplant operation the heart from the genetically modified donor pig had carried a porcine cytomegalovirus to Mr. Bennett's body, although there was never evidence the virus infected other organs or played a major role in his death.



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The new xenotransplant recipient, Lawrence Faucette of Frederick, Md., is benefiting from that experience, which was documented in journal reports. Mr. Faucette had been turned down by UMMC "and several other leading transplant hospitals due to his pre-existing peripheral vascular disease and complications with internal bleeding," notes a UMMC press release describing his procedure.

The patient "is currently breathing on his

own, and his heart is functioning well without any assistance from supportive devices," says the statement. Despite a few setbacks, Mr. Faucette is "on the right track," said Muhammad M. Mohiuddin, MBBS, surgeon and xenotransplantation program director at the University of Maryland, Baltimore, in an interview.

"We're taking one day at a time. His immune system is still intact, despite the heavy immune suppression," he told this news organization. His heart didn't carry a virus and "has not shown any signs of rejection so far." Dr. Mohiuddin said, "is very hopeful that we will be able to at least mobilize the patient, and he can be discharged. But it's a little too early to call."

Mr. Faucette, as part of his immunosuppressant regimen, is receiving tegoprubart (Eledon Pharmaceuticals), an investigational antibody that blocks CD40 ligand. His predecessor Mr. Bennett, in contrast, had received a blocker of the CD40 receptor (Kiniksa Pharmaceuticals) along with other more familiar immunosuppressants.

The new anti-CD40-ligand blocker, Eledon said, is in phase 1 studies looking at efficacy in patients with conventional kidney transplants. ■

DISE continued from page 12

at a single academic medical center between June 2020 and November 2022. The mean age of participants was 53.5 years, mean body mass index (BMI) was 29.7 kg/m², and 67% were male. The average apnea-hypopnea index (AHI) was 30.7 events/hour. Researchers used a polysomnography platform to capture data on nasal airflow, thoraco-abdominal effort belt signals, and videoendoscopy.

A total of 47 patients (46%) had at least one SCent. The average time to the first SCent was just under 6 minutes, and average transition to obstructive pathology in these patients occurred between 7 and 8 minutes. Using the one-sided prediction interval, at least 95% of patients were expected to transition to obstructive pathology within 12-13 minutes, Dr. Rodin said. In addition, 29 of the 46 patients with SCent (63%) showed significant variability between central/mixed VOTE scores and obstructive VOTE scores. No statistically significant differences were noted between patients with and without SCent in terms of demographics or AHI.

Surprising prevalence of SCents

"We anecdotally noted that SCents seemed to be somewhat common during the initial period of DISE, but were surprised that we saw at least one SCent in almost 50% of our DISE population," Dr. Rodin said. "We also saw that the majority

of these SCents eventually transitioned to obstructive events after approximately 12 minutes, which is often past the average duration of normal DISE exams." The high frequency of differing VOTE scores between SCents and obstructive events also was unexpected, she added. Within the changes in VOTE scores as defined in the study, "there was a higher tendency for SCents to have more complete tongue base collapse compared to no or partial collapse in obstructive events, and to transition from anterior-posterior velum to concentric velum collapse during the obstructive event."

This outcome could potentially affect a patient's candidacy for hypoglossal nerve stimulator therapy, she explained.

The takeaway from the current study is an increased awareness of the prevalence and timing of SCents in OSA patients, said Dr. Rodin. Clinicians who offer DISE and positive airway pressure alternatives also should be mindful of clinical signs of effort, by monitoring the chest and abdomen during DISE in the absence of respiratory effort belts.

The study findings also suggest that clinicians consider extending the minimum DISE duration to 10 minutes to ensure that the majority of SCents have passed, and delay VOTE scoring until patients transition to obstructive events, she added.

As for additional research, Dr. Rodin said: "If we could repeat the study with a standardized protocol

of target-controlled infusion of propofol, that would further bolster the data." However, TCI is not approved in the United States.

"Our propofol dosing technique was not standardized across all patients, which in theory could account for more SCents if patients were more sedated," Dr. Rodin noted. "However, we did not see a difference in average bispectral index levels across all patients."

Other limitations of the current study included an inability to visualize the entire upper airway to achieve a complete VOTE score for every patient, which could have led to underestimation of the VOTE difference frequency, she added.

Data inform team approaches to DISE

As DISE procedures become more widespread, "it is paramount that we understand the risks associated with these procedures to increase safety, improve shared decision-making, and encourage a team-based approach in the operating room with our anesthesia colleagues," said Daniel M. Zeitler, MD, from the University of Washington and Virginia Mason Medical Center, both in Seattle, who served as a moderator for the session in which the study was presented.

"I was surprised by these data for two reasons," Dr. Zeitler said in an interview. "We typically don't wait more than a few minutes between induction of anesthesia and the

initiation of the airway procedure. This study calls that practice into question, and the duration of time before the onset of a sentinel event was much longer than I would have expected," he said.

Second, "I was quite surprised that there were no differences in the demographics or AHI between the two groups; this reminds us that AHI and BMI alone may not be themselves predictive of risk and all patients should be assessed similarly."

"Otolaryngologists performing DISE need to be aware of these data, communicate them to the involved teams, including anesthesia, nursing, and postanesthesia care units, and remember to delay the manipulation of the airway long enough to minimize the risk of a sentinel event," Dr. Zeitler said. "Perhaps this also means we need improved intraoperative monitoring for these patients, including respiratory airflow and effort monitoring."

For further research, "we need to increase the number of patients, perform a multicenter study, and expand the study to a wider range of ages, BMI, and AHI," he added. A recommended algorithm for these cases in order to standardize the practice would be useful.

The study received no outside funding. Dr. Rodin and Dr. Zeitler reported no relevant financial relationships. Several coauthors disclosed funding and relationships with multiple companies unrelated to the current study. ■

Dietary changes may improve lung health

BY NEIL OSTERWEIL

AT CHEST 2023 ■ HONOLULU – What we eat and what’s in the gut may influence lung health for better or worse, suggest new data from an ongoing study of lung function in New York City firefighters who were at the World Trade Center site on Sept. 11, 2001, and the days immediately following.

Among NYC firefighters enrolled in the randomized FIREHOUSE (Food Intake Restriction for Health Outcome Support and Education) study who took part in a microbiome substudy, those who followed a low-calorie, Mediterranean-style diet had higher levels in stools samples at 6 months of *Bacteroides ovatus*, a bacterial species associated with protection against bowel inflammation.

In contrast, participants who followed a usual-care diet had elevated 6-month levels of a species associated with high-fat diets and inflammation, reported Rachel Lam, a

Participants in the LoCalMed group had significant decreases in BMI and increases in FEV₁.

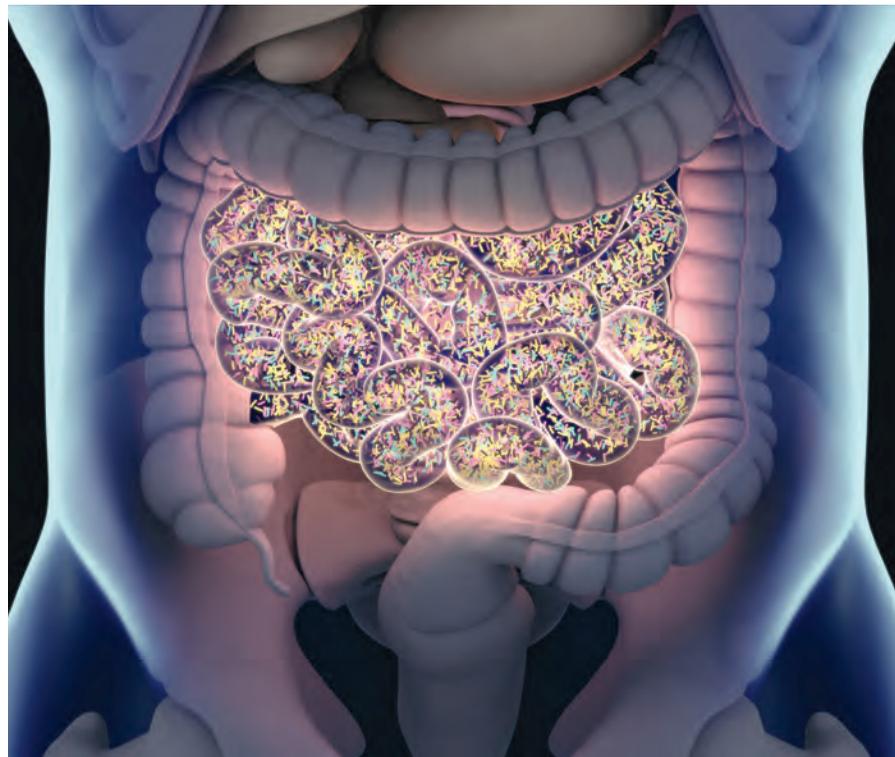
predoctoral fellow in the Nolan Lab at NYU Langone Medical Center, at the annual meeting of the American College of Chest Physicians (CHEST).

“Overall, we found that, in our validation cohort, *Bacteroides ovatus* was increased in the LoCalMed arm after 6 months, and this bacterial species is associated with fewer negative health effects,” she said.

Ms. Lam noted that, in a murine model of high-fat diets, mice gavaged with *Bacteroides ovatus* had reductions in body mass index (BMI) and decreased serum LDL cholesterol and triglyceride levels.

FIREHOUSE cohort

Senior author Anna Nolan, MD, whose lab members study predictors of lung function loss in a cohort of firefighters who were exposed to the particulate matter clouding the air of lower Manhattan on Sept. 11 and the ensuing days, told this news organization that the findings, while preliminary, support previous research findings on potential links



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between intestinal microbiota and lung function.

“It’s interesting that we saw this done in other models, like mouse models and such, where certain bacteria were viewed as healthy for the system, and if they were able to bring that bacteria out in larger amounts they saw anti-inflammatory effects, so we’re hoping to mirror that and also do a mouse model,” she said.

Dr. Nolan’s group has previously shown that markers for the metabolic syndrome, inflammation, and vascular injury detected in serum samples taken within 6 months of Sept. 11 were predictive for later abnormal lung function. In addition, their group has found that elevated serum levels of an LDL metabolite after intense World Trade Center dust exposure is a risk factor for future impaired lung function as measured by forced expiratory volume in 1 second (FEV₁).

In the FIREHOUSE trial, 89 patients were randomly assigned either to a technology-supported educational and behavioral intervention targeting calorie restriction for weight loss while following a low-calorie Mediterranean diet, or to usual care. The usual-care arm included participants who were informed about their weight, BMI, and other standard measures at annual visits and were given general advice about healthy eating, but were not assigned to a specific diet.

Participants in the LoCalMed group had significant decreases in BMI and increases in FEV₁,

compared with those in the usual-care group. In addition, the LoCalMed group had improved vascular health, better dietary habits, decreases in fats and calories from sweets, and decreases in inflammation as measured by a lower white blood cell count.

Microbiome substudy

At CHEST 2023, Ms. Lam reported on microbiome pilot and validation substudies of FIREHOUSE.

‘Clearly diet is influencing the type of bacteria in the biome in the gut, and perhaps some are favorable, and some are not favorable.’ –Samuel Evans, MD

The pilot study included five patients in each arm. The validation sample included 15 participants in the Mediterranean-diet group and 16 in the usual-care diet group.

Each participant’s microbiome was assessed with genomic sequencing with sequences aligned to a bacterial database. The number and diversity of bacterial species in each sample were determined with the Chao1 Index and Shannon Index, respectively.

There were no significant differences among the study groups in mean age, exposure at the World

Trade Center site, or years of service.

Although bacterial diversity did not differ between the study arms either at baseline or at 6 months, in both groups it significantly decreased over time ($P = .02$ in the pilot, $P < .0001$ in the validation arm).

In the pilot study, there was an increase over 6 months in the usual-care arm only of *Bilophila wadsworthia*, a species associated with high-fat diets and inflammation.

In the validation study, patients in the LoCalMed arm had significant reductions in *Ruminococcaceae* ($P = .015$) and increases in both *B. ovatus* ($P = .03$) and *Alistipes shahii* ($P = .038$), a recently identified species with uncertain protective or pathogenic potential.

In contrast, there were no significant increases in species in the usual-care group, but there were significant declines in several other bacterial species; Ms. Lam, however, did not say whether these changes had clinical significance. “Future studies will assess microbial association with clinical outcomes,” Ms. Lam said.

Confounding factors

Samuel Evans, MD, a pulmonologist at Straub Medical Center in Honolulu who moderated the oral abstract session where the data were presented, commented that the data are interesting but added that associations are difficult to determine given the heterogeneity of exposures that firefighters encounter.

“I think it’s interesting that clearly diet is influencing the type of bacteria in the biome in the gut, and perhaps some are favorable, and some are not favorable,” he told this news organization “We already know that the Mediterranean diet is associated with better health outcomes, so it makes sense, but can we tease out in the microbiome which bacteria are harmful and which are helpful?” He noted that there are a lot of confounding factors and that “it’s hard to find the right signal when you have so many variables.”

The FIREHOUSE study is supported by the Centers for Disease Control and Prevention’s National Institute of Occupational Safety & Health and the National Heart, Lung, and Blood Institute. Ms. Lam, Dr. Nolan, and Dr. Evans report no relevant financial relationships. ■

CRITICAL CARE COMMENTARY

Sedative use in older adults after critical illness

BY LISA D. BURRY, PHARMD, PHD; AND DAVID R. WILLIAMSON, MSCPHARM, PHD

Patients admitted to ICUs require modifications to their medication regimen due to their critical illness and rapidly changing clinical status. Modifications to medication regimens may include stopping home medications for chronic conditions, dose adjustments for altered organ function, or initiating new treatments for acute illness(es). Common examples of changes to a critically ill patient's medication regimen are stopping a chronic antihypertensive drug in the setting of shock, holding an oral medication that cannot be crushed or administered through a feeding tube, and initiating sedatives and analgesics to support invasive mechanical ventilation. Medication regimens are especially vulnerable to errors and omissions at transition points (i.e., ICU to ward transfers and home discharge). As critical illness resolves and patients transition to different care teams, the hospital discharge medication regimen may differ from the preadmission list with the omission of prehospital medications and/or the continuation of acute medications no longer needed without thorough medication review and reconciliation.

While admitted to ICU, many critically ill patients – particularly those who are mechanically ventilated – receive intravenous or enteral sedatives such as benzodiazepines and antipsychotics. Sedatives are prescribed to more than two-thirds of critically ill patients for disturbing symptoms of agitation, delirium, anxiety, and insomnia and to facilitate invasive procedures (Burry LD, et al. *J Crit Care*. 2017;42:268). Current sedation practice guidelines endorse the use of sedatives when indicated for the shortest duration possible, given the known associated serious short- and long-term adverse drug events (Devlin JW, et al. *Crit Care Med*. 2018;46[9]:e825). Previous research has demonstrated that benzodiazepines initiated in-hospital are often continued on discharge for older adults and that patients from the

ICU are at greater risk of benzodiazepine continuation than patients hospitalized without an ICU admission (Scales DC, et al. *J Gen Intern Med*. 2016;31[2]:196; Bell C, et al. *J Gen Intern Med*. 2007;22[7]:1024). This is particularly concerning for older adults as sedatives have been associated with serious adverse events in community-dwelling older adults, including falls and cognitive impairment (American Geriatrics Society. *J Am Geriatr Soc*. 2015;63[11]:2227).

Until recently, it was unknown which ICU survivors were at risk of new sedative prescriptions after hospital discharge and if all sedative drug classes were similarly continued. In a recent issue of the journal *CHEST*[®], we addressed the clinical question “Among sedative-naïve older adult ICU survivors, how common is the receipt of new and persistent sedative prescriptions, and what factors are associated with the receipt of such prescriptions?” (Burry LD, et al. *Chest*. 2023;163[6]:1425). We conducted a population-based cohort study using health administrative data between 2003 and 2019 in Ontario, Canada. Among sedative-naïve older adults who had survived a hospitalization with ICU admission, we determined the frequency and risk factors associated with filled outpatient sedative prescriptions within 1 week of hospital discharge and persistent sedative prescriptions up to 6 months post-discharge. The cohort of patients included all adults aged 66 years or more, who were discharged alive from the hospital and who were sedative-naïve prior to hospitalization. Sedative-naïve status was defined as no sedative prescription filled for any class, dose, or duration in the 180 days before hospital admission. The proportion of ICU survivors who filled a sedative prescription within 1 week of hospital discharge was the primary outcome. The secondary outcomes were the proportion of patients that filled each sedative class (e.g., antipsychotic, benzodiazepine, nonbenzodiazepine sedative) within 1 week of hospital discharge and persistent sedative prescription (additional prescriptions filled within 6 months after discharge).

The cohort included 250,428



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sedative-naïve older adults. The mean age was 75.8 years, 61.0% were male, 26.3% received invasive mechanical ventilation, and 14.8% had sepsis. In total, 6.1% (n=15,277) of patients filled a sedative prescription within 1 week of discharge; 57.7% (n = 8824) filled a benzodiazepine, 18.0% (n = 2749) filled a non-benzodiazepine sedative, 17.9% (n = 2745) filled an antipsychotic, and 6.2% (n = 959) filled more than 1 sedative drug class. Most patients filled prescriptions on the day of discharge (median 0 days (interquartile range (IQR) 0-3). The study found considerable variation in the primary outcome across the 153 hospitals: 2.1% (95% confidence interval [CI] 1.2% to 2.8%) to 44.0% (95% CI 3.0% to -57.8%) filled a sedative prescription within a week of hospital discharge. The factors strongly associated with an increased odds of a sedative prescription filled within a week of discharge included: discharge to long-term care (adjusted OR (aOR) 4.00, 95% CI 3.72 to 4.31), receipt of inpatient geriatric (aOR 1.95, 95% CI 1.80 to 2.10) or psychiatry consultation (aOR 2.76, 95% CI 2.62, 2.91), mechanical ventilation (aOR 1.59, 95% CI 1.53 to 1.66), and admitted ≥ 7 days to the ICU (aOR 1.50, 95% CI 1.42 to 1.58). Among hospital factors, a community hospital (vs academic) (aOR 1.40, 95% CI 1.16 to 1.70) and rural location (vs urban) (aOR 1.67, 95% CI 1.36 to 2.05) were also associated with new sedative prescriptions. Even after adjusting for patient and site characteristics, there was considerable remaining variability between sites quantified by the median odds ratio (aMOR) of 1.43. By drug class, there were similar findings with the exception of different associations for sex and frailty. For benzodiazepine prescriptions, female sex was associated with increased odds of a prescription (aOR 1.13, 95% CI 1.08 to 1.18), while frailty was inversely associated (aOR 0.82, 95%

CI 0.75 to 0.89). The opposite associations were identified for antipsychotics: female sex (aOR 0.75, 95% CI 0.69 to 0.81) and frailty (aOR 1.41, 95% CI 1.28 to 1.55). No associations were identified for sex and frailty and non-benzodiazepine sedative prescriptions.

Persistent sedative prescription was common as 55% met the definition of persistence, filling a median of 2 prescriptions (IQR 1,3) in the 6 months after hospital discharge. The factors associated with persistent sedative prescriptions were similar to those identified above except female sex was associated with persistent sedative prescription (sHR 1.07, 95% CI 1.02 to 1.13). Those who filled an antipsychotic prescription (sHR 1.45, 95% CI 1.35 to 1.56), a non-benzodiazepine sedative prescription (sHR 1.44, 95% CI 1.34 to 1.53), or prescriptions for more than 1 sedative class filled (sHR 2.16, 95% CI 1.97 to 2.37) were more likely to fill persistent prescriptions compared with those who filled a prescription for a benzodiazepine alone as their first sedative.

In summary, 1 in 15 sedative-naïve older adults filled a sedative prescription within a week of hospital discharge following a critical illness, and many continued to fill sedative prescriptions in the next 6 months. We were able to identify factors associated with new sedative prescriptions that could be targeted for stewardship programs or quality improvement projects that focus on medication safety and reconciliation. Medication stewardship and reconciliation processes have been broadly studied in many patient care settings but not the ICU. There is still much to determine regarding de-escalating and discontinuing sedatives as critical illness resolves and patients are liberated from intensive clinical interventions as well as the consequences of sedative exposure after hospital discharge for this population. ■

SLEEP STRATEGIES

New pharmacological interventions for residual excessive daytime sleepiness in OSA

BY ASHESHA MECHINENI, MD; AND ASHIMA SAHNI, MD, FCCP

Residual excessive daytime sleepiness (REDS) is defined as the urge to sleep during the day despite an intention to remain alert after optimal treatment of obstructive sleep apnea (OSA). This is a distressing outcome with an estimated prevalence of 9% to 22% among patients with OSA (Pépin JL, et al. *Eur Respir J*. 2009;33[5]:1062). The pathophysiology of the condition is complex, and experimental studies conducted on animal models have demonstrated that chronic sleep fragmentation and chronic intermittent hypoxia can result in detrimental effects on wake-promoting neurons. Additionally, there is evidence of heightened oxidative stress and alterations in melatonin secretion, with the severity and duration of the disease playing a significant role in the manifestation of these effects (Javaheri S, et al. *Chest*. 2020;158[2]:776). It is considered a diagnosis of exclusion, with the assessment being mostly subjective. Prior to diagnosing REDS, it is crucial to optimize positive airway pressure (PAP) therapy and nocturnal ventilation, ensure sufficient adherence to sleep hygiene practices, and exclude the presence of other sleep disorders. The Epworth Sleepiness Scale (ESS) score is widely utilized as a primary clinical tool in the assessment of sleepiness. To enhance the precision of this score, it is advantageous to take input from both family members and friends. Additional objective assessments that could be considered include the utilization of the Multiple Sleep Latency Test (MSLT) or the Maintenance of Wakefulness Test (MWT).

Due to the socioeconomic and public health considerations of REDS, pharmacological therapy is crucial to its management after exhausting conservative measures. Off-label use of traditional central nervous system stimulants, like amphetamine or methylphenidate, in these patients is almost extinct. The potential for abuse and negative consequences outweighs the potential benefits. FDA-approved medications for treatment of REDS in OSA

include modafinil, armodafinil, and solriamfetol in the United States.

Historically, modafinil and armodafinil are the first-line and most commonly used wake-promoting agents. Both agents bind to the dopamine transporter and inhibit dopamine reuptake. They have demonstrated efficacy in reducing EDS and improving wakefulness in patients with OSA treated with CPAP. A meta-analysis of 10 randomized, placebo-controlled trials of modafinil and armodafinil found that they were better than placebo by 2.2 points on the ESS score and 3 minutes on the MWT (Maintenance of Wakefulness Test) (Chapman JL, et al. *Eur Respir J*. 2016;47[5]:1420). Both drugs have common adverse effects of headache, nausea, nervousness, insomnia, dizziness, rhinitis, and diarrhea. Drug interaction with CYP3A4/5 substrates and oral contraceptives is a concern with these medications. In 2010, the European Medicines Agency restricted the use of modafinil only to patients with narcolepsy, considering its cardiovascular and neuropsychiatric risks (European Medicines Agency website; press release, July 22, 2010).

Solriamfetol is the newest medication being utilized for EDS in OSA and is approved in both the United States and Europe for this indication. It is a dopamine and norepinephrine reuptake inhibitor with a simultaneous effect on both transporters. It has been effective in improving wakefulness and reducing sleepiness in patients with residual OSA. In the landmark trial TONES 3, dose-dependent (37.5, 75, 150, and 300 mg/day) effects were observed, with improvements in ESS scores of -1.9 to -4.7 points and sleep latency in MWT by 4.5 to 12.8 minutes (Schweitzer PK, et al. *Am J Respir Crit Care Med*. 2019;199[11]:1421). The current recommended dosing for REDS in OSA is to start with the lowest dose of 37.5 mg/day and increase to the maximum dose of 150 mg/day by titrating up every 3 days if needed. A recent meta-analysis showed an indirect treatment comparison between efficacy and safety among the medications solriamfetol, modafinil, and armodafinil (Ronnebaum S, et al. *J Clin Sleep Med*. 2021;17[12]:2543). Six parallel-arm,



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placebo-controlled, randomized, controlled trials were looked at. The ESS score, MWT20 sleep latency, and CGI-C (Clinical Global Impression of Change) all got better in comparison to the placebo. Relative to the comparators and placebo at 12 weeks, solriamfetol at 150 mg and 300 mg had the highest degree of improvement in all the outcomes studied. Common adverse effects of solriamfetol include headache, nausea, decreased appetite, insomnia, dry mouth, anxiety, and minimal

increase in blood pressure and heart rate. The adverse effects in terms of blood pressure and heart rate change have a dose-dependent relationship, and serial vitals monitoring is recommended for patients every 6 months to a year. This medication is contraindicated in patients receiving concomitant monoamine oxidase inhibitors (MAOIs) or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reactions. Solriamfetol is

OSA continued on following page



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Gen Z is hooked on vaping

Exploring the obstacles to nicotine cessation among teens

BY DENNY WATKINS

Pulmonologist Evan Stepp, MD, FCCP, has a teenage daughter who doesn't smoke or vape – as far as he knows, Stepp will admit – but the statistics on youth smoking are alarming enough to have him worried.

On one hand, fewer Americans are smoking today than ever before. Since 1992, the percentage of people who told Gallup that they'd had a cigarette in the past week has dropped from 28% to 11%. Meanwhile, the rate of new lung cancer cases declined from 65 per every 100,000 people in 1992 to 34 per 100,000 in 2020, according to the National Cancer Institute.

While those statistics are worth celebrating, they hide an alarming reality: A disproportionate number of teens and young adults today are addicted to nicotine.

According to a November 2022 report from the Centers for Disease Control and Prevention (CDC), 1 in 6 high school students and 1 in 20 middle schoolers are using a nicotine product at least once every day.

"It's a completely different picture for nicotine cessation in youth," Dr. Stepp, who is an associate professor at National Jewish Health in Denver, said. "Because of the fact that the nicotine addiction is occurring in a developing brain, which raises many other nicotine-related harms."

Why teens vape

Today's teens are smoking less actual tobacco, and, instead, overwhelmingly prefer e-cigarettes or vaping. In fact, 85% of high school-aged smokers and 72% of middle school smokers reach for a vape over regular cigarettes or smokeless tobacco, according to the CDC.

It's not hard to understand why: e-cigarettes use a heating element to turn a nicotine-infused liquid into an aerosol, with no open flame, ash, or lingering smoke. The vapes themselves are easy to conceal, and if someone needed to hide an e-cigarette from particularly perceptive parents or teachers, they can find vapes built into hoodies, fake smartwatches, and USB drives.

Plus, the liquids often come in flavors like fruit, bubble gum, mint, and vanilla, because

unflavored nicotine isn't exactly appealing. "Huge concentrations of nicotine salts are just miserable to breathe in," Dr. Stepp said. "Flavors are necessary to make these products palatable, and those flavors end up being a huge draw for youth users to get exposed to nicotine addiction."

Challenges surrounding smoking cessation in youth

The powerful effect of nicotine in youth means the need for effective cessation strategies is both more urgent and more difficult. But while physicians can prescribe to adults the antidepressants varenicline and bupropion, along with nicotine replacement therapy, to help ease withdrawal symptoms, the US Food and Drug Administration (FDA) has not approved those medications for anyone under the age of 18.

Research on cessation medications in young people is limited: A recent meta-analysis found only four studies on people between the ages of 12 and 21. In teens, antidepressants seem to help quitting for the first few weeks but are unproven as a long-term solution.

"That really has been a challenge for the 1 in 6 high school students who are current users of tobacco products," said pediatrician, Susan Walley, MD, a co-author of the American Academy of Pediatrics' recent position papers on children and smoking.

"One of the things that is important to keep at the forefront of the conversation is that nicotine addiction is a chronic medical disease, and it's a form of substance abuse," Dr. Walley said. "We know that we need more research in adolescent tobacco cessation, and it really is about the funding, about research dollars."

Without medications, smoking cessation in teens relies largely on counseling strategies. A 2017 review published by Cochrane Library found that group counseling was the most effective quitting method, with teens participating in group sessions 35% more likely to stop using nicotine products up to a year later, compared with teens who did not receive any counseling.

Counseling can help educate teens (and parents) on some of the realities of e-cigarettes,

bridging the gap between well-established anti-smoking campaigns and the anti-vape campaigns that have yet to catch up.

"We have done a great job promoting cigarette use as dangerous," Dr. Walley said. "[But] many teens who would never pick up a cigarette – because they know the health risks – are vaping."

How to get a teen to quit

Cessation and prevention strategies are closely linked, and interventions can start in middle school-aged children up through high school and young adults. Simply asking a 12-year-old, "Do you know anyone who smokes?" can help start a conversation that leads to an attempt to quit.

Teens may be compelled to smoke through digital advertising and influencer endorsements on social media platforms, but Gen Z is turned off by the idea that it's being manipulated by the tobacco industry. Juul, for example, is partially owned by Altria, which makes Marlboros, and Vuse is wholly owned by R.J. Reynolds, which makes Camel cigarettes.

"If you can get somebody to understand that Big Tobacco is trying to manipulate you as a young person to want to illegally obtain and use their products, which are incredibly addictive, thus ensuring you will remain a loyal customer, that could be the thing that pushes them over the hump," Dr. Stepp said. "You push it away like you would push away a parent trying to tell you how to park a car in the driveway."

And just because a smoker relapses, it doesn't mean the cessation was a complete failure. The younger someone is when they stop smoking, the less likely they are to suffer from the long-term health consequences of smoking, according to a 2021 study in the *Journal of the American Medical Association*. "With the right counseling," Dr. Walley said, "each relapse is an opportunity for losing the habit permanently." ■

This article was adapted from the Summer 2023 online issue of CHEST Advocates. For the full article – and to engage with the other content from this issue – visit <https://chestnet.org/chest-advocates>.

OSA continued from previous page

renally excreted, so dose adjustment is needed in patients with moderate to severe renal impairment. It is not recommended for use in end-stage renal disease (eGFR <15 mL/min/1.73 m²) (SUNOSI. Full prescribing information. Axsome; revised 06/2023. <https://www.sunosihcp.com/assets/files/sunosi.en.uspi.pdf>. Accessed: Sept 24, 2023). Solriamfetol demonstrates a comparatively shorter half-life when compared with traditional pharmaceuticals like modafinil and

armodafinil, implying the possibility of a decreased duration of its effects. The effect in question may exhibit interpersonal diversity in its impact on quality of life when applied in a therapeutic setting.

Pitolisant is another potential medication to treat REDS in patients with OSA. While only approved for treating EDS and cataplexy in adult US patients with narcolepsy, it is currently approved for REDS in OSA in Europe (Ozawade. European Medicines Agency. Last updated 12/05/2022. <https://www.ema.europa.eu/en/medicines/human/EPAR/ozawade#product-information-section>. Accessed: Oct 2, 2023). It is a selective histamine H3 receptor antagonist and an inverse agonist of the presynaptic H3 receptor. The fact that this medication is not scheduled and has a negligible or nonexistent risk of abuse is one of its advantages. It is dosed once daily, and the most frequent adverse effects include headaches and insomnia. A prolonged QT interval was observed in a few patients; caution is needed with concomitant use of other medications

with known similar effects. Dosage modification is recommended in patients with moderate hepatic impairment and moderate to severe renal impairment. Drug interactions are also observed with the concomitant use of CYP2D6 inhibitors and CYP3A4 inducers. Pitolisant may reduce the efficacy of hormonal contraception, including up to 21 days after its discontinuation (WAKIX. Full prescribing information. Harmony biosciences; revised 12/2022. <https://wakixhcp.com/pdf/wakix-tablets-pi.pdf>. Accessed: Sept 24, 2023). ■

PRESIDENT'S REPORT

525,600 minutes ... how does one measure a year as President?

BY DOREEN J. ADDRIZZO-HARRIS, MD, FCCP

As we find ourselves in November, on the heels of yet another exceptional CHEST Annual Meeting, I cannot help but use my last column as CHEST President to reflect on a year well spent.

For the first time since CHEST 2011, when I was the Scientific Program Committee Vice Chair, I was able to return to beautiful Hawai'i as the organization's President, which was such a big coincidence that it felt almost like fate.

During my time on stage at the CHEST 2023 Opening Session, I reflected on the last (at the time) 9 months and shared how truly humbled I have been to lead such a group of leaders and doers. I'm continually amazed at the energy of our members and our staff. In my 25 years as a member, I thought I knew all that CHEST did, but there is so much more happening than any one person realizes. From creating and implementing patient care initiatives to drafting and endorsing statements advocating for better access to health care, there is a tremendous amount accomplished by this organization every year.

One notable accomplishment of this particular year is that not only was CHEST 2023 our largest meeting ever, but I'm proud to share that we also had more medical students, residents, and fellows than any other year, with over 2,000 attendees in-training.

This is a great reflection of the work we've been doing to expand the CHEST community – both to physicians earlier in their careers and also to the whole care team. We are putting a dedicated focus toward welcoming and creating a sense of belonging for every clinician. The first step toward this inclusion is the creation of the new CHEST interest groups – Respiratory Care, which is dedicated to the field, and Women in Chest Medicine, which is a more inclusive evolution of the previous Women & Pulmonary group.

This year, we also established CHEST organizational values. The result of a tremendous effort from



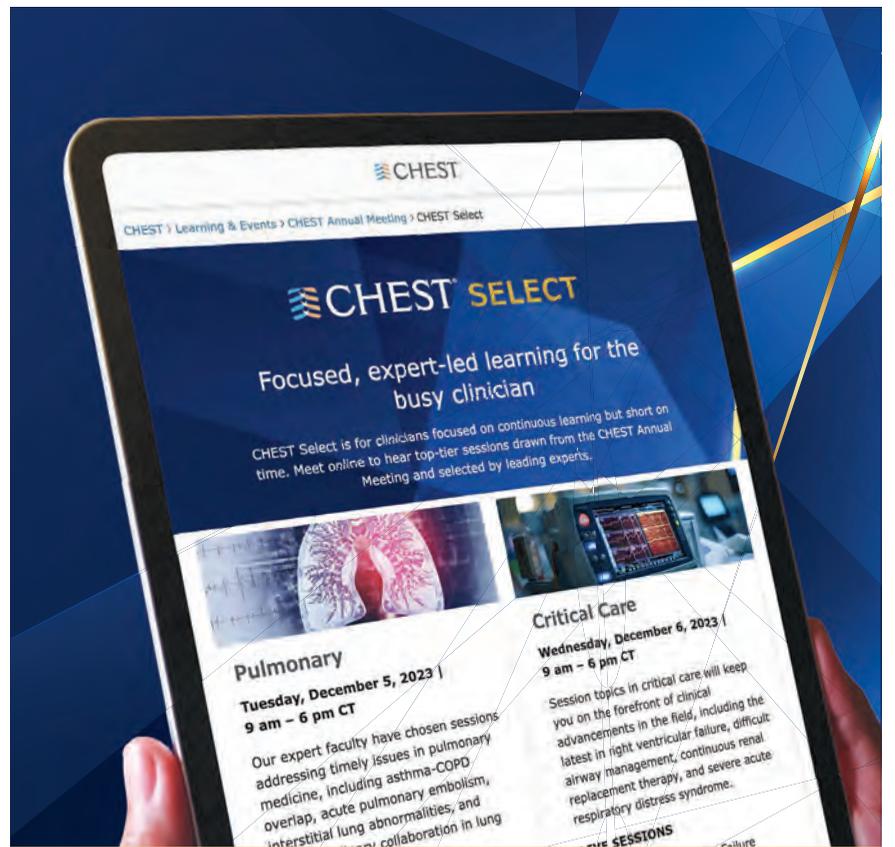
Dr. Doreen J. Addrizzo-Harris

an advisory committee, CHEST leaders, members, and staff, these values – Community, Inclusivity, Innovation, Advocacy, and Integrity – are reflective of the CHEST organization and will guide decisions for years to come.

They also serve to elevate the work we are doing in social responsibility and health equity, within both of which we've made great strides. CHEST philanthropy evolved from what was known as the CHEST Foundation, with a new strategic focus, and we continue working to create opportunities to expand diversity within health care, including the new CHEST mentor/mentee sponsorship fellowship in partnership with the Association of Pulmonary and Critical Care Medicine Program Directors.

Though I could go on for eternity describing all we did at CHEST this year, the reality is that at the end of the next month, as we ring in the new year, I will cede the presidency to the incredibly accomplished and capable Jack Buckley, MD, MPH, FCCP, who will take the reins of our great organization.

For now, in my parting words to you, I encourage everyone to stay in touch. I am always reachable by email and would love to hear your thoughts on CHEST – reflections on this past year, ideas about where we're going, and suggestions for what we're missing. The role of the President (and, to some extent, the Immediate Past President) is to be a steward of the needs of the CHEST members, and it's been a true honor being your 2023 CHEST President. ■



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ILD: Time lost is lung lost

First launched in 2022 in partnership with Three Lakes Foundation, Bridging Specialties™: Timely Diagnosis for ILD is a collaborative initiative hinged on bringing together pulmonary and primary care experts. To shorten the time to diagnosis for interstitial lung diseases (ILDs) like pulmonary fibrosis, the initiative illustrates that there is a need for clinicians to work collaboratively, utilizing the unique strengths of all involved. The steering committee of experts from both fields created a clinician-facing toolkit that, with support of two quality improvement grants, will be introduced into health care institutions in 2024.

Kavitha Selvan, MD, Pulmonary and Critical Care Fellow at the University of Chicago School of Medicine, and Amirahwaty Abdullah, MBBS, Assistant Professor & Critical Care Medicine Associate Program Director at the West Virginia University School of Medicine, are the recipients of the grants. Each recipient will receive funding to implement strategic quality improvement projects designed to work closely with primary care partners and address the needs of their communities to shorten the time to diagnosis for patients with ILD.

Dr. Selvan's project leverages the diverse population of Chicago and will engage primary care physicians by working closely with the Medical Director of the Primary Care Group within the University of Chicago. "There is a growing body

of research that illustrates vast racial and ethnic disparities in ILD outcomes, including time to diagnosis and survival. The diverse community we serve in Chicago provided the inspiration for our project, which we hope will enable us to take a meaningful step toward achieving equity in health care," Dr. Selvan said. "Through close collaboration with the dedicated physicians in our Primary Care Group, we aim to increase recognition of signs and symptoms suggestive of ILD earlier in the course of disease and streamline the thoughtful, multidisciplinary care our patients need."

Affecting 400,000 people in the United States, ILDs are often overlooked as a potential diagnosis given their rarity. A proper diagnosis for this disease is further complicated by ubiquitous presenting symptoms that are common in many other diseases, including asthma, COPD, and cardiac conditions, and often leads to a misdiagnosis. This delay in diagnosis, or an outright misdiagnosis, leads to additional delays in receiving proper treatment and, subsequently, a degradation in the patient's quality of life. For Dr. Abdullah, the rarity of the disease is not the issue; rather, there is an access issue. Because of this, their project will focus on telemedicine implementation to meet the needs of their area. "While ILD is a rare disease, the state of West Virginia has a disproportionately increased prevalence due to a variety of societal factors," Dr. Abdullah



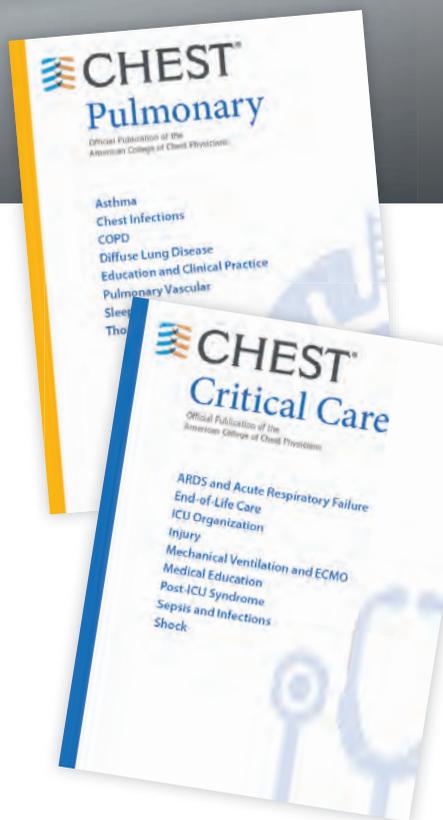
maglime/Getty Images

said. "Despite this prevalence, there is one ILD clinic in the state of West Virginia in comparison to 1,253 primary care providers throughout the state. To address this gap, the project will focus on expanding telemedicine capabilities in order to reach these patients virtually through their primary care physicians who would help us to facilitate the video-assisted visits."

To learn more about the toolkit they will be implementing, visit the CHEST website. ■

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NETWORKS

Flu, RSV, inpatient vaccines, and more...

Chest Infections & Disaster Response Network**Chest Infections Section Update on seasonal flu, RSV infections, and vaccines**

November 12 marks World Pneumonia Day, and while it has long been recognized that viruses play a significant role in causing pneumonia, awareness has surged due to the COVID-19 pandemic. Furthermore, with the advent of rapid molecular diagnostics, the contribution of respiratory viral pathogens in pneumonia has become clearer (Seema J, et al. *N Engl J Med*. 2015 Jul 30;373[5]:415-27). Despite COVID-19 remaining a substantial threat, infection rates with other respiratory viruses are on the rise and will continue to increase during colder months. Here, we will provide an update on influenza and RSV:

Two new vaccines have become available to prevent RSV-associated lower respiratory tract diseases, boasting a vaccine effectiveness of over 80% for the first and over 70% for the second.

Currently, influenza activity in the United States is low (National Center for Immunization and Respiratory Diseases. FluView. 2023 Oct 4. <https://www.cdc.gov/flu/weekly/index.htm>). Vaccination coverage for US adults during the previous influenza season stood at 47% (Centers for Disease Control and Prevention. FluVaxView Vaccination Dashboard. 2023 Oct 4. <https://www.cdc.gov/flu/fluview/dashboard/vaccination-dashboard.html>). Hospitalizations were estimated to range between 300,000 and 650,000, a significant increase from the 2021-2022 season, which saw about 100,000 hospitalizations (Centers for Disease Control and Prevention. Preliminary In-Season Estimates of Influenza Burden. 2023 Oct 4. <https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm>). Data from the Southern Hemisphere's recent influenza season indicates a 52% vaccine efficacy in preventing influenza-associated hospitalizations (Fowlkes AL, et al. *MMWR Morb Mortal Wkly Rep*.

2023 Sep 15;72[37]:1010-5). Influenza hospitalization rates are likely returning to higher pre-COVID-19 levels.

Respiratory Syncytial Virus (RSV) is a seasonal pathogen causing substantial morbidity and mortality. This year, two new vaccines have become available to prevent RSV-associated lower respiratory tract diseases, boasting a vaccine effectiveness of over 80% for the first and over 70% for the second season post-administration (Melgar M, et al. *MMWR Morb Mortal Wkly Rep*. 2023 Jul 21;72[29]:793-801). The CDC's Advisory Committee on Immunization Practices recommends a single dose for adults over 60, and one vaccine is FDA-approved for pregnant individuals (32-36 weeks gestation) to provide passive infant immunity.

In summary, both the current influenza vaccine and the new RSV vaccines demonstrate effectiveness and are strongly recommended, alongside an updated COVID-19 vaccine.

John Huston, MD
Jamie Felzer, MD, MPH – Section Fellow-in-Training
Charles Dela Cruz, MD – Section Member-at-Large
Sebastian Kurz, MD, FCCP – Network Member-at-Large

Chest Infections & Disaster Response Network Disaster Response & Global Health Section**The crucial roles of inpatient vaccinations in preventing respiratory viral illnesses**

In recent years, the importance of inpatient vaccinations against respiratory viral illnesses has become increasingly clear. As the world grapples with the ever-present threat of contagious diseases like influenza, COVID-19, Respiratory Syncytial Virus (RSV) and other respiratory viruses, the significance of vaccinating individuals during hospital stays cannot be overstated. Notably, the rates of inpatient vaccinations have significantly increased in recent years.

Numerous studies have demonstrated the success of various strategies to boost vaccine delivery to hospitalized patients. These strategies include personalized catch-up plans, electronic medical record (EMR) prompts, visual reminders,

staff education and training, and allowing nonphysicians to screen and order vaccines. The implementation of nonphysician protocols has proven effective in increasing inpatient influenza vaccinations in multiple studies (Mihalek AJ, et

Inpatient vaccinations against respiratory viral illnesses are supported by a growing body of evidence.

al. *Hosp Pediatr*. 2021 Dec 1. doi: 10.1542/hpeds.2021-005924; Skull S, et al. *J Paediatr Child Health*. 1999;35[5]:472).

Optimizing the delivery of vaccines to hospitalized patients carries substantial public health benefits. This is especially vital for patients who face challenges accessing primary care and during periods of health care systems disruptions, such as those experienced during

the COVID-19 pandemic.

In conclusion, inpatient vaccinations against respiratory viral illnesses are supported by a growing body of evidence. These vaccinations not only prevent disease transmission within health care facilities but also protect vulnerable patients, alleviate the burden on health care systems and with the recent approval of the RSV vaccine, we have a new tool to combat respiratory viruses effectively. As we continue to navigate the challenges posed by respiratory viruses, prioritizing inpatient vaccinations is a wise and necessary step toward a healthier, safer future for all.

Stella Ogake, MD – Section Member-at-Large

Sleep Network Non-Respiratory Sleep Section**Seasonal variations in sleep architecture**

Do you feel like you sleep worse in

NETWORKS *continued on following page*

This month in the journal CHEST®**Editor's picks**

BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

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By Kerollos Nashat Wanis, MD, PhD, et al.

Lower vs Higher Fluid Volumes in Adult Patients With Sepsis: An Updated Systematic Review With Meta-Analysis and Trial Sequential Analysis

By Praleene Sivapalan, MD, et al.

Noninvasive Oxygenation Strategies in Adult Patients With Acute Hypoxemic Respiratory Failure: A Systematic Review and Network Meta-Analysis

By Tyler Pitre, MD, et al.

Effectiveness of Flexible Bronchoscopy Simulation-Based**Training: A Systematic Review**

By Eveline C. F. Gerretsen, MSc, et al.

Climate Change for the Pulmonologist: A Focused Review

By Bathmapriya Balakrishnan, MBMS, FCCP, et al.

Addressing Mental Health Needs Among Frontline Health Care Workers During the COVID-19 Pandemic

By Traci N. Adams, et al.

Lung Transplantation for Pulmonary Arterial Hypertension

By Nicholas A. Kolaitis, MD, MAS

Observation, Aspiration, or Tube Thoracostomy for Primary Spontaneous Pneumothorax: A Systematic Review, Meta-Analysis, and Cost-Utility Analysis

By Gilgamesh Eamer, MD, et al.

NETWORKS *continued from previous page*

the spring and have more difficulty keeping your schedule on track? There are new data to support the way you feel based on our deeper understanding of seasonal variations in sleep architecture.

Patients in a recent study had 43 minutes less total sleep time and approximately 30 less minutes of REM sleep in the late spring when compared with the winter (Seidler A, et al. *Front Neurosci*. 2023 Feb 17;17:1105233). Accumulation of decreased sleep time and quality can lead to the sensation of 'running-on-empty' by early spring.

Experts believe these seasonal variations in sleep architecture are mainly secondary to circadian shifts.

Experts believe these seasonal variations in sleep architecture are mainly secondary to circadian shifts. Our social synchronization overrides our natural alignment with daylight patterns and can lead to known consequences of circadian misalignment. Common consequences of poor circadian alignment include worsening sleep disturbances, cognitive impairments, occupational mistakes, and metabolic and mental health disturbances (Schmal C, et al. *Front Physiol*. 2020 Apr 28;11:334; Boivin D, et al. *J Biol Rhythms*. 2022 Feb;37[1]:3-28).

The effects of circadian misalignment can be particularly dramatic in children receiving less than their age-appropriate hours of sleep. Children with sleep deprivation are at increased risk of attention, behavior, and learning problems (Paruthi S, et al. *J Clin Sleep Med*. 2016;12[6]:785-6).

To improve circadian alignment in spring, it is recommended to achieve morning bright light exposure and perform regular exercise. The elimination of daylight savings time to a consensus of permanent standard time will optimize circadian alignment.

Christopher Izzo, DO – Section Fellow-in-Training

William Healy, MD – Section Member-at-Large

Mariam Louis, MD – Section Chair

**Thoracic Oncology Network
Ultrasound & Chest
Imaging Section**
Thoracic ultrasound advancements for the assessment and management of pleural disorders
Thoracic ultrasound (TUS) is standard of care for the detection of

pleural effusion and guidance of pleural procedures. Recent advancements have further expanded the utility of TUS. TUS has better diagnostic performance than CT scan or chest radiograph for predicting complicated parapneumonic effusion (Svigals PZ, et al. *Thorax*.

2017;72[1]:94-5). This is likely because of better visualization of septation, but there are still limitations. In a study of 300 pleural ultrasounds, TUS was found to be inadequately reliable in the diagnosis of transudative pleural effusion as 56% of anechoic effusions were

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exudative, but complex appearing pleural effusion on TUS was found to have high predictive value for the diagnosis of exudative pleural effusion (Shkolnik B, et al. *Chest*. 2020;158[2]:692-7).

TUS may diagnose nonexpandable lung prior to drainage in

malignant pleural effusions. Using M-mode to assess lung motion and speckled tracking for the assessment of lung stain, blunted cardio-phasic response of the lung was highly specific for the diagnosis of non-expandable lung (Salamonsen MR, et al. *Chest*. 2014;146[5]:1286-93).

TUS can also be used to assess the success of pleurodesis as measured by the adherence score (abolishment of pleural sliding). TUS guided pleurodesis approach was shown to decrease the hospital length of stay in patients undergoing pleurodesis for malignant pleural effusion

(Psallidas I, et al. *Lancet Respir Med*. 2022;10[2]:139-48). Point-of-care TUS is evolving, and adapted use focusing on patient-centered outcomes will further enhance the utility of this indispensable tool.

Amit Chopra, MD, FCCP
Nicholas Villalobos, MD

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Biologics tied to fewer asthma hospitalizations

BY JIM KLING

MDedge News

AT CHEST 2023 ■ HONOLULU – In a real-world study of asthma patients, treatment with biologics following

an exacerbation was associated with better health care utilization outcomes.

The data fill a gap, according to Sushan Gupta, MD, who presented the results at the annual meeting of

the American College of Chest Physicians. “There’s some ample real-world data that shows that biologics reduce the incidence of asthma exacerbation, but the data regarding what happens after an exacerbation

is still lacking, especially real-world data,” said Dr. Gupta, who is a resident at Carle Foundation Hospital in Champaign, Ill.

The findings were encouraging. “Patients with severe asthma on

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'Patients with severe asthma on biologics fare well even after an exacerbation event.'

—Sushan Gupta, MD

biologics fare well even after an exacerbation event, which includes a reduced incidence of hospitalization, ICU admission, and need for mechanical ventilation. We did not have any patient in the biologic group that required intubation, so that is pretty significant as compared to other patients who did not receive biologics," said Dr. Gupta.

The results weren't surprising, but underscore the benefits of biologics, according to Brittany Duchene, MD, who moderated the session where the results were presented. "I think it reinforced that they're really good drugs," said Dr. Duchene, who is a pulmonary critical care physician at Northeastern Vermont Regional Hospital, St. Johnsbury.

Although the study was retrospective, it suggests that the threshold for initiating biologics could potentially be lowered for patients with uncontrolled asthma despite adequate use of inhalers, according to Dr. Gupta. "Should that threshold be lower, and would that improve the overall morbidity and eventually the

BIOLOGICS *continued on following page*

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health care cost of utilization? Our study does not prove any of those data, but moving forward that data will also come out.”

Dr. Duchene noted that the accumulating scientific and clinical data for biologics is “really, really strong.” She also speculated that biologics could be used increasingly in the

acute setting, which she admitted is a controversial topic. “I think there’s going to be a lot more push to early initiation, and you can see from the [new] study that it decreased a lot of hospitalizations.”

Dr. Gupta emphasized the need for prospective studies, and Dr. Duchene agreed that any such change would need to be patient

centric, considering the diversity of available biologics. “It depends what their true issue is. The broader the biologic [mechanism of action], probably the more success you’ll have. I’ve found there’s not a pure allergic or a pure eosinophilic asthma patient. They’re usually more a combination.”

Some key questions remain about

biologics treatment, especially in the long term. These include when a patient should be switched from one biologic to another, and whether biologic treatment should be continued over the patient’s lifetime and potential long-term side effects. “I think that data is still evolving and will come to us with time,” said Dr. Gupta.

The researchers analyzed retrospective data from 316 asthma patients treated with biologics and 9,645 treated with nonbiologic therapy between February 2018 and February 2023 at a tertiary care teaching hospital in the Midwest.

The threshold for initiating biologics could potentially be lowered for patients with uncontrolled asthma despite adequate use of inhalers.

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There was a higher proportion of females in the biologics (69.7%) and nonbiologics groups (63.8%, $P = .032$), but there was no significant difference in the proportion of Whites in the biologics and nonbiologics groups (78.2% vs 74.3%, $P = .103$).

The lack of a difference in racial groups was a surprise, according to Dr. Duchene, especially since other studies have noted disparities in biologic therapy among asthma patients.

Among the biologics group, 0.9% were hospitalized during the study period, compared with 6.5% of the nonbiologics group ($P = .00006$). They also had fewer ICU visits (0.3% vs 1.8%; $P = .04$).

Dr. Gupta’s team attempted to subdivide the data by individual biologic, but there was no statistical significance in outcomes between biologics, perhaps because of the relatively small sample size.

Dr. Gupta noted that his group’s results are generally similar to other studies, including a U.S. study that found a decrease in exacerbation rates after starting or switching biologics and a slightly higher prevalence of biologics use among White patients (77% of biologic users versus 71% of nonbiologics users) (*Ann Allergy Asthma Immunol.* 2021 Nov;127[5]:579-87.e1). A study in southwestern England found fewer ED visits and hospitalizations among patients on biologics.

Dr. Gupta and Dr. Duchene have no relevant financial disclosures. ■

Respiratory infections, asthma rise before T2D onset

BY BECKY MCCALL

HAMBURG, GERMANY – Respiratory tract infections and asthma are 10 times more prevalent at type 2 diabetes diagnosis, compared with matched controls without a diagnosis, shows a longitudinal study looking at comorbidities both 25 years before and 25 years after a type 2 diabetes diagnosis.

About 40% of people had respiratory tract infections at the time of diagnosis with type 2 diabetes, compared with 4% who were not diagnosed. Likewise, ear, nose, and throat infections were present in 20% of people at type 2 diabetes diagnosis, compared with around 2% who were not diagnosed. A similar pattern was seen with

Five years prior to diagnosis, respiratory tract infections were documented in around 23% of patients who were later diagnosed with type 2 diabetes versus 2.5% in those not diagnosed.

asthma. The data suggest that sub-acute inflammation manifesting in asthma, as well as the onset of asthma or an acute infection, may be a precursor to a type 2 diabetes diagnosis. “We have also found that in the years prior to diagnosis there are associations with infections and inflammatory disorders to a much greater degree than in those people who do not get a diabetes diagnosis but who have very similar demographics,” Adrian Heald, MD, study lead and diabetes consultant from Salford (England) Royal Hospital, said in an interview.

Five years prior to diagnosis, respiratory tract infections were documented in around 23% of patients who were later diagnosed with type 2 diabetes versus 2.5% in those not diagnosed, and a similar pattern was seen for ear, nose, and throat infections and asthma. The findings suggest that patients reporting infections, in addition to other known risk factors for type 2 diabetes, might benefit from diabetes tests and early interventions, if needed.

“These novel insights offer a fascinating and fresh perspective on the onset and natural progression to type 2 diabetes and beyond, suggesting

an early phase of inflammation-related disease activity long before any clinical diagnosis of type 2 diabetes is made.” Dr. Heald points out that clinicians may intervene to stave off progression to a type 2 diabetes diagnosis in at-risk patients. “At this point, an intervention could relate to lifestyle changes and involve highlighting to the patient that the morbidity they have already accumulated is suggestive of diabetes risk,” he said, adding that, “they may have dyslipidemia, hypertension, and most often excess weight so annual checks of their HbA1c, weight management, and blood pressure would need checking,” he explained.

Moderator Coen Stehouwer, MD, professor of internal medicine at Maastricht (the Netherlands) University, commented, “Before clinical diagnosis of type 2 diabetes there is often a lengthy period of undiagnosed disease and before that, prediabetes, because glucose can be abnormal up to 10 years prior to clinical diagnosis.” But he added that, “It’s not entirely clear whether the rise seen before clinical diagnosis in this study correlates with undiagnosed diabetes or prediabetes or even if it precedes type 2 diabetes – it might be because inflammation is a common origin for type 2 diabetes and various comorbidities. This might explain how they go together.”

Longitudinal study 25 years before and 25 years after type 2 diagnosis

Dr. Heald presented the findings at the annual meeting of the European Association for the Study of Diabetes. The work was also published in *Diabetes Therapy* (2023 Sep 14. doi: 10.1007/s13300-023-01463-9). The researchers wanted to investigate the pattern of comorbidities in the years and decades prior to a diagnosis of type 2 diabetes as well as after: “With the database we used, called DARE [Diabetes Alliance for Research in England], we are able to explore phenomena longitudinally going right back to the beginning of their digital health records, looking at phenotypes over time.”

By mapping significant health issues in people who went on to develop type 2 diabetes alongside those that did not, Dr. Heald managed to develop a continuum spanning 25 years prior and 25 years after diagnosis of type 2 diabetes. The researchers also examined relationships between sociodemographic factors and longitudinal

health outcomes of relevance to cardiac conditions and lower respiratory tract infections. His talk in Hamburg primarily addressed clinical phenotypes before the point of diagnosis. Data were drawn from 1,932 people with (1,196) and without (736) type 2 diabetes. Participants were aged 66-67 years (50-52 years at diagnosis), 43%-46% were women, and lived in Greater Manchester, England. In the years leading up to type 2 diagnosis, individuals consistently exhibited an increase in several clinical phenotypes, reported Dr. Heald. He added, “immediately prior to type 2 diagnosis, there was a significantly greater proportion of hypertension at 35%; respiratory tract infection at 34%; heart disease at 17%; ear, nose, and throat infection at 19%; and asthma at 12%. And by comparison, the corresponding disease trajectory in matched controls was much less dramatic.” He emphasized, “There is a huge difference in people who went on to receive a diagnosis of type 2 diabetes and those who did not, and not just what we’d expect – so hypertension for example or manifestations of renal disease, but

importantly inflammatory disorders are more common.”

In addition, a larger signal for ischemic heart disease was seen just before type 2 diabetes diagnosis. These data suggest longitudinal clinical histories prior to a diagnosis of type 2 diabetes might offer new information, both genetic and non-genetic, about development of type 2 diabetes in relation to comorbidities. After type 2 diabetes diagnosis, the proportion of people exhibiting coronary artery disease, hypertension, chronic kidney disease, retinopathy, and infections climbed rapidly before plateauing, reported Dr. Heald. “We also know that individuals with coronary artery disease are more highly represented in socially disadvantaged groups, and this is borne out in the data at 25 years prior and after type 2 diagnosis.”

Dr. Heald has received speaker fees or contributed to advisory boards from Lilly, AstraZeneca, Janssen, Bristol-Myers Squibb, Besins, Bayer, Sanofi, and Recordati, as well as research grants from Novo Nordisk, Pfizer, and Besins. Dr. Stehouwer has declared no relevant conflicts. ■

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PULMONARY MEDICINE

Aspergillosis tied to poor outcomes in influenza

BY HEIDI SPLETE
MDedge News

FROM THE JOURNAL CHEST ■

Critically ill influenza patients with associated pulmonary aspergillosis were more than twice as likely to die in intensive care than those without the infection, based on data from a meta-analysis of over 1,700 individuals. Reports of influenza-associated pulmonary aspergillosis are rising in critically ill patients, but data on risk factors, clinical features, and outcomes are limited, Lawrence Y. Lu, MD, of The Prince Charles Hospital, Brisbane, Australia, and colleagues wrote. In addition, diagnosis of IAPA can be challenging, and many clinicians report low awareness of the condition.

In a study published in the journal *Chest* (2023 Sep 22. doi: 10.1016/j.chest.2023.09.019), the researchers reviewed data from 10 observational studies including 1,720 critically ill influenza patients aged 16 years and older; of these, 331 had IAPA, for a prevalence of 19.2%. The primary outcomes were all-cause mortality in the hospital and ICU. Secondary outcomes included ICU length of stay, hospital length of stay, and the need for supportive care. Mortality among flu patients in the ICU was significantly higher for those with IAPA than those without IAPA (45.0% vs. 23.8%, respectively), as was all-cause mortality (46.4% vs. 26.2%, respectively; odds ratio, 2.6; $P < .001$ for ICU and all-cause mortality).

Factors significantly associated

with an increased risk for IAPA included organ transplant (OR, 4.8), hematogenous malignancy (OR, 2.5), immunocompromise (OR, 2.2), and prolonged corticosteroid use prior to hospital admission (OR, 2.4). IAPA also was associated with more severe disease, a higher rate of complications, longer ICU stays, and a greater need for organ supports, researchers noted. Clinical features not significantly more common in patients with IAPA included fever, hemoptysis, and acute respiratory distress syndrome.

The findings were limited by factors including the retrospective design of the studies and inability to control for all potential confounders. Other limitations included the variations in study design, variability of practice patterns across locations, and inclusion of data mainly from countries of high socioeconomic status. “Given the apparent waning of the COVID-19 pandemic and re-emergence of influenza, our analysis also revealed other gaps in the current literature, including the need to validate newer diagnostic methods and to develop a system to measure severity of IAPA,” the researchers added.

The study results reflect IAPA prevalence from previous studies, and support the need for a lower threshold for IAPA testing and initiation of antifungal treatment, even with limited data for clinical guidance, they concluded. The study received no outside funding. The researchers had no financial conflicts to disclose. ■

LONG COVID

People with long COVID have specific blood biomarkers

BY RALPH ELLIS

People with long COVID have specific biomarkers in their blood, according to a study published in *Nature* (2023 Sep 25. doi: 10.1038/s41586-023-06651-y). The findings may be a step toward creating blood tests to positively identify people with long COVID, researchers said. “This is a decisive step forward in the development of valid and reliable blood testing protocols for long COVID,” said

David Putrino, PhD, lead author and professor of rehabilitation and human performance and director of the Abilities Research Center at Icahn Mount Sinai Health System, New York.

Researchers from the Icahn School of Medicine at Mount Sinai and Yale School of Medicine looked at blood samples from about 270 people between January 2021 and June 2022. The people had never been infected with COVID, had

LONG COVID continued on following page

New RSV vaccine will cut hospitalizations, study shows

BY MEGAN BROOKS

The newly approved respiratory syncytial virus vaccine administered during pregnancy reduces the clinical and economic burden of lower respiratory tract disease caused by RSV, according to research presented at an annual scientific meeting on infectious diseases. “With RSV maternal vaccination that is associated with clinical efficacy of 69% against severe RSV disease at 6 months, we estimated up to 200,000 cases can be averted, and that is associated with almost \$800 million in total,” author Amy W. Law, PharmD, director of global value and evidence at Pfizer, noted during a news briefing. The challenge, said Natasha Halasa, MD, MPH, professor of pediatrics, division of pediatric infectious diseases at Vanderbilt University, Nashville, Tenn., is that uptake of maternal vaccines and vaccines in general is “not optimal,” making awareness of this maternal RSV vaccine important. Most children are infected with RSV by age 2 years.

In the randomized, double-blind, placebo-controlled phase 3 study, Pfizer’s maternal RSV vaccine had an almost 82% efficacy against severe RSV infection in infants from birth through their first 90 days, and a 69% efficacy against severe disease through 6 months of life. In the trial, 7,400 women received a single dose of the vaccine in the late second or third trimester. There were no safety signals for the mothers or infants. The U.S. Food and Drug Administration approved the vaccine, known as Abrysvo, in August, to be given between weeks 32 and 36 of pregnancy.

Dr. Law and colleagues modeled the potential public health impact

of the maternal RSV vaccine among all pregnant women and their infants born during a 12-month period in the United States. The model focused on severe RSV disease in babies requiring medical attention. According to their model, without widespread use of the maternal RSV vaccine, 48,246 hospitalizations, 144,495 emergency department encounters, and 399,313 outpatient clinic visits are projected to occur annually among the U.S. birth cohort of 3.7 million infants younger than 12 months. With widespread use of the vaccine, annual hospitalizations resulting from infant RSV would fall by 51%, emergency department encounters would decline by 32%, and outpatient clinic visits by 32%, or a direct medical cost decrease of about \$692 million and indirect nonmedical cost of roughly \$110 million.

Dr. Law noted two caveats to the data: “Protections are based on year-round administration of the vaccine to pregnant women at 32-36 weeks’ gestational age, and this is also assuming 100% uptake,” she told the briefing. Dr. Halasa noted the peak age for severe RSV illness is 3 months and it’s tough to identify infants at highest risk for severe RSV.

The FDA in July approved AstraZeneca’s monoclonal antibody nirsevimab (Beyfortus) for the prevention of RSV in neonates and infants entering their first RSV season, and in children up to 24 months who remain vulnerable to severe RSV disease through their second RSV season. The study was funded by Pfizer. Dr. Law is employed by Pfizer. Dr. Halasa has received grant and research support from Merck. ■

LONG COVID *continued from previous page*

fully recovered from an infection, or still showed symptoms at least 4 months after infection. Using machine learning, research teams differentiated between people with and without long COVID with 96% accuracy based on features in the blood samples, according to a news release from Mount Sinai. People with long COVID had abnormal T-cell activity and low levels of the hormone cortisol. Cortisol helps people feel alert and awake, which

would explain why people with long COVID often report fatigue, NBC News said in a report on the study. “It was one of the findings that most definitively separated the folks with long COVID from the people without long COVID,” Dr. Putrino told NBC News. The study also found that long COVID appears to reactivate latent viruses including Epstein-Barr and mononucleosis, the study said. The blood tests could allow doctors to come up with specialized treatments in

Wastewater can signal upswing in flu, RSV

BY MEGAN BROOKS

Wastewater monitoring can accurately gauge influenza A and B and respiratory syncytial virus (RSV) at the population level, and help inform public response to common seasonal illnesses, according to research reported at an annual scientific meeting on infectious diseases.

The analysis of wastewater in Calgary (Alta.) found a “positive correlation” between positivity rates for these three viruses in wastewater and weekly laboratory-confirmed clinical cases and test positivity rates, study investigator Kristine Du, with Cumming School of Medicine, University of Calgary, told this news organization. Wastewater monitoring of viral activity has become an established tool for COVID-19 pandemic monitoring, providing a leading indicator to cases and hospitalizations. However, less is known about its potential for monitoring endemic respiratory viruses.

The new study shows wastewater-based surveillance is a “robust and adaptable” tool for community-level surveillance of seasonal respiratory viruses – “one that can complement health care clinical testing because it’s independent from testing biases, and we can actually correlate our cases very well with it,” Ms. Du said during a preconference media briefing. For the study, Ms. Du and colleagues assessed the occurrence of influenza A, influenza B, and RSV RNA in all three wastewater treatment plants in Calgary between March 2022 and April 2023 and its correlation with clinical disease. They found that viral signals in Calgary’s wastewater for influenza

A and B and RSV correlated significantly with weekly confirmed clinical cases in Calgary residents. Influenza A peaked in Calgary’s wastewater between November and December 2022; influenza B peaked between February and April 2023; and RSV between November 2022 and February 2023.

“Wastewater gives us unbiased, objective, and comprehensive data.

Wastewater monitoring of viral activity has become an established tool for COVID-19 pandemic monitoring, providing a leading indicator to cases and hospitalizations.

It can be used in addition to other testing for assessing the community burden that disease may have, and it is complementary to clinical testing,” Ms. Du said. Their team, she added, is continuing to proactively monitor wastewater for influenza and RSV, as well as other agents of “pandemic potential to make sure we know what could affect humans – and make sure everyone is aware of that.”

Briefing moderator Belinda Ostrowsky, MD, MPH, Albert Einstein College of Medicine, New York, commented, “Wastewater surveillance illustrates how understanding community levels of viral trends can identify hotspots, inform local public health decision-making, and prepare clinicians and hospitals for potential outreach.” The study had no commercial funding. Ms. Du and Dr. Ostrowsky report no relevant financial relationships. ■

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