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Hospital health care workers are shown during an intubation procedure. The patient has COVID-19.

Tempura/Getty Images

COVID-19 ICU visit restrictions add to staff stress, burnout

BY NEIL OSTERWEIL

FROM CHEST 2021 ■ During the COVID-19 pandemic, visitation in intensive care units has been restricted for obvious safety reasons, but such restrictions have contributed to the already serious strains on staff, results of a survey indicate.

Among 91 residents, nurse practitioners, and physician assistants who work in ICUs in the Emory Healthcare system in Atlanta, two-thirds agreed that visitation restrictions were necessary, but nearly three-fourths said that the restrictions had a negative effect on their job satisfaction, and slightly more than half reported experiencing

symptoms of burnout, wrote Nicole Herbst, MD, and Joanne Kuntz, MD, from Emory University School of Medicine.

“Because families are not present at bedside, restrictive visitation policies have necessitated that communication with families be more intentional and planned than before the COVID-19 pandemic.

Understanding the ways these restrictions impact providers and patients can help guide future interventions to improve communication with families and reduce provider burnout,” the authors wrote in a poster at the annual meeting of the American College of Chest Physicians (CHEST).

ICU RESTRICTIONS // continued on page 6

New bronchoscopic interventions appear promising for patients with COPD

BY ANDREW D. BOWSER

FROM CHEST 2021 ■ Several emerging bronchoscopic treatments have the potential to improve the quality of life for patients with chronic obstructive pulmonary disease, an investigator reported at the annual meeting of the American College of Chest Physicians.

Targeted lung denervation is one promising novel therapeutic option that is safe and may improve clinical outcomes according to investigator Christian Ghattas, MD.

Data from an ongoing phase 3 randomized controlled trial may provide new information on the efficacy of targeted lung denervation in patients with chronic obstructive pulmonary disease (COPD), said Dr. Ghattas, assistant professor of medicine and associate program director for the interventional pulmonary fellowship at the Ohio State University Medical Center in Columbus.

“Outcome data of longer follow-up on previously treated patients will provide us with more

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information on the durability and the effect of this treatment,” Dr. Ghattas said in an online presentation at the CHEST meeting, which was held virtually this year. Meanwhile, a few compelling bronchoscopic treatment modalities for patients with chronic bronchitis are in

earlier stages of clinical development. “Larger randomized, controlled trials are ongoing to confirm the available data and to evaluate treatment durability,” said Dr. Ghattas.

Targeted lung denervation

The targeted lung denervation sys-

tem under study (dNerva[®], Nuvaira) involves the use of a radiofrequency catheter to ablate the peribronchial branches of the vagus nerve, Dr. Ghattas said.

The goal of disrupting pulmonary nerve input is to achieve sustained bronchodilation and reduce mucus

secretion, thereby simulating the effect of anticholinergic drugs, he added. In pilot studies, the targeted lung denervation system demonstrated its feasibility and safety, while modifications to the system reduced the rate of serious adverse events,

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according to Dr. Ghattas.

In the AIRFLOW-1 study, which evaluated the safety of the latest generation version of the system, 30 patients with COPD were randomized to targeted lung denervation at one of two doses, 29 or 32 watts.

Of those 30 patients, 29 (96.7%) had procedural success, meaning



the catheter was inserted, guided to its intended location, and removed intact with no reported in-hospital serious adverse events, according to results published in *Respiration* (2019;98:329-39).

There was no difference between arms in the primary endpoint, which was the rate of adverse airway effects requiring intervention that were associated with targeted lung denervation, investigators reported. Four such events occurred, in 3 of 15 patients treated with 32 watts and 1 of 15 patients treated with 29 watts.

Procedural success, defined as device success without an in-hospital serious adverse event, was 96.7% (29/30). The rate of targeted lung denervation-associated adverse airway effects requiring intervention was 3/15 in the 32 W versus 1/15 in the 29 W group ($P = .6$). However, serious gastric events were noted in five patients, prompting safety improvements and procedural enhancements that reduced both gastrointestinal and airway events, according to the study report.

Further data are available from AIRFLOW-2, a randomized, sham-

controlled trial enrolling patients with symptomatic COPD.

In that study, targeted lung denervation plus optimal drug treatment led to fewer respiratory ad-

verse events of interest, including hospitalizations for COPD exacerbation, according to a report on the study that appears in the *American Journal of Respiratory and Critical Care Medicine* (2019. doi: 10.1164/rccm.201903-0624OC).

Respiratory adverse events occurred in 32% of treated patients versus 71% of sham-treated patients in a predefined 3- to 6.5-month postprocedure window, the report says.

Currently underway is AIRFLOW-3, a randomized study of targeted lung denervation versus sham procedure in patients with COPD. The study has a primary outcome measure of moderate or severe COPD exacerbations over 12 months and is slated to enroll 480 patients.

To be eligible for AIRFLOW-3, patients must have had at least two moderate or one severe COPD exacerbation in the previous year, Dr. Ghattas said.

Metered cryospray

One novel intervention with the potential to benefit patients with chronic bronchitis is metered cryospray (RejuvenAir), which works by delivering liquid nitrogen to the tracheobronchial airways, according to Dr. Ghattas.

This targeted delivery ablates abnormal epithelium, facilitating the regeneration of healthy mucosa, according to investigators in a recently published single-arm prospective trial.

Metered cryospray was safe,

Continued on following page

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Valid concerns, negative effects

“During the COVID pandemic, we fell back into old ways of doing things, where parents were restricted from the bedsides of patients in the intensive care unit. And I think we have shown over the last decade that family presence at the bedside significantly improves outcomes for patients and also helps clinicians caring for those patients,” commented Christopher Carroll, MD, FCCP, from Connecticut Children’s Medical Center, Hartford, in an interview.

“We had good reason to exclude visitors because we were worried about their own safety and their own health, but now 18 months into this pandemic, we know how to prevent COVID. We know now how to safely walk into the room of a patient who has COVID and walk out of it and not get infected. There’s no reason why we can’t relax these restrictions and allow families to be there with their loved ones,” continued Dr. Carroll, who was not

involved in the study.

With visitation limited or banned outright, ICU staff have had to replace face-to-face discussion with more intentional, planned, and time-consuming methods, such as telephone calls and online video.

At the time of the survey, only two visitors were allowed to see patients in end-of-life situations in Emory ICUs. Exceptions to this rule were rare.

Study details

ICU staff members were asked about their communication practices, their attitudes about the effect of the restrictions on communication with families and job satisfaction, and their symptoms of burnout, using a validated single-item measure.

A total of 91 practitioners completed most of the survey questions. The results showed that more than half of all respondents (57.9%) reported spending more time com-

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feasible, and linked to clinically meaningful improvements in patient-reported outcomes among patients with COPD, according to authors of the study, which appears in the European Respiratory Journal (2020 Dec 20. doi: 10.1183/13993003.00556-2020).

In the study, 34 of 35 participants received three treatments 4-6 weeks apart.

Investigators reported that at 3 months there were significant reductions in the COPD Assessment Test that were durable to 6 months, and changes in the St. George’s Respiratory Questionnaire and the Leicester Cough Questionnaire that were durable to 9 months.

There were 14 serious adverse events, none of which were device or procedure related, according to investigators.

An ongoing randomized study called SPRAY-CB is comparing metered cryospray to sham procedure in an anticipated 210 patients with COPD with chronic bronchitis.

Bronchial rheoplasty

Bronchial rheoplasty (RheOx, Gala Therapeutics) is another promising intervention under investigation for the treatment of chronic bronchitis, according to Dr. Ghattas.

This system delivers nonthermal pulsed electrical energy, Dr. Ghattas said, with the intention of ablating goblet cells in the airways.

“The preclinical studies have demonstrated epithelial ablation, followed by regeneration of normalized epithelium,” he said in his presentation.

In 12-month results of multicenter clinical trial, bronchial rheoplasty was technically feasible and safe, with reductions in goblet cell hyperplasia and changes in patient-reported quality of life following the procedure, investigators wrote in the American Journal of Respiratory and Critical Care Medicine (2020. doi: 10.1164/rccm.201908-1546OC).

The mean goblet cell hyperplasia score was reduced by 39% from baseline to treatment, according to study results. Four procedure-related serious adverse events were observed through 6 months, and there were no procedure- or device-related serious adverse events over the next 6 months. Mild hemoptysis occurred in 47% of patients, investigators reported.

A larger randomized, double-blind prospective trial with a sham control arm is underway and will include 270 patients, according to Dr. Ghattas. “We’re going to have to wait for the results,” he said.

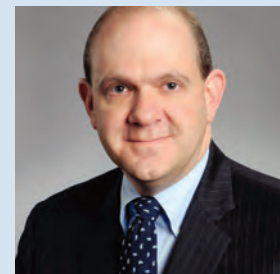
Dr. Ghattas reported serving as a site principal investigator for clinical trials involving the bronchoscopic interventions he discussed, including AIRFLOW-3 (evaluating the targeted lung denervation system), SPRAY-CB (metered cryospray), and RheSolve (bronchial rheoplasty).

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Higher mortality for ECMO-treated patients in 2nd wave

BY NEIL OSTERWEIL

FROM CHEST 2021 ■ For patients with refractory acute respiratory distress syndrome (ARDS) caused by COVID-19 infections, extracorporeal membrane oxygenation (ECMO) may be the treatment of last resort.

But for reasons that aren't clear, in the second wave of the COVID-19 pandemic at a major teaching hospital, the mortality rate of patients on ECMO for COVID-induced ARDS was significantly higher than it was during the first wave, despite changes in drug therapy and clinical management, reported Rohit Reddy, BS, a second-year medical student, and colleagues at Thomas Jefferson University Hospital in Philadelphia.

During the first wave, from April to September 2020, the survival rate of patients while on ECMO in their ICUs was 67%. In contrast, for patients treated during the second wave, from November 2020 to March 2021, the ECMO survival rate was 31% ($P = .003$).

The 30-day survival rates were also higher in the first wave compared with the second, at 54% versus 31%, but this difference was not statistically significant.

"More research is required to develop stricter inclusion/exclusion criteria and to improve pre-ECMO management in order to improve outcomes," Mr. Reddy said in a narrated poster presented at the annual meeting of the American College of Chest Physicians, held virtually this year.

ARDS severity greater

ARDS is a major complication of COVID-19 infections, and there is evidence to suggest that COVID-as-

sociated ARDS is more severe than ARDS caused by other causes, the investigators noted.

"ECMO, which has been used as a rescue therapy in prior viral outbreaks, has been used to support certain patients with refractory ARDS due to COVID-19, but evidence for its efficacy is limited. Respiratory failure remained a highly concerning complication in the second wave of the COVID-19 pandemic, but it is unclear how the evolution of the disease and pharmacologic utility has affected the clinical utility of ECMO," Mr. Reddy said.

To see whether changes in disease course or in treatment could explain changes in outcomes for patients with COVID-related ARDS,

ECMO mortality rates were significantly higher during the second wave. During the first wave, 33% of patients died while on ECMO, compared with 69% in the second wave ($P = .03$).

the investigators compared characteristics and outcomes for patients treated in the first versus second waves of the pandemic. Their study did not include data from patients infected with the Delta variant of the SARS-CoV-2 virus, which became the predominant viral strain later in 2021.

The study included data on 28 patients treated during the first wave, and 13 during the second. The sample included 28 men and 13 women with a mean age of 51 years.

All patients had venovenous ECMO, with cannulation in the femoral or internal jugular veins;

some patients received ECMO via a single double-lumen cannula.

There were no significant differences between the two time periods in patient comorbidities prior to initiation of ECMO.



Patients in the second wave were significantly more likely to receive steroids (54% vs. 100%; $P = .003$) and remdesivir (39% vs. 85%; $P = .007$). Prone positioning before ECMO was also significantly more frequent in the second wave (11% vs. 85%; $P < .001$).

Patients in the second wave stayed on ECMO longer – median 20 days versus 14 days for first-wave patients – but as noted before, ECMO mortality rates were significantly higher during the second wave. During the first wave, 33% of patients died while on ECMO, compared with 69% in the second wave ($P = .03$). Respective 30-day mortality rates were 46% versus 69% (ns).

Rates of complications during ECMO were generally comparable between the groups, including acute renal failure (39% in the first wave vs. 38% in the second), sepsis (32% vs. 23%), bacterial pneumonia (11% vs. 8%), and gastrointestinal bleeding (21% vs. 15%). However, significantly more patients in the second wave had cerebral vascular accidents (4% vs. 23%; $P = .050$).

Senior author Hitoshi Hirose, MD, PhD, professor of surgery at Thomas Jefferson University, said in an interview that the difference in outcomes was likely caused by changes in pre-ECMO therapy between the first and second waves.

"Our study showed the incidence of sepsis had a large impact on the

patient outcomes," he wrote. "We speculate that sepsis was attributed to use of immune modulation therapy. The prevention of the sepsis would be key to improve survival of ECMO for COVID 19."

"It's possible that the explanation for this is that patients in the second wave were sicker in a way that wasn't adequately measured in the first wave," CHEST 2021 program cochair Christopher Carroll, MD, FCCP, from Connecticut Children's Medical Center in Hartford, said in an interview.

The differences may also have been attributable to changes in virulence, or to clinical decisions to put sicker patients on ECMO, he said.

Casey Cable, MD, MSc, a pulmonary disease and critical care specialist at Virginia Commonwealth Medical Center in Richmond, also speculated in an interview that second-wave patients may have been sicker.

"One interesting piece of this story is that we now know a lot more – we know about the use of steroids plus or minus remdesivir and proning, and patients received a large majority of those treatments but still got put on ECMO," she said. "I wonder if there is a subset of really sick patients, and no matter what we treat with – steroids, proning – whatever we do they're just not going to do well."

Both Dr. Carroll and Dr. Cable emphasized the importance of ECMO as a rescue therapy for patients with severe, refractory ARDS associated with COVID-19 or other diseases.

Neither Dr. Carroll nor Dr. Cable were involved in the study.

No study funding was reported. Mr. Reddy, Dr. Hirose, Dr. Carroll, and Dr. Cable disclosed no relevant financial relationships.

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municating with families than they had the previous year.

A large majority (90.5%) also said that video communication (for example, with a tablet, personal device, or computer) was as effective or more effective than telephone communication.

In all, 64.3% of practitioners agreed that visitation restrictions were appropriate, but 71.4% said that the restrictions had a negative effect on their job satisfaction, and 51.8% reported experiencing symptoms of burnout, such as stress, low energy, exhaustion, or lack of motivation.

Casey Cable, MD, a pulmonary disease and critical care specialist at Virginia Common-

wealth Medical Center, Richmond, who was not involved in the study, did her fellowship at Emory. She told this news organization that the study findings might be skewed a bit by subjective impressions.

"I work in a level I trauma unit providing tertiary medical care, and we're using more video to communicate with family members, more iPads," she said. "Their finding is interesting that people felt that they were communicating more with family members, and I wonder if that's a type of recall bias, because at the bedside, you can have a conversation, as opposed to actively talking to family members by calling them, videoing them, or whatnot, and I think that sticks in our head more, about putting in more effort.

I don't know if we are spending more time communicating with family or if that's what we just recall."

She agreed with the authors that visitation restrictions have a definite negative effect on job satisfaction and that they cause feelings of burnout.

"It's tough not having families at bedside and offering them support. When visitors are not able to see how sick their family members are, it complicates discussions about end-of-life care, transitioning to comfort care, or maybe not doing everything," she said.

No funding source for the study was reported. Dr. Herbst, Dr. Kuntz, Dr. Carroll, and Dr. Cable have disclosed no relevant financial relationships.

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COVID-19

Comorbidities, not race, primary to ICU outcomes?

BY NEIL OSTERWEIL

FROM CHEST 2021 ■ Racial/ethnic disparities in COVID-19 mortality rates may be related more to comorbidities than to demographics, suggest authors of a new study.

Researchers compared the length of stay in intensive care units in two suburban hospitals for patients with severe SARS-CoV-2 infections.

Their study shows that, although the incidence of comorbidities and rates of use of mechanical ventilation and death were higher among Black patients than among patients of other races, length of stay in the ICU was generally similar for patients of all races. The study was conducted by Tripti Kumar, DO, from Lankenau Medical Center, Wynnewood, Pa., and colleagues.

“Racial disparities are observed in the United States concerning COVID-19, and studies have discovered that minority populations are at ongoing risk for health inequity,” Dr. Kumar said in a narrated e-poster presented during the annual meeting of the American College of Chest Physicians (CHEST).

“Primary prevention initiatives should take precedence in mitigating the effect that comorbidities have on these vulnerable populations to help reduce necessity for mechanical ventilation, hospital length of stay, and overall mortality,” she said.

At the time the study was conducted, the COVID-19 death rate in the United States had topped 500,000 (as of this writing, it stands at 726,000). Of those who died, 22.4% were Black, 18.1%

were Hispanic, and 3.6% were of Asian descent. The numbers of COVID-19 diagnoses and deaths were significantly higher in U.S. counties where the proportions of Black residents were higher, the authors note.

To see whether differences in COVID-19 outcomes were reflected in ICU length of stay, the researchers conducted

a retrospective chart review of data on 162 patients admitted to ICUs at Paoli Hospital and Lankenau Medical Center, both in the suburban Philadelphia town of Wynnewood.

All patients were diagnosed with COVID-19 from March through June 2020.

In all, 60% of the study population were Black, 35% were White, 3% were Asian, and 2% were Hispanic. Women composed 46% of the sample.

The average length of ICU stay, which was the primary endpoint, was similar among Black patients (15.4 days), White patients (15.5 days), and Asian patients (16 days). The shortest average hospital stay was among Hispanic patients, at 11.3 days.

The investigators determined that among all races the prevalence of type 2 diabetes, obesity, hypertension, and smoking was highest among Black patients.

Overall, nearly 85% of patients required mechanical ventilation. Among the patients who required it, 86% were Black, 84% were White, 66% were Hispanic, and 75% were Asian.

Overall mortality was 62%. It was higher among Black patients, at 60%, than among White patients, at

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VIEW ON THE NEWS

Sachin Gupta, MD, FCCP, comments: More data are becoming available that attempt to address the impact on race and outcomes. Some aspects to keep in mind for population studies such as this include the racial mix and socioeconomic status of the sample population and timing of the analysis during the pandemic. The study findings themselves may imply structural racism, and adjusting for socioeconomic status may be a method to explore that further. Given the small sample size, and the limitations that Dr. Haynes in his commentary also brings up, results such as these should be interpreted cautiously.



Unvaccinated 20 times more likely to die of COVID-19

BY CAROLYN CRIST

During the month of September, Texans who weren't vaccinated against COVID-19 were 20 times more likely to die from COVID-19 and related complications than those who were fully vaccinated, according to a new study from the Texas Department of State Health Services.

The data also showed that unvaccinated people were 13 times more likely to test positive for COVID-19 than people who were fully vaccinated.

"This analysis quantifies what we've known for months," Jennifer Shuford, MD, the state's chief epidemiologist, told the Dallas Morning News.

"The COVID-19 vaccines are doing an excellent job of protecting

people from getting sick and from dying from COVID-19," she said. "Vaccination remains the best way to keep yourself and the people close to you safe from this deadly disease."

As part of the study, researchers analyzed electronic lab reports, death certificates, and state immunization records, with a particular focus on September when the contagious Delta variant surged across

Texas. The research marks the state's first statistical analysis of COVID-19 vaccinations in Texas and the effects, the newspaper reported.

The protective effect of vaccina-

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33%. The investigators did not report mortality rates for Hispanic or Asian patients.

Demondes Haynes, MD, FCCP, professor of medicine in the Division of Pulmonary and Critical Care and associate dean for admissions at the University of Mississippi Medical Center and School of Medicine, Jackson, who was not involved in the study, told this news organization that there are some gaps in the study that make it difficult to draw strong conclusions about the findings.

"For sure, comorbidities contribute a great deal to mortality, but is there something else going on? I think this poster is incomplete in that it cannot answer that question," he said in an interview.

He noted that the use of retrospective rather than prospective data makes it hard to account for potential confounders.

"I agree that these findings show the potential contribution of comorbidities, but to me, this is a little incomplete to make that a definitive statement," he said.

"I can't argue with their recommendation for primary prevention – we definitely want to do primary prevention to decrease comorbidities. Would it decrease overall mortality? It might, it sure might, for just COVID-19 I'd say no, we need more information."

No funding source for the study was reported. Dr. Kumar and colleagues and Dr. Haynes reported no relevant financial relationships.

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tion was most noticeable among younger groups. During September, the risk of COVID-19 death was 23 times higher in unvaccinated people in their 30s and 55 times higher for unvaccinated people in their 40s.

In addition, there were fewer than 10 COVID-19 deaths in September

among fully vaccinated people between ages 18-29, as compared with 339 deaths among unvaccinated people in the same age group.

Then, looking at a longer time period – from Jan. 15 to Oct. 1 – the researchers found that unvaccinated people were 45 times more likely to contract COVID-19 than fully vaccinated people. The pro-

TECTIVE effect of vaccination against infection was strong across all adult age groups but greatest among ages 12-17.

“All authorized COVID-19 vaccines in the United States are highly effective at protecting people from getting sick or severely ill with COVID-19, including those infected with Delta and other known vari-

ants,” the study authors wrote. “Real world data from Texas clearly shows these benefits.”

About 15.6 million people in Texas have been fully vaccinated against COVID-19 in a state of about 29 million residents, according to state data. About 66% of the population has received at least one dose, while 58% is fully vaccinated.

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Researchers assess SSRIs for possible treatment value

BY MEGAN BROOKS

New evidence suggests selective serotonin reuptake inhibitors (SSRI) may be associated with lower COVID-19 severity.

A large analysis of health records shows patients with COVID-19 taking an SSRI were significantly less likely to die of COVID-19 than a matched control group. “We can’t tell if the drugs are

causing these effects, but the statistical analysis is showing significant association. There’s power in the numbers,” Marina Sirota, PhD, University of California San Francisco, said in a statement.

The study was published online in JAMA Network Open (2021 Nov 15. doi: 10.1001/jamanetworkopen.2021.33090). Investigators analyzed data

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from the Cerner Real World Data COVID-19 de-identified electronic health records database of 490,373 patients with COVID-19 across 87 health centers, including 3,401 patients who were prescribed SSRIs.

When compared with matched patients with COVID-19 taking SSRIs, patients taking fluoxetine were 28%

less likely to die (relative risk [RR], .72; 95% CI, 0.54-0.97; adjusted $P = .03$) and those taking either fluoxetine or fluvoxamine were 26% less likely to die (RR, 0.74; 95% CI, 0.55-0.99; adjusted $P = .04$) versus those not on these medications.

Patients with COVID-19 taking any kind of SSRI were 8% less likely to die than the matched controls

(RR, 0.92; 95% CI, 0.85-0.99; adjusted $P = .03$).

“We observed a statistically significant reduction in mortality of COVID-19 patients who were already taking SSRIs. This is a demonstration of a data-driven approach for identifying new uses for existing drugs,” Dr. Sirota told this news organization.

“Our study simply shows an association between SSRIs and COVID-19 outcomes and doesn’t investigate the mechanism of action of why the drugs might work. Additional clinical trials need to be carried out before these drugs can be used in patients going forward,” she cautioned.

“There is currently an open-label trial investigating fluoxetine to reduce intubation and death after COVID-19. To our knowledge, there are no phase 3 randomized controlled trials taking place or planned,” study investigator Tomiko Oskotsky, MD, with UCSF, said in an interview.

The current results “confirm and expand on prior findings from observational, preclinical, and clinical studies suggesting that certain SSRI antidepressants, including fluoxetine or fluvoxamine, could be beneficial against COVID-19,” Nicolas Hoertel, MD, PhD, MPH, with Paris University and Corentin-Celton Hospital in France, writes in a linked editorial.

Dr. Hoertel notes that the anti-inflammatory properties of SSRIs may underlie their potential action against COVID-19, and other potential mechanisms may include reduction in platelet aggregation, decreased mast cell degranulation, increased melatonin levels, interference with endolysosomal viral trafficking, and antioxidant activities.

“Because most of the world’s population is currently unvaccinated and the COVID-19 pandemic is still active, effective treatments of COVID-19 – especially those that are easy to use, show good tolerability, can be administered orally, and have widespread availability at low cost to allow their use in resource-poor countries – are urgently needed to reduce COVID-19-related mortality and morbidity,” Dr. Hoertel points out.

“In this context, short-term use of fluoxetine or fluvoxamine, if proven effective, should be considered as a potential means of reaching this goal,” he adds.

The study was supported by the Christopher Hess Research Fund and, in part, by UCSF and the National Institutes of Health. Dr. Sirota has reported serving as a scientific advisor at Aria Pharmaceuticals.

Dr. Hoertel has reported being listed as an inventor on a patent application related to methods of treating COVID-19, filed by Assistance Publique-Hopitaux de Paris, and receiving consulting fees and nonfinancial support from Lundbeck.

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 **CHEST**™ Physician
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Rhinovirus and enterovirus thrived as others faded

BY MARCIA FRELICK

Comparison of children positive for viruses over four seasons

The common-cold viruses rhinovirus (RV) and enterovirus (EV) continued to circulate among children during the COVID-19 pandemic while there were sharp declines in influenza, respiratory syncytial virus (RSV), and other respiratory viruses, new data indicate.

Researchers used data from the Centers for Disease Control and Prevention's New Vaccine Surveillance Network. The cases involved 37,676 children in seven geographically diverse U.S. medical centers between December 2016 and January 2021. Patients presented to emergency departments or were hospitalized with RV, EV, and other acute respiratory viruses.

The investigators found that the percentage of children in whom RV/EV was detected from March 2020 to January 2021 was similar to the percentage during the same months in 2017-2018 and 2019-2020. However, the proportion of children infected with influenza, RSV, and other respiratory viruses combined dropped significantly in comparison to the three prior seasons.

Danielle Rankin, MPH, lead author of the study and a doctoral candidate in pediatric infectious disease at Vanderbilt University, in Nashville, Tenn., presented the study on Sept. 30 during a press conference at IDWeek 2021, an annual scientific meeting on infectious diseases.

"Reasoning for rhinovirus and enterovirus circulation is unknown but may be attributed to a number

of factors, such as different transmission routes or the prolonged survival of the virus on surfaces," Ms. Rankin said. "Improved understanding of these persistent factors of RV/EV and the role of nonpharmaceutical interventions on transmission dynamics can further guide future prevention recommendations and guidelines."

Coauthor Claire Midgley, PhD, an epidemiologist in the Division of Viral Diseases at the CDC, told reporters that further studies will assess why RV and EV remained during the pandemic and which virus types within the RV/EV group persisted.

"We do know that the virus can spread through secretions on people's hands," she said. "Washing kids' hands regularly and trying not to touch your face where possible is a really effective way to prevent transmission," Dr. Midgley said.

"The more we understand about all of these factors, the better we can inform prevention measures."

Andrew T. Pavia, MD, chief, division of pediatric infectious diseases, University of Utah, Salt Lake City, who was not involved in the study, told this news organization that

rhinoviruses can persist in the nose for a very long time, especially in younger children, which increases the opportunities for transmission.

"Very young children who are unable to wear masks or are unlikely to wear them well may be acting as the reservoir, allowing transmission in households," he said. "There is also an enormous pool of diverse rhinoviruses, so past colds provide limited immunity, as everyone has found out from experience."

Martha Perry, MD, associate professor at the University of North Carolina at Chapel Hill and chief of adolescent medicine, told this news organization that some of the differences in the prevalence of viruses may be because of their seasonality.

"Times when there were more mask mandates were times when RSV and influenza are more prevalent," said Dr. Perry, who was not involved with the study. "We were masking more intently during those times, and there was loosening of restrictions when we see more enterovirus, particularly because that tends to be more of a summer/fall virus."

She agreed that the differences

may result from the way the viruses are transmitted.

"Perhaps masks were helping with RSV and influenza, but perhaps there was not as much hand washing or cleansing as needed to prevent the spread of rhinovirus and enterovirus, because those are viruses that require a bit more hand washing," Dr. Perry said. "They are less aerosolized and better spread with hand-to-hand contact."

Dr. Perry added that, on the flip side, "it's really exciting that there are ways we can prevent RSV and influenza, which tend to cause more severe infection."

Ms. Rankin said limitations of the study include the fact that, from March 2020 to January 2021, health care-seeking behaviors may have changed because of the pandemic and that the study does not include the frequency of respiratory viruses in the outpatient setting.

The sharp 2020-2021 decline in RSV reported in the study may have reversed after many of the COVID-19 restrictions were lifted this summer.

This news organization reported in June of this year that the CDC has issued a health advisory to notify clinicians and caregivers about an increase in cases of interseasonal RSV in parts of the southern United States.

The CDC has urged broader testing for RSV among patients presenting with acute respiratory illness who test negative for SARS-CoV-2.

The study's authors, Ms. Pavia, and Dr. Perry have disclosed no relevant financial relationships.

Virus type	2017-2018	2018-2019	2019-2020	2020-2021
RV/EV	29.0%	34.4%	30.4%	29.6%
RSV	16.7%	18.2%	20.5%	1.2%
Influenza	8.4%	4.7%	10.5%	2.6%
Other respiratory viruses*	15.3%	14.0%	14.0%	6.1%

*These include human metapneumovirus, parainfluenza types 1-4, and adenovirus.

Note: Based on data for 37,676 children from seven geographically diverse U.S. medical centers.

Source: Ms. Rankin, Dr. Midgley

MDedge News

Dupilumab-improved lung function lasts in children with moderate to severe asthma

BY ANDREW D. BOWSER

MDedge News

FROM CHEST 2021 ■ Add-on treatment with dupilumab may improve lung function in children aged 6-11 years with uncontrolled moderate to severe type 2 inflammatory asthma, results from a randomized, placebo-controlled, phase 3 study show.

Improvements in lung function parameters were observed as early as 2 weeks and persisted over the 52-week treatment period among children in the LIBERTY ASTHMA VOYAGE study, according to investigator Leonard B. Bacharier, MD, of Monroe Carell Jr. Children's Hospital at Vanderbilt University Medical Center, Nashville, Tenn.

"Dupilumab led to clinically meaningful rapid

and sustained improvements in lung function parameters," Dr. Bacharier said in an online poster presentation at the annual meeting of the American College of Chest Physicians, held virtually this year.



The improvements in forced expiratory volume in 1 second (FEV₁) and other measures reported for children with moderate to severe asthma who have the type 2 phenotype, which is the most common driver of pediatric asthma, according to Dr. Bacharier.

"Many children with moderate to severe asthma have abnormal lung function, and this can be

a risk factor for future lung disease in adulthood," Dr. Bacharier said in his presentation.

The VOYAGE continues

The findings presented at the meeting build on another report earlier this year from the LIBERTY ASTHMA VOYAGE study demonstrating that add-on dupilumab treatment led to a significant improvement versus placebo in FEV₁ up to 12 weeks.

"We now have a long-term data on this drug as well, showing its efficacy over a period of time," said Muhammad Adrish, MD, MBA, FCCP, associate professor of pulmonary, critical care, and sleep medicine at Baylor College of Medicine, Houston.

Continued on following page

Placebo beat risankizumab for severe asthma in adults

BY WALTER ALEXANDER

Placebo treatment was found to be superior to treatment with risankizumab for adults with severe persistent asthma in a phase 2a clinical trial. The randomized, double-blind, multicenter trial assessed risankizumab efficacy and safety in 214 adults with severe persistent asthma. The results were reported in the *New England Journal of Medicine* (2021 Oct 28. doi: 10.1056/NEJMoa2030880).

Risankizumab is a humanized, monoclonal antibody directed against subunit p19 of interleukin-23. It is approved for the treatment of moderate to severe psoriasis. Christopher E. Brightling, MD, and colleagues investigated whether targeting interleukin-23 in asthma patients would improve disease control and reduce airway inflammation.

Study details

Patients received either 90 mg of risankizumab (subcutaneous) (n = 105) or placebo (n = 109) once every 4 weeks. Time to first asthma worsening was the primary endpoint. Worsening was defined as decline from baseline on 2 or more consecutive days. Deterioration was defined as a decrease of at least 30% in the morning peak expiratory flow or an increase from baseline of at least 50%

in rescue medication puffs over 24 hours. In addition, a severe asthma exacerbation or an increase of 0.75 or more points on the five-item Asthma Control Questionnaire (scores range from 0 to 6, with higher scores indicating less control) were considered

“The findings not only failed to show benefit for any outcome but also showed asthma worsening occurred earlier and more frequently in those treated with risankizumab versus placebo.”

to be evidence of worsening. Annualized rate of asthma worsening was a secondary endpoint.

The mean age of the patients was 53 years; 66.5% of the patients were women.

Disappointing results

In the risankizumab group, median time to first asthma worsening was 40 days, significantly worse than the 86 days reported for the placebo group (hazard ratio, 1.46; 95% confidence interval, 1.05-2.04; $P = .03$). For annualized asthma worsening, the rate ratio for the comparison of risankizumab with placebo was 1.49 (95% CI, 1.12-1.99).

Among key secondary endpoints, the adjusted mean change in trough

forced expiratory volume in 1 second (FEV₁) from baseline to week 24 was -0.05 L in the risankizumab group and -0.01 L in the placebo group. The adjusted mean change in FEV₁ after bronchodilator use from baseline to week 24 was -0.10 L in the risankizumab group and -0.03 L in the placebo group.

Sputum transcriptomic pathway analysis showed that genes involved in the activation of natural killer cells and cytotoxic T cells and the activation of type 1 helper-T and type 17 helper-T transcription factors were downregulated by risankizumab. Rates of adverse events were similar among patients receiving risankizumab and those taking placebo.

Further trials unwarranted

“The findings not only failed to show benefit for any outcome but also showed asthma worsening occurred earlier and more frequently in those treated with risankizumab versus placebo,” Dr. Brightling, of the University of Leicester (England) said in an interview. “This study does not support any further trials for anti-IL23 in asthma.” Dr. Brightling speculated on the cause of accelerated asthma worsening with risankizumab.

“We found that the gene expression of key molecules involved in our response to infection was de-

creased in airway samples in those treated with risankizumab versus placebo. It is possible that the increased asthma worsening following risankizumab was related to this suppression of antimicrobial immunity,” he said.

He noted that risankizumab did not affect type 2/eosinophilic inflammation, which is the target for current asthma biologics, or gene expression of T2 molecules. “That suggests that this type of inflammation would have continued in the asthma patients during the trial irrespective of receiving risankizumab or placebo,” he said.

Caution with studying biologicals

Downstream biologic responses to risankizumab were detectable, Philip G. Bardin, PhD, and Paul S. Foster, DSc, observed in an accompanying editorial, but there was no discernible clinical benefit, implying attenuation of apposite pathways (*N Engl J Med*. 2021 Oct 28. doi: 10.1056/NEJMe2114472).

Dr. Bardin and Dr. Foster stated that, generally, the reasons for risankizumab's poorer outcomes compared to placebo are unclear. “Overall, these findings support a cautious approach in future research investigating biologic therapies in asthma,” they concluded.

The clinical trial was sponsored and funded by BI/AbbVie.

Continued from previous page

“I think that's pretty exciting, and that's another step toward precision medicine in treatment of asthma,” Dr. Adrish, who is vice-chair of CHEST's Airways Disorders NetWork Steering Committee and was not involved in the study.

Dupilumab received Food and Drug Administration approval in 2018 as add-on maintenance therapy for the treatment of patients aged 12 years or older with moderate to severe asthma that has an eosinophilic phenotype or that is dependent on oral corticosteroid treatment.

In March 2021, Sanofi and Regeneron announced that the FDA had accepted for review a supplemental Biologics License Application (sBLA) for dupilumab as an add-on treatment in children aged 6-11 years with uncontrolled moderate to severe asthma.

That sBLA is supported by data from the LIBERTY ASTHMA VOYAGE study, Sanofi and Regeneron said.

In results of the phase 3 study that Dr. Bacharier presented in May at the American Thoracic Society International Conference, add-on dupilumab dosed every 2 weeks significantly improved percent predicted prebronchodilator FEV₁ by an additional 5.21 percentage points versus placebo at week 12.

Dupilumab and the type 2 phenotype

The new data reported at the CHEST meeting come from a prespecified analysis evaluating the impact of dupilumab on lung function over a 52-week treatment period in patients with a T2 inflammatory asthma phenotype.

“Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin-4 and -13, key and central drivers of T2 inflammation in multiple diseases,” Dr. Bacharier and coinvestigators reported in their study abstract.

Of 408 patients in the study, 350 met the T2-phenotype criteria, including 236 in the dupilumab arm and 114 in the placebo arm.

Patients met T2-phenotype criteria if they had blood eosinophils of at least 150 cells/mcL or fractional exhaled nitric oxide FeNO of at least 20 parts per billion at baseline, investigators said.

Dr. Bacharier and coinvestigators reported on several different endpoints, including absolute and percent predicted prebronchodilator FEV₁, percent predicted postbronchodilator FEV₁, prebronchodilator forced expiratory flow at 25%-75% of pulmonary volume (FEF_{25%-75%}), and forced vital capacity (FVC).

Dupilumab, when compared with placebo, significantly improved prebronchodilator FEV₁ in

pediatric patients with uncontrolled moderate to severe type 2 asthma, according to Dr. Bacharier.

“Patients receiving dupilumab experienced rapid improvements by week 2, and this was sustained for up to 52 weeks,” he said.

The prebronchodilator FEV₁ improved from baseline for dupilumab versus placebo, with a least-squares mean difference of 0.06 L at week 2, which reached 0.17 L by week 52, according to their data. Similarly, postbronchodilator FEV₁ improved from baseline for dupilumab, with a least-squares mean difference versus placebo of 0.09 L at week 52.

Dupilumab compared to placebo also significantly improved percent predicted FEF_{25%-75%} and percent predicted FVC over the 52-week treatment period, according to Dr. Bacharier.

“Dupilumab led to significant, rapid, and sustained improvements in multiple aspects of lung function in children aged 6-11 years,” Dr. Bacharier added in a CHEST press release that described the findings.

The LIBERTY ASTHMA VOYAGE study was sponsored by Sanofi and Regeneron Pharmaceuticals. Dr. Bacharier provided disclosures related to AstraZeneca, GlaxoSmithKline, Regeneron Pharmaceuticals, Sanofi, CF Foundation, DBV Technologies, NIH, and Vectura.

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Pulmonary rehab: Similar benefit for both IPF and COPD

BY WALTER ALEXANDER

MDedge News

FROM THE JOURNAL CHEST® ■ Patients with idiopathic pulmonary fibrosis (IPF) complete and respond to pulmonary rehabilitation at rates similar to patients with chronic obstructive pulmonary disease (COPD), according to results of a real-world study. The findings reported in an article published in the journal *CHEST* (2021 Nov. doi: 10.1016/j.chest.2021.10.021) reinforce pulmonary rehabilitation's benefits for this population.

A progressive decline in respiratory and physical function characterizes IPF, with median survival from diagnosis of 3-5 years, according to Claire Nolan, PhD, of Harefield Hospital, Middlesex, England, and colleagues. The effects of pharmacologic therapies on IPF on symptom burden and quality of life are modest, although lung function decline may be slowed.

Supporting evidence for pulmonary rehabilitation benefit in IPF is more modest than it is for COPD, for which exercise capacity, dyspnea, and health-related quality of life improvement have been demonstrated.

"We did not design a randomized, controlled trial," Dr. Nolan said in an interview, "as it was considered unethical by the local ethics committee to withhold pulmonary rehabilitation based on clinical guidance in the United Kingdom." She pointed out that initial pulmonary rehabilitation trials in COPD included an intervention (pulmonary rehabilitation) and a control (standard medical care) arm.

The study aims were to compare the effects of pulmonary rehabilitation with real-world data between IPF and COPD with respect to magnitude of effect and survival. The authors' hypothesis

was that IPF patients would have a blunted response to pulmonary rehabilitation with reduced completion rates, compared with a matched COPD group, and with increased mortality.

Study details

Investigators use propensity score matching of 163 IPF patients with a control group of 163 patients with COPD referred to pulmonary rehabilitation. Completion rates, responses, and survival

"Our study demonstrates that people with IPF have similar clinical benefits and completion rates to those with COPD. These data reinforce the importance of referral to and engagement in pulmonary rehabilitation amongst the IPF population."

status were recorded for 1 year following pulmonary rehabilitation discharge. The 8-week outpatient program was composed of two supervised exercise and education sessions with additional unsupervised home-based exercise each week.

While spirometry data, as expected, showed a higher proportion of IPF patients using supplemental oxygen, pulmonary rehabilitation completion rates were similar for both groups (IPF, 69%; COPD, 63%; $P = .24$) and there was no between-group difference in the number of sessions attended ($P = .39$).

Medical Research Council (muscle strength), incremental shuttle walk test (ISW), and Chronic Respiratory Questionnaire total score improved significantly in both groups, again with no significant difference between groups.

Over the study course, there was progressive,

significant worsening of the percent of predicted forced vital capacity, prescription supplemental oxygen, resting peripheral oxygen saturation, exercise capacity, health-related quality of life, and pulmonary rehabilitation adherence across groups of responders ($n = 63$; 38%), nonresponders ($n = 50$; 31%) and noncompleters ($n = 50$; 31%).

Among the IPF patients, 6 died before completing pulmonary rehabilitation, with 42 (27%) dying during follow-up.

Benefits of rehabilitation

Multivariable analyses showed that noncompletion and nonresponse were associated with significantly higher risk of all-cause mortality at 1 year. Also, time to all-cause mortality was shorter ($P = .001$) for noncompleters and nonresponders, compared with completers. A trend toward higher completion rates in the IPF group, compared with the COPD group, may be explained, the researchers wrote, by fewer hospitalizations over the prior 12 months in the IPF group.

"Although many programs are designed for people with COPD," Dr. Nolan and colleagues concluded, "our study demonstrates that people with IPF have similar clinical benefits and completion rates to those with COPD. These data reinforce the importance of referral to and engagement in pulmonary rehabilitation amongst the IPF population."

These findings, Dr. Nolan emphasized, emerged from a single center, and validation in other settings is needed.

This study was funded by a National Institute for Health Research Doctoral Research Fellowship (2014-07-089) and a Medical Research Council New Investigator Research Grant (98576).

Genomic classifier is one piece of the ILD diagnosis puzzle

BY ANDREW D. BOWSER

MDedge News

FROM CHEST 2021 ■ Although genomic testing is useful when an interstitial lung disease diagnosis is uncertain, the testing results themselves aren't sufficient to make



the diagnosis, Daniel Dilling, MD, FCCP, said in a presentation at the annual meeting of the American College of Chest Physicians, which was held virtually.

The genomic classifier (Envisia, Veracyte) helps differentiate idiopathic pulmonary fibrosis (IPF) by detecting usual interstitial pneumonia (UIP), the hallmark pattern of this interstitial lung disease.

However, UIP is just one piece of

the larger diagnostic puzzle, according to Dr. Dilling, professor of medicine in the interstitial lung disease program at Loyola University Medical Center in Maywood, Ill.

"Remember, it's just a pattern, and not a diagnosis of IPF," Dr. Dilling said in his presentation.

Genomic classifier results correlate well with both histologic and radiographic UIP pattern, studies show. However, Dr. Dilling said the value of the genomic classifier is not in isolation.

"We don't use this in a vacuum," he said. "It increases our confidence and consensus, but it has to be incorporated into a multidisciplinary discussion group."

Part of the diagnostic pathway

Dr. Dilling said the genomic classifier should be considered part of a diagnostic pathway in uncertain

cases, particularly when the risk of surgical lung biopsy is high.

Current clinical practice guidelines recommend surgical lung biopsy for histopathologic diagnosis

"The final decision regarding whether or not to perform a [surgical lung biopsy] must be based on the balance between benefits to establish a secure diagnosis and the potential risks."

when clinical and radiologic findings are not definitive for IPF, the speaker said.

However, surgical lung biopsy carries some risk, and sometimes it can't be done, he added.

In his presentation, Dr. Dilling

cited a systematic review and meta-analysis of 23 studies looking at surgical lung biopsy for the diagnosis of interstitial lung diseases.

The postoperative mortality rate was 3.6% in that meta-analysis, published in 2015 in the *Journal of Thoracic and Cardiovascular Surgery* (2015 Jan 7. doi: 10.1016/j.jtcvs.2014.12.057).

"The final decision regarding whether or not to perform a [surgical lung biopsy] must be based on the balance between benefits to establish a secure diagnosis and the potential risks," authors wrote at the time.

Mortality risk is higher in immunocompromised and acutely ill patient populations, according to Dr. Dilling, who added that as many of 19% of the patients will have complications from surgical lung biopsy.

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Life-threatening paradoxical bronchospasm may escape recognition in patients with COPD or asthma

BY ANDREW D. BOWSER

MDedge News

FROM CHEST 2021 ■ A rare and potentially life-threatening adverse effect of bronchodilator therapy may be overlooked among patients with chronic obstructive pulmonary disease (COPD) or asthma, according to a researcher who reviewed spirometry test results from U.S. military veterans.

Nearly 1.5% of the tests met the criteria for paradoxical bronchospasm, which refers to airway constriction that may rapidly occur after inhalation of a short-acting beta2 agonist (SABA) such as albuterol.

However, none of those reports alluded to paradoxical bronchospasm, said investigator Malvika Kaul, MD, fellow in the department of pulmonary and critical care at the University of Illinois at Chicago and the Jesse Brown Veterans Affairs Medical Center, also in Chicago.

“Paradoxical bronchospasm was neither recognized nor reported in any spirometry test results,” Dr. Kaul said in an online poster presentation at the annual meeting of the American College of Chest Physicians, held virtually this year.

By recognizing paradoxical bronchospasm, health care providers could address its clinical implications and identify potential alternative management options, according to Dr. Kaul.

“We hope in the future, education of clinicians about this phenomena is emphasized,” Dr. Kaul said in her presentation.

Recognizing paradoxical bronchospasm

In an interview, Dr. Kaul said she began researching paradoxical bronchospasm after encountering a patient who had an acute reaction to albuterol during a pulmonary function test.

“I was not taught about it, and I wasn’t recognizing that pattern very frequently in my patients,” she said.

Prescribing information for Food and Drug

Administration–approved SABAs include a warning that life-threatening paradoxical bronchospasm may occur, said Dr. Kaul.

If paradoxical bronchospasm occurs, the patient should discontinue the medication immediately and start on alternative therapy, according to the available prescribing information for albuterol sulfate.

Paradoxical bronchospasm has been linked to worsened respiratory outcomes, including more frequent exacerbations, in patients with obstructive lung diseases, according to Dr. Kaul.

Two previous large studies pegged the prevalence of paradoxical bronchospasm at around 4.5% in patients with COPD or asthma, but “it has not been

Nearly 1.5% of the tests met the criteria for paradoxical bronchospasm.

Paradoxical bronchospasm has been linked to worsened respiratory outcomes, including more frequent exacerbations, in patients with obstructive lung diseases.

reported or addressed in high-risk population, such as veterans who have high prevalence of obstructive lung diseases like COPD,” Dr. Kaul said.

Latest study results

Dr. Kaul described a retrospective analysis of 1,150 pre- and postbronchodilator spirometry tests conducted in patients with COPD or asthma at the Jesse Brown VA Medical Center between 2017 and 2020.

A positive paradoxical bronchodilator response was defined as a decrease of least 12% and 200 mL in forced expiratory volume in 1 second and forced vital capacity from baseline after four puffs of albuterol were inhaled, Dr. Kaul said.

Out of 18 reviewed spirometry results that met the criteria, none of the test results reported or

recognized paradoxical bronchospasm, according to Dr. Kaul.

Those meeting the criteria were predominantly COPD patients, according to Dr. Kaul, who said 12 had an underlying diagnosis COPD, 4 had asthma, and 2 had COPD and asthma.



Of the 18 patients, 13 were African American, and all but 1 of the 18 patients had a current or past smoking history, according to reported data.

A history of obstructive sleep apnea was reported in nine patients, and history of gastroesophageal reflux disease was also reported in nine patients. Eleven patients had emphysema.

Greater awareness needed

Results of this study emphasize the need to recognize potential cases paradoxical bronchospasm in clinical practice, as well as a need for more research, according to Allen J. Blaivas, DO, FCCP, chair of the CHEST Airway Disorders NetWork.

“It’s something to be on the alert for, and certainly be aware that, if your patient is telling you that they feel worse, we shouldn’t just pooh-pooh it,” said Dr. Blaivas, who is medical director of the intensive care unit at the East Orange campus of the VA New Jersey Health Care System.

Further research could focus on breaking down whether patients with suspected paradoxical bronchospasm are using metered-dose inhalers or nebulizers, whether or not they are also taking inhaled corticosteroids, and whether prospective testing can confirm paradoxical bronchospasm in patients who report tightness after using a SABA, he said in an interview.

Dr. Kaul and coauthor Israel Rubinstein, MD, had no relevant relationships to disclose. Dr. Blaivas had no relevant relationships to disclose.

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Genomic classifier studies

In a proof-of-principle study, published in 2017 in *Annals of the American Thoracic Society* (2017 Nov. doi: 10.1513/AnnalsATS.201612-947OC), authors described how they used machine learning to train an algorithm to distinguish UIP from non-UIP pattern in tissue obtained by transbronchial biopsy (TBB).

The top-performing algorithm distinguished UIP from non-UIP conditions in single TBB samples with specificity of 86% and sensitivity of 63%, according to investigators, who said at the time that independent validation would be needed before the genomic clas-

sifier could be applied in clinical settings.

In a prospective validation study, published in 2019 in *The Lancet Respiratory Medicine* (2019 Apr 1. doi: 10.1016/S2213-2600[19]30059-1), the genomic classifier identified UIP in TBB samples from 49 patients with a specificity of 88% and sensitivity of 70%.

Excluding patients with definite or probable UIP as shown on high-resolution computed tomography, results show that the classifier had a sensitivity of 76%. The specificity was 88%, and positive predictive value was 81%.

“The performance of the test is good, even in that scenario,” Dr. Dilling said.

Real-world results

Dr. Dilling also highlighted a “real-world” study, published earlier in 2021, demonstrating that UIP pattern recognized by a genomic classifier had encouraging sensitivity and specificity when combined with high-resolution CT and clinical factors.

That study included 96 patients who had both diagnostic lung pathology and a transbronchial lung biopsy for molecular testing with the classifier.

The classifier had a sensitivity of 60.3% and a specificity of 92.1% for histology-proven UIP pattern, investigators said in their report, which appears in the *American Journal of Respiratory and Critical Care*

Medicine (2020 Jul 28. doi: 10.1164/rccm.202003-0877OC).

Local radiologists identified UIP with a sensitivity of 34.0% and specificity of 96.9%. But adding genomic classifier testing to local radiology testing increased the diagnostic yield, investigators said, with a sensitivity of 79.2% and specificity of 90.6%.

“This might suggest that the implementation of this into a local [multidisciplinary discussion] with your local radiology expertise might really improve your recognition of UIP,” Dr. Dilling said.

Dr. Dilling reported disclosures related to Bellerophon, Boehringer Ingelheim, Genentech, Nitto Denko, and Lung Bioengineering.

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Interpreting pulmonary function tests through race/ethnicity may perpetuate health disparities

BY WALTER ALEXANDER

FROM THE JOURNAL CHEST® ■

The use of race/ethnicity in medicine to explain and interpret pulmonary function test (PFT) differences between individuals may contribute to biased medical care and research. Furthermore, it may perpetuate health disparities and structural racism, according to a study published in CHEST (2021. doi: 10.1016/j.chest.2021.08.053).

Current practices of PFT measurement and interpretation are imperfect in their ability to accurately describe the relationship between function and health outcomes, according to Nirav R. Bhakta, MD, University of California, San Francisco, and colleagues.

The authors summarized arguments against using race-specific equations, while voicing genuine concerns about removing race from PFT interpretations, and described knowledge gaps and critical questions needing to be addressed for remediation of health disparities.

“Leaving out the perspectives of practicing pulmonologists and physiologists has global relevance for increasingly multicultural communities in which the range of values that represent normal lung function is uncertain,” Dr. Bhakta said in an interview.

A lesson in history

Tracing the history of spirometry, the authors stated that observations about vital lung capacity showing differences attributable to height, age, sex, and occupation (e.g., typesetter vs. firefighter) were then extended to include social classes and ultimately race. Whites showed greater average vital capacity for the same sex, height, and age than non-Whites.

While some investigators pointed to environmental sources (such as early life nutrition, respiratory illness, air pollution, exercise, and altitude), research into their mechanisms and magnitudes of effect was not pursued, but rather “a narrative of innate differences took hold,” Dr. Bhakta and colleagues reported.

That sort of narrative risks comparison with those used to uphold slavery and structural racism in the past. More recently, such a narrative was used to deny disability claims of Welsh versus English White miners, and was expanded to interpret algo-

rithms designed to predict expected lung function.

Use of standing height questioned

The current practice of using normalized standard height for lung function comparisons misses racial and ethnic differences in the proportion of sitting height to standing height shown in multiple studies, the authors stated. These

Using sitting height instead of standing height reduces lung volume differences up to 50% between White and Black populations, they noted, and socioeconomic variables, such as poverty and immigration status, accounted further for the differences seen.

comparisons may ignore effects on standing height of early-life nutrition, genetics, lung-specific factors such as respiratory infections and exposures to indoor and outdoor pollution, physical activity, and high altitude. Using sitting height instead of standing height reduces lung volume differences up to 50% between White and Black populations, they noted, and socioeconomic variables, such as poverty and immigration status, accounted further for the differences seen. Population differences disappeared by as much as 90% when chest measurements used to estimate surface area or volume were more finely detailed.

The researchers warned, however, that, “because current clinical and policy algorithms rely so heavily on the comparison of an individual’s observed lung function to that which is expected for similar people without typical respiratory disease, an abrupt change to not using race/ethnicity, if not paired with education and a reform of existing algorithms and policies, is also expected to have risks on average to groups of non-White individuals.”

That could lead to potential challenges for some groups ranging from the ability to obtain employment in certain occupations, to being considered for potentially curative lung resections, or having access to home assisted-ventilation and rehabilitation programs.

“An abrupt change to not using race/ethnicity and taking a society’s overall average as the reference range also has the potential to lead to delayed care, denial of

disability benefits, and higher life insurance premiums to White individuals.”

Evidence base is limited

“Although evidence demonstrates differences in lung function between racial/ethnic groups, the premise that dividing lung function interpretation up by racial/ethnic background is helpful in the clinical setting is not a proven one.”

The authors cited some evidence that lung function interpretation without consideration of race/ethnicity has superior prognostic ability (Int J Epidemiol. 2012;41[3]:782-90; Am J Epidemiol. 1998;147[11]:1011-8).

In addition, research has shown only a weak relationship between lung function and work ability, according to the authors. More appropriate ways of assessing expected lung function for an individual in the absence of a diagnoses are under study.

Offering an alternative

As an alternative to race, Dr. Bhakta and colleagues proposed using a range of values that include individuals across many global populations while still adjusting for sex, age, and height. The resultant value would represent a diverse population average and widen the limits of normal that can be expected in otherwise-healthy people.

The approach would include PFTs with other factors for clinical decision-making, but would allow clinicians and patients to appreciate the limitations of interpretation based on comparison to reference values. However, such an approach may miss pathophysiologically reduced lung function in some individuals, in which case lifesaving therapies, such as chemotherapy, lung cancer resection, and bone marrow transplantation could be withheld. In other instances the consequence would be overtesting and diagnosis, they acknowledged.

The authors further discussed

general concerns about the use of race in interpretation of PFTs, addressing limits/considerations as well as knowledge and practice gaps.

For example, one particular concern involves the fact that race does not capture acculturation and mixed ancestry. The limit/consideration is the need to discover mechanisms for differences and to suggest societal interventions, and the knowledge gap pertains to ignorance regarding mechanisms leading to differences in lung function.

For the concern that race is not a proxy for an individual’s genetics, the limit/consideration is that race captures only some genetics and the gap is the need for better genetic information. As an antidote to over reliance on lung function thresholds (without supporting data), they urged outcomes-based standards rather than comparisons with reference populations.

New thinking needed

Dr. Bhakta and colleagues pointed out that the forced expiratory volume in 1 second/forced vital capacity ratios important for diagnosis of obstructive lung disease are similar between racial/ethnic categories, underscoring the need for education about limitations of thresholds and reference values with regard to race, particularly as they are used to detect mild disease.

Ignoring race, on the other hand, can lead to unnecessary testing and treatment (with concomitant side effects), and anxiety.

“Reporting through race-based algorithms in the PFT laboratory risks portraying racial disparities as innate and immutable. By anchoring on the improved prediction of lung function from racial/ethnic-specific reference equations, we miss how the significant residual variation still leaves much uncertainty about the expected value for an individual,” the authors concluded.

“Given their origin and historical and current use in society, these racial/ethnic labels are better used to identify the effects of structural racism on respiratory health in research and ensure adequate representation in research, rather than in clinical algorithms.”

One of the authors is a speaker for MGC Diagnostics. The others indicated that they had no relevant disclosures.

Electronic 'nose' sniffs out sarcoidosis

BY JIM KLING

FROM THE JOURNAL CHEST® ■ An electronic nose (eNose) that measures volatile organic compounds (VOCs) emitted from the lungs successfully distinguished sarcoidosis from interstitial lung disease (ILD) and healthy controls, according to a report in the journal *CHEST* (2021 Oct 28. doi: 10.1016/j.chest.2021.10.025).

The approach has the potential to generate clinical data that can't be achieved through other noninvasive means, such as the serum biomarker soluble interleukin-2 receptor (sIL-2R). sIL-2R is often used to track disease activity, but it isn't specific for diagnosing sarcoidosis, and it isn't available worldwide.

Sarcoidosis is a granulomatous inflammatory disease with no known cause and can affect most organs, but an estimated 89%-99% of cases affect the lungs. There is no simple noninvasive diagnostic test, leaving physicians to rely on clinical features, biopsies to obtain tissue pathology, and the ruling out of other granulomatous diagnoses.

The challenge is more difficult because sarcoidosis is a heterogeneous disease, with great variation in the organs affected, severity, rate of progression, and therapy response.

In the new study, a cross-sectional analysis showed that exhaled breath analysis using an eNose had excellent sensitivity and specificity for distinguishing sarcoidosis from ILD and healthy controls, and identified sarcoidosis regardless

of pulmonary involvement, pulmonary fibrosis, multiple organ involvement, immunosuppressive treatment, or whether or not pathology supported the diagnosis.

The eNose technology produces a "breath-print" after combining information from a broad range of VOCs. The information originates from an array of metal-oxide semiconductor sensors with partial specificity that artificial intelligence processes to discern patterns. Overall, the system functions similarly to the mammalian olfactory system. The artificial intelligence views it as a "breath-print" that it can compare against previously learned patterns.

"It is a quite easy, simple, and quick procedure, which is noninvasive. We can collect a lot of data from the VOCs in the exhaled breath because there are several sensors that cross-react. We can create breath profiles and group patients to see if profiles differ. Ultimately, we can use the profiles to diagnose or detect disease in the earlier stage and more accurately," said Iris van der Sar, MD. Dr. van der Sar is the lead author on the study and a PhD candidate at Erasmus Medical Center in Rotterdam, The Netherlands.

The study requires further prospective validation, but the technology could have important clinical benefits, said senior author and principal investigator Marlies Wijsenbeek, MD, PhD, head of the Interstitial Lung Disease Center at Erasmus Medical Center. "If we in future can avoid a biopsy, that would be most attractive."

"We hope to come to a point-of-care device that can be used to facilitate early diagnosis at low burden for the patient and health care system," said Karen Moor, MD, PhD, and post-doc on this project. The researchers also hope to determine if the eNose can help evaluate a patient's response to therapy.

Studies of eNose technology in other chronic diseases have shown promising results, but not all results have been validated yet in independent or external cohorts.

The current study included 569 outpatients, 252 with sarcoidosis and 317 with ILD, along with 48 healthy controls. The researchers constructed a training set using 168 patients with sarcoidosis and 32 healthy controls, and a validation set using 84 patients with sarcoidosis and 16 healthy controls. The eNose differentiated between patients and controls in both groups, with an area under the curve of 1.00 for each regardless of pulmonary involvement or treatment.

It also distinguished those with sarcoidosis and pulmonary involvement from those with ILD, with an AUC of 0.90 (95% confidence interval, 0.87-0.94) in the training set, and an AUC of 0.87 (95% CI, 0.82-0.93) in the validation set.

It differentiated between pulmonary sarcoidosis and hypersensitivity pneumonitis in the training set (AUC, 0.95; 95% CI, 0.90-0.99) and the validation set (AUC, 0.88; 95% CI, 0.75-1.00).

The authors reported having no relevant financial disclosures.

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High triglycerides in normal-weight men with OSA

BY WALTER ALEXANDER

MDedge News

In men with a normal waist circumference, obstructive sleep apnea (OSA) metrics were positively associated with serum triglycerides, according to results of a study published in *Nature and Science of Sleep* (2021.13:1771-82).

Layla B. Guscoth, MD, of the South Australian Health and Medical Research Institute and Faculty of Health and Medical Sciences, University of Adelaide, and colleagues assessed unselected male community-dwelling participants in the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) and the Florey Adelaide Male Aging Study (FAMAS) studies.

They examined the association of OSA and nocturnal hypoxemia with serum lipid profiles, and suggested that the cardiometabolic risk profiles of healthy weight individuals with OSA require clinical attention, according to the researchers.

The partial or complete obstruction of upper airways found in the OSA syndrome results in intermittent hypoxia, accompanied variably by sleep fragmentation and daytime sleepiness. While the prevalence of moderate to severe OSA was 49.7% in the Swiss HypnoLaus cohort, it was 74.7% in men aged 40 or older (or having OSA syndrome according to ICD-3 criteria). Dr. Guscoth and colleagues point out, however, that OSA is frequently underdiagnosed or unrecognized in clinical settings, and that OSA has been implicated in development of cardiovascular conditions. Furthermore, the nocturnal hypoxemia resulting from OSA during rapid eye movement (REM) sleep is longitudinally associated with cardiovascular disease and its risk factors (hypertension, insulin resistance, metabolic syndrome, and carotid atherosclerosis).

Study details

Prior research suggests that intermittent hypoxemia activates the sympathetic nervous system, increases oxidative stress and systemic inflammation, and that when chronic, reduces clearance of triglyceride-rich lipoproteins and inhibits adipose tissue lipoprotein lipase activity. To clarify inconsistent results in studies investigating potential OSA-dyslipidemia associations, and to confirm research suggesting an independent association with severe OSA (apnea-hypopnea index [AHI] ≥ 30 /h),

the authors conducted analyses stratified by waist circumference to observe an obesity-independent association between OSA metrics and dyslipidemia.

The investigators assessed 753

MAILES participants (mean age 60.8 years) who underwent full in-home polysomnography (Embletta X100). They looked at triglycerides, high- and low-density lipoprotein, total cholesterol, associations between

lipids and continuous measures of nocturnal hypoxemia (oxygen desaturation index [ODI], AHI, and REM-AHI), and adjusted for chronic conditions, risk behavior, and socio-demographic factors.

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Mean waist circumference was 99.3 cm and OSA (AHI ≥ 10) prevalence was 52.6%. No significant associations were found between OSA metrics and lipid measures in an overall analysis, nor in a sensitivity analysis excluding lipid-lowering therapies.

In a covariate adjusted analysis stratified according to waist circum-

ference (<95 cm, 95-100 cm, >100 cm) to minimize the contribution of obesity to hypertriglyceridemia, triglyceride levels were positively associated with AHI, ODI, and REM-AHI in the participants with a waist circumference <95 cm ($P < .05$), but not in participants with waist circumferences of 95-100 cm or >100 cm.

Worse during REM

The authors observed also that OSA during REM sleep is marked by longer obstructive events with greater oxygen desaturations. Obstructive events during REM sleep, research has shown, may be more harmful than obstructive events during non-REM sleep with respect to hypertension, cardiovascular disease, and

glycemic control in type 2 diabetes.

Looking at clinical categories of OSA, Dr. Guscoth and colleagues found that severe OSA was significantly associated with higher likelihood of triglyceride levels that were ≥ 1.7 mmol/L (odds ratio, 4.1, 95% confidence interval, 1.1-15.5, $P = .039$). Analysis according to waist

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circumference confirmed the relationship only among men with waist circumference <95 cm.

Clinical concern

“We therefore suggest that, with our data unstratified by weight circumference, metabolic derangements associated with insulin resistance

induced by intermittent hypoxia due to OSA cannot be separated from the predominant effect of visceral obesity. When stratified by weight circumference, our data show that these derangements in triglycerides are observed only in lean participants where obesity does not have a dominant effect,” the researchers concluded.

“These findings of high prevalence

of metabolic risk in lean patients with OSA, I find very worrying,” coauthor Sarah Appleton, PhD, Flinders Medical Center, Adelaide, Australia, said in an interview. She cited a study showing a 61% risk of dyslipidemia in lean patients with OSA (AHI >5/hr, body mass index <25kg/m², and waist <80 cm in women, <90 cm in men), and two of three

metabolic syndrome components in 64%. “Annual fasting blood tests would identify metabolic problems such as elevated fasting glucose and triglyceride levels,” she noted.

This work was supported by a National Health and Medical Research Council of Australia Project Grant. There were no relevant conflicts reported.

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One-quarter of lung cancer patients alive at 5 years

BY PAM HARRISON

In recent years, the survival rate for patients with lung cancer has increased to the point where now, almost one-quarter of patients

with lung cancer are alive 5 years after being diagnosed. This new statistic is highlighted in the State of Lung Cancer report from the American Lung Association, published online.

“If you look back, the 5-year survival rate has been very slowly eking up at about 1% over the years,” Andrea McKee, MD, volunteer spokesperson at the ALA, told this news organization.

The report shows that the 5-year survival rate increased by 14.5% over the past 5 years. “To see this big jump is truly remarkable, so that is something we

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are all celebrating,” she added.
“But we have to change the fatalistic thinking that both patients and primary care physicians still have about lung cancer. Most people say, ‘Everybody I know who had lung cancer died,’ and that was the way it used to be,” she commented, “but that has now changed. Lung cancer

is highly curable in its early stages, and even if not early-stage, there are treatments that are making an impact now.”

“We have to change the fatalistic thinking that both patients and primary care physicians still have about lung cancer.”

“So we’ve got to change that perception, as it does exist, even on the part of primary care providers, too,” Dr. McKee emphasized.

Lung cancer decreasing but still being diagnosed late
The report notes that the risk of being diagnosed with lung cancer varies considerably across the United States. For example, rates of lung cancer diagnoses are almost 2.5 times higher in Kentucky than in Utah. Overall, the incidence is decreasing. “Over the last 5 years,

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the rate of new cases decreased 10% nationally,” the authors point out.

However, in almost half of the cases, the disease is diagnosed in late stages.

When diagnosed at a late stage, the 5-year survival rate for lung cancer drops to only 6%, whereas when the disease is diagnosed early, the 5-year survival rate is 60%.

At present, around 24% of cases of lung cancer are diagnosed at early stages, the report notes, but again, this varies across the United States. The highest rate (30%) is in Massachusetts, and the lowest rate (19%) is in Hawaii.

The percentage of lung cancer cases diagnosed early has been steadily increasing, presumably in

part because of the introduction of low-dose CT screening for individuals at highest risk (such as smokers).

However, across the nation, only 5.7% of individuals at high risk for lung cancer underwent annual low-dose CT screening, the report notes.

“CT screening is so powerful at

saving lives that even with only 5.7% of people that we’ve been able to screen, I believe it’s making a difference,” Dr. McKee commented.

That small national percentage still represents a considerable number of patients, she noted, “so even with what we’ve done so far, I

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believe that screening is making a difference, at least within my own practice, where I'm definitely seeing it," Dr. McKee emphasized.

Recent changes to the recommendations as to who should undergo lung cancer screening "have almost doubled the size of the screening population in the U.S.," Dr. McKee

commented. "So there are now about 15 million people who need to get screened, and it again helps that primary care physicians know that screening is very powerful at detecting early-stage lung cancer," she said.

In her hospital's own screening program, among the individuals who regularly undergo screening,

the majority (88%) of lung cancer cases are detected at stage I or II, for which the cure rate is approximately 90%, she noted.

Another misconception of primary care physicians is that lung cancer screening has an unacceptably high false-positive rate. Previous reports in the medical literature suggested the rate could be as high as 96%.

"This is absolutely, positively wrong. That is not the false-positive rate; the false-positive rate for lung cancer screening is less than 10%," Dr. McKee emphasized.

"So we have to change that in the minds of primary care providers as well," she underscored.

Report highlights racial disparities

The report also highlights the racial disparities that persist in all aspects of lung cancer management – early diagnosis, surgical treatment, lack of treatment, and survival.

Black Americans are 18% less likely to be diagnosed with early-stage disease and are 23% less likely to receive surgical treatment than their White counterparts.

For example, Black Americans are 18% less likely to be diagnosed with early-stage disease and are 23% less likely to receive surgical treatment than their White counterparts. They are also 9% more likely to receive no treatment at all, and mortality from lung cancer among Black patients is 21% worse than it is for White patients.

The same trend is seen among Latinx persons, although they are just as likely as White patients to undergo surgical treatment.

First and foremost, "we have to make sure that the [Black and Latinx persons] are screened in an equal fashion," Dr. McKee said. Providing screening for communities of color is one strategy that might improve screening rates, she suggested.

So, too, can outreach programs in which lung cancer experts work with leaders within these communities, because people are more likely to listen to their leaders regarding the importance of screening for early detection of lung cancer.

Physicians also need to emphasize that, even for people who quit smoking decades ago, once those persons are in their 70s, "there is a spike again in lung cancer diagnoses, and that is true for both Black and White patients," Dr. McKee stressed.

"Again, this is something that many doctors are not aware of," she emphasized.

Dr. McKee has disclosed no relevant financial relationships.

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Fungal infection can mimic lung cancer metastases

BY ANDREW D. BOWSER

MDedge News

FROM CHEST 2021 ■ A fungal infection typically seen in the lungs may have a variety of unusual clinical presentations elsewhere in the body, even raising suspicion of cancer in some cases, a medical resident reported at the annual meeting of the American College of Chest Physicians.

In one recent and unusual presentation, a 58-year-old woman with persistent headaches had skull lesions on computed tomography (CT) was eventually diagnosed with disseminated coccidioidomycosis (Valley fever), a fungal infection endemic to the Southwestern United States.

The imaging pattern of her head CT was initially concerning for cancer metastasis, according to Sharjeel Israr, MD, a third-year internal medicine resident at Creighton University in Phoenix.

However, the subsequent chest CT revealed a suspicious chest mass. A biopsy of that mass led to the correct diagnosis of disseminated coccidioidomycosis, according to Dr. Israr, who presented the case report in an e-poster at the CHEST meeting, which was held virtually this year.

Mistaken identity

Coccidioidomycosis, caused by the fungus *Coccidioides*, usually affects the lungs, according to

the Centers for Disease Control and Prevention. However, in severe cases it can spread to other parts of the body. In those cases, it's referred to as disseminated coccidioidomycosis.

Arizona accounted for about 10,000 out of 18,000 reported Valley fever cases in 2019, according to the latest statistics from the CDC.

Coccidioidomycosis is frequently mistaken not only for cancer, but also for rheumatic conditions

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and bacterial infections, according to Valley fever specialist John Galgiani, MD, director of the Valley Fever Center for Excellence at the University of Arizona in Tucson.

"Where Valley fever is common, it should very frequently be in the differential for masses that are thought to be cancer," Dr. Galgiani said in an interview. "This case is a good example of that."

Challenging case

In an interview, Dr. Israr said the case was challenging to crack despite the fact that Valley fever is very common in Phoenix.

"It was definitely on the differential from the get-go, but it was very, very low on our differential, just based on the presentation that

she had," according to Dr. Israr.

The patient had history of diabetes and presented with headaches for 4 weeks. However, she had no pulmonary symptoms or meningeal signs, according to Dr. Israr.

A head CT revealed multiple osseous skull lesions and a left temporal lobe lesion.

"The fact that this patient had lesions in the skull, specifically, is something that raised our initial red flags for cancer – especially since she presented with just a headache as her only complaint," he said.

The imaging pattern was concerning for metastasis, according to Dr. Israr, particularly since a subsequent CT of the chest showed multiple pulmonary nodules plus a 7.7-cm mass in the right lower lobe.

Once the biopsy confirmed coccidioidomycosis, the patient was started on fluconazole 600 mg twice daily, according to Dr. Israr.

Although severe disseminated coccidioidomycosis can be difficult to treat, the lung lesion had decreased in size from 7.7 cm to 4.2 cm about 3 months later, Dr. Israr said.

"At the end of the day, she didn't have cancer, and it's something that we're treating and she's actually doing better right now," Dr. Israr said in the interview.

Dr. Israr and coauthors of the case reported they had no relevant relationships to disclose.

Common screening tool found superior to alternatives

BY KATIE ROBINSON

A newly published study that compared the accuracy of two commonly used lung cancer screening algorithms found that the American College of Radiology Lung-RADS screening tool is more accurate in detecting cancerous nodules in patients with a history of

"Lung-RADS scores exhibited excellent sensitivity and specificity for cancer in existing nodules and excellent sensitivity in new nodules, though low specificity in new nodules."

lung cancer than NELSON, a Dutch clinical trial that measures nodule volume and growth rate instead of linear measurement of nodule size as done in Lung-RADS.

The study, published in the American Journal of Roentgenology on Nov. 10, 2021 (doi: 10.2214/AJR.21.26927) was a retrospective study of 185 patients (100 women, 85 men; mean age, 66 years) who

underwent lung cancer screening at a single health care system between July 2015 and August 2018. With the use of Lung-RADS, seven cancers were downgraded to category 2. The weighted cancer risk was 5% for new nodules, 1% for stable existing nodules, and 44% for growing existing nodules.

"Lung-RADS scores exhibited excellent sensitivity and specificity for cancer in existing nodules and excellent sensitivity in new nodules, though low specificity in new nodules," wrote the authors, led by Mark M. Hammer, MD, a radiologist with Brigham and Women's Hospital in Boston.

CT scans are increasingly used for lung cancer screening, so accuracy is essential in devising an appropriate treatment plan for patients. Nearly all centers in the United States use the American College of Radiology's Lung-RADS for lung cancer screening. In Europe, many centers use the volumetric-based approach of NELSON.

Several studies have compared the performance of nodule risk assessment algorithms, but the findings are inconsistent. Lung-RADS was found to be inferior to the Van-

couver risk calculator in predicting malignancy in the National Lung Screening Trial for total nodules (Radiology. 2019 Apr;291[1]:205-11). Dr. Hammer previously report-

ed that tality was lower among participants who underwent volume CT screening than among those who underwent no screening (N Engl J Med. 2020;382:503-13).



ed that subsolid nodules classified as Lung-RADS categories 2 and 3 have a higher risk of malignancy than reported (Radiology. 2019 Nov;293[2]:441-8). Meanwhile, a study that followed 13,195 men and 2,594 women at high risk of lung cancer found that lung cancer mor-

The authors cited the retrospective design and the small sample size as study limitations. They added that pathological proof was not obtained from benign nodules, which may represent undiagnosed cancer.

The authors declared no conflict of interest.

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Transitioning from fellow to attending

BY MEREDITH K. GREER, MD

It's day 1 of "attendingship," and I'm back to wearing my white coat after years of being confident enough in myself to think I didn't need it to look like "the doctor." Is it okay to park here? Does my clinic have a staff bathroom? Will my log in work? Oh my gosh, how do I place orders?! I remember this feeling – it's intern year all over again, except there's no senior resident to rescue me now – here we go!

Starting off

As a new attending, the amount of responsibility can be intimidating and overwhelming. It is important to remember that you are not alone,

Another great source of support for me is my CHEST colleagues. If you have not already, I highly suggest joining the CHEST NetWork(s) that aligns with your career interests. This is a great way to not only network with those who share the same niche as you but also to explore academic opportunities outside of your institution.

you have a whole team supporting you whether you are in clinic or the ICU. Be sure to introduce yourself to those who you will be working with, get to know them, their roles, and figure out the best way that you can help each other with the ultimate goal of helping patients.

In addition to meeting your own team, it is important to introduce yourself to your new colleagues – especially if you are new to the institution. Drs. Fielder and Sihag suggest putting together an introductory email to those who may be referring to you that includes an overview of what you do and how you can help, as well as your contact information. They also suggest maintaining an open line of communication and keeping the referring provider updated on your mutual patient (Fiedler AG, Sihag S. *J Tho-*

rac Cardiovasc Surg. 2020 Mar;159[3]:1156-60). While this may sound antiquated, in my experience thus far, my colleagues have greatly appreciated this gesture.

Finding support

Even though you will be surrounded by a plethora of new colleagues, the transition to attending can be lonely – especially if you are moving to a new institution. Be sure to keep in touch with your co-residents, co-fellows, mentors, and, of course, your friends and family. Studies have shown that support mitigates stress and reduces job strain, which can lead to better health outcomes in the long term (Fiedler AG, Sihag S. [previous]).

Another great source of support for me is my CHEST colleagues. If you have not already, I highly suggest joining the CHEST NetWork(s) that aligns with your career interests. This is a great way to not only network with those who share the same niche as you but also to explore academic opportunities outside of your institution. Through the CHEST Home Mechanical Ventilation and Sleep NetWorks, I have gained mentors, made friends, and have become more involved in CHEST's annual meeting, chairing my first session this year.

Staying organized

Adjusting to your new schedule can be just as hard as adjusting to a new role or new institution. After years of moving through the well-oiled, regimented machine that is medical training, there are suddenly no more rotations, no more research blocks, and no more protected time for learning.

Dr. Okereke suggests creating a weekly calendar, which blocks time for not only your clinical duties but for studying (as you will be taking boards during your first year), academic endeavors (teaching and/or research), and, most importantly – for fun (Okereke I. *J Thorac Cardiovasc Surg.* 2020 Mar;159[3]:1161-2). Being cognizant about maintaining work-life balance is key once you become an attending. It is finally time to learn how to take time off, away from all things work, and to not feel guilty about it.



Dr. Greer is Assistant Professor of Medicine, Emory University Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Atlanta, GA.

Saying no

This brings me to saying "no." We are taught to say "yes" to every opportunity throughout our careers and, while that can certainly help us get far, it can also lead to burnout. Once you're an attending, you're in it for the long haul, so best to say yes to the things you are most interested in and "spark joy," as Marie Kondo says, and say no to the things that do not make you happy and are not congruent with your overall goals (Kondo, M. *Spark Joy*. Ebury Publishing; 2016). Fielder and Sihag (previous) note that your division director or chief typically has a vision in mind for you within the department. It is important to communicate with leadership so that everyone is on the same page and the administrative and academic opportunities afforded to you are in alignment with your career goals going forward.

Teaching trainees

To prepare for teaching as an attending, Dr. Greco recommends starting during your own training. She suggests cataloging your study materials and notes for later reference, curating talks throughout your training, and exploring different rounding styles prior to graduation (Greco, A. CHEST Thought Leader Blog. 2021 June).

To get more experience in formal speaking, Dr. Shen and colleagues encourage getting involved in resident noon conferences (Shen JZ, Memon AA, Lin C. *Stroke.* 2019 Sep;50[9]:e250-e252). A benefit of being a critical care attending is that you can gain experience teaching not only with

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This month in the journal CHEST®

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BY PETER J. MAZZONE, MD, MPH, FCCP

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Antithrombotic therapy for VTE disease: Second update of the CHEST guideline and expert panel report – executive summary

By Dr. S.M. Stevens, et al.

CHEST



Final rule update – November 2021

BY MICHAEL NELSON, MD,
FCCP

The 2,414 page final rule for the CMS Physician Fee Schedule (PFS) was published on November 2, 2021, and contains a number of changes that are important for pulmonary/critical care/ sleep providers.

As is typical, the rule does bring some good news, as well as decisions that are seemingly contrary to logic and precedence. Most of the changes will be effective on January 1, 2022, although some will become effective when the inpatient evaluation and management (E/M) changes take effect in 2023. For more information, please see 2021-23972.pdf (federalregister.gov).

The first change to be noted is a decrease in the conversion factor from \$34.89 to \$33.59. This is due primarily to the expiration of the 3.75% increase that was mandated by the Consolidated Appropriations Act of 2021.

On a positive note, CMS did institute a plan to update clinical labor prices over the next 4 years, which will result in an increase in reimbursement for practice expense costs.

CMS predicts that the combined impact of these changes will result in no change in reimbursement for pulmonary or critical care medicine. Unfortunately, CMS did not publish data for sleep medicine.

On a more positive note, patients hospitalized with COVID-19 who are having persistent symptoms, including respiratory dysfunction, for at least 4 weeks after hospitalization would now qualify for pulmonary rehab services.

There will be substantial changes in critical care services beginning next year.

The CPT® definition of critical care will continue to be recognized by CMS, and the list of bundled services remains the same. Providers may now report critical care services with E/M visits done on the same day.

The E/M visit must precede the critical care service, and it must be documented that the patient did not require critical care services at that time. The critical care visit must also

be billed with a -25 modifier. This also applies to multiple practitioners in the same group of the same specialty.

Critical care services provided **concurrently** by multiple practitioners of different specialties may now be billed by each individual practitioner if the services are medically necessary. There was a concern that CMS would not allow billing of critical care services during a surgical global period, but this will be allowed if the critical care services are unrelated to the general surgical procedure performed. There will be a new modifier developed to allow CMS to track this care.

If critical care management is transferred from the surgeon to an intensivist, then the latter will append modifier -55 (postoperative management only), as well as the new modifier. Finally, and most importantly, CMS now recognizes the benefit of team-based care and will allow split (or shared) billing of critical care services. Physicians and qualified nonphysician providers

(NPP) add their times to determine the level of critical care services. The provider who is responsible for more than half of the critical care time should be the billing provider.

Pulmonary rehabilitation CPT codes **94625** and **94626** were accepted by CMS but the RVU values recommended by the RUC were not. CPT code **94625** received a finalized work RVU of 0.36 and code **94626** received 0.56.

On a more positive note, patients hospitalized with COVID-19 who are having persistent symptoms, including respiratory dysfunction, for at least 4 weeks after hospitalization would now qualify for pulmonary rehab services. The current pulmonary rehabilitation HCPCS code G0424 is replaced by the two new CPT codes and should no longer be used after December 31, 2021.

These are but a few of the changes in the final rule that may impact one's practice. Additional changes may be found in the final rule link 2021-23972.pdf (federalregister.gov) and in future *CHEST Physician* editions.

TRANSITIONING *continued from previous page*

the internal medicine residents but with emergency medicine, anesthesiology, and critical care advanced practice provider residents, as well.

While lecturing is one thing, teaching on service is a whole different ball game. No matter how young, fun, and relatable you think you are, you're the boss now. You're the giver of grades and the writer of evaluations. It is important to be self-aware of your influence and be deliberate with the environment you create on rounds and in clinic. Set expectations on day 1 so that everyone understands. Be open with what you are working on. For example, I make daily goals for myself that I share with the team before rounds. Drs. Fielder and Sihag (previous) suggest sharing anecdotes from your own time in training that can help both you and your trainees remember that you were just in their shoes. Allowing yourself to be vulnerable creates a safe space in which your learners feel more comfortable doing the same.

Lastly, delegation is key. While many of us have done this since

residency, Dr. Shen et al (previous) suggest deliberately practicing this during fellowship. If you were the fellow who was able to handle a lot on your own, trust that your own fellows will be able to do that. Delegating to your trainees helps you improve personal and team efficiency, provides fellows with needed autonomy, and allows you to further grow into the role of attending physician.

Conclusion

While you may be nervous starting out, trust that you have been well trained and have the clinical knowledge and skills you need to do your job – you are ready. Get to know the staff you will be working with, your colleagues, and keep in touch with your co-trainees and mentors who have helped you along the way. Make daily goals for yourself, and make time to read and reflect so that you can continue to learn and grow. Most of all, make time for yourself, your friends, and your family, because after years of supporting you through all of your hard work, you've finally made it – congrats!

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CRITICAL CARE COMMENTARY

Decreasing the burden of postacute sequelae of SARS-CoV-2 infection: What we know

BY MICHELLE BIEHL, MD,
AND SAMAR FARHA, MD

On March 11, 2020, the World Health Organization (WHO) declared SARS-CoV-2 a pandemic. As of October 2021, there are over 240 million confirmed COVID-19 cases and over 4 million deaths globally, with the United States having the highest incidence of both cases and deaths (tinyurl.com/y9fzv4p4). As many as 87% of COVID-19 survivors experience persistent symptoms that last beyond the acute phase of illness (Carfi A, et al. *JAMA*. 2020;324[6]:603-5).

In February 2021, the National Institutes of Health (NIH) called for a consensus term to describe this protracted form of COVID-19, and defined it as Post-acute Sequelae of SARS-CoV-2 infection (PASC) (tinyurl.com/2p9x4hyj).

What are the PASC manifestations?

PASC has a heterogeneous presentation with a broad spectrum of manifestations and can vary from single to multiorgan system involvement. Commonly, PASC involves pulmonary abnormalities (shortness of breath, exercise intolerance, abnormal pulmonary functional test [PFT] and chest imaging), neurocognitive impairments (difficulty concentrating and memory loss), mental health disorders (anxiety, depression, and post-traumatic stress disorder), functional mobility impairments, as well as general and constitutional symptoms (fatigue and muscle weakness) (Groff D, et al. *JAMA Netw Open*. 2021;4[10]). The most prevalent pulmonary physiologic impairment is reduced diffusion capacity that has been shown to be associated with the severity of acute illness, while the most common radiologic abnormalities on chest CT scan are ground glass opacities. Some studies have shown a temporal improvement in pulmonary physiology and exercise capacity; however, persistent physiological and radiographic abnormalities

persist in some patients up to 12 months after discharge (Wu X, et al. *Lancet Respir Med*. 2021;9:747-54). An abnormal or persistent hyper-inflammatory state, viral-induced autoimmune reaction, and ongoing viral activity have been proposed as possible biological mechanisms for PASC; however, the pathophysiology remains mostly unknown.

Who does PASC affect?

PASC affects patients irrespective of premorbid condition and severity of symptoms in the acute phase. It spans from those who had mild disease not requiring hospitalization to those who had critical illness requiring ICU management. COVID-19 ICU survivors seem to have an overlap of PASC and post-intensive care syndrome (PICS), defined by new or worsening physical, cognitive, and/or psychiatric impairments after critical illness. (Biehl M, et al. *Cleve Clin J Med*. 2020 Aug 5).

Who do we evaluate for PASC?

Given the complexity and chronicity of the associated symptoms and their impact on several major organ systems, a comprehensive and multidisciplinary approach is essential to assist with diagnosis and management of PASC. Listening empathically to patients and acknowledging their symptoms are key factors. Access to ambulatory care, establishment of rapport, effective collaboration and coordination of care among different disciplines, management of comorbidities, continuity of care, access to rehabilitation programs, and reduction of disease burden are some of the principles that guided the creation of dedicated COVID-19 clinics throughout the world. The most common services offered are primary care, pulmonology, cardiology, mental health, neurology, speech and language pathology, physical and occupational therapy, pharmacy, and case management. The involvement of specialties varies depending on the specific

Continued on following page

Education enhances learning with interactive discussions

If you've ever wondered about the content creation process that goes into exam study material, SEEK is offering you an insider perspective.

Recently added to the SEEK Library, CHEST SEEK™ Peer Review Discussions are behind-the-scenes recordings of the deliberations and debates between SEEK Editorial Board members as they review their draft questions. Each video showcases CHEST authors reviewing and finessing a case-based chest medicine question to prepare for

its inclusion in printed SEEK books and the electronic library.

With an opportunity to glean invaluable knowledge from distinguished practitioners in the pulmonary, critical care, and sleep medicine fields, SEEK Peer Review Discussions can be used to help supplement board exam study, advance one's clinical knowledge, and learn from the peer review process for their own professional development.

"The opportunity to observe how much critical

review there is from a scientific content standpoint – and also from a test creation standpoint – is really interesting," said CHEST SEEK Sleep Editor and President-Elect David Schulman, MD, MPH, FCCP.

"Many of us on SEEK have written for some of the standardized exams that readers will take," he said. "Somebody can learn how writers come up with wrong answers and think, 'If I can see how this test is constructed, I may have a better

Continued on following page

PASC continued from previous page

patient's needs (Parker A, et al. *The Lancet Respir Med.* 2021;S2213-2600[21]00385-4).

The development of diagnostic and care pathways by different specialties ensures standardization of clinical assessment and management while allowing for individualized care. The commonly used tools to assess the respiratory system are the 6-minute walk test, PFT, chest imaging including radiographs and high-resolution CT scan, ventilation perfusion scan, and echocardiography. Some patients exhibit persistent cardiopulmonary symptoms with no evidence of organ injury. These patients have persistent exertional and functional limitation with normal PFT, resting echocardiography, and chest imaging. Cardiopulmonary exercise testing (CPET) and, more specifically, invasive CPET can be used to further investigate the decreased exercise capacity. CPET studies have identified an augmented exercise hyperventilation, and the causes of exercise limitation varied from anemia and reduced oxygen extraction by peripheral muscles to deconditioning, obesity, and lower ventilatory efficiency. A study looking at invasive CPET showed reduced peak exercise aerobic capacity in post COVID-19 patients compared with control participants and was associated with impaired systemic oxygen extraction and an exaggerated hyperventilatory response (Singh, et al. *Chest.* 2021;S0012-3692[21]03635). A subset of COVID-19 survivors presents with symptoms of autonomic dysfunction such as orthostatic intolerance and postural orthostatic tachycardia. These symptoms have been reported after other viral infections and could be secondary to gastrointestinal fluid loss, prolonged bed rest, and deconditioning of the cardiovascular system. More research is needed to

characterize the dysautonomia in patients post-COVID-19.

What is the treatment?

Therapies depend on symptoms and organ involvement. The duration of pulmonary symptoms in long-haulers is not yet known, with cough and exercise intolerance/dyspnea ranking among the most common complaints in these patients. Exercise therapy plays an essential part in the rehabilitation of long-haulers, and several studies are underway to assess different exercise and rehabilitation programs. For most patients with normal laboratory, physiologic, and imaging tests, post-COVID-19 clinics are offering physical therapy, occupational therapy, and neuropsychologic rehabilitation. While steroids have been shown to improve mortality in hospitalized patients with COVID-19 requiring mechanical ventilation or supplemental oxygen, their role in outpatient COVID-19 infections and for post-COVID-19 lung disease/organizing pneumonia remains unclear. In a UK study of patients admitted to the hospital with COVID-19 disease of varying severity, interstitial abnormalities were noted in ~5% of patients at 6 weeks postdischarge and in 10.8% of patients with persistent respiratory symptoms (Myall, et al. *Ann Am Thorac Soc.* 2021;18[5]:799). The most common radiologic findings (in > 50% of cases) were consistent with organizing pneumonia. Patients with persistent physiologic abnormalities and interstitial findings improved with steroids. However, since the trajectory of the disease is unknown, further studies are required to understand the natural history of the disease and assess treatment strategies in patients with persistent inflammatory lung changes. Several studies looking at systemic or inhaled steroids in different phases



Dr. Biehl (left) is Staff Physician, Pulmonary & Critical Care Medicine, Director, Post-ICU Recovery Clinic Respiratory Institute, Cleveland Clinic; Dr. Farha (right) is with Respiratory and Lerner Institutes, Cleveland Clinic.

of COVID-19 infection and varying disease severity are ongoing (ClinicalTrials.gov). Antifibrotics used to treat idiopathic pulmonary fibrosis and progressive fibrotic ILD are also being investigated in COVID-19 lung disease. The rationale for their use is to treat and prevent severe COVID-19 lung injury and prevent lung fibrosis.

The role of vaccinations

Whether patients who were infected with COVID-19, and, more specifically, patients with long-term symptoms post-COVID-19, should get vaccinated is actively being investigated. Vaccinations are protective at preventing infections and severe illness. Studies showed that patients who had COVID-19 infection and got vaccinated had a significantly higher antibody response than previously uninfected vaccine recipients. A review showed that the protective effect of prior SARS-CoV-2 infection on reinfection is high and similar to that of vaccination. However, a recent study of hospitalized patients revealed higher rates of COVID-19 among unvaccinated adults with previous infection compared with vaccinated adults (<http://dx.doi.org/10.15585/mmwr.mm7044e1>). On the other hand, the impact of vaccine on long-hauler symptoms has raised interest. A UK survey (not peer-reviewed) on more than 800 long-haulers reported

about 57% with overall improvement in their symptoms, 24% no change, and 19% with worsening symptoms after their first dose of vaccine, suggesting that the chances of experiencing an overall worsening of symptoms after vaccination is small, with more than half experiencing improvement (go.nature.com/3yfqem2). While awaiting longitudinal trials, the main argument to guide vaccination in long-haulers is that COVID-19 vaccinations provide protection from reinfection and appear to have the potential to improve symptoms.

The availability of a patient's support system, peer support, and patient advocacy groups assist in providing equitable care and are critical in sustaining the recovery of COVID-19 survivors. Providing social, financial, and cultural support is imperative in decreasing the burden of COVID-19. The dedicated post-COVID-19 clinics will not only offer care to COVID-19 survivors, but will also help our understanding of the determinants and course of PASC, and will provide opportunities for research. Long-term longitudinal observational studies and clinical trials are critical to identify those at high risk for PASC, clarify the extent of health consequences attributable to COVID-19, and define best practices for COVID-19 survivors.

Faster testing possible for secondary ICU infections

BY SHEENA MEREDITH,
MBBS, MPHIL

The SARS-CoV-2 pandemic has given added impetus for metagenomic testing using nanopore sequencing to progress from a research tool to routine clinical application. A study led by researchers from Guy's and St. Thomas' NHS Foundation Trust has shown the potential for clinical metagenomics to become a same-day test for identifying secondary infection in ventilated ICU patients. Getting results in hours rather than days would help to ensure rapid treatment with the correct antibiotic, minimize unnecessary prescriptions, and thus reduce the growing menace of antimicrobial resistance.

SARS-CoV-2 put strain on ICUs

The researchers point out that the setting of an intensive care unit involves frequent staff-patient contact that imparts a risk of secondary or nosocomial infection. In addition, invasive ventilation may introduce organisms into the lungs and lead to ventilator-acquired pneumonia. This carries a high mortality and is responsible for up to 70% of antimicrobial prescribing, with current guidelines requiring empiric antibiotics pending culture results, which typically takes 2-4 days.

Many of these infection problems worsened during SARS-CoV-2. Expanded critical care capacity raised the risk of nosocomial infections, with attendant increased antimicrobial prescriptions and the threat of antimicrobial resistance. In addition, treatment of COVID-19 patients with steroid therapy potentially exacerbates bacterial or fungal infections.

The researchers noted that the pandemic thus reinforced "a need for rapid comprehensive diagnostics to improve antimicrobial stewardship and help prevent emergence and transmission of multi-drug-resistant organisms."

"As soon as the pandemic started,

our scientists realized there would be a benefit to sequencing genomes of all bacteria and fungi causing infection in COVID-19 patients while on ICU," said Jonathan Edgeworth, PhD, London, who led the research team.

"Within a few weeks we showed

A single sample can provide enough genetic sequence data to compare pathogen genomes with a database and accurately identify patients carrying the same strain, enabling early detection of outbreaks.

it can diagnose secondary infection, target antibiotic treatment, and detect outbreaks much earlier than current technologies – all from a single sample."

Proof-of-concept study

The team performed a proof-of-concept study of nanopore metagenomics sequencing – a type of DNA sequencing that allows direct rapid unbiased detection of all organisms present in a clinical sample – on 43 surplus respiratory samples from 34 intubated COVID-19 patients with suspected secondary bacterial or fungal pneumonia. Patients were drawn from seven ICUs at St. Thomas' Hospital, London over a 9-week period between April 11 and June 15 2020, during the first wave of COVID-19.

Their median age was 52, 70% were male, 47% White, and 44% Black or minority ethnicities. Median length of stay was 32 days and mortality 24%. Samples sent for metagenomic analysis and culture included 10 bronchoalveolar lavages, 6 tracheal aspirates, and 27 non-direct bronchoalveolar lavages.

The study showed that an 8-hour metagenomics workflow was 92% sensitive (95% CI, 75%-99%) and 82% specific (95% CI, 57%-96%) for bacterial identification, based on

culture-positive and culture-negative samples, respectively.

The main Gram-negative bacteria identified were *Klebsiella* spp. (53%), *Citrobacter* spp. (15%), and *E. coli* (9%). The main Gram-positive bacteria were *S. aureus* (9%), *C. striatum* (24%) and *Enterococcus* spp. (12%). In addition, *C. albicans*, other *Candida* spp. and *Aspergillus* spp. were cultured from 38%, 15%, and 9% of patients, respectively.

In every case, the initial antibiotics prescribed according to prevailing guideline recommendations would have been modified by metagenomic sequencing demonstrating the presence or absence of β -lactam-resistant genes carried by *Enterobacterales*.

Next day results of sequencing also detected *Aspergillus fumigatus* in four samples, with results 100% concordant with quantitative PCR for both the 4 positive and 39 negative samples. It identified two multi-drug-resistant outbreaks, one involving *K. pneumoniae* ST307 affecting 4 patients and one a *C. striatum* outbreak involving 14 patients across three ICUs.

Thus, a single sample can provide enough genetic sequence data to compare pathogen genomes with a database and accurately identify patients carrying the same strain, enabling early detection of outbreaks. This is the first time this combined benefit of a single test has been demonstrated, the team say.

Gordon Sanghera, CEO of Oxford Nanopore (England) commented that "rapidly characterizing co-infections for precision prescribing is a vital next step for both COVID-19 patients and respiratory disease in general."

Andrew Page, PhD, of the Quadram Institute, Norwich, England, said: "We have been working on metagenomics technology for the last 7 years. It is great to see it applied to patient care during the COVID-19 pandemic."

He said in an interview: "The pandemic has accelerated the tran-

sition from using sequencing purely in research labs to using it in the clinic to rapidly provide clinicians with information they can use to improve outcomes for patients."

Potential to inform prescribing and infection control

"Clinical metagenomic testing provides accurate pathogen detection and antibiotic resistance prediction in a same-day laboratory workflow, with assembled genomes available the next day for genomic surveillance," the researchers say.

The technology "could fundamentally change the multidisciplinary team approach to managing ICU infections." It has the potential to improve initial targeted antimicrobial treatment and infection control decisions, as well as help rapidly detect unsuspected outbreaks of multi-drug-resistant pathogens.

Prof. Edgeworth told this news organization that, since the study, "secondary bacterial and fungal infections have increased, perhaps due to immunomodulatory treatments or just the length of time patients spend in an ICU recovering from COVID-19. This makes rapid diagnosis even more important to ensure patients get more targeted antibiotics earlier, rather than relying on generic guidelines." The team is "planning to move respiratory metagenomics into pilot service under our Trust's quality improvement framework," he revealed. This will enable them to gather data on patient benefits.

"We also need to see how clinicians use these tests to improve antibiotic treatment, to stop antibiotics when not needed, or to identify outbreaks earlier, and then how that translates into tangible benefits for individual patients and the wider NHS."

He predicts that the technique will revolutionize the approach to prevention and treatment of serious infection in ICUs, and it is now planned to offer it as a clinical service for COVID-19 and influenza

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chance of doing well on it."

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"The audience gets to see that these big names you see on the page – authors, coauthors, and editors – are just normal people like anybody else," Dr. Schulman said. "They joke around a little bit, and they push each other a little bit. I think get-

ting to see under the hood of CHEST and seeing what leadership is like is a really valuable experience."

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Fluoroquinolones linked to the risk of sudden death for those patients on hemodialysis

BY MEGAN BROOKS

Oral fluoroquinolone therapy to treat a respiratory infection is associated with an increased risk of sudden cardiac death (SCD) in patients on hemodialysis, particularly those taking other QT-prolonging medications, a large observational study suggests.

In many cases, the absolute risk is relatively small, and the antimicrobial benefits of a fluoroquinolone may outweigh the potential cardiac risks, the researchers say.

However, in many cases, the absolute risk is relatively small, and the antimicrobial benefits of a fluoroquinolone may outweigh the potential cardiac risks, the researchers say.

“Pathogen-directed treatment of respiratory infections is of the utmost importance. Respiratory fluoroquinolones should be prescribed whenever an amoxicillin-based antibiotic offers suboptimal antimicrobial coverage and clinicians should consider electrocardiographic monitoring,” first author Magdalene M. Assimon, PharmD, PhD, University of North Carolina, Chapel Hill, told this news organization.

The study was published online in JAMA Cardiology (2021. doi: 10.1001/jamacardio.2021.4234).

Nearly twofold increased risk

The QT interval-prolonging potential of fluoroquinolone antibiotics are well known. However, evidence linking respiratory fluoroquinolones to adverse cardiac outcomes in the

hemodialysis population is limited.

These new observational findings are based on a total of 626,322 antibiotic treatment episodes among 264,968 adults (mean age, 61 years; 51% men) receiving in-center hemodialysis – with respiratory fluoroquinolone making up 40.2% of treatment episodes and amoxicillin-based antibiotic treatment episodes making up 59.8%.

The rate of SCD within 5 days of outpatient initiation of a study antibiotic was 105.7 per 100,000 people prescribed a respiratory fluoroquinolone (levofloxacin or moxifloxacin) versus with 40.0 per 100,000 prescribed amoxicillin or amoxicillin with clavulanic acid (weighted hazard ratio, 1.95; 95% confidence interval, 1.57-2.41).

The authors estimate that one additional SCD would occur during a 5-day follow-up period for every 2,273 respiratory fluoroquinolone treatment episodes. Consistent associations were seen when follow-up was extended to 7, 10, and 14 days.

“Our data suggest that curtailing respiratory fluoroquinolone prescribing may be one actionable strategy to mitigate SCD risk in the hemodialysis population. However, the associated absolute risk reduction would be relatively small,” wrote the authors.

They noted that the rate of SCD in the hemodialysis population exceeds that of the general population by more than 20-fold. Most patients undergoing hemodialysis have at least one risk factor for drug-induced QT interval-prolongation.

In the current study, nearly 20% of hemodialysis patients prescribed a respiratory fluoroquinolone were taking other medications with known risk for torsades de pointes.

“Our results emphasize the im-

portance of performing a thorough medication review and considering pharmacodynamic drug interactions before prescribing new drug therapies for any condition,” Dr. Assimon and colleagues advised.

They suggest that clinicians consider electrocardiographic monitoring before and during fluoroquinolone therapy in hemodialysis patients, especially in high-risk individuals.

Valuable study

Reached for comment, Ankur Shah, MD, of the division of kidney diseases and hypertension, Brown University, Providence, R.I., called the analysis “valuable” and said the results are “consistent with the known association of cardiac arrhythmias with respiratory fluoroquinolone use in the general population, postulated to be due to increased risk of torsades de pointes from QTc prolongation. This abnormal heart rhythm can lead to sudden cardiac death.

“Notably, the population receiving respiratory fluoroquinolones had a

higher incidence of cardiac disease at baseline, but the risk persisted after adjustment for this increased burden of comorbidity,” Dr. Shah said in an interview. He was not involved in the current research.

Dr. Shah cautioned that observational data such as these should be considered more “hypothesis-generating than practice-changing, as there may be unrecognized confounders or differences in the population that received the respiratory fluoroquinolones.

“A prospective randomized trial would provide a definitive answer, but in the interim, caution should be taken in using respiratory fluoroquinolones when local bacterial resistance patterns or patient-specific data offer another option,” Dr. Shah concluded.

Dr. Assimon reported receiving grants from the Renal Research Institute (a subsidiary of Fresenius Medical Care), and honoraria from several nephrology-related societies. Dr. Shah has disclosed no relevant financial relationships.

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patients during the coming winter.

In addition, he said: “It can be equally applied to other samples such as tissue fluids and biopsies, including those removed at operation. It therefore has potential to impact on diagnostics for many clinical services, particularly if the progress is maintained at the current pace.”

The study was published in Genome Med 13, 182 (2021). <https://doi.org/10.1186/s13073-021-00991-y>.

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