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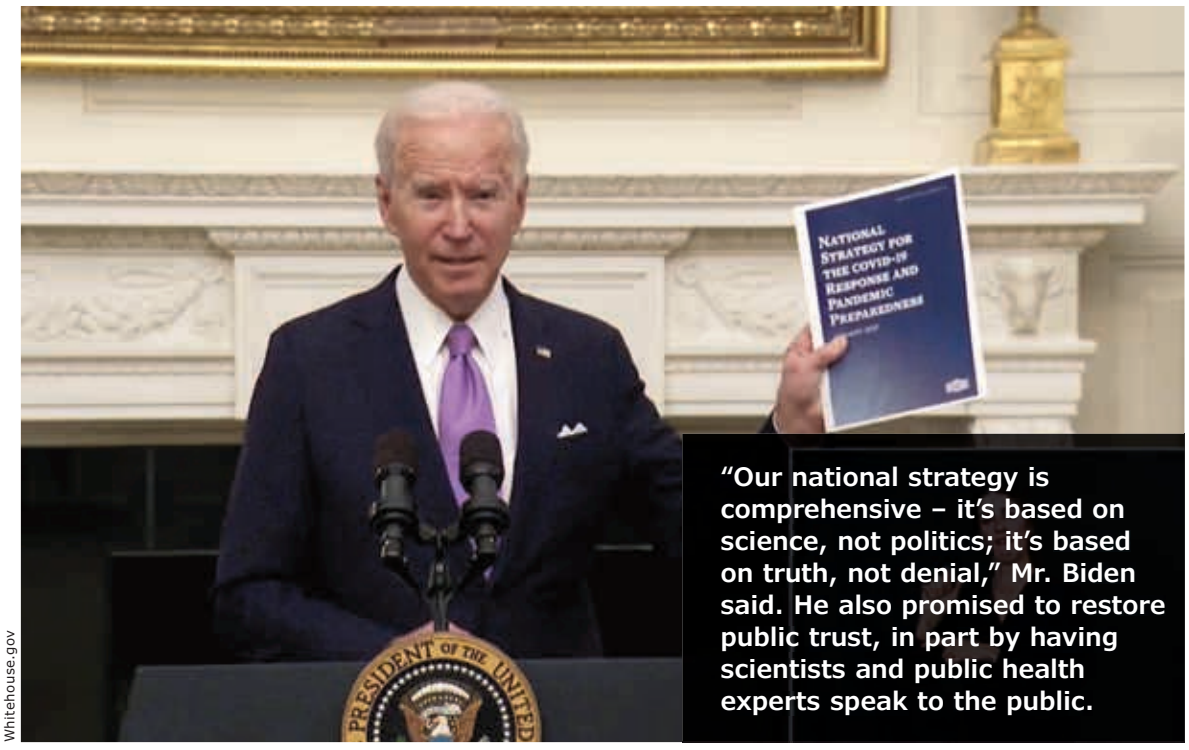

Whitehouse.gov

"Our national strategy is comprehensive – it's based on science, not politics; it's based on truth, not denial," Mr. Biden said. He also promised to restore public trust, in part by having scientists and public health experts speak to the public.

New administration, new strategy to fight COVID-19 pandemic

BY ALICIA AULT

President Biden signed 10 new executive orders on his second day in office that are designed to help roll out his broader plan to fight COVID-19.

"For the past year, we couldn't rely on the federal government to act with the urgency and focus and coordination we needed, and we have seen the tragic cost of that failure," Mr. Biden said in remarks from the White House, unveiling his 198-page National Strategy for the COVID-19 Response and Pandemic Preparedness.

He said in a press briefing on Jan. 21 that as many as 500,000 Americans will have died by February. "It's going to take months for us to turn things around," he said.

"Our national strategy is comprehensive – it's based on science, not politics; it's based on truth, not denial," Mr. Biden said. He also promised to restore public trust, in part by having scientists and public health experts speak to the public. "That's why you'll be hearing a lot more from Dr. Fauci again, not from the president," he said, adding that the experts will be "free from political interference."

While the president's executive orders can help accomplish some of the plan's proposals, the majority will require new funding from Congress and will be included in the $1.9 trillion Ameri-

STRATEGY // *continued on page 6*

Coronasomnia: Sleeplessness, self-medicating worry experts

BY NEIL OSTERWEIL
MDedge News

Among the many losses suffered by millions worldwide during the COVID-19 pandemic, the loss of sleep may be the most widespread, with potentially long-lasting, negative consequences on physical, mental, and emotional health, sleep researchers have found.

Results from multiple studies and surveys conducted during the pandemic show that a majority of subjects report clinically meaningful changes in sleep quality, sleep patterns, and sleep disturbances, a condition dubbed "coronasomnia."

For example, a cross-sectional international survey conducted from late March through late April 2020 found that, among more than 3,000 responders from 49 countries, 58% reported dissatisfaction with their sleep, and 40% reported a decrease in sleep quality during the pandemic, compared with pre–COVID-19 sleep, according to Uri Mandelkorn of the Natural Sleep Clinic in Jerusalem, and colleagues.

"In particular, this research raises the need to screen for worsening sleep patterns and use of

SELF-MEDICATION // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Pulmonary Perspectives®

Bronchiolitis: Rare diseases, diagnostic challenges, and few proven therapies

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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

Anaphylaxis after COVID-19 vaccine rare but rising

BY KERRY DOOLEY YOUNG

Health care providers should be ready to treat rare cases of anaphylaxis following administration of COVID-19 vaccines, federal medical officials have urged. The officials also stressed the importance of continuing vaccinations, despite reports of the rare side effect.

There have been 29 cases of anaphylaxis to date following administration of a COVID-19 vaccine, officials from the Centers for Disease Control and Prevention said in a call with reporters on Jan. 6.

The severe allergic reaction, which appears to be rare, can happen with either the Pfizer-BioNTech vaccine or the rival Moderna product. The Food and Drug Administration granted emergency-use authorizations for these two vaccines in December 2020.

Even with the cases seen to date, the COVID-19 vaccines remain a "good value proposition," Nancy Messonnier, MD, director of the CDC's National Center for Immunization, said in the call.

There have been about 11.1 cases of anaphylaxis per million doses with the Pfizer-BioNTech COVID-19 vaccine, which is higher than the estimated 1.3 cases per million doses with influenza vaccines, she said. But she said the low risk of anaphylaxis must be balanced against the threat of COVID-19, which currently claims about 3,000 lives a day in the United States. In addition, many people are reporting long-term complications with COVID-19 even if they recover.

Kept in context, the data on anaphylaxis should not scare people away from getting a COVID-19 vaccine, she added.

"Their risk from COVID and poor outcomes is still more than the risk of a severe outcome from the vaccine," Dr. Messonnier said. "And fortunately, we know how to treat anaphylaxis."

ROBEO/THINKSTOCK

"Anybody administering vaccines needs not just to have the EpiPen available, but frankly, to know how to use it."

Dr. Messonnier urged health care workers administering COVID-19 vaccines to be prepared.

"Anybody administering vaccines needs not just to have the EpiPen available, but frankly, to know how to use it," Dr. Messonnier said.

MMWR details

The CDC on Jan. 6 also provided an update on anaphylaxis in Morbidity and Mortality Weekly Report.

The information included in the report was based on cases reported with the Pfizer-BioNTech vaccine – the first to get emergency-use authorization from the FDA. On the call with reporters, CDC officials confirmed there have been additional reports since then and anaphylaxis has been reported with both the Pfizer-BioNTech and Moderna vaccines. CDC officials said they could not give a breakdown of how many cases were linked to each of these products at this time.

Between Dec. 14 and 23, 2020, monitoring by the Vaccine Adverse Event Reporting System detected 21 cases of anaphylaxis after administration of a reported 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine. Most reactions – 71% – occurred within 15 minutes of vaccination.

A version of this article originally appeared on Medscape.com.

Coordinated strategy expected // continued from page 1

can Rescue package that Mr. Biden hopes legislators will approve.

Ten new orders

The 10 new pandemic-related orders Mr. Biden signed on Jan. 21 follow 2 he signed on his first day in office.

One establishes a COVID-19 Response Office responsible for coordinating the pandemic response across all federal departments and agencies and also reestablishes the White House Directorate on Global Health Security and Biodefense, which was disabled by the Trump administration.

The other order requires masks and physical distancing in all federal buildings, on all federal lands, and by federal employees and contractors.

Among the new orders will be directives that:

- Require individuals to also wear masks in airports and planes, and when using other modes of public transportation including trains, boats, and intercity buses, and also require international travelers to produce proof of a recent negative COVID-19 test prior to entry and to quarantine after entry.
- Direct federal agencies to use all powers, including the Defense Production Act, to accelerate manufacturing and delivery of supplies such as N95 masks, gowns, gloves, swabs, reagents, pipette tips, rapid test kits, and nitrocellulose material for rapid antigen tests, and all equipment and material needed to accelerate manufacture, delivery, and administration of COVID-19 vaccine.
- Create a Pandemic Testing Board to expand supply and access, to promote more surge capacity, and to ensure equitable access to tests.
- Facilitate discovery, development, and trials of potential COVID-19 treatments, as well as expand access to programs that can meet the long-term health needs of those recovering from the disease.
- Facilitate more and better data sharing that will allow businesses, schools, hospitals, and individuals to make real-time decisions based on spread in their community.
- Direct the Education and Health & Human Services departments to provide schools and child-care operations guidance on how to reopen and operate safely.
- Direct the Occupational Safety and Health Administration to immediately release clear guidance for employers to keep workers safe and to enforce health and safety requirements.

The plan also sets goals for vaccination – including 100 million shots in the administration's first 100 days. President Biden had already previewed his goals for vaccination, including setting up mass vaccination sites and mobile vaccination sites. During his remarks, Mr. Biden said that he had already directed the Federal Emergency Management Agency to begin setting up the vaccination centers.

The administration is also going to look into improving reimbursement for giving vaccines. As a start, the HHS will ask the Centers for Medicare & Medicaid Services to consider if a higher rate "may more accurately compensate providers," according to the Biden plan.

"But the brutal truth is it will take months before we can get the majority of Americans vaccinated," said Mr. Biden.

As part of the goal of ensuring an equitable pandemic response, the president will sign an order that establishes a COVID-19 Health Equity Task Force. The task force is charged with providing recommendations for allocating resources and funding in communities with inequities in COVID-19 outcomes by race, ethnicity, geography, disability, and other considerations.

Finally, the administration has committed to being more transparent and sharing more information. The national plan calls for the federal government to conduct regular, expert-led, science-based public briefings and to release regular reports on the pandemic. The administration said it will launch massive science-based public information campaigns – in multiple languages – to educate Americans on masks, testing, and vaccines, and also work to counter misinformation and disinformation.

The American Academy of Family Physicians applauded Mr. Biden's initiative. "If enacted, this bold legislative agenda will provide much-needed support to American families struggling during the pandemic – especially communities of color and those hardest hit by the virus," Ada D. Stewart, MD, AAFP president, said in a statement.

Dr. Stewart also noted that family physicians "are uniquely positioned in their communities to educate patients, prioritize access, and coordinate administration of the COVID-19 vaccines," and urged the administration to ensure that family physicians and staff be vaccinated as soon as possible, to help them "more safely provide care to their communities."

A version of this article originally appeared on Medscape.com.

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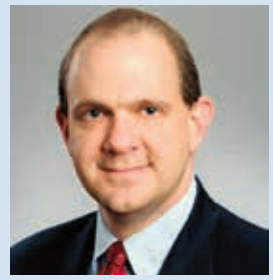

David A. Schulman, MD, FCCP, is Editor in Chief of *CHEST Physician*.

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Self-medicating can lead to longer-term sleep problems // continued from page 1

sleeping aids in the more susceptible populations identified in this study, namely, women and people with insecure livelihoods or those subjected to strict quarantine. Health care providers should pay special attention to physical and psychological problems that this surge in sleep disturbances may cause," they wrote. The report is in the Journal of Clinical Sleep Medicine (2021;17[1]:45-53).

Sleeping, more or less

A coauthor of that study, David Gozal, MD, FCCP, a pediatric pulmonologist and sleep medicine specialist at the University of Missouri in Columbia, said that the pandemic has had paradoxical effects on sleeps patterns for many.

"At the beginning, with the initial phases of lockdown for COVID, for most of the people whose jobs were not affected and who did not lose their jobs, [for whom] there was not the anxiety of being jobless and financially strapped, but who now were staying at home, there was actually a benefit. People started reporting getting more sleep and, more importantly, more vivid dreams and things of that nature," he said in an interview.

"But as the lockdown progressed, we saw progressively and increasingly more people having difficulty falling asleep and staying asleep, using more medicines such as hypnotics to induce sleep, and we saw a 20% increase in the overall consumption of sleeping pills," he said.

Similar results were seen in a cross-sectional survey of 843 adults in the United Kingdom, which showed that nearly 70% of participants reported a change in sleep patterns, only 45% reported having refreshing sleep, and 46% reported being sleepier during lockdown than before. Two-thirds of the respondents reported that the pandemic affected their mental health, and one-fourth reported increased alcohol consumption during lockdown. Those with suspected COVID-19 infections reported having more nightmares and abnormal sleep rhythms (J Thorac Dis. 2020;12[Suppl 2]:S163-75).

It is possible that the effects of COVID-19 infection on sleep may linger long after the infection itself has resolved, results of a cohort study from China suggest. As reported in The Lancet (2021 Jan 8. doi: 10.1016/S0140-6736[20]32656-8), among 1,655 patients discharged from the Jin Yin-tan Hospital in Wuhan, China, 26% reported sleep disturbances 6 months after acute COVID-19 infection.

Self-medicating

Among 5,525 Canadians surveyed from April 3 through June 24, 2020, a large proportion reported the use of pharmacologic sleeps aids (J Sleep Res. 2020 Nov 17. doi: 10.1111/jsr.13231), said Tetyana Kendzerska, MD, PhD, assistant professor of medicine in the division of respirology at the University of Ottawa.

"At the time of the survey completion, 27% of participants reported taking sleeping aids (prescribed or [over] the counter); across the entire sample, 8% of respondents reported an increase in the frequency of sleeping medication use during the outbreak compared to before the outbreak," she said in an interview.

Many people resort to self-medicating with over-the-counter preparations such as melatonin and pain-relief nighttime formulations containing diphenhydramine (Benadryl), a first-generation antihistamine with sedative properties, noted Kannan Ramar, MBBS, MD, a critical care, pulmonary, and sleep medicine specialist at the Mayo Clinic in Rochester, Minn., and current president of the American Academy of Sleep Medicine.

KLEBERCORDEIRO/GETTY IMAGES

"There may be an increase in individuals who may require professional guidance to taper off from sleeping medications started or increased during the pandemic. While some of these sleep problems may be transient, it should be a high priority to ensure they do not evolve into chronic sleep disorders."

"When people are self-medicating for what they think is difficulty sleeping, the concern is that even if a diagnosis of insomnia has been established, there could be another, ongoing sleep disorder that may be undiagnosed, which might be causing the problem with insomnia," he said in an interview.

Causing concern

"For those people who have COVID, we have seen quite a few sleep issues develop. Those were not reported in the actual study, but in the clinic and subsequent studies published from other places," Dr. Gozal said.

"People who suffered from COVID, and even people who supposedly did very well and were virtually asymptomatic or maybe had only a headache or fever but did not need to go to the hospital, many of those people reported either excessive sleepiness for a long period of time, and would sleep 2 or 3 hours more per night. Or the opposite was reported: There were those that after recovering reported that they couldn't sleep – they were sleeping 4 or 5 hours when they normally sleep 7 or 8," he said.

It's also unclear from current evidence whether the reported uptick in sleep problems is related to stress or, in patients who have had COVID-19 infections, to physiologic causes.

Dr. Gozal said that insomnia in the time of COVID-19 could be attributed to a number of factors such as less daily exposure to natural light from people sheltering indoors, stress related to financial or health worries, depression, or other psychological factors. It's also, possible, however, that COVID-19–related physiological changes could contribute to sleep disorders, he said, pointing to a recent study in the Journal of Experimental Medicine (2021;218 [3]: e20202135) showing that SARS-CoV-2, the virus that causes COVID-19, can bind to neurons and cause metabolic changes in both infected and neighboring cells.

"It could be that in some instances – not very commonly – the virus will affect areas that control sleep in our brain, and that therefore we may see too much or too little sleep, and how to differentiate between all of these is the area that clearly needs to be explored, particularly in light of the finding that the virus can bind to brain cells and can induce substantial issues in the brain cells."

Affecting immunity

It has been well documented that, in addition to being, as Shakespeare called it, "the balm of hurt minds," sleep has an important role in supporting the immune system.

"Sleep and immunity go together," Dr. Ramar said. "When people have adequate sleep, their immune system is boosted. We know that there are good data from hepatitis A and hepatitis B vaccinations, and recently on flu vaccination, that if people get sufficient duration of sleep before and after they receive the shot, their likelihood of building an immune response to that particular vaccination tends to go up."

Dr. Kendzerska said, "In our study, we did find that, among other factors, having a chronic illness was associated with new sleep difficulties during the pandemic. We did not look separately if sleep difficulties were associated with the COVID-19 infection or symptoms, but this is a great question to address with longitudinal data we have."

Mitigating coronasomnia

All three sleep experts contacted for this article agreed that, for patients with insomnia, mitigating stress through relaxation techniques or cognitive-behavioral therapy is more beneficial than medication.

"Medications, even over-the-counter medications, all have side effects, and if one is taking a medication that has stimulants in place, such as pseudoephedrine in antihistamine combinations, that can potentially contribute to or exacerbate any underlying sleep disorders," Dr. Ramar said.

Dr. Kendzerska recommended reserving medications such as melatonin, a chronobiotic therapy, for patients with sleep disorders related to circadian rhythm problems, including a sleep phase delay. Supplemental, short-term treatment with hypnotic agents such as zolpidem (Ambien), eszopiclone (Lunesta), or zaleplon (Sonata) should be used only as a last resort, she said.

Sleep medicine specialists recommend good sleep hygiene as the best means of obtaining restful sleep, including regular bed and wake times, limited exposure to stressful news (including COVID-19 stories), reduced consumption of alcohol and stimulants such as coffee or caffeine drinks, limited use of electronic devices in bed or near bedtime, and healthy lifestyle, including diet and exercise.

"It is also foreseeable that there may be an increase in individuals who may require professional guidance to taper off from sleeping medications started or increased during the pandemic. While some of these sleep problems may be transient, it should be a high priority to ensure they do not evolve into chronic sleep disorders," Dr. Kendzerska and colleagues wrote.

chestphysiciannews@chestnet.org

ACC guidance embraces new heart failure strategies

BY TED BOSWORTH
MDedge News

The newly updated expert consensus from the American College of Cardiology for management of heart failure with reduced ejection fraction includes several new guideline-directed medical therapies among other substantial changes relative to its 2017 predecessor.

The advances in treatment of heart failure with reduced ejection fraction (HFrEF, left ventricular ejection fraction </= 40%) have resulted in a substantial increase in complexity in reaching treatment goals, according to the authors of the new guidance. Structured similarly to the 2017 ACC Expert Consensus Decision Pathway (J Am Coll Cardiol. 2018;71:201-30), the update accommodates a series of practical tips to bring all patients on board with the newer as well as the established therapies with lifesaving potential.


Dr. Fonarow


Dr. Maddox

The potential return from implementing these recommendations is not trivial. Relative to an ACE inhibitor and a beta-blocker alone, optimal implementation of the current guideline-directed medical therapies (GDMT) "can extend medical survival by more than 6 years," according to Gregg C. Fonarow, MD, chief of cardiology at the University of California, Los Angeles.

A member of the writing committee for the 2021 update, Dr. Fonarow explained that the consensus pathway is more than a list of therapies and recommended doses. The detailed advice on how to overcome the barriers to GDMT is meant to close the substantial gap between current practice and unmet opportunities for inhibiting HFrEF progression.

"Optimal GDMT among HFrEF patients is distressingly low, due in part to the number and complexity of medications that now constitute GDMT," said the chair of the writing committee, Thomas M. Maddox, MD, executive director, Healthcare Innovation Lab, BJC HealthCare/Washington University, St. Louis. Like Dr. Fonarow, Dr. Maddox emphasized that the importance of the update for the practical strategies it offers to place patients on optimal care.

In the 2017 guidance, 10 pivotal issues were tackled, ranging from advice of how to put HFrEF patients on the multiple drugs that now constitute optimal therapy to when to transition patients to hospice care. The 2021 update covers the same ground but incorporates new information that has changed the definition of optimal care.

Perhaps most importantly, sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNi), and sodium-glucose transporter 2 (SGLT2) inhibitors represent major new additions in HFrEF GDMT. Dr. Maddox called the practical information about how these should be incorporated into HFrEF management represents one of the "major highlights" of the update.

Two algorithms outline the expert consensus recommendations of the order and the dose of the multiple drugs that now constitute the current GDMT. With the goal of explaining exactly how to place patients on all the HFrEF therapies associated with improved outcome, "I think these figures can really help us in guiding our patients to optimal medication regimens and dosages," Dr. Maddox said. If successful, clinicians "can make a significant difference in these patients' length and quality of life."

Most cardiologists and others who treat HFrEF are likely aware of the major improvements in outcome documented in large trials when an ARNi and a SGLT2 inhibitor were added to previously established GDMT, but the update like the 2017 document is focused on the practical strategies of implementation, according to Larry A. Allen, MD, medical director of advanced heart failure at the University of Colorado at Denver, Aurora.

"The 2017 Expert Consensus Decision Pathway got a lot of attention because it takes a very practical approach to questions that clinicians and their patients have to tackle everyday but for which there was not always clean answers from the data," said Dr. Allen, a member of the writing committee for both the 2017 expert consensus and the 2021 update. He noted that the earlier document was one of the most downloaded articles from the ACC's journal in the year it appeared.

"There is excellent data on the benefits of beta-blockers, ARNi, mineralocorticoid antagonists, and SGLT2 inhibitors, but how does one decide what order to use them in?" Dr. Allen asked in outlining goals of the expert consensus.

chestphysiciannews@chestnet.org

SOURCE: Maddox TM et al. J Am Coll Cardiol. 2021 Jan 11. doi: 10.1016/j.jacc.2020.11.022.

VIEW ON THE NEWS

Jonathan Ludmir, MD, comments: The ACC 2021 Expert Consensus Decision Pathway successfully and succinctly highlights all of the key features of how to successfully provide comprehensive GDMT for HFrEF patients. In addition to optimizing GDMT, early referral to heart failure specialists and consideration of advanced therapies are critical. I hope initiation of GDMT will not be delayed. Physicians should feel empowered to initiate GDMT in HFrEF patients in order to avoid care delays. I hope it can be effectively distributed and implemented by all health care providers managing heart failure patients.

Fatigue, insomnia plague survivors of severe COVID-19

BY RICHARD FRANKI
MDedge News

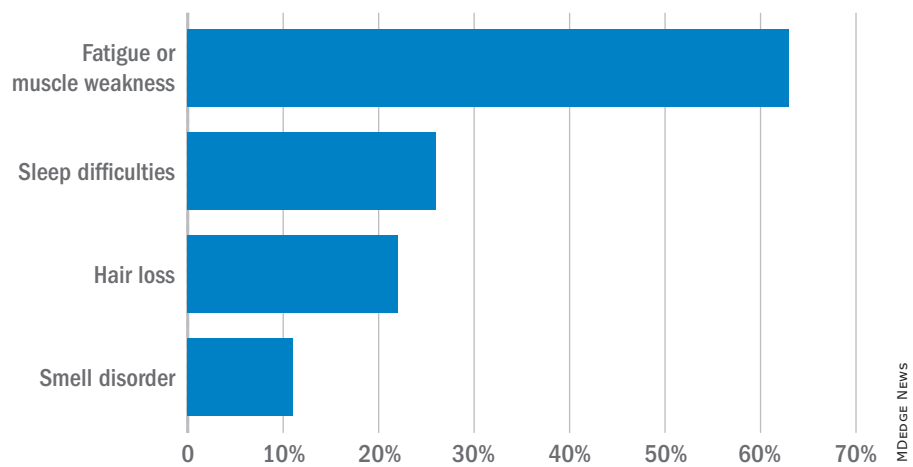
Three-quarters of patients hospitalized with COVID-19 were still experiencing at least one symptom of the infection 6 months after being discharged, according to a follow-up study involving 1,733 patients.

"Patients with COVID-19 had symptoms of fatigue or muscle weakness, sleep difficulties, and anxiety or depression," and those with "more severe illness during their hospital stay had increasingly impaired pulmonary diffusion capacities and abnormal chest imaging manifestations," Chaolin Huang, MD, of Jin Yin-tan Hospital in Wuhan, China, and associates wrote in The Lancet (2021 Jan 8. doi: 10.1016/S0140-6736[20]32656-8).

Fatigue or muscle weakness, reported by 63% of patients, was the most common symptom, followed by sleep difficulties, hair loss, and smell disorder. Altogether, 76% of those examined 6 months after discharge from Jin Yin-tan Hospital – the first designated for patients with COVID-19 in Wuhan – reported at least one symptom, they said. Symptoms were more common in women than men: 81% vs. 73% had at least one symptom, and 66% vs. 59% had fatigue or muscle weakness, the investigators said.

rfranki@mdedge.com

Symptoms persisting 6 months after severe COVID-19 infection



Note: Based on follow-up data for 1,733 patients discharged from Jin Yin-tan Hospital in Wuhan, China, between Jan. 7 and May 29, 2020.

Source: Lancet 2021 Jan 8. doi: 10.1016/S0140-6736(20)32656-8

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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.

BFR0001-0716-01

Screening paused during pandemic concerns

BY JIM KLING
MDedge News

FROM THE JOURNAL *CHEST*® ▪ The COVID-19 pandemic led to a drastic reduction in lung cancer screening, but the rate of decline was similar between Whites and non-Whites and between rural and nonrural populations. All groups saw their rates of lung cancer screening (LCS) return to near prepandemic levels by June 2020, according to a new analysis of two academic and two community imaging sites in North Carolina.

The study was led by Louise Henderson, PhD, of the Lineberger Comprehensive Cancer Center, and M. Patricia Rivera, MD, FCCP, of the department of medicine, division of pulmonary disease and critical care medicine, both at the University of North Carolina at Chapel Hill. The findings appeared online in Chest (2021 Jan 5. doi: 10.1016/j.chest.2020.12.033).

"I am [not] surprised by the decline, but I am certainly reassured," Abbie Begnaud, MD, FCCP, said in an interview. Dr. Begnaud is assistant professor of medicine at the University of Minnesota, Minneapolis. She was not involved in the study.

Dr. Begnaud said that the findings were similar to what she has seen at her own institution. Although the rebound in screening was good to see, it nevertheless suggests that screening is still lagging. "During the ramp-up period, they got back to nearly prepandemic levels, but you might have liked to see that the numbers were even higher. In theory, if you had several months of people who should have been getting screened who didn't, if they were all getting caught up, you might have seen higher numbers after that," said Dr. Begnaud.


Dr. Begnaud

The current winter surge in cases is likely to have long-lasting impact on lung cancer screening as well. Although she hasn't seen a similar decline yet, Dr. Begnaud expects it's coming. "I think we'll see a major decline even throughout this year in screening until we are squarely out of the pandemic." Things could be particularly challenging for resource-poor settings. "If physical resources (CT scanners) and human resources (techs, radiologists, primary care providers) are overworked, they may not have the bandwidth for 'elective' and preventive care," said Dr. Begnaud.

Two previous studies looked at changes in lung cancer screening after the onset of the pandemic, but neither examined patient characteristics or risk factors. The current study included 3,688 screening exams (52.3% first-time exams), and divided them up into the pre-COVID-19 era (Jan. 1 to March 2, 2019), the beginning of the pandemic (March 3 to March 29, 2020), the shutdown period (March 30 to May 21, 2020) and the ramp-up period (May 22 to Sept. 30, 2020).

The largest reduction of screening volume occurred during the beginning of the pandemic, at –33.6% (95% confidence interval, –11.9% to –55.3%). By June, the reduction in volume was –9.1%, compared with pre-COVID-19 levels (95% CI, –4.7% to –23.0%). In the period between June and September 2020, the overall rate was similar to pre-COVID-19 levels (–15.3% change; 95% CI, –7.8% to 38.4%).

The researchers found no differences in screening changes among patient groups based on age, sex, race, smoking status, body mass index, COPD status, hypertension, or patient residence. The proportion of exams that were first-time screens was highest before the pandemic (53.8%), and declined at the beginning of the pandemic (50.7%), during shutdown (49.7%), and during the ramp-up period (48.6%). The difference between the prepandemic and ramp-up period in terms of first-time screens was statistically significant ($P = .0072$).

The investigators offered a couple of caveats: "Our results do not demonstrate differences in LCS volumes pre- versus during COVID among non-White patients or rural patients, both of which have persistently experienced disparities in lung cancer outcomes and other cancer screening modalities. Additionally, our results do not suggest that patients at high risk of COVID

Continued on following page

NSCLC deaths continue to drop, driving down national cancer mortality rates

BY PAM HARRISON

For the second year in a row, mortality from cancer has fallen in the United States, driven largely by reductions in the incidence of, and death from, non–small cell lung cancer (NSCLC) in men and women, according to a new report from the American Cancer Society.

The study was published online Jan. 12 in CA: A Cancer Journal for Clinicians (doi: 10.3322/caac.21654).

"Mortality rates are a better indicator of progress against cancer than incidence or survival because they are less affected by biases resulting from changes in detection practices," wrote the authors, led by Rebecca Siegel, MPH, American Cancer Society, Atlanta.

"The overall drop of 31% as of 2018 [since the early 1990s] translates to an estimated 3,188,500 fewer cancer deaths (2,170,700 in men and 1,017,800 in women) than what would have occurred if mortality rates had remained at their peak," the researchers added.

Lung cancer accounted for 46% of the total decline in cancer mortality in the past 5 years, with a record, single-year drop of 2.4% between 2017 and 2018.

The recent and rapid reductions in lung cancer mortality reflect better treatments for NSCLC, the authors suggested. For example, survival rates at 2 years have increased from 34% for patients diagnosed with NSCLC between 2009 and 2010 to 42% for those diagnosed during 2015 and 2016 – an absolute gain of 5%-6% in survival odds for every stage of diagnosis.

On a more somber note, the authors warned that COVID-19 is predicted to have a negative impact on both the diagnosis and outcomes of patients with cancer in the near future.

"We anticipate that disruptions in access to cancer care in 2020 will lead to downstream increases in advanced stage diagnoses that may impede progress in reducing cancer mortality rates in the years to come," Ms. Siegel said in a statement.

New cancer cases

The report provides an estimated number of new cancer cases and deaths in 2021 in the United States (nationally and state-by-state) based on the most current population-based data for cancer incidence through 2017 and for mortality through 2018. "An estimated 608,570 Americans will die from cancer in 2021, corresponding to more than 1600 deaths per day," Ms. Siegel and colleagues reported.

The greatest number of deaths are predicted to be from the most common cancers: Lung, prostate, and colorectal cancer in men and lung, breast, and colorectal cancer in women, they added. However, the mortality rates for all four cancers are continuing to fall.

Survival rates at 2 years have increased from 34% for patients diagnosed with NSCLC between 2009 and 2010 to 42% for those diagnosed during 2015 and 2016.

As of 2018, the death rate from lung cancer had dropped by 54% among males and by 30% among females over the past few decades, the investigators noted.

Mortality from female breast cancer has dropped by 41% since 1989; by 52% for prostate cancer since 1993; and by 53% and 59% for colorectal cancer for men (since 1980) and women (since 1969), respectively.

"However, in recent years, mortality declines have slowed for breast cancer and [colorectal cancer] and have halted for prostate cancer," the researchers noted.

In contrast, the pace of the annual decline in lung cancer mortality doubled among men from 3.1% between 2009 and 2013 to 5.5% between 2014 and 2018, and from 1.8% to 4.4% among women during the same time intervals.

Increase in incidence at common sites

Despite the steady progress in mortality for most cancers, "rates continue to increase for some common sites," Ms. Siegel and colleagues reported.

For example, death rates from uterine corpus cancer have accelerated from the late 1990s at twice the pace of the increase in its incidence. Death rates also have increased for cancers of the oral cavity and pharynx – although in this cancer, increases in mortality parallel an increase in its incidence.

"Pancreatic cancer death rates [in turn] continued to increase slowly in men ... but remained stable in women, despite incidence [rates] rising by about 1% per year in both sexes," the authors observed.

Meanwhile, the incidence of cervical cancer, although declining for decades overall, is increasing for patients who present with more distant-stage disease as well as cervical adenocarcinoma, both of which are often undetected by cytology.

"These findings underscore the need for more targeted efforts to increase both HPV [human papillomavirus] vaccination among all individuals aged [26 and younger] and primary HPV testing or HPV/cytology co-testing every 5 years among women beginning at age 25," the authors emphasized.

On a more positive note, the long-term increase in mortality from liver cancer has recently slowed among women and has stabilized among men, they added.

Once again, disparities in both cancer occurrence and outcomes varied considerably between racial and ethnic groups. For example, cancer is the leading cause of death in people who are Hispanic, Asian American, and Alaska Native. Survival rates at 5 years for almost all cancers are still higher for White patients than for Black patients, although the disparity in cancer mortality between Black persons and White persons has declined to 13% from a peak of 33% in 1993.

Geographic disparities in cancer mortality rates still prevail; the rates are largest for preventable cancers such as lung and cervical cancer, for which mortality varies by as much as fivefold across states.

And although cancer remains the second most common cause of death among children, death rates from cancer have continuously declined over time among both children and adolescents, largely the result of dramatic declines in death rates from leukemia in both age groups.

The study authors have disclosed no relevant financial relationships.

A version of this article originally appeared on Medscape.com.

Continued from previous page

complications (i.e., patients who are obese, have COPD or hypertension) were less likely to undergo LCS." The study demonstrated, rather, that a similar impact of the COVID-19 crisis on lung cancer screening was felt across all patient subgroups.

The study was funded by The National Cancer Institute. Dr. Rivera served as an advisory board member for Biodesix and bioAffinity Technologies, and served on an advisory research panel for Johnson & Johnson. Dr. Begnaud has no relevant financial disclosures.

chestphysiciannews@chestnet.org

This month in the journal *CHEST*®

Editor's picks

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

How I Do It

How I Do It: Approach to Eosinophilia Presenting with Pulmonary Symptoms. *By Dr. P. Khoury.*

Original Research

The COVID-19 Pandemic's Impact on Critical Care Resources and Providers: A Global Survey. *By Dr. S. Wahlster, et al.*

Effectiveness of Proton Pump Inhibitors in Idiopathic Pulmonary Fibrosis: A Population-Based Cohort Study. *By Dr. S. Suissa, et al.*

Research Letter

COVID-19 Acute Myocarditis and Multisystem Inflammatory Syndrome in Adult Intensive and Cardiac Care Units. *By Dr. G. Hékimian et al.*

Guidelines and Consensus Statements

Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjögren's. *By Dr. K. Hammitt, et al.*

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

RELEASE THE POWER OF PROTECTION WITH BREZTRI[1]

In Study 1 (52 weeks), BREZTRI significantly reduced the annual rate of moderate or severe exacerbations by 24% vs LAMA/LABA (rate ratio=0.76; 95% CI: 0.69, 0.83; *P*<0.0001) and 13% vs ICS/LABA (rate ratio=0.87; 95% CI: 0.79, 0.95; *P*=0.0027).[1]*

Annual rate estimate: BREZTRI 1.08 (n=2137); LAMA/LABA 1.42 (n=2120); ICS/LABA 1.24 (n=2131).[1]

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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.

*Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in hospitalization or death.

Study 1 was a 52-week, Phase 3, randomized, double-blind, parallel-group, multicenter study of 8588 patients with moderate to very severe COPD that compared BREZTRI MDI 320/18/9.6 (n=2157) with budesonide/glycopyrrolate/formoterol fumarate MDI 160/18/9.6 (n=2137), glycopyrrolate/formoterol fumarate MDI 18/9.6 (n=2143), and budesonide/formoterol fumarate MDI 320/9.6 (n=2151), each administered as 2 inhalations twice daily. Patients were current or former smokers with a smoking history of ≥10 pack-years, aged 40-80 years, with symptomatic COPD despite receiving 2 or more inhaled maintenance therapies, and a history of ≥1 moderate or severe exacerbation(s) in the previous year. The primary endpoint was the estimated annual rate of moderate or severe COPD exacerbations.[1]

BREZTRI is administered as 2 inhalations twice daily.

Reference: 1. BREZTRI AEROSPHERE [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

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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In case you missed it: CHEST 2020 Award Recipients

ANNUAL AWARDS

Master FCCP
Nancy A. Collop MD, Master FCCP

College Medalist Award
Neil R. MacIntyre, MD, FCCP

Distinguished Service Award
Lisa K. Moores, MD, FCCP

Master Clinician Educator
William F. Kelly, MD, FCCP
David A. Schulman, MD, MPH, FCCP

Early Career Clinician Educator
Subani Chandra, MD, FCCP

Alfred Soffer Award for Editorial Excellence
Barbara Anderson, CHEST Staff
Laura Lipsey, CHEST Staff

Presidential Citation
Mangala Narasimhan, DO, FCCP
Renli Qiao, MD, PhD, FCCP

HONOR LECTURE AND MEMORIAL AWARDS

Edward C. Rosenow III, MD, Master FCCP/Master Teacher Endowed Honor Lecture
Evolving Therapies in ANCA-Associated Vasculitides
Joseph P. Lynch, III, MD, FCCP
The lecture is generously funded by the CHEST Foundation.

Distinguished Scientist Honor Lecture in Cardiopulmonary Physiology
Helping the Dyspneic Patient: Clinical Physiology Matters!
Denis E. O'Donnell, MD, MBBCh, FCCP
The lecture is generously funded by the CHEST Foundation.

Presidential Honor Lecture
COPD Management: We've Come So Far
Darcy D. Marciniuk, MD, Master FCCP

Thomas L. Petty, MD, Master FCCP Memorial Lecture
Real World Research - What Would Dr. Petty Say?
Mary Hart, RRT, MS, FCCP
The lecture is generously funded by the CHEST Foundation.

Margaret Pfrommer Endowed Memorial Lecture in Home-Based Mechanical Ventilation
Navigating to Home NIV Nirvana: What Would Margaret Do?
Peter C. Gay, MD, MS, FCCP
The Margaret Pfrommer Endowed Memorial Lecture in Home-Based Mechanical Ventilation is generously supported by International Ventilator Users Network of Post-Polio Health International and the CHEST Foundation.

Pasquale Ciaglia Memorial Lecture in Interventional Medicine
Raising the Bar: The Interventional Pulmonary Outcomes Group
Lonny B. Yarmus, DO, MBA, FCCP
The lecture is generously funded by the CHEST Foundation.

Roger C. Bone Memorial Lecture in Critical Care
To SIRS with Love: Dr. Roger Bone's Continued Influence on Early Sepsis Care
Emanuel P. Rivers, MD, MPH, FCCP
The lecture is generously funded by the CHEST Foundation.

Murray Kornfeld Memorial Founders Lecture
Our Pneumonia Journey: The Lungs and Beyond
Marcos I. Restrepo, MD, PhD, FCCP
The lecture is generously funded by the CHEST Foundation.

CHEST FOUNDATION GRANT AWARDS

The GlaxoSmithKline Distinguished Scholar in Respiratory Health
Deepa Gotur, MD, FCCP
Cytokine Release in SARS COV2 Viral Illness and Trends of Inflammasome Expression in Acute Respiratory Distress Syndrome Manifestations and Management
This grant is supported by an endowed fund from GlaxoSmithKline.

CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
Paul R. Ellis, MBChB
Cardiovascular Outcomes and Phenotypes in Pulmonary Exacerbations of Alpha-1 Antitrypsin
This grant is jointly supported by the CHEST Foundation and the Alpha-1 Foundation.

CHEST Foundation Research Grant in Women's Lung Health
Shannon E. Kay, MD
Sex-specific Gene Expression in Asthma
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
Davide Biondini, MD, PhD
Role of the Immune Check Points (CTLA-4 and PD-1) in the Development or Evasion of Smoking-Induced Chronic Obstructive Pulmonary Disease

Andrew J. Gangemi, MD
Are Sleep Health, Nicotine Metabolism, and Airway Inflammation Mechanisms for Differences in Lung Function between African American and Non-Hispanic White Smokers? A Proof-of-Concept Examination
These grants are supported by AstraZeneca LP.

CHEST Foundation Research Grant in Critical Care
Mounica Vallurupalli, MD
Evaluating the Impact of Clonal Hematopoiesis on Host Immune Response During Sepsis
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Lung Cancer
Stefanie Mason, MD
Implications of Longitudinal Muscle-Mass Trajectories in Lung Cancer
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Venous Thromboembolism
Jansen N. Seheult, MD, MBBCh
Untangling the NET: Neutrophil Activation as the Driver of Venous Thromboembolism in Coronavirus Disease 2019
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Nontuberculous Mycobacteria Diseases
Bryan A. Garcia, MD
Longitudinal Proteomic Endotyping of Patients with Nontuberculous Mycobacterial Lung Infections
This grant is supported by Insmed Incorporated.

CHEST Foundation Research Grant in Cystic Fibrosis
Jeffrey Barry, MD
Eosinophilia as a Biomarker for Worse Outcomes in Cystic Fibrosis

Kristina Montemayor, MD
The Association of Sex Hormones and Respiratory Morbidity in Individuals with Cystic Fibrosis
These grants are supported by Vertex Pharmaceuticals.

John R. Addrizzo, MD, FCCP Research Grant in Sarcoidosis
Changwan Ryu, MD
Extracellular Matrix Proteins as a Biomarker for Stage IV Sarcoidosis
This grant is in honor of John R. Addrizzo, MD, FCCP and is jointly supported by the Addrizzo family and the CHEST Foundation.

CHEST Foundation Research Grant in Severe Asthma
Isaretta L. Riley, MD, MPH
Coping with Asthma through Life Management (CALM)
This grant is funded by AstraZeneca LP.

CHEST Foundation Research Grant in Pulmonary Fibrosis
Sarah Beshay, MD
COPA Syndrome-Associated Mutations in Lung Transplant Recipients for Pulmonary Fibrosis

Erica D. Farrand, MD
The Future of Telehealth in Interstitial Lung Disease
These grants are supported by Boehringer Ingelheim Pharmaceuticals and Genentech, Inc.

CHEST Foundation Research Grant in Sleep Medicine
Tetyana Kendzerska, MD, PhD
The Role of Sleep and Circadian Disturbances in Cancer Development and Progression: A Historical Multicenter Clinical Cohort Study

Nancy Stewart, DO
Improving COPD/OSA Overlap Syndrome Pre-Discharge Care Delivery
These grants are funded by Jazz Pharmaceuticals, Inc.

CHEST Foundation and Association of Critical Care Medicine Program Directors Award Research Grant in Medical Education
Ilana R. Krumm, MD
What's good about Soul Food? Discovering and Analyzing Elements of an ICU Team Group Discussion Which Improve Provider Wellness
This grant is jointly supported by the CHEST Foundation and APCCMPD.

CHEST Foundation and American Thoracic Society Research Grant in Diversity
Thomas S. Valley, MD, MSc
Understanding Differences in Delivery of Care Processes for Respiratory Failure by Race/Ethnicity
This grant is jointly supported by

the CHEST Foundation and ATS.

CHEST Foundation Research Grant in COVID-19

David Furfaro, MD
Subphenotypes, Inflammatory Profiles, and Antibody Response in COVID-19 ARDS

This grant is supported by the CHEST Foundation.

CHEST Foundation and American Thoracic Society Grant in COVID-19 and Diversity

Peter D. Jackson, MD
The Effect of the COVID-19 Pandemic on Tuberculosis Care in Uganda

This grant is jointly supported by the CHEST Foundation and ATS.

CHEST Foundation Research Grant in Ultrasonography and COVID-19

Marjan M. Islam, MD
Thoracic Ultrasound in COVID-19: A Prospective Study Using Lung and Diaphragm Ultrasound in Evaluating Dyspnea in ICU Survivors with COVID-19 in a Post-ICU Clinic

Siddharth Dugar, MBBS
Spontaneous Echo Contrast in Lower Extremity and Correlation with Venous Velocity and Subsequent Deep Venous Thrombosis in Critically Ill COVID-19 Patients

This grant is jointly supported by the CHEST Foundation and FUJIFILM SonoSite.

CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP

Ivan Nemorin, MBA, MS, RRT
Healthier Homes for Children-Community Asthma Prevention Program

Joseph Huang, MD
East Africa Training Initiative (EATI)

Aninda Das, MD, MBBS
Screening for Childhood Tuberculosis in Children 0-4 years of Age with Moderate to Severe Malnutrition in a Rural District of West Bengal, India

Trishual Siddharthan, MD
Establishing a Pulmonary and Critical Care Training Program in Uganda

Marina Lima, MD, MSc
Asmaland: The First Gamified Pediatric Asthma Educational Program in Portuguese

Roberta M. Kato, MD
Lung Power

These grants are supported by the CHEST Foundation.

Alfred Soffer Research Award Winners

Mazen O. Al-Qadi, MD: Respiratory variation in right atrial pressure predicts right ventricular dysfunction in patients with pre-capillary pulmonary hypertension
Valerie G. Press, MD: Cost saving simulation for the transition from nebulizer to combination of nebulizer and metered-dose inhalers (MD)

Young Investigator Award Winners

Gabriel E. Ortiz Jaimes, MD: Correlation of cardiac output measurement by goal-directed echocardiography performed by intensivists vs pulmonary artery catheter
Palakkumar Patel, MD: Impact of having pulmonary hypertension in patients admitted with acute exac-

Continued on following page

PULMONARY PERSPECTIVES®

Bronchiolitis: Rare diseases, diagnostic challenges, and few proven therapies

BY BRIAN R. POOLE, MD, AND SEAN J. CALLAHAN, MD

What's in a name?

Bronchiolitis, a group of diseases also referred to as "small airways diseases," is characterized by inflammation and/or fibrosis in airways less than 2 mm in diameter. In pediatric patients, it is most commonly related to acute viral infections, while in adults, it is often associated with chronic diseases. Bronchiolitis is a well-recognized complication in a significant number of patients who have undergone lung or stem cell transplantation. Common associations also include connective tissue diseases, environmental or occupational inhalation exposures, aspiration, drug toxicity, and infections. Diagnosing bronchiolitis can be challenging for clinicians, and few treatment options exist apart from treating identifiable underlying etiologies. More research is needed into noninvasive diagnostic techniques and treatment modalities.

The terminology used to describe bronchiolitis has evolved over time. Bronchiolitis is now used to describe conditions where the primary pathologic condition is damage to the bronchiolar epithelium not attributable to a larger parenchymal disease (such as hypersensitivity pneumonitis). This change in nomenclature explains why the condition formerly known as "bronchiolitis obliterans organizing pneumonia" (BOOP) is now simply recognized as "organizing pneumonia." Despite several proposed classification schemes focusing on histopathology, there is no consensus regarding the different subtypes of bronchiolitis, leading to confusion in some cases. Recently, authors have attempted to distinguish cases based on three main histologic patterns (Urisman A, et al. *Surg Pathol Clin*. 2020;13[1]:189).

- **Obliterative/constrictive bronchiolitis (OB)** – the terms "obliterative" and "constrictive" are used interchangeably throughout pulmonary literature. It is characterized by fibroblast-rich tissue accumulation in the subepithelium of bronchioles leading to progressive narrowing of the lumen. In addition to the transplant setting, it is often seen in patients with rheumatoid arthritis or other connective tissue diseases, inhalational exposures, or acute respiratory infections. More recently, clinicians have recognized diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) as a rare condition causing OB with potentially effective treatment.
- **Follicular bronchiolitis (FB)** – features peribronchiolar inflammation with subepithelial lymphoid deposits leading to luminal obstruction. FB is chiefly associated with conditions of impaired immunity or chronic airway infection, such as autoimmune connective tissues diseases (especially rheumatoid arthritis and Sjogren's), severe combined immunodeficiency, HIV, cystic fibrosis, and primary ciliary dyskinesia.
- **Diffuse panbronchiolitis (DBP)** – features bilateral bronchiolar lesions with lymphocytic inflammation of the bronchiolar wall, as well as peribronchiolar inflammation and accumulation of interstitial foamy macrophages. Patients afflicted with DBP may suffer repeated bacterial colonization or infection. There is a higher prevalence of DBP in Asia where it was first identified in the 1960s, potentially due to several HLA alleles that are more common in Asia.

In patients who have continued lung function decline, a systematic review concluded that extracorporeal photopheresis had the most robust evidence for efficacy.

In addition to the above terminology, the transplant-setting diagnosis "bronchiolitis obliterans syndrome" (BOS) is used to denote progressive obstructive lung disease for which there is not another cause aside from chronic graft rejection. For these patients, clinicians assume the underlying disease entity is OB, but they often lack histopathologic confirmation.

Diagnosis is challenging

Symptoms of bronchiolitis are typically dyspnea and cough, and patients may often be diagnosed with asthma or COPD initially. Pulmonary function testing may show signs of obstruction, restriction, or mixed disease with or without a reduction in Dlco. Chest radiography often appears normal, but high-resolution CT may show expiratory air trapping and centrilobular nodules. Advanced imaging modalities may augment or replace CT imaging in diagnosing bronchiolitis: investigators are evaluating pulmonary MRI and fluoroscopy with computerized ventilation analysis in clinical trials (NCT04080232).

Currently, open or thoracoscopic lung biopsy is typically required to make a definitive diagnosis. Because bronchiolitis is a patchy and heterogeneous process, transbronchial biopsy may provide insufficient yield, with a sensitivity of 29% to 70%

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erbation of copd in their healthcare utilization and readmission: a us population cohort study

Top 5 abstract posters

Winner: **Amr Alwakeel, MD:** Impact of a pleural care program on the pathway to definitive palliation of malignant pleural effusions: a pre-and post study

Winner: **Konstantinos Zorbas, MD:** A simple prediction score for postoperative death after decortication

Winner: **Yichen Wang, MD, MSC:** Coronavirus-related hospital admissions in the united states in 2016-2017

Runner up: **Daniel Ospina-Delgado, MD:** Characterization of laryngeal disorders in patients with excessive central airway collapse

Runner up: **Vishal Vashistha, MD:** Treatment patterns among lower-income indian patients with metastatic non-small cell lung cancer harboring egfr mutations or alk rearrangements

Case report poster winners

Faiza Khalid, MD: Forme fuste of intermediate syndrome (ims) in organophosphate poisoing (opp): expert opinion guideline without clear end-point.

William Meng, MD: Vingt mille lieues sous les mers: a poisonous guest from the blue sea toxic inhalation of coral palytoxin

Dhruv Amratia, MD: Pulmonary blastoma: a rare form of lung cancer

Melinda Becker, MD: Ecmo-assisted bronchoscopy for near-complete tracheal obstruction

Brittany Blass, PA-C: A case of autoimmune pulmonary alveolar proteinosis with underlying monoclonal b-cell lymphocytosis

Abigayle Sullivan, MD: Bird fancier's lung: an underdiagnosed cause of shortness of breath

Nitin Gupta, DO: Successful emergent coronary artery bypass in a woman with postpartum spo ntaneous coronary artery dissection

Michelle Miles, DO: GI variant of lemierre syndrome: complete occlusion of superior mesenteric vein in a 30-year-old with appendiceal abscess

Adarsha Ojha, MD: Bleeding lung and bloating gut: lane hamilton syndrome

Abdul Siddiqui, MD: A case of e-cigarette or vaping product use-associated lung injury in an infrequent vape user

James Dugan, MD: Emphysema with placental transmogrification and lipomatous change

Daniel Condit, MD: Duplicate inferior vena cava as a potential pathway for recurrent pulmonary embolism

CHEST 2020 CHEST Challenge

1st Place
Case Western Reserve University (MetroHealth)
Enambir Josan, MD
Ishan Lalani, MD, MPH
Faisal Qadir, MD
Program Director: Ziad Shaman, MD, FCCP

2nd Place
SUNY Downstate
Suchit Khanijao, MD
Chetana Pendkar, MBBS
Ayla Zubair, MBBS
Program Director: Robert Foronjy, MD

3rd Place
NYP Brooklyn Methodist Hospital
John Gorski, MD
Sandi Khin, MD
Kinjal Patel, MD
Program Director: Anthony Saleh, MD, FCCP

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CHEST Foundation vision for 2021 and beyond

BY IAN NATHANSON, MD, FCCP
President, CHEST Foundation

In the year of COVID-19, we saw unprecedented changes in our environment and social interactions. Almost nothing was as it should be—sports championships in a "bubble," social distancing, limited travel, economic hardships, and, of course, the devastating effects on the health of people all over the world. CHEST did not shy away from the challenges of COVID-19. Instead, we accelerated our focus on education, patient care, research, and advocacy to assist clinicians caring for affected patients. The CHEST Foundation, the philanthropic arm of CHEST, contributed to this effort by funding research and community service grants and distributing over 14,000 pieces of PPE to health workers and the public.

Amid social protests, CHEST issued statements supporting inclusion and diversity and called for improving health care disparities. To better understand how these important issues interact, the CHEST Foundation began conducting listening tours across the country to learn what is important to patients and what barriers they face. These lessons will influence how the foundation implements its current programs and designs future programs. Over the next few months, the CHEST Foundation will set in motion a course of action to support valuable programs in these areas. We will focus on three main themes.


Dr. Nathanson

First, we will utilize the strength of CHEST by inviting fellows to participate in CHEST Foundation activities and serve on our committees. By creating an atmosphere of inclusion and collegiality, we believe that fellows will better understand the CHEST Foundation's goals and commit themselves to strengthening the foundation for years to come.

Second, we want to establish relationships with organizations outside of CHEST. Although our partnerships with health care industry organizations are strong, we have few robust alliances in the non-endemic space. Corporations espouse wellness, and we have experts all over the world who can address the needs and concerns of these companies. Preliminary exploration tells us that non-endemic corporations have an interest in what we can offer.

Third, we want to grow the corpus of the CHEST Foundation. Dreams without funding become only aspirations, but dreams with funding become reality. Without a solid corpus, we operate on a short-term plan. CHEST has some of the most influential leaders in the fields of pulmonary, critical care, and sleep medicine. Together, we can develop programs that can significantly impact the lives of the people we serve.

The CHEST Foundation looks forward to building on past successes and tackling new challenges. On behalf of CHEST's Board of Trustees and the gifted staff, I invite you to join us to reach these goals.

Continued from page 18

reported in lung transplant literature (Urisman A, et al. *Surg Pathol Clin*. 2020;13[1]:189).

Recent studies have demonstrated transbronchial cryobiopsy to be a promising alternative to surgical biopsy, owing to larger tissue samples than conventional transbronchial lung biopsies. For example, in a recent case series four patients underwent transbronchial cryobiopsy. The procedure yielded adequate tissue for diagnosis of a chronic bronchiolitis in each case (Yamakawa H, et al. *Internal Med Advance Publication*. doi: 10.2169/internalmedicine.6028-20.

Treatment options are growing

Evidence for treatment of bronchiolitis remains limited. Options are extrapolated from lung transplant patients, where incidence of BOS ranges from 50% at 5 years to 76% at 10 years post transplant. Guidelines recommend a 3-month minimum trial of azithromycin, which has been shown to slow or reverse decline of lung function in some patients. Modification of immunosuppression is also recommended. In patients who have continued lung function decline, a systematic review concluded that extracorporeal photopheresis had the most robust evidence for efficacy with stabilized lung function and improved overall survival (Benden C, et al. *J Heart Lung Transplant*. 2017;36[9]:921). Other salvage therapies that have lower-quality evidence of benefit include total lymphoid irradiation, montelukast, and aerosolized cyclosporine.

In patients who have undergone hematopoietic stem cell transplant, steroids are typically the first line treatment for OB as it is thought to be a form of chronic graft-vs-host disease (GVHD). Ruxolitinib, a selective JAK1/2 inhibitor, demonstrated significant improvement overall in patients with steroid-refractory acute GVHD in a recent randomized clinical trial, although the trial did not examine its effect on pulmonary manifestations (Zeiser R, et al. *N Engl J Med*. 2020;382[19]:1800). To date, retrospective observational studies of ruxolitinib in patients with lung GVHD have shown conflicting results regarding benefit. Investigators are currently studying ruxolitinib in a phase II trial for patients with BOS following stem cell transplant (NCT03674047).

DIPNECH is unique from other bronchiolitis entities, as small airways dysfunction develops as a result of neuroendocrine cell proliferation in the airway mucosa, ultimately leading to bronchial narrowing. It most commonly presents in middle-aged nonsmoking women with years of chronic cough and dyspnea. While it has an indolent course in many patients, some patients develop progressive symptoms and obstructive lung disease. DIPNECH is considered a precursor to other pulmonary neuroendocrine tumors. The lesions demonstrate somatostatin receptor expression in many cases, prompting the use of somatostatin analogues as treatment. In the largest published case series, 42 patients from three different institutions were identified who were treated with somatostatin analogues for a mean of 38.8 months at the time of review. Symptomatic improvement was seen in 33 of the 42 (79%), and of the 15 with posttreatment PFT data, 14 (93%) showed improvement in PFTs (Al-Toubah,

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CHEST NETWORKS

Home O_2 in COPD. Eradicating COVID-19. mRNA and beyond. COVID-19 treatment, so far.

Airways Disorders

Updated guidelines on the use of home O_2 in COPD: A much needed respite

The use of long-term oxygen therapy (LTOT, oxygen prescribed for at least 15 h/day) in patients with COPD and chronic hypoxemia has been standard of care based on trials from the 1980s that conferred a survival benefit with the use of continuous oxygen (*Ann Internal Med.* 1980;93[3]:391-8.

More recently, LTOT has not shown to improve survival or delay time to the hospitalization in patients with stable COPD and resting or exercise-induced moderate desaturation *(N Engl J Med.* 2016;375[17]:1617-27). Thus far, existing recommendations had been semi-inclusive in patient selection. A fundamental lack of evidence-based clinical practice guidelines prompted additional research into patient selection, portable oxygen technology, advocacy for improved oxygen therapy financing, and updating of policies (Jacobs et al. *Ann Am Thorac Soc.* 2018;15[12]:1369-81). With over a million patients in the United States being prescribed home oxygen and reported disconnect in-home oxygen needs/experiences across disease processes, lifestyles, and oxygen supply requirements, the 2020 American Thoracic Society (ATS) workshop on optimizing home oxygen therapy sought to answer critical questions in the use of LTOT for COPD patients (AlMutairi, et al. *Respir Care.* 2018;63[11]:1321-30; Jacobs, et al. *Am J Respir Crit Care Med.* 2020;202[10]:e121-e141).


Dr. Vijaykumar


Dr. Narendra

Based on a thorough systematic review of available literature, the committee made strong recommendations (moderate-quality evidence) for LTOT use in COPD with severe chronic resting hypoxemia ($PaO_2 \leq 55$ mm Hg or $SpO_2 \leq 88\%$), conditional recommendations for the following: (1) Against LTOT use in COPD with moderate chronic resting hypoxemia [SpO_2 89%-93% (low-quality evidence)]; (2) Ambulatory oxygen use in adults with COPD with severe exertional hypoxemia (moderate-quality evidence); and (3) Liquid oxygen use in patients who are mobile outside the home and require >3 L/min of continuous-flow oxygen during exertion (very-low-quality evidence). The review identified a dire need to develop a more robust evidence-based practice and incorporate shared decision-making while highlighting the deficit of conclusive data supporting supplemental oxygen for patients with exertional desaturation.

Kadambari Vijaykumar, MD
Fellow-in-Training Member
Dharani Kumari Narendra, MBBS, FCCP
Steering Committee Member

Chest Infections

Eradicating COVID-19 scourge: It is up to all of us — get vaccinated!

2021 brings hope, spurred by the availability of several effective COVID-19 vaccines – unprecedented scientific advances, considering that these vaccines were developed in record time. We have stark choices: while some individuals ignore scientific evidence and refuse to take the vaccine, we from the Chest Infections NetWork urge an alternative and imperative choice. As health providers caring for COVID-19 patients, we first-hand witness the horrors of dying alone in a hospital bed – far away from beloved ones. I have a sticker on my car that says: If you do not like your mask, you will not like my ventilator. With the advent of vaccines, I plan on replacing this sticker: If you do not want to get vaccinated, you will not like my ventilator. When the vaccine became available at my institution, I was the first to roll up my sleeve and feel the pinch in my upper arm. I urge you all to do the same. Make a difference, do your part – get vaccinated.


Dr. Restrepo

Marcos I. Restrepo, MD, PhD, FCCP
Chair

Clinical Pulmonary Medicine

COVID-19 vaccines – mRNA and beyond

We currently have two COVID-19 mRNA vaccines with US FDA emergency use authorization (EUA) for use in individuals less than or equal to age 18 years – Pfizer and Moderna. They work by introducing mRNA into a muscle cell that instructs the host cell ribosomes to express Sars-CoV-2 spike proteins, thereby triggering a systemic immune response.


Dr. Farmer


Dr. Subramanian

Phase 3 trial demonstrated vaccine efficacy of 95% with both vaccines. Besides injection site pain, common side effects were fatigue, headache, chills, and myalgias, more frequent after dose two.

Both are two-dose regimens, with Pfizer's 21 days apart and requires storage at -75 C, and Moderna's 28 days apart, requiring storage at -20 C.

With reports of anaphylaxis reactions, CDC has issued a warning with a contraindication to the vaccine if there is severe allergic reaction after the first dose or a history of allergy to any of its components, including polyethylene glycol (PEG), or polysorbate, due to potential cross-reactive hypersensitivity with PEG.

Presently in development are three more vaccines. AstraZeneca (AZ) and Johnson & Johnson (JnJ) use an adenovirus vector. Both vaccines are stable at standard refrigerator temperatures. AZ's results were mixed – with two, full-size doses efficacy at 62% effective, but with a half-dose followed by a full dose, efficacy was 90%. Novavax candidate works differently - it's a protein subunit vaccine and uses a lab-made version of the SARS-CoV-2 spike protein, mixed with an adjuvant to help trigger the immune system. Results from all trials are eagerly awaited.

Mary Jo S. Farmer, MD, PhD, FCCP
Steering Committee Member
Shyam Subramanian, MD, FCCP
Chair

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T, et al. *Chest*. 2020;158[1]:401). Other small studies have demonstrated varying results with symptomatic improvement in 29% to 76% of patients and improvement or stability of PFTs in 50% to 100% of patients (Samhouri BF, et al. *ERJ Open Res*. 2020;6[4]:527).

For patients who have not undergone lung transplant, and who do not have an identifiable exposure or underlying rheumatologic condition, a similar 3-month minimum trial of macrolide antibiotics is reasonable. Macrolides have been shown to double long-term survival rates to over 90% in patients with DPB. Evidence in this patient population is quite limited, and further research is needed to determine effective therapies for patients.

What's next for bronchiolitis?

While clinicians currently have few tools for diagnosing and treating these uncommon diseases, in the coming years, we should learn whether novel imaging modalities or less invasive procedures can aid in the diagnosis. Physicians hope these advances will preclude the need for invasive biopsies in more patients going forward. We should also learn whether newer, targeted agents like ruxolitinib are effective for BOS in patients with stem cell transplant. If so, this finding may open it and similar agents to investigation in other forms of bronchiolitis.

Dr. Poole and Dr. Callahan are with University of Utah Health, Salt Lake City, Utah.

Continued from previous page

Clinical Research and Quality Improvement

COVID-19 treatment, so far!

COVID-19 has turned rapidly into a fatal illness, causing over 1.8 million deaths worldwide so far. The pandemic has also showed us the power of adaptive trials, multi-arm trials, and the role for collaboration across the global scientific community.


Dr. Syed

A few significant studies are worth mentioning.

Initial therapies were with hydroxychloroquine and azithromycin, but showed no clinical improvement (Cavalcanti AB. *N Engl J Med.* 2020;383[21]:2041). Remdesivir, now standard of care, is based on the ACTT-1 trial, a double-blind randomized controlled trial (RCT), showing improved recovery time (Beigel JH, et al. *N Engl J Med*. 2020;383[19]:1813). The RECOVERY trial, a large clinical trial in the United Kingdom, demonstrated a mortality benefit (rate ratio 0.83) with dexamethasone at 28 days in those with moderate to severe COVID-19 pneumonia. Lopinavir-ritonavir combination failed to show benefit in the same trial (Horby P, et al. *N Engl J Me*d. 2020 Jul 17. doi: 10.1056/NEJMoa2021436). Baricitinib has been shown to decrease recovery time, especially in patients with high oxygen need (Kalil AC, et al. *N Engl J Med.* 2020 Dec 11. doi: 10.1056/NEJMoa2031994).

Possible future therapies include antiviral monoclonal antibodies, bamlanivimab (Chen P, et al. *N Engl J Med.* 2020; online ahead of print); early convalescent plasma (Libster R, et al. *N Engl J Med.* 2021 Jan 6. doi: 10.1056/NEJMoa2033700); and casirivimab-imdevimab (Baum A, et al. *Science*. 2020 Nov 27 doi: 10.1126/science.abe2402). Development of mRNA COVID-19 vaccines can help with primary prevention and herd immunity (Polack FP, et al. *N Engl J Med*. 2020;383[27]:2603; Baden LR, et al. *N Engl J Med.* 2020; Dec 30; doi: 10.1056/NEJMoa2035389).

We are starting to understand why COVID-19 infection is more pathogenic in some, how to predict development of severe disease, and how to best treat respiratory failure. Defeating the pandemic will require ongoing international collaboration in research, development, and resource allocation.

Muhammad Hayat Syed, MBBS
Ankita Agarwal, MD
Fellows-in-Training Members

Critical Care

Awake proning in COVID-19

Prone positioning has been shown to improve pulmonary mechanics in intubated patients with acute respiratory distress syndrome (ARDS). Proposed mechanisms for these benefits include shape matching, reversing the pleural pressure gradient, homogenizing distribution of pleural pressures, reducing the impact of the heart and abdomen on the lungs, and maintaining distribution of perfusion. Application of prone positioning has also been shown to reduce mortality in severe ARDS (Guérin, et al. *N Engl J Med*. 2013;368(23):2159-68). With the COVID-19 pandemic, clinicians have extrapolated that nonintubated patients with severe hypoxia may benefit from awake proning in the hopes of improving oxygenation and decreasing need for intubation. But, what's the evidence so far?


Dr. Pendleton


Dr. Kaul

In small studies, awake proning has been shown to improve oxygenation (PaO_2/FIO_2 ratio) and work of breathing in patients with COVID-19 who were severely hypoxic and could tolerate proning receiving high flow nasal oxygen (HFNO) or noninvasive ventilation (Weatherald, et al. *J Crit Care.* 2021;61:63-70). However, other studies were less conclusive. In a study by Elharrar, et al (*JAMA*. 2020;323(22):2336-2338), oxygenation only improved in 25% of those who were proned, and this improvement was not sustained in half of patients after they were re-supined. Additionally, a recent prospective, observational study from Spain did not show benefit to awake proning in patients receiving HFNO with respect to need for intubation or risk of mortality (Ferrando, et al. *Crit Care.* 2020;24(1):597).

It remains unclear whether these

physiologic and short-term clinical benefits will prevent the need for mechanical ventilation and/or improve long-term outcomes, including mortality. The other nuances of application of prone positioning in spontaneously breathing patients, such as the optimal duration, positioning, clinical setting, termination criteria, and adverse effects will only become clearer with time and more robust studies. Currently, more than 60 studies examining the role of prone positioning in COVID-19 were enrolling or recently completed. Hopefully, more robust trials will provide evidence about the effectiveness of this therapy in this population. Finally, head over to CHEST's COVID-19 Resource Center (https://www.chestnet.org/Guidelines-and-Resources/COVID-19/Resource-Center) to access a downloadable infographic describing the application of prone positioning.

Kathryn Pendleton, MD
Viren Kaul, MD
Steering Committee Members

Home-Based Mechanical Ventilation and Neuromuscular Disease

New horizons in home ventilation

Phasing out a particular ventilator (Philips Respironics Trilogy 100 ventilator) has everyone on a steep learning curve with the replacement (Trilogy EVO). Most features are replicated in the EVO, including volume/pressure control and pressure-supported modes, mouthpiece ventilation, active/passive circuit capability, and portability (11.5 lb). Upgrades include longer battery life (15 hours; 7.5 hours internal/7.5 hours detachable) and use in pediatric patients now greater than or equal to 2.5 kg.

A significant improvement in the workhorse AVAPS-AE mode is the addition of inspiratory time control on patient-initiated breaths. In AVAPS-AE (without PC-enabled), patient-initiated breaths remain flow-cycled; however, the inspiratory time control can be achieved using Timax/Timin setting for patients with neuromuscular respiratory failure and COPD (Coleman et al. *Ann Am Thorac Soc.* 2019;16(9):1091-98; Nicholson, et al. *Ann Am Thorac Soc.* 2017;14(7):1139-46).

Pressure control (PC) can now be enabled in AVAPS-AE to allow fixed Ti for both patient-initiated and device-initiated breaths, advantageous in neuromuscular disease and obesity-hypoventilation syndrome (Nicholson, et al. *Ann Am Thorac Soc.* 2017;14(7):1139-46; Selim, et al., *Chest*. 2018;153(1):251-65).

Other significant improvements include lower flow trigger sensitivity to accommodate patients with severe respiratory muscle weakness, a fast start AVAPS with rapid breath-to-breath 3 cm H_20 increases for the first minute to rapidly reach target tidal volume, and breath-to-breath auto-EPAP sensing of upper airway resistance to maintain airway patency for patients with upper airway obstruction.


Dr. Provost


Dr. Hilbert

Internal bluetooth transmission to cloud-based monitoring (Care Orchestrator™) expands access to patients without wi-fi or cellular service. New monitoring modules, SpO_2 and $EtCO_2$, and transcutaneous CO_2 monitoring (Sentec), transmit to cloud-based monitoring (EVO $EtCO_2$ spring 2021).

These welcome improvements allow clinicians to better match ventilator settings to the patients' evolving physiology and provide flexibility and connectivity to optimize long-term care.

Karin Provost, DO, PhD
Steering Committee Member
Janet Hilbert, MD
NetWork Member

Online resources
EVO e-learning curriculum (https://www.learningconnection.philips.com/en/trilogyevo-education)

Interprofessional Team

Interprofessional team approach to palliative extubation

The emotional burden of caring for patients at the end of life affects all members of the care team. Palliative (or compassionate) extubation consists of the withdrawal of mechanical ventilation when the absolute priority in care delivery is to afford comfort and allow for natural death to occur. Rapid withdrawal of ventilatory support may lead to significant respiratory distress, and the critical care team has an obligation to ensure patient comfort during the dying process (Truog RD, et al. *Crit Care Med*. 2008;36[3]:953). Registered nurses (RN) are primarily responsible for the titration of sedation/analgesia and should be included in discussions regarding medication selection. It is imperative that neuromuscular blockade is absent, and benzodiazepines and/or opioids should be initiated prior to palliative extubation (Lanken PN, et al. A*m J Respir Crit Care Med*. 2008;177:912). Respiratory therapists (RT) are responsible for endotracheal tube removal despite rare participation in end-of-life discussions (Grandhige AP, et al. *Respir Care*. 2016;61[7]:891). It is recommended that an experienced physician, RN, and RT be readily available to respond quickly to any signs of distress (Downar J, et al. *Intensive Care Med*. 2016;42:1003). Regular debriefing sessions exploring team actions and communication dynamics are advised following end-of-life care (Ho A, et al. *J Interprof Care*. 2016;30[6]:795-803). Palliative extubation demands meticulous planning and clear communication among all team members (physician, RN, RT) and the patient's family. Poor planning may result in physical and emotional suffering for the patient and difficult bereavement for the family (Coradazi A, et al. *Hos Pal Med Int J*. 2019;3[1]:10-14). Interprofessional team-based care results from intentional teams that exhibit collective identity and shared responsibility for the patients they serve (Core Competencies for Interprofessional Education Collaborative Practice, 2016). An inclusive and interprofessional approach to withdrawal of mechanical ventilation is key to both quality patient care and provider wellbeing.

Rebecca Anna Gersten, MD
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