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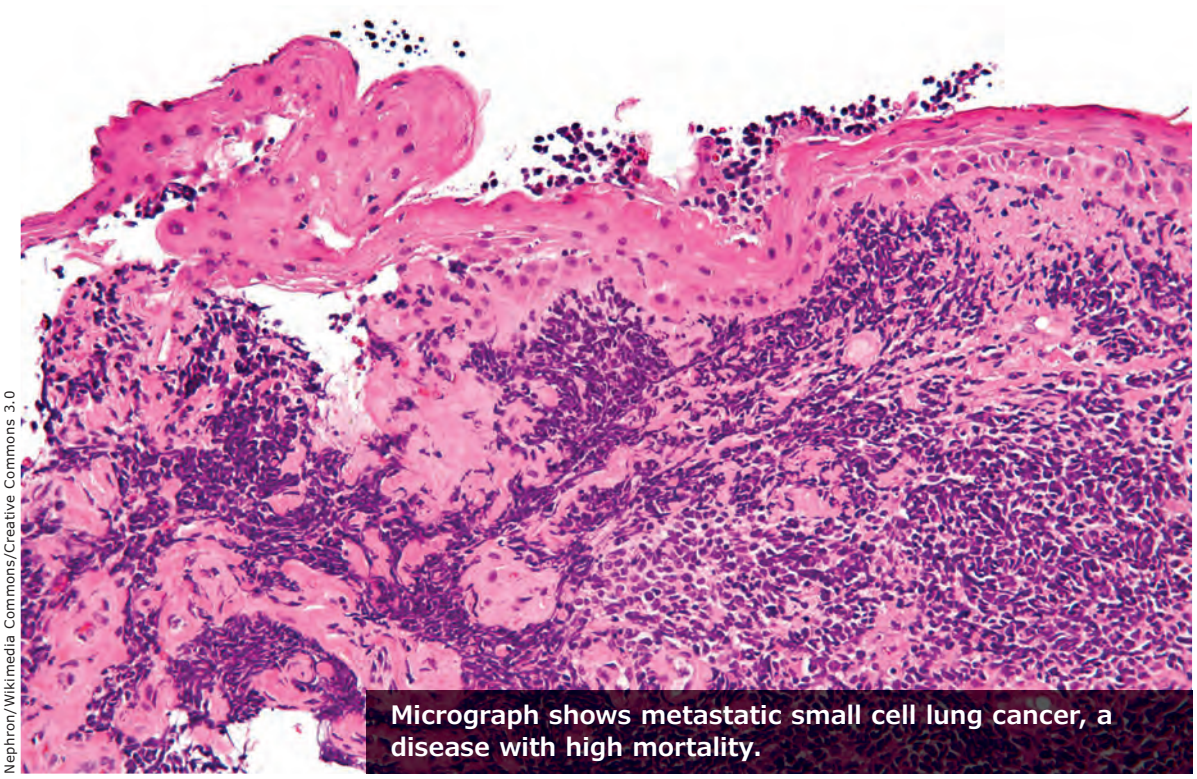

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Micrograph shows metastatic small cell lung cancer, a disease with high mortality.

Urine metabolites could predict end of life in lung cancer

BY LIAM DAVENPORT

Lung cancer patients could soon have their risk of dying over the following 3 months accurately predicted by analyzing their urine samples, which could allow them to better prepare for their end of life, say U.K. researchers.

Seamus Coyle, PhD, a consultant in palliative medicine at the Clatterbridge Cancer Centre, Liverpool, and colleagues studied urine samples from more than 100 lung cancer patients, deriving a model for end of life based on their metabolite profile.

This model allowed the patients to be divided into high- and low-risk groups for dying over the following 3 months, with an accuracy of 88%.

The model "predicts dying … for every single day for the last 3 months of life," Dr. Coyle said.

"That's an outstanding prediction," Dr. Coyle added, "based on the fact that people actively die over 2 to 3 days on average," while "some die over a day."

He continued: "It's the only test that predicts dying within the last 2 weeks of life, and that's what I'm passionate about: the earlier recognition of dying."

The research was presented at the 2021 American Society of Clinical Oncology Annual Meeting.

END OF LIFE // *continued on page 4*

Nasal swab test helps identify malignant lung nodules

BY ROXANNE NELSON, RN, BSN

A simple nasal swab may help in the diagnosis of lung cancer in smokers who have undergone CT screening and had lung nodules detected on the scan.

Only about 5% of the nearly 1.6 million lung nodules identified as incidental findings on low-dose CT screening tests will turn out to be malignant. The new test helps to distinguish between benign and malignant nodules, say researchers reporting a validation study.

The results show that the test identified those at low risk for cancer with a sensitivity of 96.3% and specificity of 41.7%, as well as identifying those as high risk, with a specificity of 90.4% and sensitivity of 58.2%.

The Percepta nasal swab is a first-of-its-kind genomic test, says the manufacturer Veracyte.

It is based on "field of injury" technology, which examines genomic changes in the lining of the respiratory tract for evidence of active cancer cells, coupled with a machine learning model that includes factors such as age, gender, and smoking history.

SWAB TEST // *continued on page 6*

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INDICATION

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

SELECT IMPORTANT SAFETY INFORMATION

Elevated liver enzymes and drug-induced liver injury (DILI): DILI has been observed with Esbriet. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3x ULN (3.7%) compared with placebo patients (0.8%). Increases in ALT and AST ≥3x ULN were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with Esbriet, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) vs placebo (1%). Patients should avoid or minimize exposure to sunlight and sunlamps, regularly use sunscreen (SPF 50 or higher), wear clothing that protects against sun exposure, and avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal (GI) disorders: Patients treated with Esbriet had a higher incidence of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease (GERD), and abdominal pain. GI events required dose reduction or interruption in 18.5% of 2403 mg/day Esbriet-treated patients, compared with 5.8% of placebo patients; 2.2% of 2403 mg/day Esbriet-treated patients discontinued treatment due to a GI event, vs 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modification may be necessary.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, GERD, sinusitis, insomnia, weight decreased, and arthralgia.

Drug Interactions:

CYP1A2 inhibitors: Concomitant use of Esbriet and strong CYP1A2 inhibitors (e.g., fluvoxamine) is not recommended, as CYP1A2 inhibitors increase systemic exposure of Esbriet. If discontinuation of the CYP1A2 inhibitor prior to starting Esbriet is not possible, dosage reduction of Esbriet is recommended. Monitor for adverse reactions and consider discontinuation of Esbriet.

Concomitant use of ciprofloxacin (a moderate CYP1A2 inhibitor) at the dosage of 750 mg BID and Esbriet are not recommended. If this dose of ciprofloxacin cannot be avoided, dosage reductions of Esbriet are recommended, and patients should be monitored.

Moderate or strong inhibitors of both CYP1A2 and other CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

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ESBRIET OFFERS ESTABLISHED SAFETY BUILT ON MULTIPLE CLINICAL STUDIES

Esbriet was rigorously analyzed in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients with idiopathic pulmonary fibrosis (IPF)[1]

Serious adverse events (AEs), including elevated liver enzymes and drug-induced liver injury, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet[1]

The most common AEs (>1%) leading to discontinuation were rash and nausea. The most common AEs (>3%) leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

Some AEs with Esbriet were mild to moderate, occurred early, and decreased over time[1,2]

Photosensitivity reactions and GI events typically occurred in the first 3 to 6 months of treatment and infrequently led to discontinuation

<9% of photosensitivity events and <8% of GI events in three phase 3 trials were severe. The remaining photosensitivity and GI events were mild to moderate in severity[2]

>1400 patients were evaluated for safety of Esbriet, with >170 on treatment for more than 5 years in clinical trials[1]

Dose modifications, interruptions, and discontinuations with Esbriet 267 mg may help manage potential AEs like GI events and photosensitivity reactions[1]

Demonstrated efficacy

In ASCEND and CAPACITY 004, Esbriet delayed disease progression by slowing lung function decline vs placebo[1,3]

In CAPACITY 006, no statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed[1,4]

Learn more at **EsbrietHCP.com**

CYP1A2 inducers: Concomitant use of Esbriet and strong CYP1A2 inducers should be avoided, as CYP1A2 inducers may decrease the exposure and efficacy of Esbriet.

Specific Populations:

Mild to moderate hepatic impairment: Esbriet should be used with caution in patients with Child Pugh Class A and B. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

Severe hepatic impairment: Esbriet is not recommended for patients with Child Pugh Class C. Esbriet has not been studied in this patient population.

Mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} <30 mL/min) renal impairment: Esbriet should be used with caution. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

End-stage renal disease requiring dialysis: Esbriet is not recommended. Esbriet has not been studied in this patient population.

Smokers: Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when on Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

Study design: The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[1] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide (%DL_{co}) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[1,3] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[1,4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1] **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.[1]**

References: 1. Esbriet Prescribing Information. Genentech, Inc. July 2019. **2.** Data on file. Genentech, Inc. 2019. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083–2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760–1769.

Esbriet® (pirfenidone) tablets 267 mg 801 mg

'Promising and important pilot study'

Nathan Pennell, MD, PhD, an ASCO expert, told this news organization that "predicting the actual 'time' someone has left is more of an art than a science."

He added that, "For people who may be closer to death, this would potentially allow more focus on supportive care and allow families and patients to plan more accurately for supporting their loved one through the dying process."

He continued that, "While this is a promising and important pilot study, there is more work to be done before this could be used in practice."

"If someone has a high risk score for dying, could medical intervention to treat an infection or some other modifiable action change that 'fate'?"

For example, the treatment status of the patients was not clear.

"Were these patients all in hos-

pice, or were some undergoing treatment which, if effective, could 'rescue' them from their poor prognostic state?"

Dr. Pennell continued: "Would measuring kidney function be just as good? Is this something that could be intervened upon?

"For example, if someone has a high risk score for dying, could medical intervention to treat an infection or some other modifiable action change that 'fate'?"

Death 'difficult' to predict

Dr. Coyle began by saying that, while for him recognizing that a patient is dying is the start of good end-of-life care, "recognizing dying accurately, when someone is in the last days of life, is difficult."

He noted that the 2019 National Audit of Care at the End of Life found that people were recognized to be dying at median of 34 hours before death, with 20% recognized in the last 8 hours.

Moreover, by the time their condition was recognized, 50% of people who are dying "are unconscious and unable to be involved in any conversation that [is] pertinent to them."

In an attempt to better predict the onset of dying, the researchers conducted a prospective, longitudinal study in which 424 urine samples were collected from 162 lung cancer patients from six centers.

Of those, 63 patients gave a sample within the last 28 days of life, and 29 within the last week of life.

Urine samples were analyzed using a liquid chromatography quadrupole time-of-flight mass spectrometer for 112 patients, who had a median age of 71 years and a range of 47-89 years, and 40.2% were female.

The most common diagnosis was non–small cell lung cancer, in 55.4%, while 19.6% had small cell lung cancer.

More than 50% of the patients who were designated in the highest-risk group died within 1 week of their urine sample being taken, and 100% had died within 3 weeks.

By performing Cox Lasso regression analysis on the "hundreds of metabolites" identified in the urine samples, the team were able to develop an End of Life Metabolome (ELM) profile that predicted an individual's risk of dying over the following 3 months, according to the researchers.

Kaplan-Meier analysis allowed the patients to be divided into five risk groups based on their ELM ($P < .001$ for trend), which showed that all patients in the lowest-risk group were still alive after more than 2 months following the urine sample.

In contrast, more than 50% of the patients who were designated in the highest-risk group died within 1 week of their urine sample being taken, and 100% had died within 3 weeks.

Calculating the area under the receiver operating characteristic curve revealed that the ELM was able to predict the risk of dying for every day for the last 3 months of life with an accuracy of 88%.

ELM is being validated in a new cohort of lung cancer patients and it is being assessed in multiple cancers.

The study was funded by the Wellcome Trust UK and North West Cancer Research UK. No relevant financial relationships were declared.

chestphysiciannews@chestnet.org

Swab test // *continued from page 1*

Veracyte hopes to begin to make the test available to a select number of sites in the second half of 2021. "The test is intended to be performed in the physician's office on patients referred with suspicious lung nodules found on CT scans," said Giulia C. Kennedy, PhD, chief scientific officer and chief medical officer at Veracyte. "This could include patients with nodules found through screening programs, as well as incidentally."

"It will be made available as a laboratory developed test in the U.S. through Veracyte's centralized CLIA laboratory," she said in an interview. "In global markets, we will offer the test as an IVD product that can be performed on the nCounter instrument by laboratories locally. Outside of the United States, the test will require a CE mark, which we are equipped to support."

Results with the test were presented during the American Society of Clinical Oncology 2021 Annual Meeting, which was held virtually this year.

It was first tested in a training set, which consisted of more than 1,100 patients. All were current or former smokers who had a lung nodule detected on chest CT scanning and were followed for up to 1 year or until a final diagnosis of lung cancer or benign disease.

Brushings of the nasal epithelium were prospectively collected in patients with lung nodules from multiple cohorts.

A total of 502 genes were used in the classifier, and performance was evaluated in an independent clinical validation set consisting of 249 patients.

The test identified true benign patients as low risk with 41.7% specificity and 96.3% sensitivity, resulting in a negative predictive value of 97.1% in a population with a cancer prevalence of 25%. The risk of malignancy for patients in this low-risk group was less than 3%, and for this group, clinical guidelines recommend surveillance.

Patients with true malignancies were identified as high risk, with 58.2% sensitivity and 90.4% specificity, resulting in a positive predictive value of 67.0% in a population with 25% cancer prevalence.

The risk of malignancy for patients deemed to be high risk by the classifier was 67.0%, which exceeds the current guideline threshold for consideration of surgical resection or other ablative therapy if a staging evaluation confirms early-stage disease, the authors point out.

The remaining patients, who did not meet the stringent cut-offs for low or high risk, were identified as intermediate risk. In this population, the prevalence of malignancy for patients identified as intermediate risk was 20.7%, which is consistent with guidelines that provide a range for intermediate-risk patients as between 5% and 65% for whom diagnostic biopsy is recommended.

Help guide decisions, more data needed

Approached by this news organization for independent comment, Alexander Spira, MD, PhD, medical oncologist, Virginia Cancer Specialists, Fairfax, explained that the study provides an interesting way to look at a common finding and lung nodules and to predict whether further workup should be done.

"This could provide a role in reassurance that patients who fall into the low-risk category could be observed with serial imaging rather than proceeding to immediate biopsy," he said. "It falls in under the 'field of injury' principle."

Dr. Spira noted that although the low-risk group appears to have a negative predictive value of >90%, it doesn't mean that the patient would require no further workup. "It would require CT surveillance rather than proceeding to immediate biopsy, and at this point it does appear promising, but I would want further follow-up in terms of outcomes," he said.

"This does not apply to nonsmokers, which is of increasing prevalence, but with the increased use of CT screening for patients with a history of tobacco use, it may indeed have a role." He also pointed out that while the idea is to avoid biopsies, the smaller lesions are the ones that are concerning.

"They are often tough to get at, and it would also depend on patient choice and anxiety as well, given the chance of being in that low percentage that the test misses," said Dr. Spira. "Lastly, many pulmonologists are ordering PET scans in lieu of a biopsy, and this may also help."

The bottom line is that this may help guide clinical decisions, but more data are needed. "Even in the low-risk category, 9.4% of patients had a malignancy, which is still a high miss rate," he added.

The study was funded by Veracyte. Dr. Kennedy is employed by Veracyte. Dr. Spira has reported no relevant financial relationships.

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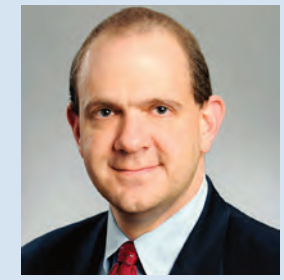

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Conflicting medical opinions: black lungs, big coal, and bias

BY DONAVYN COFFEY

In 2008, the U.S. Department of Labor paid for Tony Adams, a 48-year-old coal miner, to have a chest x-ray. His doctor found stage I black lung disease. Yet Mr. Adams' claim for medical benefits was denied. This was because the insurance group that represented his employer hired a different – more credentialed – doctor as its medical expert. That doctor said he saw no such evidence. The judge ruled in favor of the mining company on the basis of the latter's "expertise."

Before he died 5 years later, at age 53, Mr. Adams went through this process again. In fact, he did it four more times. Each time, his doctor found evidence of black lung, but the company's medical expert did not. He died without receiving benefits. Among the causes of death listed on his autopsy were cardiopulmonary arrest and coal worker's pneumoconiosis (CWP): black lung.

Since his death in 2013, two judges have awarded Mr. Adams' benefits to his widow, Linda. Both times, the mining company appealed the decision, most recently in December 2020. She's not giving up. "Two weeks before he died, he told me, 'I'm going to die of black lung,' " Linda recalled. " 'But I don't want you to give up on black lung. There are too many people screwing these miners out of what they deserve.' "

There has long been suspicion among miners and their advocates that doctors used by coal companies to fight claims like Mr. Adams's are in the pocket of "Big Coal." At the very least, some say these physicians are swayed by their client's preference when reading a coal miner's chest x-ray. A recent study published in Annals of the American Thoracic Society provides empirical evidence that these doctors' conflicts of interest – namely, that parties representing coal companies hired them – appears to influence their medical opinion (doi: 10.1513/AnnalsATS.202010-1350OC).

Proof of a 'broken system'

The Annals study examined 63,780 radiograph classifications made by 264 physicians – all certified as B-readers, a certification by the National Institute for Occupational Safety and Health for physicians who demonstrate proficiency in classifying radiographs of pneumoconiosis. The results showed that doctors hired by miners identified black lung 49% of the time; those hired by coal companies identified black lung only 15% of the time.

Doctors hired by miners identified black lung 49% of the time; those hired by coal companies identified black lung only 15% of the time.

The study also found that B-readers contracted by employers read results differently for different clients. The same doctors were significantly less likely to say a miner's lungs were negative for CWP when they were hired by the DOL (77.2%) than when they were hired by a coal company or its insurers (90.2%).

The bias does appear to work both ways: B-readers hired by miners and miners' attorneys were more likely to find evidence of black lung when they worked with plaintiffs. However, a much higher number of doctors appeared to be biased in favor of the companies. "There were 3X more B-readers providing 8X more classifications among those affiliated with employers compared to those affiliated with miners," the study concluded.

The authors suggest that one reason for this was the difference in pay. Some company-hired doctors made as much as $750 per reading, about 10 times what miner-hired doctors were paid.

"We knew [about the potential bias] from our work over the decades taking care of these guys," said Robert A. Cohen, MD, a pulmonologist and the study's senior author. "But then you see it with *P* values that are incredibly statistically significant ..."

The study finally put numbers to a problem that many working with black lung claims had always assumed. Those within the system

Continued on following page

Continued from previous page

are accustomed to seeing names of the same doctors on documents and reports, with little to no overlap between those hired by the defense and the plaintiffs.

"The vast majority of the time, we know what a report will say based on the doctor's name," said Evan Smith, JD, advocacy director at AppalReD Legal Aid, in Prestonsburg, Ky. It is far more surprising, he said, when a defense-hired doctor agrees with a miner-hired doctor.

Over the years, Katherine DePonte, MD, a radiologist and B-reader in West Virginia, has often seen an "almost textbook appearance" of CWP, only to later learn that "another radiologist read it as negative." She explained, "They would use some other term, like 'old granulomatous disease.' "

Employer-hired doctors often do acknowledge the same lung damage on the radiograph as miner-hired docs; they simply don't attribute it to coal dust. Common "alternative diagnoses" include chronic obstructive pulmonary disease or histoplasmosis. "I know a number don't believe this disease of coal worker pneumoconiosis exists [at all]," Dr. DePonte said.

What's inarguable is that, even as coal mining in Appalachia is on the decline, black lung disease is on the rise. NIOSH now estimates that it affects over 20% of long-term (25+ years) coal workers in central Appalachia. That's the highest prevalence in a quarter of a century.

Mr. Smith said that at its most basic level, these doctors' conflicts of interest "lead to people who have the disease that these benefits are for, having them denied." People like Tony Adams. Whether the doctors involved are complicit or just conservative, critics say they have become a fixture of a broken system.

Financial bias or difference of opinion?

Broken system or not, evidence suggests that the problem can't be blamed solely on medical experts. Dr. DePonte primarily reads for the DOL and miners. "Not that I necessarily chose that," she said. "You get pigeonholed."

Some say that the bias demonstrated by the Annals study is at least partially driven by the litigation process itself. It is an adversarial system. As such, attorneys on both sides are naturally inclined to seek out doctors who will best support their clients' cases. Doctors with a legitimately conservative perspective on what constitutes black lung are more sought after by the coal companies' attorneys.

"It can often be impossible to tell whether the money is driving a change in the behavior or if the behavior is causing them to be sought out," said Matt McCoy, PhD, a medical ethicist who specializes in conflicts of interest at the University of Pennsylvania, Philadelphia.

Although some believe that certain doctors are driven purely by financial incentive and offer a specific reading to secure repeat business, B-readers can end up working exclusively for companies because of other reasons. Wes Addington, JD, an attorney at the Appalachian Citizens' Law Center, Whitesburg, Ky., said some doctors appear to have an authentically different – often antiquated – view of the disease.

National Archives/Wikimedia Commons/Public Domain

This human lung is shriveled and hardened from black lung disease, often associated with mining.

Perhaps the most extreme example is Paul Wheeler, MD, a highly credentialed Johns Hopkins radiologist who was exposed for false medical testimony in Chris Hamby's 2013 Pulitzer Prize reporting. In 1,500 readings, Dr. Wheeler never diagnosed a single case of severe black lung. And yet, Dr. Cohen, Mr. Addington, Mr. Smith, and other experts all agree that Dr. Wheeler appeared to wholeheartedly believe that his view of black lung was accurate. That made him a valuable asset to mining companies.

Since Dr. Wheeler's exposure, there has been a greater sense of accountability among B-readers, said John Cline, JD, a West Virginia–based attorney who represents miners with federal black lung claims. "Radiologists were thinking, 'Somebody could be watching me.' Even if they thought they were doing this in the shadows, it made people more cautious," he said.

The data used in the Annals study predate Mr. Hamby's investigation, going back to 2000. Thus, it is possible that, as Mr. Cline argues, things may be different now. However, Lee S. Friedman, PhD, associate professor at the University of Illinois at Chicago, who is the lead author of the study, remains skeptical.

"While the Wheeler case might have dampened some physicians [who were] completely skewing their readings always negative, I think it's premature or incorrect" to say it resolved the issue, he said. "Did they all change their behavior the morning after? It doesn't seem likely, given the evidence of financial conflicts of interest and behavior that's been demonstrated."

Skewing the evidence?

Mr. Hamby's 2013 reporting also revealed that even when company-hired doctors did diagnose CWP, law firms were burying those readings. In 2016, the DOL attempted to stop this practice. The agency made suppression of written evidence illegal – emphasis on written.

Law firms can't hide positive reports, but they can prevent them. Dr. Cohen explained that now, "a doctor on the phone says, 'I will read this as positive.' Then the company says, 'No, thank you,' we will send you a check."

This practice was confirmed by Kim Adcock, MD, a retired radiologist and B-reader in Littleton, Colo., who primarily reads for 26 law firms. Some of his clients want a report no matter how he reads the radiograph. However, some want him to call them first if he's going to read the radiograph as positive. Dr. Adcock said this practice skews the dataset to make company-hired docs appear to read more negatively than they actually do.

Because the dataset used in the study is from the Federal Black Lung Program (FBLP), it includes only readings that made it to court. Dr. Adcock said he reads approximately 2,000 radiographs a year, although only a few of his readings appeared in the study's dataset, according to a search by Dr. Friedman. This difference is likely because the study evaluated only readings between 2000 and 2013, the year Dr. Adcock started B-reading.

"I think it's important to get a message that, to a certain extent, contravenes this paper. Yes, we should have some reservations about the conclusions," Dr. Adcock explained. "There are people out there attempting to do the best job they could do."

Law firms shopping for the reading they want and censoring the ones they don't might alter the FBLP data, but experts say that doesn't change the underlying problem. "In any case like this, where you're looking at individuals going up against corporations," Dr. McCoy said, "[corporations] are able to marshal their resources and hire more officials in a way claimants can't, and that's a baseline concern here."

Battling bias

Admitting bias is notoriously difficult; thus, it isn't surprising that many doctors involved refuse to believe they are influenced by money, incentives, or other biases. Dr. DePonte said she's not swayed by money, nor does she actively take a pro-miner stance. She views herself as more of an advocate for accuracy. However, she did say that it has traditionally been far more difficult for miners to prove their cases, a problem that has improved with new regulations in recent years.

In Colorado, Dr. Adcock's approach is to stay as far removed from the litigation process as possible. He said he has limited understanding of how his reports are used or how claims are filed and awarded. He leans heavily on his initial – almost instantaneous – impression of a chest x-ray.

Dr. DePonte and Dr. Adcock were both hired as experts on Tony Adams' case. In 2008, Dr. DePonte read his chest x-ray as positive for early-stage black lung (1/0). Dr. Adcock also read two of Adams' four chest x-rays, one in 2009 and the other in 2013. He read them as negative. When asked about the case, which autopsy confirmed as black lung, Dr. Adcock explained that positive histopathology doesn't mean the radiograph reading was wrong, only

that the disease didn't show on that radiograph. He said his "highest ambition" is to be "an objective finder of fact" and that he trusts the process to work out the truth.

That process didn't work in time for Tony Adams. Dr. Friedman argues that people who provide expert testimony have an ethical responsibility to know how their testimony is being used; to do otherwise, he says, is "willful ignorance." Still, the Annals study authors, along with Dr. DePonte, Mr. Cline, and West Virginia attorney Sam Petsonk, say that the process is getting fairer, thanks to new policies developed over the past 5 years by the DOL.

"The DOL has worked very hard to reconcile the final award rate (around 30%) with the incidence of disease in the population (between 20% and 25%)," Mr. Petsonk said. Although the study calls into question the integrity of the system and the doctors within it, it's critical for miners to know that the system is working and that they can get benefits, he explained. Many fear that cynicism about the system drives miners away and causes them to resort to Social Security or long-term disability.

Fixing what's broken

The Annals study's authors propose some solutions to the problems they quantified. The first is a sort of "super panel" that collectively evaluates readings. Although a completely unbiased panel would be nice, such impartiality is likely unsustainable, Mr. Smith said. He believes that over time the panel would become vulnerable to politics and would work in favor of the companies.

Even without a panel, a method to provide greater transparency could be a great start, some suggest. The DOL could make the entire FBLP database public and analyze it annually. The authors also propose a flat fee for readings. Even now, Dr. Adcock said he doesn't make anywhere close to the upper limit of $750 per readings. "My understanding is around $125 is a pretty characteristic fee [for reading a chest x-ray]," he elaborated. "Everyone I've had a conversation with is within 25 bucks [of that]."

That said, Dr. Adcock is not currently listed among the heavy readers who appear in the data used for the study; it's possible that his experience is not representative. Some readers who were included in that dataset read more than 10 times the average number of classifications per reader – the average was 242 classifications – and read 95% of chest x-rays as negative, according to Dr. Friedman. This news organization obtained the names of two doctors whose readings were 95% negative on a high volume of cases. Neither agreed to an interview.

It's possible that, if the dataset had included readings from more recent years, Dr. Adcock would have appeared more frequently, given his personal estimates. That's why the study authors recommend that the DOL conduct this kind of analysis annually in order to get an accurate picture of who is contributing to these cases, in what way, and how often.

By doing so, readers who appear biased could be identified and addressed with more regularity, according to Dr. Friedman.

Even if the rate were more consistent and the data were more frequently analyzed, the very nature of the adversarial system will put any potential solution at risk. "I'm not sure there's a foolproof system that can be devised that can't be corrupted in time," Mr. Cline said.

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PRACTICE MANAGEMENT

OSHA: COVID-19 safety rules for health workers

BY SHEILA MULROONEY ELDRED

The U.S. Occupational Safety and Health Administration issued its long-awaited Emergency Temporary Standard (ETS) for COVID-19 on June 10, surprising many by including only health care workers in the new workplace safety rules.

"The ETS is an overdue step toward protecting health care workers, especially those working in long-term care facilities and home health care who are at greatly increased risk of infection," said George Washington University, Washington, professor and former Obama administration Assistant Secretary of Labor David Michaels, PhD, MPH. "OSHA's failure to issue a COVID-specific standard in other high-risk industries, like meat and poultry processing, corrections, homeless shelters, and retail establishments is disappointing. If exposure is not controlled in these workplaces, they will continue to be important drivers of infections."

With the new regulations in place, about 10.3 million health care workers at hospitals, nursing homes, and assisted living facilities, as well as emergency responders and home health care workers, should be guaranteed protection standards that replace former guidance.

The new protections include supplying personal protective equipment and ensuring proper usage (for example, mandatory seal checks on respirators); screening everyone who enters the facility for COVID-19; ensuring proper ventilation; and establishing physical distancing requirements (6 feet) for unvaccinated workers. It also requires employers to give workers time off for vaccination. An antiretaliation clause could shield workers who complain about unsafe conditions.

"The science tells us that health care workers, particularly those who come into regular contact with the virus, are most at risk at this point in the pandemic," Labor Secretary Marty Walsh said on a press call. "So following an extensive review of the science and data, OSHA determined that a health care–specific safety requirement will make the biggest impact."

But questions remain, said James Brudney, JD, a professor at Fordham Law School in New York and former chief counsel of the U.S. Senate Subcommittee on Labor. The standard doesn't amplify or address existing rules regarding a right to refuse unsafe work, for example, so employees may still feel they are risking their jobs to complain, despite the antiretaliation clause.

And although vaccinated employees don't have to adhere to the same distancing and masking standards in many instances, the standard doesn't spell out how employers should determine their workers' vaccination status – instead leaving that determination to employers through their own policies and procedures. (California's state OSHA office rules specify the mechanism for documentation of vaccination.)

The Trump administration did not issue an ETS, saying OSHA's general duty clause sufficed. President Biden took the opposite approach, calling for an investigation into an ETS on his first day in office. But the process took months longer than promised.

"I know it's been a long time coming," Mr. Walsh acknowledged. "Our health care workers from the very beginning have been put at risk.

While health care unions had asked for mandated safety standards sooner, National Nurses United, the country's largest labor union for registered nurses, still welcomed the rules.

"An ETS is a major step toward requiring accountability for hospitals who consistently put their budget goals and profits over our health and safety," Zenei Triunfo-Cortez, RN, one of NNU's three presidents, said in a statement June 9 anticipating the publication of the rules.

The rules do not apply to retail pharmacies, ambulatory care settings that screen nonemployees for COVID-19, or certain other settings in which all employees are vaccinated and people with suspected or confirmed COVID-19 cannot enter.

The agency said it will work with states that have already issued local regulations, including two states that issued temporary standards of their own, Virginia and California.

Employers will have 2 weeks to comply with most of the regulations after they're published in the Federal Register. The standards will expire in 6 months but could then become permanent, as Virginia's did in January.

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Obstructive sleep apnea linked to COVID-19 risk

BY JIM KLING

Greater severity of obstructive sleep apnea (OSA) is associated with a higher risk of contracting COVID-19, and positive airway pressure (PAP) treatment may counter that risk, according to a retrospective analysis from the records of Kaiser Permanente Southern California.


Dr. Hwang

OSA patients often worry that PAP therapy might increase risk of severe COVID-19, said Dennis Hwang, MD, who presented the study at the American Thoracic Society's virtual international conference (Abstract A1108). But the findings should be reassuring. "If you have obstructive sleep apnea, and you're supposed to be using PAP, we recommend that you continue using PAP. It's good for your overall wellness and reducing the risk of cardiovascular disease, but as it relates to COVID-19, it's possible that it could protect. And there doesn't appear to be any risk of increased severity of illness (with use of PAP)," Dr. Hwang said in an interview. He is medical director of sleep medicine for Kaiser Permanente San Bernardino County and cochair of sleep medicine for Kaiser Southern California.

He noted that the retrospective nature of the study makes it difficult to pin down whether PAP therapy is truly protective, "but I think there's enough that we've been able conceptually to understand, to suggest that a direct causative relationship is possible," said Dr. Hwang.

The results may imply that OSA patients should pay special attention to their OSA when there's concern about exposure to an infectious agent like SARS-CoV-2. "The intermittent hypoxia at night, which can linger over to the day as increased sympathetic activity, increased heart rate. All of these are stresses to the body. So if you're going to get infected, you want to start at a healthier level. You want to eliminate your sleep apnea to help reduce your risk of morbidity," said Esra Tasali, MD, who was asked to comment on the study. Dr. Tasali is associate professor of medicine at the University of Chicago, and director of the Sleep Research Center there.

During the Q&A session after the talk, audience members asked about the timing of PAP use during COVID-19 infection, for example how often it was used during the asymptomatic phase of infection and if PAP has a positive effect. The data were not available, but "I think that the way to go is to understand this chronology," said Dr. Tasali.

The researchers examined records between 2015 and 2020, using sleep study data, remotely collected daily PAP data, and electronic health records, all from Kaiser Permanente Southern California. Included subjects were adults who had enrolled before Feb. 1, 2020, and had sleep diagnostic or PAP data on record by March 1, 2020. The researchers analyzed PAP adherence between March 1, 2020, and the time of COVID-19 diagnosis, or until the study ended on July 31, 2020.

Patients were defined as being untreated (< 2 hours/night PAP), moderately treated (2-3.9 hours/night), or well treated (4 or more hours/night). Apnea hypopnea index (AHI) was used to determine severity. The analysis included 81,932 patients (39.8% were women, mean age was 54.0 years, 9.9% were Black, and 34.5% were Hispanic). A total of 1.7% of subjects without OSA experienced COVID-19 infection, compared to 1.8% with OSA; 0.3% with OSA were hospitalized and 0.07% underwent intensive care or died.

There were some differences between the two groups. The non-U.S. population was younger (mean age 47.0 vs. 54.5 years), was less likely to be men (44% vs. 60.3%), had a lower mean body mass index (30.4 vs. 34.3), had fewer comorbidities according to the Charleston Comorbidity Index (1.3 vs. 2.0), and were less likely to have hypertension (5.6% vs. 12.4%; $P < .0001$ for all).

Infection rates were higher in patients with more severe OSA. The rates in untreated mild, moderate, and severe OSA were 2%, 2%, and 2.4%, respectively. The rate among all treated patients was 1.4% ($P < .0001$). Infection rates also dropped with better treatment: untreated, 2.1%; moderately treated, 1.7%; and well treated, 1.3% ($P < .0001$).

Not having OSA was associated with a lower infection risk than was having OSA (odds ratio [OR], 0.82; 95% confidence interval, 0.70-0.96). Compared to untreated patients, there was lower infection risk in the moderately treated (OR, 0.82; 95% CI, 0.65-1.03) and well treated (OR, 0.68; 95% CI, 0.59-0.79) groups. Higher infection rates were associated with obesity, higher Charlson Comorbidity score (> 2; OR, 1.29; 95% CI, 1.09-1.53), Black (OR, 1.51; 95% CI, 1.24-1.84) and Hispanic (OR, 2.23; 95% CI, 1.96-2.54) ethnicities, and Medicaid enrollment. Increasing age was associated with lower risk of infection, with each 5-year increment linked to reduced risk (OR, 0.88; 95% CI, 0.86-0.90). Dr. Hwang suggested that the age association may be because older individuals were more likely to follow social distancing and other precautions.

A multivariate analysis found that OSA was associated with infection risk according to OSA severity, including mild (OR, 1.21; 95% CI, 1.01-1.44), and moderate to severe (OR, 1.27; 95% CI, 1.07-1.51). There was no association between hospitalization rate or ICU admission/death and presence of OSA or PAP adherence in the data presented, but Dr. Hwang said that an updated analysis suggests that OSA may be associated with a risk of greater COVID-19 severity.

The control group was composed of individuals who had undergone sleep testing, but found to not have OSA. Still, they aren't necessarily representative of the general population, since symptoms likely drove them to testing. A high percentage were also obese, and the average BMI was 30. "It's certainly not a 'normal population,' but the advantage of what we did in terms of using this control group is that they underwent sleep testing, so they were proven to have no obstructive sleep apnea, whereas if we used a general population, we just don't know," said Dr. Hwang.

The study received technical and data support from Somnoware, and was funded by Kaiser Permanente. Dr. Tasali has no relevant financial disclosures.

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OSA: Heart rate change may signal CPAP benefit

BY JIM KLING

Some nonsleepy patients with coronary artery disease and obstructive sleep apnea (OSA) may receive cardiovascular benefit from continuous positive airway pressure (CPAP) therapy, according to a post hoc analysis of the RICCADSA clinical trial. That study found no benefit among patients overall, but the new analysis found that patients whose heart rate increases (delta heart rate, or dHR) more than average during apnea or hypopnea experienced fewer cardiovascular or cerebrovascular events during apnea or hypopnea when treated with CPAP.

Although RICCADSA showed no benefit, an analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) and the Sleep Heart Health Study (SHHS) cohorts found that elevated pulse rate response to respiratory events was associated with greater risk of cardiovascular disease (CVD) morbidity and mortality. But the effect was seen only in nonsleepy patients. "We hypothesized that pulse rate response to apneas would predict which patients with OSA may most benefit from CPAP treatment. Now, our study suggests that there is, in fact, a subgroup of nonsleepy patients with OSA for whom CPAP could provide a reduction in risk, specifically those with a higher pulse rate response to their respiratory events," Ali Azarbarzin, PhD, said in an interview.

Dr. Azarbarzin presented the study at the American Thoracic Society's virtual international conference (Abstract A1103). He is in the division of sleep and circadian disorders at Brigham and Women's Hospital, and is assistant professor of medicine at Harvard Medical School, both in Boston.

The study is in line with recent efforts to subgroup OSA patients to determine which are at higher risk of cardiovascular events and other complications, and which are most likely to respond to treatment, according to Esra Tasali, MD, of the University of Chicago, who moderated the session where the study was presented. "The field is really urgently in need of coming up with new methods, and I think this study is getting a handle on that," said Dr. Tasali in an interview.

Continued on page 16

BREZTRI is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

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In Study 1 (52 weeks), BREZTRI significantly reduced the annual rate of moderate or severe COPD exacerbations vs LAMA/LABA (rate ratio=0.76; *P*<0.0001) and ICS/LABA (rate ratio=0.87; *P*=0.0027).[2]
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IMPORTANT SAFETY INFORMATION

- BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients
- BREZTRI is not indicated for treatment of asthma. Long-acting beta$_2$-adrenergic agonist (LABA) monotherapy for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD
- BREZTRI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BREZTRI is NOT a rescue inhaler. Do NOT use to relieve acute symptoms; treat with an inhaled short-acting beta$_2$-agonist
- BREZTRI should not be used more often than recommended; at higher doses than recommended; or in combination with LABA-containing medicines, due to risk of overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation
- Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap
- Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI
- Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy
- Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur
- If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy
- Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider alternative therapy
- Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles

ICS=inhaled corticosteroids; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

Study 1 design[2]: 52-week, Phase 3, randomized 1:1:1:1, double-blind, multicenter, parallel-group trial of 8588 patients with moderate to very severe COPD, comparing BREZTRI MDI 320/18/9.6 mcg (n=2157), BUD/GLY/FORM MDI 160/18/9.6 mcg (n=2137), GLY/FORM MDI 18/9.6 mcg (n=2143), and BUD/FORM MDI 320/9.6 mcg (n=2151), each administered BID. Patients were 40-80 years of age, smoking history of ≥10 pack-years, symptomatic COPD while receiving ≥2 inhaled maintenance therapies, and had a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the annual rate of moderate or severe COPD exacerbations. Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations as those resulting in hospitalization or death.

BREZTRI is administered as 2 inhalations twice daily.

References: 1. BREZTRI AEROSPHERE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very severe COPD. *N Engl J Med.* 2020;383(1):35-48.

BREZTRI is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

- Decreases in bone mineral density have been observed with long-term administration of ICS. Assess initially and periodically thereafter in patients at high risk for decreased bone mineral content
- Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow-angle glaucoma may occur, so use with caution. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI long term. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if symptoms occur
- Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines
- Be alert to hypokalemia or hyperglycemia
- Most common adverse reactions in a 52-week trial (incidence ≥ 2%) were upper respiratory tract infection (5.7%), pneumonia (4.6%), back pain (3.1%), oral candidiasis (3.0%), influenza (2.9%), muscle spasms (2.8%), urinary tract infection (2.7%), cough (2.7%), sinusitis (2.6%), and diarrhea (2.1%). In a 24-week trial, adverse reactions (incidence ≥ 2%) were dysphonia (3.3%) and muscle spasms (3.3%)
- BREZTRI should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors and tricyclic antidepressants, as these may potentiate the effect of formoterol fumarate on the cardiovascular system
- BREZTRI should be administered with caution to patients being treated with:
  - Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
  - Adrenergic drugs (may potentiate effects of formoterol fumarate)
  - Xanthine derivatives, steroids, or non-potassium sparing diuretics (may potentiate hypokalemia and/or ECG changes)
  - Beta-blockers (may block bronchodilatory effects of beta-agonists and produce severe bronchospasm)
  - Anticholinergic-containing drugs (may interact additively). Avoid use with BREZTRI
- Use BREZTRI with caution in patients with hepatic impairment, as budesonide and formoterol fumarate systemic exposure may increase. Patients with severe hepatic disease should be closely monitored

Please see Brief Summary of Prescribing Information on adjacent pages.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

BREZTRI AEROSPHERE™
(budesonide 160 mcg, glycopyrrolate 9 mcg and formoterol fumarate 4.8 mcg) Inhalation Aerosol

AstraZeneca

BREZTRI AEROSPHERE™

(budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION.

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

BREZTRI AEROSPHERE is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Limitations of Use:

BREZTRI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma *[see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information]*.

CONTRAINDICATIONS

BREZTRI AEROSPHERE is contraindicated in patients who have demonstrated hypersensitivity to budesonide, glycopyrrolate, formoterol, or any of the excipients *[see Warnings and Precautions (5.11) and Description (11) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations, Death

The safety and efficacy of BREZTRI AEROSPHERE in patients with asthma have not been established. BREZTRI AEROSPHERE is not indicated for the treatment of asthma.

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

Deterioration of Disease and Acute Episodes

BREZTRI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BREZTRI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BREZTRI AEROSPHERE in this setting is not appropriate.

BREZTRI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREZTRI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning treatment with BREZTRI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREZTRI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREZTRI AEROSPHERE no longer controls symptoms, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. The daily dosage of BREZTRI AEROSPHERE should not be increased beyond the recommended dose.

Avoid Excessive Use of BREZTRI AEROSPHERE and Avoid Use with other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, BREZTRI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Patients using BREZTRI AEROSPHERE should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Oropharyngeal Candidiasis

BREZTRI AEROSPHERE contains budesonide, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products containing budesonide. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREZTRI AEROSPHERE continues. In some cases, therapy with BREZTRI AEROSPHERE may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following administration of BREZTRI AEROSPHERE to help reduce the risk of oropharyngeal candidiasis.

Pneumonia

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap.

In a 52-week trial of subjects with COPD (n = 8,529), the incidence of confirmed pneumonia was 4.2% for BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n = 2144), 3.5% for budesonide, glycopyrrolate and formoterol fumarate [BGF MDI 160 mcg/18 mcg/9.6 mcg] (n = 2124), 2.3% for GFF MDI 18 mcg/9.6 mcg (n = 2125) and 4.5% for BFF MDI 320 mcg/9.6 mcg (n = 2136).

Fatal cases of pneumonia occurred in 2 subjects receiving BGF MDI 160 mcg/18 mcg/9.6 mcg, 3 subjects receiving GFF MDI 18 mcg/9.6 mcg, and no subjects receiving BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg.

In a 24-week trial of subjects with COPD (n = 1,896), the incidence of confirmed pneumonia was 1.9% for BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n = 639), 1.6% for glycopyrrolate and formoterol fumarate [GFF MDI 18 mcg/9.6 mcg] (n = 625) and 1.9% for budesonide and formoterol fumarate [BFF MDI 320 mcg/9.6 mcg] (n = 320). There were no fatal cases of pneumonia in the study.

Immunosuppression and Risk of Infections

Patients who are using drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREZTRI AEROSPHERE may provide control of COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their healthcare practitioner for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREZTRI AEROSPHERE. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREZTRI AEROSPHERE. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

Transfer of patients from systemic corticosteroid therapy to BREZTRI AEROSPHERE may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

Corticosteroid Withdrawal Symptoms

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Inhaled budesonide is absorbed into the circulation and can be systemically active. Effects of budesonide on the HPA axis are not observed with the therapeutic doses of budesonide in BREZTRI AEROSPHERE. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9) and Drug Interactions (7.1) in the full Prescribing Information]*.

Because of the possibility of significant systemic absorption of ICS, patients treated with BREZTRI AEROSPHERE should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects, such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be initiated as needed.

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of BREZTRI AEROSPHERE with long-term ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Paradoxical Bronchospasm

As with other inhaled therapies, BREZTRI AEROSPHERE can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs following dosing with BREZTRI AEROSPHERE, it should be treated immediately with an inhaled, short-acting bronchodilator; BREZTRI AEROSPHERE should be discontinued immediately and alternative therapy should be instituted.

Hypersensitivity Reactions including Anaphylaxis

Immediate hypersensitivity reactions have been reported after administration of budesonide, glycopyrrolate or formoterol fumarate, the components of BREZTRI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips, and face), urticaria, or skin rash, BREZTRI AEROSPHERE should be stopped at once and alternative treatment should be considered *[see Contraindications (4) in the full Prescribing Information]*.

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*.

If such effects occur, BREZTRI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, BREZTRI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREZTRI AEROSPHERE and periodically thereafter. If significant reductions in BMD are seen and BREZTRI AEROSPHERE is still considered medically important for that patient's COPD therapy, use of therapy to treat or prevent osteoporosis should be strongly considered.

In a subset of COPD patients in a 24-week trial with a 28-week safety extension that evaluated BREZTRI AEROSPHERE 320/18/9.6 mcg and GFF MDI 18/9.6 mcg, the effects on BMD endpoints were evaluated. BMD evaluations were performed at baseline and 52-weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean percent changes in BMD from baseline was -0.1% for BREZTRI AEROSPHERE 320/18/9.6 mcg and 0.4% for GFF MDI 18/9.6 mcg *[see Clinical Studies (14) in the full Prescribing Information]*.

Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. BREZTRI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI AEROSPHERE long term.

In a 52-week trial that evaluated BREZTRI AEROSPHERE 320/18/9.6 mcg, GFF MDI 18/9.6 mcg, and BFF MDI 320/9.6 mcg in subjects with COPD, the incidence of cataracts ranged from 0.7% to 1.0% across groups.

Worsening of Urinary Retention

BREZTRI AEROSPHERE, like all therapies containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Coexisting Conditions

BREZTRI AEROSPHERE, like all therapies containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonists may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist therapies may produce transient hyperglycemia in some patients.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression and risk of infections *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10) in the full Prescribing Information]*
- Hypersensitivity reactions including anaphylaxis *[see Contraindications (4) and Warnings and Precautions (5.11) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma and cataracts *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BREZTRI AEROSPHERE is based on the safety data from one 52-week exacerbation trial (Trial 1) and one 24-week lung function trial with a 28-week safety extension study, resulting in up to 52 weeks of treatment (Trial 2). In Trials 1 and 2, a total of 2783 subjects have received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg *[see Clinical Studies (14) in the full Prescribing Information]*.

In Trials 1 and 2, subjects received one of the following treatments: BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg, glycopyrrolate and formoterol fumarate [GFF MDI 18 mcg/9.6 mcg], or budesonide and formoterol fumarate [BFF MDI 320 mcg/9.6 mcg]. Each treatment was administered twice daily.

In Trial 1, a 52-week, randomized, double-blind clinical trial, a total of 2144 subjects with COPD received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (mean age: 64.7 years, 84.9% Caucasian, 59.7% male across all treatments) *[see Clinical Studies (14) in the full Prescribing Information]*.

In Trial 2, a 24-week, randomized, double-blind clinical trial, with a 28-week long-term safety extension resulting in up to 52 weeks of treatment, a total of 639 subjects received at least 1 dose of BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (mean age: 65.2 years, 50.1% Caucasian, 71.2% male across all treatments) *[see Clinical Studies (14) in the full Prescribing Information]*.

The incidence of adverse reactions from the 52-week trial (Trial 1) is presented in Table 1 for subjects treated with BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg, GFF MDI 18 mcg/9.6 mcg, or BFF MDI 320 mcg/9.6 mcg.

Table 1: Adverse reactions occurring at an incidence of ≥ 2% of subjects and more common in BREZTRI AEROSPHERE compared to GFF MDI and BFF MDI (Trial 1)

Adverse Reaction	BREZTRI AEROSPHERE[1] 320 mcg/18 mcg/9.6 mcg N=2144 (%)	GFF MDI[1] 18 mcg/9.6 mcg N=2125 (%)	BFF MDI[1] 320 mcg/9.6 mcg N=2136 (%)
Upper Respiratory Tract Infection	123 (5.7)	102 (4.8)	115 (5.4)
Pneumonia	98 (4.6)	61 (2.9)	107 (5.0)
Back pain	67 (3.1)	55 (2.6)	64 (3.0)
Oral candidiasis	65 (3.0)	24 (1.1)	57 (2.7)
Influenza	63 (2.9)	42 (2.0)	61 (2.9)
Muscle spasms	60 (2.8)	19 (0.9)	53 (2.5)
Urinary tract infection	58 (2.7)	60 (2.8)	41 (1.9)
Cough	58 (2.7)	50 (2.4)	51 (2.4)
Sinusitis	56 (2.6)	47 (2.2)	55 (2.6)
Diarrhea	44 (2.1)	37 (1.7)	38 (1.8)

[1] BREZTRI AEROSPHERE = budesonide/glycopyrrolate/formoterol fumarate 320 mcg/18 mcg/9.6 mcg; GFF MDI = glycopyrrolate/formoterol fumarate 18 mcg/9.6 mcg; BFF MDI = budesonide/formoterol fumarate 320 mcg/9.6 mcg; all treatments were administered twice daily.

In 24-week data from Trial 2, adverse reactions that occurred in subjects treated with BREZTRI AEROSPHERE 320 mcg/18 mcg/9.6 mcg (n=639) at an incidence of ≥ 2% included dysphonia (3.3%) and muscle spasms (3.3%).

Additional Adverse Reactions

Other adverse reactions that have been associated with one or more of the individual components of BREZTRI AEROSPHERE include: hyperglycemia, anxiety, insomnia, headache, palpitations, nausea, hypersensitivity, depression, agitation, restlessness, nervousness, tremor, dizziness, angina pectoris, tachycardia, cardiac arrhythmias (e.g., atrial fibrillation, supraventricular tachycardia, and extrasystoles), throat irritation, bronchospasm, dry mouth, bruising, urinary retention, chest pain, sign or symptoms of systemic glucocorticoid steroid effects (e.g., hypofunctional adrenal gland), and abnormal behavior.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BREZTRI AEROSPHERE.

Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including budesonide, a component of BREZTRI AEROSPHERE, is via cytochrome P450 isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of a CYP3A4 inhibitor may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of BREZTRI AEROSPHERE with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9) in the full Prescribing Information]*.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BREZTRI AEROSPHERE, may be potentiated *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of beta$_2$-adrenergic agonists such as formoterol, a component of BREZTRI AEROSPHERE.

Non-Potassium Sparing Diuretics

The hypokalemia and/or ECG changes that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta$_2$-agonists, especially when the recommended dose of the beta$_2$-agonist is exceeded.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BREZTRI AEROSPHERE, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-adrenergic Receptor Blocking Agents

Beta-adrenergic receptor antagonists (beta-blockers) and BREZTRI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta$_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of BREZTRI AEROSPHERE with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.9, 5.10) and Adverse Reactions (6) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BREZTRI AEROSPHERE. BREZTRI AEROSPHERE contains budesonide, glycopyrrolate, and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BREZTRI AEROSPHERE. Treatment of overdosage consists of discontinuation of BREZTRI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Budesonide

If used at excessive doses for prolonged periods, systemic corticosteroid effects, such as hypercorticism may occur *[see Warnings and Precautions (5.8) in the full Prescribing Information]*.

Glycopyrrolate

High doses of glycopyrrolate, a component of BREZTRI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation, or difficulties in voiding.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta$_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest, and even death may be associated with overdosage of formoterol fumarate.

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Avoiding excess O_2 in mechanically ventilated patients

BY DOUG BRUNK

The respiratory therapists at Mount Sinai Beth Israel, New York, know when Lina Miyakawa, MD, starts a week in the ICU, because she turns down the fraction of inspired oxygen (FiO_2) levels if patients tolerate it.

"Hyperoxia in mechanical ventilation is a topic that's near and dear to my heart," Dr. Miyakawa, a pulmonary and critical care medicine specialist at Mount Sinai Beth Israel, said during SHM Converge, the annual conference of the Society of Hospital Medicine. "You can always find 'wean down FiO_2' in my consult notes."


Dr. Miyakawa

While it is believed that humans have built up evolutionary defenses against hypoxia but not against hyperoxia, medical literature on the topic of hyperoxia with supplemental oxygen is fairly young. "In medical school we were taught to give oxygen for anybody with chest pain and concern about acute coronary syndrome," she said. "This was until recent data suggested harm from liberal oxygen use."

A single-center trial of 434 critical care patients with an ICU length of stay of 72 hours or longer, examined the effects of a conservative protocol for oxygen therapy versus conventional therapy on ICU mortality (JAMA. 2016;316[15]:1583-9). The trial was stopped because the patients who were assigned to receive conservative therapy had a significantly lower mortality than the ones who received usual care ($P = .01$).

"The study was not perfect, and the premature stoppage likely exaggerated the effect size," said Dr. Miyakawa, who was not affiliated with the trial. "However, subsequent retrospective studies continue to support a benefit with conservative oxygen use, especially in different groups of patients. One of note is hyperoxia following cardiac arrest. There's something called a two-hit model that speaks to worsening ischemia with reperfusion injury after the initial hypoxic event from the cardiac arrest itself."

In a multicenter cohort study that drew from the Project IMPACT critical care database of ICUs at 120 U.S. hospitals between 2001 and 2005, researchers led by J. Hope Kilgannon, MD, tested the hypothesis that postresuscitation hyperoxia is associated with increased in-hospital mortality (JAMA. 2010;303[21]:2165-71). The study population consisted of 6,326 patients who were divided into three groups: the hypoxic group (a PaO_2 of less than 60 mm Hg); the normoxic group (a PaO_2 of 60-299 mm Hg), and the hyperoxic group (a PaO_2 of over 300 mm Hg). The mortality for the hyperoxic group was 63%, the hypoxic group at 57%, and the normoxic group at 45%.

More recently, the ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group evaluated conservative versus liberal approaches in providing oxygen to 965 patients who were mechanically ventilated between 2015 and 2018 at 21 ICUs (N Eng J Med. 2020;382:989-98). Of the 965 patients, 484 were randomly assigned to the conservative oxygen group (defined as an SpO_2 of 97% or lower) and 481 were assigned to the usual oxygen group (defined as having no specific measures limiting FiO_2 or the SpO_2). The primary outcome was the number of ventilator-free days from randomization until day 28, while the secondary outcome was mortality at 180 days. The researchers also performed a subgroup analysis of patients at risk for hypoxic-ischemic encephalopathy.

No significant differences were observed in the number of ventilator days between the two group (a median of 21 days in the conservative oxygen group versus 22 days in the usual oxygen group, respectively; $P = .80$) nor in mortality at 180 days (35.7% vs. 34.5%). However, in the subgroup analysis, patients with hypoxic-ischemic encephalopathy were noted to have more ventilator-free days (21 vs. 0 days), improved 180-day mortality (43% vs. 59%), and less functional impairment (55% vs. 68%) in the conservative-oxygen group.

"The results of this study suggest that conservative oxygen therapy has no additional advantage over standard oxygen therapy, but there may be benefits in those vulnerable to hyperoxia, which warrants further investigation," Dr. Miyakawa said. "There are a few points to note on this topic. First, many of the previous studies had more liberal oxygen strategies than the ones used in this study, which could be the reason why we are seeing these results. In addition, O_2 titration relies on imperfect approximations. PaO_2 cannot be measured continuously; we really depend on the SpO_2 on a minute-by-minute basis. Critically ill patients can also undergo episodes of hypoperfusion and shock state minute-by-minute. That's when they're at risk for hypoxemia. This would not be captured continuously with just O_2 saturations."

Dr. Miyakawa also highlighted the Liberal Oxygenation versus Conservative Oxygenation in Acute Respiratory Distress Syndrome trial ($LOCO_2$) a prospective, multicenter, randomized, open-label trial involving patients with ARDS. It was carried out at 13 ICUs in France between June 2016 and September 2018 in an effort determine whether conservative oxygenation would reduce mortality at 28 days compared with the usual liberal oxygen strategy (N Eng J Med. 2020;382:999-1008). The researchers detected a signal of increased mortality in the conservative oxygen group (34% vs. 27%), which led to a premature stoppage of the trial. "I'd like to postulate that the higher incidence of proning in the liberal oxygenation group compared to the conservative oxygen group (51% to 34%) may be the reason for the difference in mortality," said Dr. Miyakawa, who was not affiliated with $LOCO_2$. "This is supported from the 2013 PROSEVA Study Group, which reported that prone positioning in ARDS significantly decreases 28- and 90-day mortality" (see N Engl J Med. 2013; 368:2159-68).

She said that future trials on this topic "will have to address how a particular [oxygenation] target is both set and achieved in each group of patients, particularly those with specific organ injuries. In the meantime, in my opinion, avoiding excess oxygen seems sensible."

Dr. Miyakawa reported having no financial disclosures.

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"I think that this is really pointing toward a new area that the whole (sleep field) is moving toward, which is better phenotyping of sleep apnea so that we can come up with more personalized treatments," said Dr. Tasali.


Dr. Tasali

The patients who appeared to gain a cardiovascular benefit from CPAP represented about 16% of trial participants. Dr. Azarbarzin refrained from making clinical recommendations, citing the need for more data. The team next plans to reproduce the findings in additional, larger trials such as the SAVE and ISAACC trials. "Ultimately, our goal is to confirm our findings in a future randomized controlled trial of CPAP by enrolling participants based on their pulse rate response," said Dr. Azarbarzin.

The RICCADSA study was a single center randomized, controlled trial with 226 patients with coronary artery disease and OSA who were randomized to CPAP or no CPAP treatment. In the overall population, CPAP treatment was not associated with a statistically significant change in repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality (hazard ratio, 0.79; $P = .435$). That study assumed that the effect of OSA on CVD is similar across all subgroups of dHR.

The mean increase in heart rate was 7.1 beats per minute (BPM; standard deviation, 3.7). Each standard deviation increase in dHR was linked to greater CVD risk (HR, 1.45; $P = .029$). For each standard deviation decrease in dHR, treatment with CPAP decreased the CVD risk (HR, 0.54; $P = .043$).

For patients with a low dHR of 4 BPM, the hazard ratio for CVD was 0.8 with no CPAP treatment and 1.2 for CPAP treatment. For those at the mean value of 7 BPM, the HRs were 1.1 and 0.9, respectively. For those with a high dHR, (10 BPM), the HR was 1.6 without treatment and 0.7 with CPAP.

"We modeled delta heart rate interaction with CPAP, which was significant. What this means is that for someone with a mean delta heart rate of 7 beats per minute, the risk reduction [with CPAP] is similar to what RICCADSA reported. But if you look at those with high delta heart rate, the risk reduction was significantly larger. It was actually a more than 50% reduction of risk with CPAP treatment," said Dr. Azarbarzin.

Dr. Azarbarzin has consulted for Somnifix and Apnimed and has received grants from Somnifix. Dr. Tasali has no financial disclosures.

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Telemedicine is poised to drive new models of care

BY TED BOSWORTH

Telemedicine has been proposed as a solution for an array of health care–access problems over decades of gradual growth. The ramping up of telemedicine during the COVID-19 pandemic greatly expanded the evidence of its feasibility and what appears to be its inevitable incorporation into models of care, according to an update at the Health Policy and Advocacy Conference (HPAC) sponsored by the American College of Chest Physicians.

"The cat is out of the bag," said Jaspal Singh, MD, FCCP, professor of medicine, Atrium Health, Charlotte, N.C. Due to changes in access and reimbursement to telemedicine driven by the pandemic, he said, "we now have permission to explore new models of care."

Prior to February 2020, telemedicine was crawling forward at a leisurely pace, according to Dr. Singh. After March 2020, it broke into a run due to enormous demand and met by a rapid response from the U.S. Congress. The first of four legislative bills that directly or indirectly supported telemedicine was passed on March 6.

The Centers for Medicare & Medicaid Services (CMS) responded in kind, making modifications in a number of rules that removed obstacles to telehealth. One modification on April 6, for example, removed the requirement for a preexisting relationship between the clinician and patient, Dr. Singh said. The CMS also subsequently modified reimbursement policies in order to make telemedicine more tenable for physicians.

Given the risk of contagion from face-to-face encounters, telemedicine in the early days of the pandemic was not just attractive but the only practical and safe approach to medical care in many circumstances. Physicians and patients were eager for health care that did not require in-office visits even though many critical issues for telemedicine, including its relative effectiveness, had not yet been fully evaluated.

Much has been learned regarding the feasibility and acceptability of telemedicine during the pandemic, but Dr. Singh noted that quality of care relative to in-person visits remains weakly supported for most indications. Indeed, he outlined a sizable list of incompletely resolved issues, including optimal payment models, management of privacy concerns, and how to balance advantages to disadvantages.

For patients and physicians, the strengths of telemedicine include greater convenience made possible by the elimination of travel and waiting rooms. For the health care system, it can include less infrastructure and overhead. For many physicians, telemedicine might be perceived as more efficient.

Many physicians and patients will have a different perception of telemedicine after the widespread exposure to this type of care.

On the other hand, some patients might feel that a clinical encounter is incomplete without a physical examination even when the physician does not feel the physical examination is needed, according to Dr. Singh. He cited a survey suggesting nearly half of patients expressed concern about a lack of connection to health care providers following a virtual visit.

In the same 2020 National Poll on Healthy Aging 2020 survey conducted by the University of Michigan, 67% of respondents reported that the quality of care was not as good as that provided by in-patient visits, and 24% expressed concern about privacy.

However, at the time the poll was taken in May 2020, experience with telemedicine among many of the respondents may have been limited. As telemedicine is integrated into routine care, perceptions might change as experience increases.

A distinction between telemedicine in routine care and telemedicine as a strategy to respond to a pandemic is important, Dr. Singh indicated. Dr. Singh was the lead author for a position paper on telemedicine for the diagnosis and treatment of sleep disorders from the American Academy of Sleep Medicine 5 years ago (J Clin Sleep Med. 2015;11:1187-98), but he acknowledged that models of care might differ when responding to abnormal surges in health care demand.

The surge in demand for COVID-19–related care engendered numerous innovative solutions. As examples, Dr. Singh recounted how a virtual hospital was created at his own institution. In a published study, 1,477 patients diagnosed with COVID-19 over a 6-week period remained at home and received care in a virtual observation unit (VCU) or a virtual acute care unit (VACU) (Ann Intern Med. 2020;174:192-9). Only a small percentage required eventual hospital admission. In the VACU, patients were able to receive advanced care, including IV fluids and some form of respiratory support.

It is unclear how the COVID-19 pandemic will change telemedicine. Now, with declining cases of the infection, telemedicine is back to a walk after the sprint required during the height of the pandemic, according to Dr. Singh. However, Dr. Singh thinks many physicians and patients will have a different perception of telemedicine after the widespread exposure to this type of care. In terms of the relative role of in-patient and virtual visits across indications, "we do not know how this will play out, but we will probably end up toggling between the two."

This is an area that is being followed closely by the CHEST Health Policy and Advocacy Committee, according to Kathleen Sarmiento, MD, FCCP, director, VISN 21 Sleep Clinical Resource Hub for the San Francisco VA Health Care System. A member of that Committee and moderator of the session in which Dr. Singh spoke, Dr. Sarmiento called the effort to bring permanent coverage of telehealth services "the shared responsibility of every medical society engaged in advocacy."

She cautioned that there might be consequences that require analysis to develop policies that are in the best interests of effective care. The "ACCP [CHEST], along with its sister societies, does have a role in supporting the evaluation of the impact of these changes on both patients and providers in the fields of pulmonary medicine, critical care, and sleep medicine."

Dr. Singh reports a financial relationship with AstraZeneca. Dr. Sarmiento reports no relevant financial relationships.

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NetWorks

Eosinophils in COVID-19. Long COVID-19. Sedation practices post-pandemic. Establishing NIV clinics. More. . .

Airways Disorders

Eosinophils in COVID-19

Using peripheral blood eosinophilia (PBE) as a treatable biomarker of airway inflammation in patients with COPD has become an area of controversy in pulmonary medicine.

The proponents find a role for PBE testing in initiation and withdrawal of inhaled corticosteroids (ICS) and as a target for monoclonal antibodies in future studies.[1] Post hoc analyses showed that variable doses of ICS/LABA combination compared with LABA alone in COPD patients were associated with much higher exacerbation reduction in patients with eosinophils counts of ≥2% and magnitude of effect proportionally increased from 29% to 42% with increasing eosinophil count from ≥2% to ≥6% suggesting a dose-response relationship.[2] A post hoc analysis of the WISDOM trial showed increased risk of exacerbation after ICS discontinuation in COPD patients with high eosinophils (≥300 cells/mcL or ≥4%) while exacerbation risk was not increased in patients with low eosinophils (<150 cells/mcL or <2%).[3]

Dr. Abbas

The opponents of eosinophil-guided therapy object that the level of evidence is weak as this is based on the post hoc analyses of randomized control trials on patients with increased exacerbation risk at baseline, which in itself is an independent predictor of future exacerbations.[4] Some observational studies failed to find increased risk of exacerbation with higher eosinophil count while others found that higher eosinophil count was associated with increased survival and better quality of life.[5,6] Anti-eosinophilic biologics have failed to show consistent benefit in exacerbation reduction in COPD patients so far, despite showing a reduction in the PBE.[7-9]

The GOLD COPD Guidelines support the use of ICS in patients with eosinophils >300 cells/mcL especially with a history of exacerbation and recommend against ICS in patients with eosinophils <100 cells/mcL.[10]

Farrukh Abbas, MD
Steering Committee
Fellow-in-Training
Allen J. Blaivas, MD, FCCP
NetWork Chair

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Clinical Research

Long-COVID: COVID-19 disease beyond the pandemic

There are increasing reports of persistent multi-organ symptoms following COVID-19 infection.

In December 2020, the National Institute for Health and Care Excellence (NICE) developed guidelines, based primarily on expert opinion, to define and manage ongoing symptomatic COVID-19 (symptoms for 4-12 weeks after infection) and post-COVID syndrome (symptoms present for > 12 weeks without alternative explanation) (www.nice.org.uk/guidance/ng188). Subsequently, the National Institutes of Health (NIH), released in February 2021 an initiative to study Post-Acute Sequelae of SARS-CoV2 infection (PASC) (https://tinyurl.com/92kpfwsn). Symptoms can include, respiratory (cough, shortness of breath), cardiac (palpitations, chest pain), fatigue and physical limitations, and neurologic (depression, insomnia, cognitive impairment) (*Lancet* 2020 Dec 12;396[10266]:1861). The majority of patients with post-COVID syndrome have microbiological recovery (PCR negative), and often have radiological recovery. Risk factors include older age, female sex, and comorbidities (Raveendran AV. *Diabetes Metab Syndr*. 2021 May-June;15[3]:869-75).

Diagnosis and access to care pose significant challenges for post-COVID syndrome, and it is difficult to estimate exactly how many are affected – one report from Italy found that up to 87% of discharged hospitalized patients had persistent symptom(s) at 60 days (Carfi A. *JAMA* 2020 Aug;324[6]:603-5). Thus far, management recommendations include a multidisciplinary approach to evaluation, symptomatic treatment, organ specific treatment (for example, consideration of corticosteroids for persistent inflammatory interstitial lung disease) (Myall KJ. *Ann Am Thorac Soc*. 2021 May;8[5]:799-806), physical/occupational therapy, and psychological support. Many institutions have established, or are working to establish post-COVID clinics (*Aging Clin Exp Res*. 2020 Aug;32[8]:1613-20). Currently, the NIH is offering funding opportunities and there are many clinical trials across the world actively recruiting patients.

Ankita Agarwal, MD
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Critical Care

Sedation practices in the ICU: Moving past the COVID-19 pandemic

The COVID-19 pandemic brought unprecedented change to critical care practice patterns, and sedation practices in the intensive care unit are no exception. In a large cohort analysis of over 2,000 adults with COVID-19 (Pun BT, et al. *Lancet Respir Med*. 2021;9[3]:239-50), 64% of patients received benzodiazepines (median of 7 days), and patients were deeply sedated. More than half of the patients were delirious, with benzodiazepine use associated with increased incidence of delirium.

Dr. Cable

These observations represent a significant departure from well-established pre-COVID best-practices in sedation: light targets, daily sedation interruption, and avoiding continuous benzodiazepine infusions whenever possible (Girard TD, et al. *Lancet*; 2008;371[9607]:126-34; Fraser GL, et al. *Crit Care Med*;2013 Sep;41[9 Suppl 1]:S30-8; Riker RR, et al. *JAMA*;2009;301[5]:489-99).

As COVID-19 case counts begin to improve in many of our communities, we have the opportunity to refocus on best sedation practices and build on a growing body of recent evidence. The MENDS2 trial, completed pre-COVID-19, assigned mechanically ventilated patients with sepsis to either propofol or dexmedetomidine and showed no difference in delirium or coma in this cohort of lightly sedated patients (Hughes CG, et al. *N Engl J Med*. 2021;384[15]:1424-36). Furthering this point, Olsen et al. found no difference in outcomes when mechanically ventilated patients were randomized to no sedation vs light sedation (Olsen HT, et al. *N Engl J Med*; 2020;382[12]:1103-11).

While the evidence surrounding sedation strategies in the critically ill continues to grow, one thing is certain: promoting lighter sedation targets and reengaging in sedation-related best practices following the COVID-19 pandemic will continue to play a vital role in improving both short- and long-term outcomes for our critically ill patients.

Casey Cable, MD, MSc
Steering Committee Member
Kyle Stinehart, MD
Steering Committee Member

Home Mechanical Ventilation

How to initiate a chronic respiratory failure clinic

Noninvasive ventilation (NIV) is an established treatment for chronic hypercapnic respiratory failure from neuromuscular disorders, COPD, obesity hypoventilation syndrome (OHS), and restrictive thoracic disorders. Previously, hospital admission was considered essential for setup of chronic NIV but with advances in the modes of ventilation and remote monitoring, hospital admission has become less justifiable, especially in countries with centralized medical systems and presence of centers of excellence for home ventilation (Van Den Biggelaar

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RJM, et al. *Chest.* 2020;158[6]:2493-2501); Duiverman ML, et al. *Thorax*. 2020;75:244-52). In the United States, where centralized health care is atypical, management of NIV has been disparate with no clear consensus on practice patterns. Thus, we hope to provide some guidance toward the establishment of such clinics in the U.S.

Dr. Sahni

Prior to developing an NIV clinic, establishing a referral source from neuromuscular, rehabilitation/spinal cord injury, bariatric surgery, and COPD programs is important. After this, collaboration with a respiratory therapist through durable medical equipment is essential to building a robust care team. These companies are also important for assisting in remote monitoring, providing overnight pulse oximetry/CO_2 monitoring, mask fitting, and airway clearance. Clinicians are encouraged to develop protocols for initiation and titration of NIV and mouthpiece ventilation. Clinics should provide spirometry, maximal inspiratory pressure, transcutaneous CO_2, and/or blood gas testing. Additionally, in this patient population, wheelchair scales are necessary. Clinical workflow should include a review of NIV downloads, identify asynchronies and troubleshoot it in timely and reliable manner (Blouet S, et al. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2577-86). Lastly, effort should be made for an adequate assessment of the home situation including layout of home along with family support utilizing social worker and palliative care team. Due to patient mobility, we encourage continued availability of telehealth for these patients.

In summary, strong clinical infrastructure, a robust care team, and an efficient, secure, reliable telemonitoring system are key to provide better care to this vulnerable patient population.

Ashima S. Sahni, MD, MBBS, FCCP
NetWork Member
Amen Sergew, MD
Steering Committee Member

Interstitial and Diffuse Lung Disease

Treatment for pulmonary hypertension secondary to interstitial lung disease

The development of pulmonary hypertension (PH) in patients with interstitial lung disease (ILD) (PH-ILD) is associated with increased supplemental oxygen requirements, reduced functional status, and decreased survival (King CS, et al. *Chest*. 2020;158[4]:1651).

Dr. Shifren

An inhaled formulation of treprostinil (Tyvaso) is the first treatment option approved by the FDA for patients with PH-ILD, including those with idiopathic pulmonary fibrosis, connective tissue disease-associated ILD, and combined pulmonary fibrosis and emphysema (www.tyvaso.com/pdf/TYVASO-PI.pdf). Approval was based on results from the INCREASE trial (Waxman A, et al. *N Engl J Med*. 2021;384[4]:325), a phase III multicenter, randomized, double-blinded study comparing the inhaled formulation to placebo in 326 patients over a 16-week period. Participants in the treatment arm were given up to 12 breaths of the formulation per session, four times per day. Subjects treated with this inhaled formulation met the primary study endpoint, an increase in 6-minute walk distance (6MWD) from baseline to week 16, walking 21 m farther than placebo-treated control subjects. Furthermore, patients receiving the new formulation had a decrease in NT-proBNP levels (compared with increases in the placebo arm) and a reduction in clinical worsening (23% of inhalation formulation-treated vs. 33% of placebo-treated subjects). This formulation of treprostinil was well-tolerated with a safety profile consistent with common prostacyclin-related adverse events, including cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Its approval will dramatically alter the ILD treatment landscape. It now necessitates the use of PH screening in this patient population. However, care will need to be exercised in appropriate patient selection for treatment, using the study inclusion and exclusion criteria as a starting point. Appropriate use of this formulation will hopefully help mitigate the negative outcomes impacting patients with PH-ILD.

Rebecca Anna Gersten, MD
Adrian Shifren, MD
Steering Committee Members

NetWorks Challenge

Get active while funding CHEST Foundation microgrants

The NetWorks Challenge 2021 is kicking off in July with a 25k to celebrate the Foundation's 25th anniversary. This year, we're asking each NetWork to participate in a physical challenge, virtually. Make your way to 25k by walking, running, biking – or any activity that suits you.

Through the challenge, you can engage in friendly competition while supporting the goals of the Foundation. This year, money raised will directly help us in addressing health disparities through our microgrants program and will support travel grants for doctors-in-training looking to attend CHEST 2021.

With your help, by participating in the NetWorks Challenge, we can fund grants that aim to lend a hand to those who need it the most. Expanding research capabilities, improving patient care, and giving access to medical equipment are just a few ways microgrants from the CHEST Foundation have been used in the past.

Salim Surani, MD, MSc, FCCP, is a long-time supporter of the NetWorks Challenge and the Foundation's grants program. "Whatever the Foundation pays in terms of grants and awards not only impacts the recipient but also the community as a whole ... For me, it was a no-brainer to get involved in an organization that actually raises funding to support community, education, and research," Dr. Surani said.

With your support, during the NetWorks Challenge, we can provide grants to more clinicians looking to make a difference in chest medicine. Encourage your NetWork members to join you in the race to 25k.

"When you work within the NetWorks and join together, and work along with the CHEST Foundation, the impact is much more powerful. I always believed that it is a privilege for us that we have the outlet at the CHEST Foundation to provide grants," Dr. Surani said.

To learn more about this initiative and this year's NetWorks Challenge, visit the CHEST Foundation's website at https://foundation.chestnet.org/.

FROM THE BOARD OF REGENTS

In person board meetings resume – June 2021

BY DAVID A. SCHULMAN, MD, MPH, FCCP

The CHEST Board of Regents met in mid-June for its first in-person meeting in more than a year. It served as a lovely reminder that not only are in-person meetings a more effective way to conduct the business of the College, but that the members of the board have really missed seeing each other without an intervening screen and webcam.

First on the agenda was a recap by the CHEST Presidents of their recent strategic retreat. Most relevant to the organization was a recommendation that we revise the manner by which the CHEST strategic plan is set.

If the last year has taught us anything, it is that planning for the future is essential, but we must also allow for flexibility.

If the last year has taught us anything, it is that planning for the future is essential, but we must also allow for flexibility when external forces change what the future holds.

Accordingly, we will be replacing the former 5-year planning cycle with a more nimble annual review. From a member's standpoint, this means that you will see more frequent revisions of those plans (Strategic Plan, American College of Chest Physicians, https://www.chestnet.org/About/Overview/Strategic-Plan).

Over the last year, the CHEST Foundation has sponsored a series of "listening tours," which has allowed our members and leaders to hear from many of our patients who feel disenfranchised from the medical system because of struggles with communication, finances, and access, among other issues.

The willingness of our patients to share their struggles with us has inspired the Foundation to try to make inroads into these, better navigating these barriers.

In direct response to what we've heard, the team is designing programs to help our caregivers focus on the psychological, social, environmental, and personal factors that impact our patients' ability to obtain the critical health care that all need and deserve.

Our ability to execute and deliver such programs is contingent on successful fundraising efforts. Ian Nathanson, who is the President of the CHEST Foundation, reviewed fundraising progress with the board.

Over these long months, donors, participants, and friends of the Foundation have participated in virtual events that were designed to foster engagement as well as comradery through this difficult time.

This June, we held a virtual and in-person Belmont Stakes event that has shown that we can adapt to challenging times and that our membership is still incredibly supportive of the Foundation's mission.

Thank you to all of you who participated in or donated to the CHEST Foundation over the last year!

The last 18 months have had a marked impact on our ability to provide the live, interactive learning experiences for which CHEST is known, but all of the efforts in the remote learning space have yielded impressive increases in both the number of remote learning opportunities available and the breadth of our members who are taking advantage of them.

As one example, the number of CHEST podcast views quadrupled last year compared with those in 2019.

Although CHEST reopened its headquarters for live learning opportunities this summer, and we are looking to move significantly back toward "business as usual" with CHEST 2021 in Orlando this October, we will also be carefully considering how best to incorporate the lessons learned in the remote offering space as the world reopens in the coming year.

At the board meeting, Neil Freedman, who is the chair of CHEST's Health Advocacy and Policy Committee (HPAC), presented a review of the committee's accomplishments since its inception just over 1 year ago.

In addition to putting together a multi-society Technical Expert Panel on the use and coverage of noninvasive ventilation, HPAC worked with 18 other societies in drafting a response to the Agency for Healthcare Research and Quality's draft on coverage for CPAP therapy for obstructive sleep apnea.

For members who are interested in getting more involved in CHEST's advocacy efforts, we are seeking self-nominations for members of several working groups (nominations to open soon). In addition, there will be sessions offered during CHEST 2021 focused on our advocacy efforts and how you can participate in them, as well as best practices in the advocacy space.

For members who are interested in getting more involved in CHEST's advocacy efforts, we are seeking self-nominations for members of several working groups.

Several months ago, the Exeter Group was asked by the board to analyze how CHEST can expand our organizational efforts in diversity, equity, and inclusion (DEI). Representatives from the Exeter Group joined the meeting to provide board members with preliminary data.

Limited interviews with both members and staff have begun to provide a picture of where CHEST has already made some progress in this space, and where our ongoing challenges and opportunities for improvement still exist; it is clear that there is a wide range of opinions on these complicated issues.

As our consultants are only 1 month into this 6-month phase of the project, we expect a great deal more information to come, with a plan for ongoing surveys of and focus groups for our members; when you receive one of these requests, please make every effort to complete it as candidly as possible, regardless of your viewpoint.

The consulting work will culminate with a final presentation to the board just before the annual meeting in the fall, with specific recommendations on organizational actions that will be used to implement a multiyear DEI plan.

The Governance Committee, represented by Stephanie Levine, made several recommendations to revision of the CHEST Foundations bylaws.

Specifically, the new bylaws permit Trustees of the Foundation to be re-elected to positions on the board beyond the current 6-year maximum term after several years away from the position.

The position of President-Designate of the Foundation will also be eliminated, allowing for a 2-year term for the President-Elect of the Foundation and a 2-year term for the President of the Foundation.

One of the main challenges for an organization of 19,000 people is to ensure that we can engage as many of our members as possible. The NetWorks structure has historically been the primary mechanism for members to pursue initial leadership opportunities within the College.

CHEST Past-President Stephanie Levine previously established a working group to revisit NetWork structure in an effort to ensure ample opportunities for engagement within CHEST.

The final agenda item at this board meeting was a discussion about restructuring the CHEST NetWorks to create mechanisms that will help us balance the needs of the College with the energy of the volunteers to maximize productivity and engagement of all parties. The plan would increase the number of leadership positions available within the NetWork structure.

While the final nomenclature and distribution of NetWorks amongst the pillars has yet to be finalized, the board was supportive of this modification and expects implementation in the next 12 months, with details to be provided to the membership as they are fleshed out.

After a full day's agenda, CHEST President Steve Simpson adjourned the board meeting.

The Board of Regents will meet again remotely in August (the summer call has always been a remote meeting) and again in Orlando in October.

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SLEEP STRATEGIES

Updates on COVID-19 guidance for sleep medicine

BY IAN LEE, MD, AND SHANNON S. SULLIVAN, MD

Background

Well into its second year, the worldwide COVID-19 pandemic continues to pose substantial challenges for health care access and delivery. Regulatory agencies such as the Centers for Disease Control and Prevention (CDC) do not currently have guidance related to COVID-19 specific to sleep centers and laboratories. In March 2020, within days of the World Health Organization pandemic declaration, the American Academy of Sleep Medicine (AASM) posted detailed guidance on mitigation strategies for sleep medicine practices (COVID-19 Resources, available at aasm.org/covid-19-resources/).

This initial guidance has been previously reported in this publication (Sullivan S, Gurubhagavatula I. *CHEST Physician* 2020 May 8), and the guidance has been periodically updated during the pandemic. It was restructured in mid-2020 to include sections summarizing CDC recommendations germane for sleep practices; additional sleep medicine-specific guidance from the AASM COVID-19 Task Force (TF); and a frequently asked questions (FAQ) section. The last major update from the task force occurred on Jan. 18, 2021, though subsequent posts – especially related to recent CDC changes in masking guidelines – were made in May 2021. The purpose of this article is to summarize these updates and to call attention to areas of ongoing interest to sleep medicine. Notably, the AASM Task Force guidance is nonbinding and offered as a framework for considering best practices in this evolving situation, acknowledging the importance of weighing local factors, conditions, and regulations, as well as the interests of and risks to the patient, staff, and providers.

Key updates

Data on exposure and transmission risks specific to sleep medicine

Measures for reducing viral transmission have been central to managing the spread of the virus in clinical settings. In its last major update, the AASM TF noted that no known outbreaks of COVID-19 related to sleep center exposure have been reported. A perspective and data published in the *Journal of the American Medical Association* concluded that hospital transmission of the virus "in the setting of universal masking is likely rare, even during periods of high community prevalence." It also concluded that hospital-based outbreaks are more likely to occur in

Dr. Lee

Dr. Sullivan

small workrooms and during mealtime when staff are less adherent to masking and physical distancing (Richterman A, et al. *JAMA*. 2020;324[21]:2155-6). The TF elaborated on considerations to reduce transmission, which include not just telework and foundational infection control practices, but also broader workplace considerations such as optimizing ventilation, taking advantage of outdoor spaces (eg, for breaks and eating), scheduling to reduce interactions between personnel from different teams, minimizing contact in meeting/break rooms, removing tables and chairs from lounge areas, and following CDC guidance for effective facility operations.

Vaccination

In the January update, the AASM COVID-19 TF stated that, "sleep facility leaders should encourage staff and patients to be vaccinated in accordance with CDC guidance." The role of the sleep medicine community in encouraging healthy sleep habits before and after vaccination was emphasized, pointing to evidence linking sleep and immunity, specifically between sleep duration and vaccination response (Healthy sleep and immune response to COVID-19 vaccination. 2021 Jan. aasm.org/healthy-sleep-and-immune-response-to-covid-19-vaccination/).

In an FAQ update from March 26, 2021, considering whether continued COVID-19 testing was needed following full vaccination, the AASM advised testing prior to potential aerosol-generating procedures should be made on the basis of a risk-benefit assessment by the sleep clinician. Several considerations were highlighted, including recent COVID-19 infection, vaccination status of contacts, local prevalence of newer variants, and whether individuals are receiving positive airway pressure therapy. The TF focused on the vigilance for residents and staff in long-term care facilities, which have been associated with a number of outbreaks.

Masking in the context of the COVID-19 vaccine

The most significant change in recommendations is the recent relaxation of masking guidance by the CDC in the setting of the approval and distribution of COVID-19 vaccinations. In May, the CDC stated that fully vaccinated individuals can resume activities without masking or physically distancing except in scenarios of travel and where required by laws, regulations, and local businesses, due to the efficacy of the vaccines, increasing evidence of reduced asymptomatic carriage and transmission after vaccination, and anticipated increased uptake of vaccination. However, the CDC also noted that these updates did not apply to health care facilities, where the recommendation remains that patients and visitors should continue to mask throughout their stay. Additionally, fully vaccinated health care workers should continue to practice infection control measures while working with patients. On May 14, the AASM TF provided a detailed FAQ acknowledging the CDC's new guidance, emphasizing that masking guidance in health care facilities remains unchanged, and encouraging individuals to follow CDC guidance regarding vaccination, noting that emergence of newer variants continues to be monitored, and existing vaccines still appear to induce neutralizing antibodies even if to a somewhat lower degree. The situation for pediatric sleep centers has been highlighted in particular because the potential risk posed by newer variants to children remains under investigation, and children under age 12 are not approved for vaccination (COVID-19: FAQs for Sleep Clinicians. AASM. aasm.org/covid-19-resources/covid-19-faq/).

Important caveats to discussions around vaccination status are the lack of a centralized method to identify vaccinated individuals, the unknown duration of immunity, and reports of the use of fake vaccine cards. At this time, in health care settings, vaccination status should not exempt mask usage for any individual.

Sleep medicine care for those with COVID-19

Regarding the duration of isolation and precautions for adults with COVID-19, the TF highlighted the CDC's symptom-based strategy, rather than test-based strategy, for ending isolation of these patients, availing them of sleep medicine services in person.

In line with the CDC guidance, this approach indicates that scheduling in-person care such as polysomnography for a COVID-19–positive patient may be appropriate at least 10 days after symptom onset (or after a positive test if the patient never developed symptoms); or at least 20 days after symptom onset if the illness was severe; or if at least 90 days have elapsed since symptom onset, consider preappointment COVID-19 screening. In the context of immunocompromised individuals, involvement from infectious disease specialists may be needed to help guide decisions.

Patient communications

For many, a repercussion of the pandemic has been delaying care or avoiding addressing medical issues, including sleep disorders. The AASM encouraged practices to consider communicating with patients that delaying needed care can increase health risks; COVID-19 transmission to patients in health care settings has been low; effective safety procedures are in place; and whether remote/telehealth services are available.

Disparities in care

In addition to the specific guidance above, there are ongoing concerns regarding disparities in care resulting from a variety of sources and becoming more evident during the pandemic. Complex factors, ranging from economic, geographic, contextual, occupational, and others contribute to disparities that health care systems – and sleep medicine – have

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This month in the journal *CHEST*®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP
Editor in Chief

Hormone replacement therapy and development of new asthma.
By Dr. E. Hansen et al.

Sex and gender omic biomarkers in men and women with COPD: Considerations for precision medicine.
By Dr. D. Demeo.

Pulmonary function and radiological features in survivors of critical covid-19: A 3-month prospective cohort.
By Dr. F. Barbe et al.

Characteristics and prevalence of domestic and occupational inhalational exposures across interstitial lung diseases.
By Dr. C. Lee et al.

Identification and remediation of environmental exposures in patients with interstitial lung disease: Evidence review and practical considerations.
By Dr. M. Salisbury et al.

How we do it: Creating an organizational culture for the chest physician.
By Dr. J. Stoller et al.

Proposed quality metrics for lung cancer screening programs: A national lung cancer roundtable project.
By Dr. P. Mazzone et al.

Continued from previous page

not been able to adequately address (Jackson CL and Johnson DA. *J Clin Sleep Med*. 16[8]:1401-2). More specific differences may include internet access, reduced access due to socioeconomic barriers, transportation limitations, medical mistrust, and membership in a medically vulnerable group such as children, the elderly, and those with high acuity needs. For example, in pediatric patients there exist few evidence-based alternatives and guidelines to in-lab testing and care, which may have negatively impacted access to needed sleep medicine services (Sullivan S et al. *J Clin Sleep Med*. 2021 Mar 1;17[3]:361-2).

Economics in the COVID-19 pandemic

The economic effects of COVID-19 on medical institutions and in sleep medicine is a story that continues to unfold. Reductions in patient visits and elective procedures, infection control measures limiting capacity, increased costs to maintain such measures, and variability of responses by payer and region are just a few of the issues. The Centers for Medicare & Medicaid Services has employed waivers to increased flexibility and promote safe and effective care, including the use of telemedicine during the public health emergency, but the future of these waivers remains uncertain. Alarmingly, a sizeable portion of sleep practices reported financial solvency concerns related to the pandemic (Ramar K. *J Clin Sleep Med*. 2020;16[11]:1939-42).

Conclusion

As the COVID-19 pandemic and related public health guidance continues to evolve, sleep medicine practices continue to adapt. Vaccination, new variants, changes in mask guidance, new outbreaks around the globe, financial and staffing uncertainties, as well as addressing disparities in care and outcomes that may be augmented by the pandemic remain salient areas of ongoing development.

Dr. Lee is a Postdoctoral and Pediatric Pulmonary Fellow, Department of Pediatrics, Division of Pulmonary, Asthma, and Sleep Medicine, Stanford University School of Medicine; Dr. Sullivan is Clinical Professor, Department of Pediatrics, Division of Pulmonary, Asthma, and Sleep Medicine, and by courtesy, Division of Sleep Medicine, Department of Psychiatry, Stanford University School of Medicine, Palo Alto, CA.

Get ready for the FUN at CHEST Annual Meeting 2021 with CHEST games

This year's CHEST Annual Meeting will push the envelope of fun through various educational games and experiences for those attending on-site and online.

CHEST is supercharging the escape room experience with the expansion of two unique on-site escape scenarios to solve, First Contact and Shuttle Crash.

To build off the futuristic hands-on experiences, CHEST will be debuting intubation procedural simulations using state-of-the-art virtual reality technology.

In escape rooms, small teams work against the clock to solve a medical puzzle and unlock the final challenges. Those attending online can take a break and join the excitement with First Contact, a mission to Jupiter led by our space lieutenant, William Kelly, MD, FCCP, and faculty and staff game fleet.

To build off the futuristic hands-on experiences, CHEST will be debuting intubation procedural simulations using state-of-the-art virtual reality technology.

If you prefer to join the fun using your mobile device, CHEST is releasing daily task-based missions that you can track and complete using your phone.

These missions will include a variety of social activities designed around the conference halls, hotels, clinic, and your own home that are sure to get you moving and working as a team.

During the 4 days of the annual meeting, CHEST will also host an exclusive event called "Play With the Pros." You can test your knowledge and play alongside annual meeting cochairs, Chris Carroll, MD, FCCP, and David Zielinski, MD, FCCP, for the chance to win a grand prize. As an added bonus, CHEST is offering daily prize drawings for players and social media recognition to those who top the leaderboards in the CHEST Player Hub. The Player Hub hosts more than 10 bite-sized mobile games and is available on demand with your CHEST ID.

Additionally, live game breaks hosted by our faculty between education sessions will give you the chance to unwind and play in real time with your peers and colleagues.

On-site, CHEST invites you to shoot hoops, drive remote-controlled cars, and shuffle across the gameboard floors. From your couch or desk, you can tune in to test your knowledge in our livestreamed trivia or sign up for the chance to receive a trivia question phone call from our faculty, which is tied to a grand prize.

The opportunities to play and learn during CHEST Games are endless at CHEST 2021!

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Unlock fast, comprehensive results for critical patients with BioFire.

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1 Test. 33 Targets. ~1 Hour.

Overall 96.3% Sensitivity and 97.2% Specificity[2]

The BioFire PN Panel identifies the most common causes of lower respiratory tract infections by detecting 33 targets, including bacteria, viruses, and antimicrobial resistance genes.

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1. Novosad SA, Sapiano MR, Grigg C, et al. Vital Signs: Epidemiology of Sepsis: Prevalence of Health Care Factors and Opportunities for Prevention. MMWR Morb Mortal Wkly Rep 2016;65:864–869.
2. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Filmarray® Pneumonia (PN) Panel.
3. The stated performance is the aggregate of the prospective data from the clinical study for the BioFire® Blood Culture Identification 2 (BCID2) Panel.

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