Go to **MDedge.com/CHESTPhysician** for the latest news on the coronavirus pandemic.

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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

REUTERS/Shannon Stapleton

The triage framework starts with surge planning that includes an inventory of intensive care unit resources such as ventilators, beds, supplies, and staff that could be marshaled to meet a surge in demand, followed by establishing "identification triggers" for triage initiation by a regional authority.

COVID-19 critical care guidance includes resource triage plan

BY ANDREW D. BOWSER
MDedge News

While triage of critical care resources should be a rare event during the COVID-19 crisis, failing to prepare for the worst-case scenario could have serious consequences, according to authors of recent reports that offer advice on how to prepare for surges in demand.

Even modest numbers of critically ill COVID-19 patients have already rapidly overwhelmed existing hospital capacity in hard-hit areas including Italy, Spain, and New York City, said authors of an expert panel report released in CHEST.

"The ethical burden this places on hospitals, health systems, and society is enormous," said Ryan C. Maves, MD, FCCP, of the Naval Medical Center in San Diego, lead author of the expert panel report from the Task Force for Mass Critical Care and the American College of Chest Physicians (CHEST).

"Our hope is that a triage system can help us identify those patients with the greatest likelihood of benefiting from scarce critical care resources, including but not limited to mechanical ventilation, while still remembering our obligations to care for all patients as best we can under difficult circumstances," Dr. Maves said in an interview.

Triage decisions could be especially daunting for resource-intensive therapies such as extracorporeal membrane oxygenation (ECMO), as physicians may be forced to decide when and if to offer

TRIAGE // *continued on page 7*

Concerns for clinicians over 65 grow during pandemic

BY ALICIA GALLEGOS
MDedge News

When Judith Salerno, MD, heard that New York was calling for volunteer clinicians to assist with the COVID-19 response, she didn't hesitate to sign up.

Although Dr. Salerno, 68, has held administrative, research, and policy roles for 25 years, she has kept her medical license active and always found ways to squeeze some clinical work into her busy schedule.

"I have what I could consider 'rusty' clinical skills, but pretty good clinical judgment," said Dr. Salerno, president of the New York Academy of Medicine. "I thought in this situation that I could resurrect and hone those skills, even if it was just taking care of routine patients and working on a team, there was a lot of good I can do."

Dr. Salerno is among 80,000 health care professionals who have volunteered to work temporarily in New York during the COVID-19 pandemic as of March 31, 2020, according to New York state officials. In mid-March, New

Over 65 // *continued on page 8*

INSIDE HIGHLIGHT

NEWS FROM CHEST

FROM THE EVP/CEO

How CHEST is helping to flatten the curve

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Dear Readers: It is unlikely to surprise you that the majority of this issue of *CHEST Physician* is dedicated to the coronavirus pandemic. What may surprise you is that this was given much consideration prior to implementation. The rate at which our understanding of this virus, how it spreads, and how it is best managed is growing rapidly, so that today's information may be quickly out of date, making it a challenge to finalize a publication almost a month before it finds its way into readers' hands. That said, we at *CHEST Physician* thought it inappropriate to focus on anything other than what is clearly the greatest public health crisis of our time.

So, as you peruse these pages, note that all data herein were current as of their writing in late April. And please, above all else, stay safe.

David A. Schulman, MD, FCCP, Editor in Chief

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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:

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

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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.[4] 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.[2] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1,4] 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).[1–3] **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.[1,2]**

References: 1. Esbriet Prescribing Information. Genentech, Inc. July 2019. **2.** 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. **3.** Data on file. Genentech, Inc. 2019. **4.** 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.

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COVID-19 unusual features: 'Look for tricky symptoms'

BY M. ALEXANDER OTTO
MDedge News

The take-home message from a growing number of recent COVID-19 case reports is that the infection might be far more than a respiratory disease.

Although a cause-and-effect relationship is unknown, people with the virus have presented with or developed heart disease, acute liver injury, ongoing GI issues, skin manifestations, neurologic damage, and other problems, especially among sicker people.

For example, French physicians described an association with encephalopathy, agitation, confusion, and corticospinal tract signs among 58 people hospitalized with acute respiratory distress (N Engl J Med. 2020 Apr 15. doi: 10.1056/NEJMc2008597).

In particular, Yale New Haven (Conn.) Hospital is dealing with unexpected complications up close. Almost half of the beds there are occupied by COVID-19 patients. Over 100 people are in the ICU, and almost 70 intubated. Of the more than 750 COVID admissions so far, only about 350 have been discharged. "Even in a bad flu season, you never see something like this; it's just unheard of," said Harlan M. Krumholz, MD, a Yale cardiologist and professor of medicine helping lead the efforts there.

Kidney injuries prominent

"When they get to the ICU, we are seeing lots of people with acute kidney injuries; lots of people developing endocrine problems; people having blood sugar control issues, coagulation issues, blood clots. We are just waking up to the wide range of ways this virus can affect people. Our ignorance is profound," Dr. Krumholz said, but physicians "recognize that this thing has the capability of attacking almost every single organ system, and it may or

Dr. Harlan M. Krumholz

may not present with respiratory symptoms."

It's a similar story at Mt. Sinai South Nassau, a hospital in Oceanside, N.Y. "We've seen a lot of renal injury in people having complications, a lot of acute dialysis," but it's unclear how much is caused by the virus and how much is simply because people are so sick, said Aaron E. Glatt, MD, infectious disease professor and chair of medicine at the hospital. However, he said things are looking brighter than at Yale.

"We are not seeing the same level of increase in cases that we had previously, and we are starting to see extubations and discharges. We've treated a number of patients with plasma therapy, and hopefully that will be of benefit. We've seen some response to" the immunosuppressive "tocilizumab [Actemra], and a lot of response to very good respiratory therapy. I think we are starting to flatten the curve," Dr. Glatt said.

"Look for tricky symptoms"

The growing awareness of COVID's protean manifestations is evident in Medscape's Consult forum, an online community where physicians and medical students share information and seek advice; there's been over 200 COVID-19 cases and questions since January.

Early on, traffic was mostly about typical pulmonary presentations, but lately it's shifted to nonrespiratory involvement. Physicians want to know if what they are seeing is related to the virus, and if other people are seeing the same things.

There's a case on Consult of a 37-year-old man with stomach pain, vomiting, and diarrhea, but no respiratory symptoms and a positive COVID test. A chest CT incidental to his abdominal scan revealed significant bilateral lung involvement.

A 69-year-old woman with a his-

Continued on following page

Continued from previous page

tory of laparotomy and new-onset intestinal subocclusion had only adhesions on a subsequent exploratory laparotomy, and was doing okay otherwise. She suddenly went into respiratory failure with progressive bradycardia and died 3 days later. Aspiration pneumonia, pulmonary embolism, and MI had been ruled out. "The pattern of cardiovascular failure was in favor of myocarditis,

Dr. Aaron E. Glatt

Dr. William Shaffner

but we don't have any other clue," the physician said after describing a second similar case.

Another doctor on the forum reported elevated cardiac enzymes without coronary artery obstruction in a positive patient who went into shock, with an ejection fraction of 40% and markedly increased heart wall thickness, but no lung involvement. There are also two cases of idiopathic thrombocytopenia without fever of hypoxia.

An Italian gastroenterologist said: "Look for tricky symptoms." Expand "patient history, asking about the sudden occurrence of dysgeusia and/or anosmia. These symptoms have become my guiding diagnostic light" in Verona. "Most patients become nauseated, [and] the taste of any food is unbearable. When I find these symptoms by history, the patient is COVID positive 100%."

'Make sure that they didn't die in vain'

There was interest in those and other reports on Consult, and comments from physicians who have theories, but no certain answers about what is, and is not, caused by the virus.

Direct viral attack is likely a part of it, said Stanley Perlman, MD, PhD, a professor of microbiology and immunology at the University of Iowa, Iowa City.

The ACE2 receptor the virus uses to enter cells is common in many organs, plus there were extrapulmonary manifestations with severe acute respiratory syndrome (SARS), another pandemic caused by a zoonotic coronavirus almost 20 years ago. At least with SARS, "many organs were infected when examined at autopsy," he said.

The body's inflammatory response is almost certainly also in play. Progressive derangements in inflammatory markers – C-reactive protein, D dimer, ferritin – correlate with worse prognosis, and "the cytokine storm that occurs in these patients can lead to a degree of encephalopathy, myocarditis, liver impairment, and kidney impairment; multiorgan dysfunction, in other words," said William Shaffner, MD, a professor of preventive medicine and infectious diseases at Vanderbilt University Medical Center, Nashville, Tenn.

But in some cases, the virus might simply be a bystander to an unrelated disease process; in others, the experimental treatments being used might cause problems. Indeed, cardiology groups recently warned of torsade de pointes – a dangerously abnormal heart rhythm – with hydroxychloroquine and azithromycin.

"We think it's some combination," but don't really know, Dr. Krumholz said. In the meantime, "we are forced to treat patients by instinct and first principles," and long-term sequelae are unknown. "We don't want to be in this position for long."

To that end, he said, "this is the time for us all to hold hands and be together because we need to learn rapidly from each other. Our job is both to care for the people in front of us and make sure that they didn't die in vain, that the experience they had is funneled into a larger set of data to make sure the next person is better off."

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

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Plan for fair and equitable triage

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such support after demand outstrips a hospital's ability to provide it.

"ECMO requires a lot of specialized capability to initiate on a patient, and then, it requires a lot of specialized capability to maintain and do safely," said Steven P. Keller, MD, of the division of emergency critical care medicine in the department of emergency medicien at Brigham and Women's Hospital and Harvard Medical School, both in Boston.

Dr. Maves

Dr. Keller

Those resource requirements can present a challenge to health care systems already overtaxed by COVID-19, according to Dr. Keller, coauthor of a guidance document in Annals of the American Thoracic Society. The guidance suggests a pandemic approach to ECMO response that's tiered depending on the intensity of the surge over usual hospital volumes.

Mild surges call for a focus on increasing ECMO capacity, while a moderate surge may indicate a need to focus on allocating scarce resources, and a major surge may signal the need to limit or defer use of scarce resources, according to the guidance.

"If your health care system is stretched from a resource standpoint, at what point do you say, 'we don't even have the capability to even safely do ECMO, and so, perhaps we should not even be offering the support'?" Dr. Keller said.

Critical care guidance

The guidance from the Task Force for Mass Critical Care and CHEST offers nine specific actions that authors suggest as part of a framework for communities to establish the infrastructure needed to triage critical care resources and "equitably" meet the needs of the largest number of COVID-19 patients. "It is the goal of the task force to minimize the need for allocation of scarce resources as much as possible," the authors stated.

The framework starts with surge planning that includes an inventory of intensive care unit resources such as ventilators, beds, supplies, and staff that could be marshaled to meet a surge in demand, followed by establishing "identification triggers" for triage initiation by a regional authority, should clinical demand reach a crisis stage.

Next is preparing the triage system, which includes creating a committee at the regional level, identifying members of tertiary triage teams and the support structures they will need, and preparing and distributing training materials.

Agreeing on a triage protocol is important to ensure equitable targeting of resources, and how to allocate limited life-sustaining measures needs to be considered, the panel wrote. They also recommend adaptations to the standards of care such as modification of end-of-life care policies; support for health care workers, family, and the public; and consideration of pediatric issues including transport, concentration of care at specific centers, and potential increases in age thresholds to accommodate surges.

Barriers to triage?

When asked about potential barriers to rolling out a triage plan, Dr. Maves said the first is acknowledging the possible need for such a plan: "It is a difficult concept for most in critical care to accept – the idea that we may not be able to provide an individual patient with interventions that we consider routine," he said.

Beyond acknowledgment of need, other potential barriers to successful implementation include the limited evidence base to support development of these protocols, as well as the need to address public trust.

"If a triage system is perceived as unjust or biased, or if people think that triage favors or excludes certain groups unfairly, it will undermine any system," Dr. Maves said.

Dr. Maves and coauthors reported that some of the authors of their guidance are U.S government employees or military service members, and that their opinions and assertions do not reflect the official views or position of those institutions. Dr. Keller reported no disclosures related to the ECMO guidance.

chestphysiciannews@chestnet.org

SOURCES: Maves RC et al. Chest. 2020 Apr 11. pii: S0012-3692(20)30691-7. doi: 10.1016/j.chest.2020.03.063; Seethara R, Keller SP. Ann Am Thorac Soc. 2020 Apr 15. doi: 10.1513/AnnalsATS.202003-233PS.

Clinicians over 65 can do important administrative and telemedicine work // continued from page 1

York Governor Andrew Cuomo (D) issued a plea for retired physicians and nurses to help the state by signing up for on-call work. Other states have made similar appeals for retired health care professionals to return to medicine in an effort to relieve overwhelmed hospital staffs and aid capacity if health care workers become ill. Such redeployments, however, are raising concerns about exposing senior physicians to a virus that causes more severe illness in individuals aged over 65 years and kills them at a higher rate.


Dr. Salerno

At the same time, a significant portion of the current health care workforce is aged 55 years and older, placing them at higher risk for serious illness, hospitalization, and death from COVID-19, said Douglas O. Staiger, PhD, a researcher and economics professor at Dartmouth College, Hanover, N.H. Dr. Staiger recently coauthored a viewpoint in JAMA called "Older clinicians and the surge in novel coronavirus disease 2019," which outlines the risks and mortality rates from the novel coronavirus among patients aged 55 years and older.


Dr. Staiger

Among the 1.2 million practicing physicians in the United States, about 20% are aged 55-64 years and an estimated 9% are 65 years or older, according to the paper. Of the nation's nearly 2 million registered nurses employed in hospitals, about 19% are aged 55-64 years, and an estimated 3% are aged 65 years or older.

"In some metro areas, this proportion is even higher," Dr. Staiger said in an interview. "Hospitals and other health care providers should consider ways of utilizing older clinicians' skills and experience in a way that minimizes their risk of exposure to COVID-19, such as transferring them from jobs interacting with patients to more supervisory, administrative, or telehealth roles. This is increasingly important as retired physicians and nurses are being asked to return to the workforce."

Protecting staff, screening volunteers

Hematologist-oncologist David H. Henry, MD, said his eight-physician group practice at Pennsylvania Hospital, Philadelphia, has already taken steps to protect him from COVID exposure.


Dr. Henry

At the request of his younger colleagues, Dr. Henry, 69, said he is no longer seeing patients in the hospital where there is increased exposure risk to the virus. He and the staff also limit their time in the office to 2-3 days a week and practice telemedicine the rest of the week, Dr. Henry said in an interview.

"Whether you're a person trying to stay at home because you're quote 'nonessential,' or you're a health care worker and you have to keep seeing patients to some extent, the less we're face to face with others the better," said Dr. Henry, who hosts the Blood & Cancer podcast for MDedge News. "There's an extreme and a middle ground. If they told me just to stay home that wouldn't help anybody. If they said, 'business as usual,' that would be wrong. This is a middle strategy, which is reasonable, rational, and will help dial this dangerous time down as fast as possible."

On a recent weekend when Dr. Henry would normally have been on call in the hospital, he took phone calls for his colleagues at home while they saw patients in the hospital. This included calls with patients who had questions and consultation calls with other physicians.

"They are helping me and I am helping them," Dr. Henry said. "Taking those calls makes it easier for my partners to see all those patients. We all want to help and be there, within reason. You want to step up an do your job, but you want to be safe."

Peter D. Quinn, DMD, MD, chief executive physician of the Penn Medicine Medical Group, said safeguarding the health of its workforce is a top priority as Penn Medicine works to fight the COVID-19 pandemic.

"This includes ensuring that all employees adhere to Centers for Disease Control and Penn Medicine infection prevention guidance as they continue their normal clinical work," Dr. Quinn said in an interview. "Though age alone is not a criterion to remove frontline staff from direct clinical care during the COVID-19 outbreak, certain conditions such as cardiac or lung disease may be, and clinicians who have concerns are urged to speak with their leadership about options to fill clinical or support roles remotely."

Meanwhile, for states calling on retired health professionals to assist during the pandemic, thorough screenings that identify high-risk volunteers are essential to protect vulnerable clinicians, said Nathaniel Hibbs, DO, president of the Colorado chapter of the American College of Emergency Physicians.


Dr. Hibbs

After Colorado issued a statewide request for retired clinicians to help, Dr. Hibbs became concerned that the state's website initially included only a basic set of questions for interested volunteers.

"It didn't have screening questions for prior health problems, comorbidities, or things like high blood pressure, heart disease, lung disease – the high-risk factors that we associate with bad outcomes if people get infected with COVID," Dr. Hibbs said in an interview.

To address this, Dr. Hibbs and associates recently provided recommendations to the state about its screening process that advised collecting more health information from volunteers and considering lower-risk assignments for high-risk individuals. State officials indicated they would strongly consider the recommendations, Dr. Hibbs said.

The Colorado Department of Public Health & Environment did not respond to messages seeking comment. Officials at the New York State Department of Health declined to be interviewed for this article but confirmed that they are reviewing the age and background of all volunteers, and individual hospitals will also review each volunteer to find suitable jobs.

The American Medical Association on March 30 issued guidance for retired physicians about rejoining the workforce to help with the COVID response. The guidance outlines license considerations, contribution options, professional liability considerations, and questions to ask volunteer coordinators.

"Throughout the COVID-19 pandemic, many physicians over the age of 65 will provide care to patients," AMA President Patrice A. Harris, MD, said in a statement. "Whether 'senior' physicians should be on the front line of patient care at this time is a complex issue that must balance several factors against the benefit these physicians can provide. As with all people in high-risk age groups, careful consideration must be given to the health and safety of retired physicians and their immediate family members, especially those with chronic medical conditions."

Tapping talent, sharing knowledge

When Barbara L. Schuster, MD, 69, filled out paperwork to join the Georgia Medical Reserve Corps, she answered a range of questions, including inquiries about her age, specialty, licensing, and whether she had any major medical conditions.


Dr. Schuster

"They sent out instructions that said, if you are over the age of 60, we really don't want you to be doing inpatient or ambulatory with active patients," said Dr. Schuster, a retired medical school dean in the Athens, Ga., area. "Unless they get to a point where it's going to be you or nobody, I think that they try to protect us for both our sake and also theirs."


Dr. Buerhaus

Dr. Schuster opted for telehealth or administrative duties, but has not yet been called upon to help. The Athens area has not seen high numbers of COVID-19 patients, compared with other parts of the country, and there have not been many volunteer opportunities for physicians thus far, she said. In the meantime, Dr. Schuster has found other ways to give her time, such as answering questions from community members on both COVID-19 and non–COVID-19 topics, and offering guidance to medical students.

"I've spent an increasing number of hours on Zoom, Skype, or FaceTime meeting with them to talk about various issues," Dr. Schuster said.

As hospitals and organizations ramp up pandemic preparation, now is the time to consider roles for

Continued on following page

ABIM grants MOC extension

BY GREGORY TWACHTMAN
MDedge News

Physicians will not lose their certification if they are unable to complete maintenance of certification requirements in 2020, the American Board of Internal Medicine announced.


Dr. Baron

"Any physician who is currently certified and has a Maintenance of Certification requirement due in 2020 – including an assessment, point requirement or attestation – will now have until the end of 2021 to complete it," ABIM President Richard Baron, MD, said in a letter sent to all diplomates.

Additionally, physicians "currently in their grace year will also be afforded an additional grace year in 2021," the letter continued.

ABIM noted that many assessments were planned for the fall of 2020 and the organization will continue to offer them as planned for physicians who are able to take them. It added that more assessment dates for 2020 and 2021 will be sent out later this year.

"The next few weeks and months will challenge our health care system and country like never before," Dr. Baron stated. "Our many internal medicine colleagues – and the clinical teams that support them – have been heroic in their response, often selflessly putting their own personal safety at risk while using their superb skills to provide care for others. They have inspired all of us."

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Continued from previous page

older clinicians and how they can best contribute, said Peter I. Buerhaus, PhD, RN, a nurse and director of the Center for Interdisciplinary Health Workforce Studies at Montana State University, Bozeman. Dr. Buerhaus was the first author of the recent JAMA viewpoint "Older clinicians and the surge in novel coronavirus 2019."

"It's important for hospitals that are anticipating a surge of critically ill patients to assess their workforce's capability, including the proportion of older clinicians," he said. "Is there something organizations can do differently to lessen older physicians' and nurses' direct patient contact and reduce their risk of infection?"

Dr. Buerhaus' JAMA piece offers a range of ideas and assignments for older clinicians during the pandemic, including consulting with younger staff, advising on resources, assisting with clinical and organizational problem solving, aiding clinicians and managers with challenging decisions, consulting with patient families, advising managers and executives, being public spokespersons, and working with public and community health organizations.

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Imaging recommendations issued for COVID-19

BY MITCHEL L. ZOLER
MDedge News

FROM THE JOURNAL *CHEST* ▪ A consensus statement on the role of imaging during the acute work-up of COVID-19 patients called for liberal use in patients with moderate to severe clinical features indicative of infection, regardless of their COVID-19 test results, but limited use in patients who present with mild symptoms or are asymptomatic.

The consensus statement on The Role of Imaging in Patient Management During the COVID-19 Pandemic released by the Fleischner Society on April 7 (Chest. 2020 Apr 7. doi: 10.1016/j.chest.2020.04.003) was designed to highlight the "key decision points around imaging" in COVID-19 patients.

"We developed the statement to be applicable across settings" so that each clinic or hospital managing COVID-19 patients could decide the situations where chest radiography (CXR) or CT would work best, said Geoffrey D. Rubin, MD, professor of cardiovascular research, radiology, and bioengineering at Duke University in Durham, N.C., and lead author of the statement.

Written by 15 thoracic radiologists and 10 pulmonologists/intensivists including an anesthesiologist, a pathologist, and additional experts in emergency medicine, infection control, and laboratory medicine, and with members from any of 10 countries on three continents, the panel arrived at agreement by more than 70% for each of the 14 questions.

As effective treatments are developed, thoracic imaging may find new roles by establishing treatment response or characterizing patients as likely responders to novel therapies.

"I was impressed and a little surprised that consensus was achieved for every question" posed to the panel by the Fleischner Society for Thoracic Imaging and Diagnosis, Dr. Rubin said in an interview. The panel also placed their 14 decisions about imaging within the context of three distinct clinical scenarios chosen to mirror common real-world situations: mild COVID-19 features, moderate to severe features with no critical-resource constraints, and moderate to severe features with constrained resources.

The statement also summarized its conclusions as five main recommendations and three additional recommendations.

The statement particularly called out one of its recommendations – that a COVID-19 diagnosis "may be presumed when imaging findings are strongly suggestive of COVID-19 despite negative COVID-19 testing" in a patient who has moderate to severe clinical features of COVID-19 and whose pretest probability is high. The panel voted unanimously in favor of this concept, that imaging is "indicated" in hospitalized patients with moderate to severe symptoms consistent with COVID-19 despite a negative COVID-19 test result.


Dr. Rubin

"This guidance represents variance from other published recommendations which advise against the use of imaging for the initial diagnosis of COVID-19," the statement acknowledged and specifically cited the recommendations issued in March 2020 by the American College of Radiology.

Despite that, the ACR and Fleischner recommendations "are not at odds with one another," maintained Dr. Rubin. The panel based its take on this question on the "direct experience" of its members caring for COVID-19 patients, according to the statement.

"I wholeheartedly agree with the suggested uses of imaging outlined by the panel," commented Sachin Gupta, MD, FCCP, a pulmonologist and critical care physician in San Francisco. "The consensus statement brings a practical way to consider obtaining imaging. It leaves the door open to local standards and best judgment for using CXR or CT. Many physicians are unclear whether to image low-risk and mildly symptomatic patients. This statement gives support to a watchful waiting approach."

Another recommendation advises against daily CXR in stable, intubated COVID-19 patients. This guide "now gives backing from an important society and thought leaders while giving an explanation" for why daily imaging is problematic, he noted in an interview.


Dr. Gupta

The daily CXR in these patients adds no value, and skipping unneeded imaging minimizes SARS-CoV-2 exposure to radiology personnel, and conserves personal protection equipment, said the statement.

"The Fleischner Society is known worldwide for its recommendations. Having the society lend its weight on triage with imaging for COVID-19 patients is important. I suspect it will help standardize practice."

Dr. Gupta also highlighted that lung imaging with a portable ultrasound unit has quickly become recognized as a very useful imaging tool with increasing use as the pandemic has unfolded, an option not covered by the Fleischner statement.

Study results have "confirmed excellent sensitivity, specificity, and reproducibility" with lung ultrasound, and it's also "easy to use," Dr. Gupta said.

Ultrasound chest imaging of COVID-19 patients did not get included in the statement despite the reliance some U.S. sites have already placed on it largely because few on the panel had direct experience using it. "We didn't feel we could contribute" to a discussion of ultrasound, Dr. Rubin said.

The statement's recommendations appear to have already begun influencing practice. "The feedback I've gotten is that people are relying on them," said Dr. Rubin, and some programs have sent him screen shots of the recommendations embedded in their local electronic health record.

The authors concluded on a somber note: "The evidence base supporting the use of imaging across the scenarios presented is scant and the advice presented herein may undergo refinement through rigorous scientific investigation, exposing nuances of image interpretation that may lead to prognostic information and guide management decisions. At the time of this writing, no therapy has been confirmed to alter the course of COVID-19, there is no known cure, and there is no vaccine for prevention. As effective treatments are developed, thoracic imaging may find new roles by establishing treatment response or characterizing patients as likely responders to novel therapies."

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Imaging recommendations for acute, hospitalized COVID-19 patients

Main recommendations

- Imaging is not routinely indicated for COVID-19 screening in asymptomatic people.
- Imaging is not indicated for patients with mild features of COVID-19 unless they are at risk for disease progression.
- Imaging is indicted for patients with features of moderate to severe COVID-19 regardless of COVID-19 test results.
- Imaging is indicted for patients with COVID-19 and evidence of worsening respiratory status.
- When access to CT is limited, chest radiography may be preferred for COVID-19 patients unless features of respiratory worsening warrant using CT.

Additional recommendations

- Daily chest radiographs are not indicated in stable, intubated patients with COVID-19.
- CT is indicated in patients with functional impairment, hypoxemia, or both, after COVID-19 recovery.
- COVID-19 testing is warranted in patients incidentally found to have findings suggestive of COVID-19 on a CT scan.

SOURCE: Chest. 2020 Apr 7. doi: 10.1016/j.chest.2020.04.003

SYMBICORT 160/4.5 for reducing COPD exacerbations

HELP PREVENT COPD EXACERBATIONS WITH SYMBICORT

Symbicort 160/4.5 (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

Study 4: 12-month exacerbation clinical trial. SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations vs formoterol alone[1,2]

- In **Study 4**, COPD exacerbations were defined as worsening of COPD that required treatment with a course of oral corticosteroids and/or hospitalization

Annual rate estimate: **1.05, formoterol 4.5 mcg* (n=403)**

P<.001 vs formoterol[2]
Estimate rate ratio=0.65; 95% CI: 0.53, 0.80

Annual rate estimate: **0.68, SYMBICORT 160/4.5 mcg* (n=404)**

Study 3: 6-month exacerbation clinical trial. SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations by 26% vs formoterol (estimate rate ratio=0.74; 95% CI: 0.61, 0.91; *P*=.004)[1,2]

- Annual rate estimate was 0.94 for SYMBICORT 160/4.5 mcg* (n=606) vs 1.27 for formoterol 4.5 mcg* (n=613)
- In **Study 3**, COPD exacerbations were defined as worsening of ≥2 major symptoms (dyspnea, sputum volume, sputum color/purulence) or worsening of any 1 major symptom together with ≥1 of the minor symptoms (sore throat, colds [nasal discharge and/or nasal congestion], fever without other cause, increased cough or increased wheeze) for ≥2 consecutive days. COPD exacerbation severity was classified as moderate if symptoms required systemic corticosteroid (≥3 days) and/or antibiotic treatment, and severe if symptoms required hospitalization

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms.

*Administered as 2 inhalations twice daily.

Please see study design on adjacent pages.

IMPORTANT SAFETY INFORMATION

- Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA. When LABA are 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 to ICS alone
- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the administration of ICS
- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to ICS. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available ICS
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors

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

IMPORTANT SAFETY INFORMATION (CONT'D)

- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of ICS may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of ICS, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts
- In rare cases, patients on ICS may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce COPD exacerbations.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

COPD

Exacerbation Studies

Study 3 (RISE): A 6-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 1219 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=606) with formoterol 4.5 mcg (n=613), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >1 year, and a history of ≥1 moderate or severe COPD exacerbation in the previous year requiring treatment with systemic corticosteroids or hospitalization. The study included a 4-week run-in period, a 26-week randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of moderate and severe COPD exacerbations for SYMBICORT vs formoterol.

Study 4: A 12-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 811 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=407) with formoterol 4.5 mcg (n=404), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >2 years, and a history of ≥1 COPD exacerbation in the previous year treated with a course of systemic corticosteroids and/or antibiotics. The study included a 2-week run-in period, a 12-month randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of COPD exacerbations for SYMBICORT vs formoterol.

*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.*

References: 1. SYMBICORT [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019. **2.** Data on file, REF-16658, AZPLP.

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

AstraZeneca

Symbicort® 160/4.5
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

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

Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION. For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

SYMBICORT should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting $beta_2$-adrenergic agonist (LABA).

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. SYMBICORT 160/4.5 is also indicated to reduce exacerbations of COPD. SYMBICORT 160/4.5 is the only strength indicated for the treatment of COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. 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. When LABA are 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 to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared budesonide/formoterol (SYMBICORT) to budesonide *[see Clinical Studies (14.1) in the full Prescribing Information]*; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N =17,537)[1]	ICS (N =17,552)[1]	ICS/LABA vs ICS Hazard ratio (95% CI)[2]
Serious asthma-related event[3]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting $Beta_2$-adrenergic Agonist

1. Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
2. Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.
3. Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies

Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting $beta_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting $beta_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of SYMBICORT and Use with Other Long-Acting $Beta_2$-Agonists

As with other inhaled drugs containing $beta_2$-adrenergic agents, SYMBICORT 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 SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Pneumonia and Other Lower Respiratory Tract Infections

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

In a 6-month lung function study of 1704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month lung function study of 1964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on 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 exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, 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. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., $beta_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids 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

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. 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 SYMBICORT may provide control of asthma 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, a severe asthma attack 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 physicians 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, a severe asthma attack, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma or 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.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). 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

Budesonide, a component of SYMBICORT, will often help control asthma and COPD symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT 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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with 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 and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10) in the full Prescribing Information]*. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. 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 SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month lung function study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled

corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information]*.

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month lung function study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications 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 agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

LABA use may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression *[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]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 2 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 N = 277 %**	**160/4.5 N = 124 %**	**80 mcg N = 121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

1. All treatments were administered as 2 inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of ≥3% and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The safety data described below reflect exposure to SYMBICORT 160/4.5 in 1783 patients. SYMBICORT 160/4.5 was studied in two placebo-controlled lung function studies (6 and 12 months in duration), and two active-controlled exacerbation studies (6 and 12 months in duration) in patients with COPD.

The incidence of common adverse events in Table 3 below is based upon pooled data from two double-blind, placebo-controlled lung function clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 3 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 3 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment[1]	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 N = 771 %**	**160 mcg N = 275 %**	**4.5 mcg N = 779 %**	**N = 781 %**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

1. All treatments were administered as 2 inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, hematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

The safety findings from the two double-blind, active-controlled exacerbations studies (6 and 12 months in duration) in which 1012 adult COPD patients (616 males and 396 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily were consistent with the lung function studies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients
Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting $beta_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) 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 CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT 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]*.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5) in the full Prescribing Information]*. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol 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 abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication 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. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

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Remdesivir shows potential in COVID-19 drug trials

BY ANDREW D. BOWSER
MDedge News

While there are still no proven treatments for COVID-19, the antiviral medication remdesivir is currently the most promising therapy under investigation, according to authors of a recent review covering nearly 300 active clinical treatment trials underway for the disease.

Remdesivir, which has potent in vitro activity against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is not approved by the Food and Drug Administration and is currently being tested in randomized trials, according to the review authors, led by James M. Sanders, PhD, of the department of pharmacy at University of Texas Southwestern Medical Center, Dallas.

By contrast, oseltamivir has not demonstrated efficacy against the virus, corticosteroids are not recommended, and promising data from a small French hydroxychloroquine study are balanced by "several major limitations" including small sample size and exclusion of early dropouts from the analysis, among others, Dr. Sanders and coauthors wrote.

"These limitations coupled with concerns of additive cardiotoxicity with combination therapy [i.e., hydroxychloroquine with azithromycin] do not support adoption of this regimen without additional studies," the researchers wrote. Their report is in JAMA (2020 Apr 13. doi: 10.1001/jama.2020.6019).

Dr. Sanders and colleagues identified 291 COVID-19–specific studies listed in ClinicalTrials.gov through April 2, including 29 placebo-controlled trials.

This list might represent just a sliver of the treatments that could combat COVID-19, according to the researchers, who said more than 3,000 small-molecule drug candidates with potential activity against human coronaviruses have been identified.

Remdesivir for COVID-19

Remdesivir, an investigational nucleotide analog, is one promising agent because of its broad-spectrum and potent activity against SARS-CoV-2 and other novel coronaviruses, they said, adding that phase 1 trials demonstrated the drug was well tolerated without observed liver or kidney toxicity.

There have been "successful" case reports of remdesivir use in COVID-19, and at least five ongoing clinical trials are evaluating the drug's safety and antiviral activity in this disease. Among those studies is a National Institutes of Health–sponsored adaptive, randomized, placebo-controlled trial that will provide data on the use of remdesivir versus supportive care.

"As the results from randomized controlled trials are anticipated, inclusion of this agent for treatment of COVID-19 may be considered," Dr. Sanders and colleagues wrote in their report. To date, remdesivir remains investigational and needs to be obtained via compassionate use, through expanded access, or by participating in a clinical trial, they added.

Hydroxychloroquine and chloroquine

Among the published hydroxychloroquine studies is a "promising" 36-patient open-label nonrandomized French study, in which the antimalarial agent given every 8 hours improved virologic clearance by day 6 versus controls (70% vs. 12.5%, respectively), the review authors said. Moreover, viral clearance was 100% for 6 patients who received hydroxychloroquine plus azithromycin, compared to 57% (8 of 14) for patients treated with hydroxychloroquine alone. However, that study had several important limitations, including the small sample size, variable viral loads at baseline between groups, and a lack of safety and clinical outcomes reporting, according to the investigators. Moreover, six patients in the hydroxychloroquine group were taken out of the analysis because of early treatment stoppage due to medical intolerance or critical illness.

One prospective study including 30 patients in China demonstrated no difference in virologic outcomes for patients randomized to hydroxychloroquine plus standard of care versus standard of care alone, they added. There is also a case series of more than 100 patients with COVID-19 that reportedly improved viral clearance and reduced disease progression, though they said results haven't been published or presented beyond a news briefing in China.

Randomized, controlled trials of chloroquine and hydroxychloroquine for COVID-19 treatment are underway, and studies are planned or enrolling to look at chloroquine prophylaxis in health care personnel and hydroxychloroquine for postexposure prophylaxis, authors said.

In results from one of those randomized trials, just reported, a higher dose of chloroquine was associated with a cardiac adverse event and an increased mortality risk, leading to the closure of that study arm. In the parallel, double-blinded, phase IIb clinical trial, patients in Brazil with SARS-CoV-2 infection received low or high doses of chloroquine plus ceftriaxone and azithromycin. According to the preprint publication, a higher rate of heart rate–corrected QT interval (QTc) prolongation and a "trend toward higher lethality" was observed in the high-dose group, leading investigators to "strongly recommend" the higher dose be abandoned.

According to the researchers, more than 3,000 small-molecule drug candidates with potential activity against human coronaviruses have been identified.

"No apparent benefit of chloroquine was seen regarding lethality in our patients so far, but we will still enroll patients in the low chloroquine dose group to complete the originally planned sample size," said investigators of the study, which at the time of the report had enrolled 81 out of an anticipated 440 patients.

Other therapies under study

Treatments of note in the review included the following:

- **Tocilizumab.** This monoclonal antibody interleukin-6 receptor antagonist, approved by the FDA for treatment of rheumatoid arthritis and for cytokine release syndrome related to chimeric antigen receptor (CAR) T-cell therapy, has yielded success in small series of patients with severe cases of COVID-19, according to authors. In one 21-patient report, 91% had clinical improvement, usually after a single dose. In China, tocilizumab is included in COVID-19 treatment guidelines, and several randomized clinical trials are underway in China.
- **Immunoglobulin therapy.** Antibodies from recovered COVID-19 patients could help with free virus and infected cell immune clearance, the authors said, adding that further studies are warranted beyond a few small published case series that suggest promise. Furthermore, on March 24 the FDA released guidance for screening donors for COVID-19 convalescent plasma and on emergency investigational new drug applications based on this modality.
- **Lopinavir/ritonavir.** Despite demonstrated in vitro activity against other novel coronaviruses, there are no published in vitro data for lopinavir/ritonavir in SARS-CoV-2, and likely a "limited role" for this combination is anticipated in treating COVID-19, according to the review authors. In an open-label randomized clinical trial published in the New England Journal of Medicine (2020 Mar 18. doi: 10.1056/NEJMoa2001282), there were no differences in clinical improvement, viral clearance, or mortality for antiviral treatment versus standard care. Delayed treatment initiation may explain the ineffectiveness, though a subgroup analysis didn't show a shorter time to clinical improvement for those who got the treatment earlier.
- **Ribavirin.** Likewise, this antiviral medication has efficacy and safety data suggesting "limited value" for treatment of COVID-19. Treatment of SARS yielded "inconclusive results" for ribavirin, which was also associated with substantial toxicity that included hemolytic anemia in 60% of SARS patients.
- **Oseltamivir.** While it may treat influenza, it has no documented activity against SARS-CoV-2 in vitro: "This agent has no role in the management of COVID-19 once influenza has been excluded," said Dr. Sanders and coauthors.
- **Corticosteroids.** They could decrease inflammatory responses in the lung, but they could also lead to delays in viral clearance and increases in secondary infection risk. Guidelines for COVID-19 say to avoid corticosteroids, and the authors of the review concur, saying that potential harms and lack of proven benefit mean they usually should not be used outside of a randomized clinical trial setting.

Dr. Sanders reported no potential conflicts. Senior author James B. Cutrell, MD, also of the University of Texas Southwestern Medical Center, reported nonfinancial support from Gilead and Regeneron outside of the study. No other authors reported disclosures.

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Treating lung cancer during the pandemic

BY PAM HARRISON

Lung cancer experts in Europe issued highly considered recommendations for the management of lung cancer during the COVID-19 crisis, the main intention of which is to minimize the risk of patients getting infected by SARS-CoV-2 while in hospital receiving treatment.

The recommendations were published online April 3 in ESMO Open.

"We know that having cancer increases the risk of dying of COVID-19, although not necessarily the risk of getting the virus and we also know that having lung cancer could increase the risk of pulmonary complications from SARS-CoV-2," lead author Alfredo Addeo, MD, University Hospital of Geneva, said in an interview.

"Try to think outside the box and find a way to minimize the risk of infection, and if you have to limit treatment, discuss the pros and cons of your treatment plan with the patient."

"But patients who are often in the hospital have a higher risk of catching the virus. So this paper is not about not giving necessary treatment, it's about treating patients the best you can based on the area where you live and the resources you have and keeping patients away from the hospital as much as possible," he added.

"The main message is, try to personalize the care you deliver," Dr. Addeo said.

"Rather than remain rigid about how you've been treating patients thus far, try to think outside the box and find a way to minimize the risk of infection, and if you have to limit treatment, discuss the pros and cons of your treatment plan with the patient and make sure the message is given clearly," he emphasized.

Considering benefit

The first general concept to keep in mind is: How likely is a patient to benefit from treatment?

"All regimens with a survival benefit should be maintained and prioritised whenever possible," Dr. Addeo and colleagues observe. The other co-authors of the paper are Giuseppe Banna, MD, Ospedale Cannizzaro, Catania, Italy; Alessandra Curioni-Fontecedro, MD, University Hospital Zürich; and Alex Friedlaender, MD, University Hospital of Geneva.

For non–small cell lung cancer (NSCLC), neoadjuvant chemotherapy for locally advanced resectable disease and sequential/concurrent chemotherapy/radiation therapy for patients with stage III lung cancer – provided they have adequate respiratory function – should be started when possible and should not be stopped without justification, the authors point out.

This is also true for first-line ther-

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apy in patients with metastatic disease. Treatment should also not be stopped without good reason among patients already receiving maintenance immune checkpoint inhibitor therapy.

For small-cell lung cancer (SCLC), both first-line treatment for extensive-stage disease as well as concurrent chemotherapy/radiotherapy for patients with limited-stage disease should be started when possible, again provided they have adequate respiratory function.

Palliative or stereotactic body radiotherapy (SBRT) delivered outside the lung should also be initiated when possible in SCLC patients.

The authors caution, however, that, if palliative or SBRT outside the lung requires multiple visits to the hospital, treatment to the lung should be limited to cases with compression of airways or bleeding.

Oncologists should also try to start radiotherapy on day 1 of chemotherapy because then only 2 cycles will be needed; if radiotherapy is started with cycle 2 or is given sequentially, 3 cycles of treatment will be required.

"Fractions of SBRT could be reduced, depending on organ at risk (8 fractions to 5 or 3) while palliative RT [given] as a single fraction or two (8-10 Gy or 17 Gy, respectively) should be used where possible," the authors observe.

Concurrent chemotherapy with radiotherapy for limited-stage disease should not be stopped without justification and nor should first-line treatment for metastatic SCLC, the authors continue.

Again, however, patients must have adequate respiratory function to receive or continue with concurrent chemotherapy and radiotherapy, they add.

For patients with stage III NSCLC, concurrent chemotherapy plus radiotherapy may be considered and given preferentially or not.

Similarly, oral rather than intravenous chemotherapy may be preferred for elderly NSCLC patients or for those with an Eastern Cooperative Oncology Group performance status of 2 as well as for SCLC patients.

Delaying surgery

As a general principle, the use of neoadjuvant chemotherapy instead of adjuvant therapy following surgery can delay the need for immediate surgery. If surgery can be delayed, "the risk of a patient catching the virus several months from now might be less," Dr. Addeo noted. Thus, treating patients upfront with chemotherapy is one tactic to consider in appropriate patients.

For NSCLC patients at high risk for COVID-19, adjuvant chemotherapy should be discussed and potentially withheld, the authors observe.

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NSCLC patients at high risk for COVID-19 include those with either comorbidities such as cardiovascular or pulmonary disease as well as patients who are 70 years of age and older.

Immunotherapy should also be discussed and possibly delayed for stage III NSCLC patients following concurrent chemotherapy and radiation, they add.

Maintenance pemetrexed also may be withheld for NSCLC patients, and intervals of immunotherapy may be prolonged (e.g., nivolumab every 4 weeks and pembrolizumab every 6 weeks).

Intervals of immunotherapy should be similarly prolonged for SCLC patients, they continue.

"Shorter duration of chemotherapy (e.g., four cycles of chemotherapy instead of six) should be discussed with patients and maintenance chemotherapy can be withheld," the authors note.

Furthermore, "given the pandemic, it is highly likely that metastatic cancer patients will be less likely to be intubated or to be heavily ventilated compared to patients without any comorbidity," Dr. Addeo explained.

"So we have to acknowledge that metastatic lung cancer patients will be at higher risk of dying due to severe pulmonary COVID-19 complications," he added.

Therefore, third and further lines

of chemotherapy in both NSCLC and SCLC patients at significant COVID-19 risk should not be initiated without having a good reason to do so.

"Prophylactic cranial irradiation (PCI) is still a matter of debate [in SCLC patients]," Dr. Addeo noted.

"So the reasonable alternative is to do surveillance MRI and in 6 or 8 months, we can probably offer PCI more safely at that point," he suggested, adding that radiation therapy to the brain should be considered only if a patient develops brain metastases.

The authors also suggest that thoracic consolidation radiotherapy for extensive stage SCLC should not be initiated unless there is good reason to do so.

Patients with family members or caregivers who have tested positive for COVID-19 should themselves be tested before or during any cancer treatment.

If patients themselves then test positive and are asymptomatic, "28 days of delay should be considered before (re)starting the treatment," the authors advise.

However, two negative tests done 1 week apart should be carried out before starting or restarting treatment, they note.

The authors have disclosed no relevant financial relationships.

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

New guide on managing acute CVD during COVID-19

BY DEBRA L. BECK

The Chinese Society of Cardiology (CSC) has issued a consensus statement on the management of cardiac emergencies during the COVID-19 pandemic.

The document first appeared in the Chinese Journal of Cardiology, and a translated version was published in Circulation. The consensus statement was developed by 125 medical experts in the fields of cardiovascular disease and infectious disease. This included 23 experts currently working in Wuhan, China.

Three overarching principles guided their recommendations.

- The highest priority is prevention and control of transmission (including protecting staff).
- Patients should be assessed both for COVID-19 and for cardiovascular issues.

directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients, 332 patients with chronic fibrosing ILDs with a progressive phenotype, and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. Idiopathic Pulmonary Fibrosis: OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [*see Warnings and Precautions*]. Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype: OFEV was studied in a phase 3, double-blind, placebo-controlled trial (Study 5) in which 663 patients with chronic fibrosing ILDs with a progressive phenotype were randomized to receive OFEV 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. At 52 weeks, the median duration of exposure was 12 months for patients in both treatment arms. Subjects ranged in age from 27 to 87 years (median age of 67 years). The majority of patients were Caucasian (74%) or Asian (25%). Most patients were male (54%). The most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of patients treated with OFEV and in 5% of patients treated with placebo. No pattern was identified in the adverse events leading to death. Adverse reactions leading to permanent dose reductions were reported in 33% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (16%). Adverse reactions leading to discontinuation were reported in 20% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reaction that led to discontinuation in OFEV-treated patients was diarrhea (6%). The safety profile in patients with chronic fibrosing ILDs with a progressive phenotype treated with OFEV was consistent with that observed in IPF patients. In addition, the following adverse events were reported in OFEV more than placebo in chronic progressive fibrosing ILD: nasopharyngitis (13% vs. 12%), upper respiratory tract infection (7% vs 6%), urinary tract infection (6% vs. 4%), fatigue (10% vs. 6%), and back pain (6% vs. 5%). Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.
[b] Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.
[c] Includes hypertension, blood pressure increased, and hypertensive crisis

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions]*, non-serious and serious bleeding events, some of which were fatal [*see Warnings and Precautions*], pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS: 7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV *[see Dosage and Administration]*. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **7.2 Anticoagulants:** Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [*see Warnings and Precautions*]. **7.3 Pirfenidone:** In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone. **7.4 Bosentan:** Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized

- At all times, all interventions and therapies provided should be in concordance with directives of infection control authorities.

"Considering that some asymptomatic patients may be a source of infection and transmission, all patients with severe emergent cardiovascular diseases should be managed as suspected cases of COVID-19 in Hubei Province," noted writing chair and cardiologist Yaling Han, MD, of the General Hospital of Northern Theater Command in Shenyang, China.

In areas outside Hubei Province, where COVID-19 was less prevalent, this "infected until proven otherwise" approach was also recommended, although not as strictly.

Diagnosing CVD and COVID-19 simultaneously

In patients with emergent cardiovascular needs in whom COVID-19 has not been ruled out, quarantine in a single-bed room is needed, they wrote. The patient should be monitored for clinical manifestations of the disease, and undergo COVID-19 nucleic acid testing as soon as possible.

After infection control is considered, including limiting risk for infection to health care workers, risk assessment that weighs the relative advantages and disadvantages of treating the cardiovascular disease while preventing transmission can be considered, the investigators wrote.

At all times, transfers to different areas of the hospital and between hospitals should be minimized to reduce the risk for infection transmission.

The authors also recommended the use of "select laboratory tests with definitive sensitivity and specificity for disease diagnosis or assessment."

For patients with acute aortic syndrome or acute pulmonary embolism, this means CT angiography. When acute pulmonary embolism is suspected, D-dimer testing and deep vein ultrasound can be employed, and for patients with acute coronary syndrome, ordinary electrocardiography and standard biomarkers for cardiac injury are preferred.

In addition, "all patients should undergo lung CT examination to evaluate for imaging features typical of COVID-19. ... Chest x-ray is not recommended because of a high rate of false negative diagnosis," the authors wrote.

Intervene with caution

Medical therapy should be optimized in patients with emergent cardiovascular issues, with invasive strategies for diagnosis and therapy used "with caution," according to the Chinese experts.

Conditions for which conservative medical treatment is recommended during COVID-19 pandemic include ST-segment elevation MI (STEMI) where thrombolytic therapy is indicated, STEMI when the optimal window for revascularization has passed, high-risk non-STEMI (NSTEMI), patients with uncomplicated Stanford type B aortic dissection, acute pulmonary embolism, acute exacerbation of heart failure, and hypertensive emergency.

"Vigilance should be paid to avoid misdiagnosing patients with pulmonary infarction as COVID-19 pneumonia," they noted.

Diagnoses warranting invasive intervention are limited to STEMI with hemodynamic instability, life-threatening NSTEMI, Stanford type A or complex type B acute aortic dissection, bradyarrhythmia complicated by syncope or unstable hemodynamics mandating implan-

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Cardiac symptoms can be first sign of COVID-19

BY M. ALEXANDER OTTO
MDedge News

In about 7% of people with confirmed novel coronavirus disease 2019 (COVID-19), and 22% of the critically ill, the virus injures the heart, probably by either attacking it directly or causing a cytokine storm that leads to myocyte apoptosis, according to a report from the Columbia University Division of Cardiology in New York.

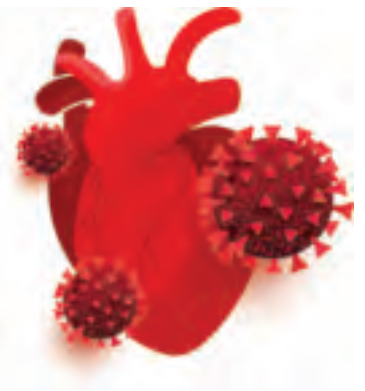
Reports from China document patients presenting with palpitations and chest pain without the typical fever and cough. Among those affected, acute myocardial injury is either apparent at presentation or develops after hospitalization.

The exact mechanism of injury is uncertain, but for now, "it appears that the incidence of fulminant myocarditis and profound cardiogenic shock is low; however, the rate of recovery and mode of treatment are yet to be determined," wrote authors led by Kevin Clerkin, MD, a cardiologist and assistant professor of medicine at Columbia (Circulation. 2020 Mar 21. doi: 10.1161/CIRCULATIONAHA.120.046941).

High-sensitivity cardiac troponin I (hs-cTnI) might be prognostic. In one Chinese study of hospitalized patients, median hs-cTnI levels were 2.5 pg/mL in survivors on day 4 of symptoms and did not change significantly during follow-up. Among people who died, day 4 hs-cTnI was 8.8 pg/mL and climbed to 290.6 pg/mL by day 22 (Lancet. 2020 Mar 11. doi: 10.1016/S0140-6736[20]30566-3).

"The rise in hs-cTnI tracks with other inflammatory biomarkers ... raising the possibility that this reflects cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury," Dr. Clerkin and colleagues wrote.

But there are also acute heart injury reports out of China, including one man who presented with chest pain and ST-segment elevation, but no coronary obstruction, and another who presented with fulminant myocarditis in addition to severe respiratory manifestations, but with no cardiac history.



Irina Shatilova/Getty Images

Both had depressed left ventricular ejection fractions, enlarged left ventricles, and elevated cardiac biomarkers, and both responded to intravenous immunoglobulin and steroids, among other treatments.

Amid a surge of COVID-19 cases at Columbia, "we have seen both forms of cardiac presentations: those presenting with cardiac predominant symptoms (none have had true [ST-segment elevation myocardial infarctions] yet, but most fall in the myopericarditis group), some of which have required mechanical circulatory support, and those who seem to have secondary myocardial injury with globally elevated inflammatory biomarkers (e.g., ferritin, interleukin-6, lactate dehydrogenase, hs-cTnI, and D-dimer)," Dr. Clerkin said in an interview.

"We are discussing each of these cases in a multidisciplinary fashion with our infectious disease, pulmonary, interventional cardiology, and cardiac surgery colleagues to try to make the best decision based on what we know and as our knowledge evolves," he said.

The exact cardiac effect of COVID-19 is unknown for now, but it is known already that it rides along with cardiovascular issues. There's a high prevalence of hypertension, diabetes, and diagnosed cardiovascular disease among patients, but it's unclear at this point if it's because the virus favors older people who happen to be more likely to have those problems or if it attacks people with those conditions preferentially.

It might be the latter. The virus that causes COVID-19, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), invades cells through angiotensin-converting enzyme (ACE) 2 receptors, which are highly expressed in the heart.

That raises the question of whether ACE inhibitors or angiotensin receptor blockers might help. However, "at this time, nearly all major societies have recommended against adding or stopping ... antagonists in this setting, unless done on clinical grounds independently of COVID-19, given the lack of evidence," Dr. Clerkin and his colleagues wrote.

As for heart transplants, the current thinking is to continue them without changes in immunosuppression so long as recipients test negative and haven't been around anyone who has tested positive for a month. If a donor had COVID-19, they should have been free of the virus by polymerase chain reaction for at least 14 days. The concern is that it might be in the donor heart.

If transplant patients come down with COVID-19, the "data to date [indicate that management] is supportive care and continuation of immunosuppression for mild COVID-19 with reduction of the antimetabolite (mycophenolate or azathioprine), and further treatment based on disease severity and drug availability. Notably, one potential treatment option for COVID-19 is protease inhibitors," the authors said, but it's important to remember that they will increase the levels of cyclosporine, tacrolimus, and other calcineurin inhibitor transplant drugs.

At Columbia, "our processes have been adjusted" for heart transplants. "For instance, nonurgent testing [before and after transplant] has been tabled, we have predominantly shifted to noninvasive screening for rejection, and each potential transplant requires more scrutiny for urgency, donor screening/risk for COVID-19, and perioperative management," Dr. Clerkin said in the interview.

There was no funding, and the authors had no disclosures.

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SOURCE: Clerkin K et al. Circulation. 2020 Mar 21. doi: 10.1161/CIRCULATIONAHA.120.046941.

Continued from previous page

tation of a device, and pulmonary embolism with hemodynamic instability for whom intravenous thrombolytics are too risky.

Interventions should be done in a cath lab or operating room with negative-pressure ventilation, with strict periprocedural disinfection. Personal protective equipment should also be of the strictest level.

In patients for whom COVID-19 cannot be ruled out presenting in a region with low incidence of COVID-19, interventions should be considered for more severe cases and undertaken only in a cath lab, electrophysiology lab, or operating room "with more than standard disinfection procedures that fulfill regulatory mandates for infection control."

If negative-pressure ventilation is not available, air conditioning (for example, laminar flow and ventilation) should be stopped.

Establish plans now

"We operationalized all of these strategies at Beth Israel Deaconess Medical Center several weeks ago, since Boston had that early outbreak with the Biogen conference, but I suspect many institutions nationally are still formulating plans," Dhruv Kazi, MD, MSc, said in an interview.

Although COVID-19 is "primarily a single-organ disease – it destroys the lungs" – transmission of infection to cardiology providers was an early problem that needed to be addressed, said Dr. Kazi. "We now know that a cardiologist seeing a patient who reports shortness of breath and then leans in to carefully auscultate the lungs and heart can get exposed if not provided adequate personal protective equipment; hence the cancellation of elective procedures, conversion of most elective visits to telemedicine, if possible, and the use of surgical/N95 masks in clinic and on rounds."

Regarding the CSC recommendation to consider medical over invasive management, Dr. Kazi noted that this works better in a setting where rapid testing is available. "Where that is not the case – as in the U.S. – resorting to conservative therapy for all COVID suspect cases will result in suboptimal care, particularly when 9 out of every 10 COVID suspects will eventually rule out."

One of his biggest worries now is that patients simply won't come. Afraid of being exposed to COVID-19, patients with MIs and strokes may avoid or delay coming to the hospital.

"There is some evidence that this occurred in Wuhan, and I'm starting to see anecdotal evidence of this in Boston," said Dr. Kazi. "We need to remind our patients that, if they experience symptoms of a heart attack or stroke, they deserve the same lifesaving treatment we offered before this pandemic set in. They should not try and sit it out."

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

Join us for CHEST Annual Meeting 2020

Registration for CHEST Annual Meeting 2020 has opened! It is important now, more than ever, to stay up to date in clinical chest education. CHEST Annual Meeting is prepared to equip attendees with the latest education and original research in the field that can be taken back home and implemented into practices.

While CHEST is excited to bring the premier event in clinical chest medicine to their Second City Home of Chicago, Illinois, this October 17-21, it is understood that now may not be the best time to be planning for a conference that is 6 months down the road. Currently, your full attention is likely on your patients, your families, your health, and your safety, and it should be! Here at CHEST, the hope is to create a "light at the end of the tunnel" to give you and your colleagues something to look forward to – an opportunity to relax, learn, explore, and reconnect with your peers in the chest medicine field.

This year's annual meeting will be filled with both new and returning educational opportunities, including CHEST Games; virtual patient tours; hands-on simulation courses; problem-based learning; and the return of FISH Bowl, an innovation competition. Along with the advanced education, there will be countless opportunities to network at after-hour events, such as the CHEST Challenge final competition, the Young Professionals Reception, and the CHEST Foundation Casino Night. Our hope is that you will be able to look ahead to October and be excited about the chance to experience everything that will be offered at CHEST 2020.

Before the meeting in October, don't forget to submit your abstracts and case reports for consideration to be presented at CHEST 2020. CHEST is excited to give you and your colleagues the opportunity to present new and original research at this year's meeting, which is why the deadline for submissions has been extended to June 1, 2020.

CHEST acknowledges that your workload is becoming increasingly heavier each day, and we are also making the safety of attendees the top priority.

That is why CHEST will be granting full refunds to any registrant who finds that they can no longer attend CHEST 2020 as the meeting approaches. Any hotel reservation that is made through CHEST's official housing site, onPeak, will be able to be changed or canceled up to 24 hours in advance of the reservation date. Visit chestmeeting.chestnet.org/hotel-accommodations for more information.

CHEST 2020 meeting chair, Victor Test, MD, FCCP, hopes to leave CHEST learners with a beacon of hope, saying, "Signing up to come to the meeting and participating may seem impossible to think about right now. We are working hard to provide a high-quality experience and are encouraging everyone to look forward to the future, which will be a lot brighter."

For all of the latest information on CHEST 2020, visit chestmeeting.chestnet.org.

Courtesy of the Chicago Architecture Foundation

FROM THE EVP/CEO

How CHEST is helping to flatten the curve

BY ROBERT MUSACCHIO, PHD

As you know, the COVID-19 pandemic has caused immense strain on global health systems. With our membership at the epicenter, many of you have experienced firsthand the shortages that result from a surging patient population – lack of personal protective equipment (PPE), access to ventilators, and increasing demand for more qualified health-care workers needed on the front lines to treat and care for patients. As the staff leader of your organization, I feel an immense responsibility to support our community through this crisis.

In recent weeks, CHEST petitioned the federal and local governments on several issues, advocating for tax relief for COVID responders, expansion of liability protections, and the development of a provider relief fund. We will continue to collaborate with other societies and push such efforts. However, we also recognize an obligation to make a more tangible, real-time difference in the circumstances of our membership and the lives of the patients you are working to save.

An opportunity arose when we received a call from Dr. Doreen Addrizzo-Harris, Immediate Past President of the CHEST Foundation and Professor of Medicine at NYU Langone Health. In late March, New York City was seeing an uptick in patients with confirmed COVID infection in critical condition that was escalating by the day. The situation was beginning to resemble the trajectory of hotspots in Wuhan, China and Italy, and it was already taking a toll on health-care teams. Dr. Adrizzo-Harris asked whether there was any way to leverage the strength of the CHEST community to provide help. Already, our headquarters team had received unsolicited offers to travel to areas in need from our members. The question was how could we more proactively identify such willing and able clinicians.

Dr. Robert Musacchio

We knew that if we could apply our knowledge and deploy our heroic members, we could develop a solution that could save lives and relieve frontline clinicians.

We quickly drew upon our existing CHEST Analytics platform to target physicians outside New York City who might be well-positioned to travel. We harnessed our communication channels to get the word out. The response was immediate, with more than 100 people completing applications to join forces with their colleagues in New York. In the first 10 days of recruitment efforts, we added an additional 250 interested volunteers to the system. The positive response from members showed both the willingness of qualified medical staff to assist on the front lines but also highlighted deficiencies in other registration systems overwhelmed with requests in the face of this pandemic. Finding certified pulmonary and critical care physicians who are willing to step in where they are needed is time- and labor-intensive and detracts from health systems' ability to focus on care. Watching the projections in other regions, we recognized other areas may soon need this same help.

With this in mind, CHEST approached ATS and our long-time partner PA Consulting to help us address the problem on a national scale. We felt we had the resources to leverage our databases and our analytic tools to create a more efficient process that would put physicians in hospitals where they could do the most good more efficiently. We knew that if we could apply our knowledge and deploy our heroic members, we could develop a solution that could save lives and relieve frontline clinicians. By leveraging the existing CHEST Analytics platform, the team created a solution that can be used by provider institutions, government agencies, and willing clinicians to quickly and effectively provide care where it is needed most. The team has engineered the solution to be scalable nationally and expandable to other critical care specialties (eg, anesthesia, emergency, nursing, respiratory therapy).

The Clinician Matching Network formally launched on April 14, 2020. It provides a two-way input that accepts sign up from individual clinicians and gathers needs and requirements from hospital systems, connecting health-care providers with the systems most in need of the specific support they are equipped to provide. We believe this has the potential to enable us to move ahead of the curve of the crisis.

I am very proud of the teams that lead this effort and have gained a greater appreciation of how CHEST, in partnership with other medical societies, can fully utilize data and analytics toward implementing public health solutions. The design and development of the Clinician Matching Network was accomplished in less than a week, leveraging a methodology that will enable the team to continuously improve and iterate through weekly releases, adding functionality quickly as the pandemic evolves.

In the weeks ahead, communications will be distributed to hospitals and hospital systems to help identify their staffing needs, encourage them to input their needs into the Clinician Matching Network, and expand the clinician-to-hospital matching effort. We aim to increase the number of collaborationg associations to grow the pool of clinicians who can be deployed to areas in need.

Please visit www.chestnet.org/clinician-matching to learn more, sign up to serve, tell us about the needs of your institution, or collaborate toward this cause.

SLEEP STRATEGIES

COVID-19 and impact on sleep medicine practices

BY SHANNON S. SULLIVAN, MD, AND INDIRA GURUBHAGAVATULA, MD, MPH

Introduction

Since reported in late 2019 in Wuhan China, the disease named "novel coronavirus disease 2019" (COVID-19), caused by the virus referred to as Severe Acute Respiratory Syndrome-causing Coronavirus-2 (SARS-CoV-2) has spread widely to many parts of the world. As of April 13, 2020, a total of 210 countries reported more than 1.9 million cases, resulting in more than 119,000 deaths.[1] All 50 states have reported cases of COVID-19 to the Centers for Disease Control and Prevention (CDC), and most US states are reporting community spread. While levels of COVID-19 activity vary by region, the CDC has reported that the US remains in the acceleration phase of the pandemic, and that widespread transmission is expected.

On March 18, the Centers for Medicare & Medicaid Services (CMS) advised[2] that all elective surgeries and nonessential medical, surgical, and dental procedures should be delayed to promote physical distancing, preserve personal protective equipment (PPE), and enable health-care workers (HCW) to redirect work to high-need areas. California was the first to issue a statewide shelter-in-place order on March 19, and by April, leaders in 42 states, the District of Columbia, and Puerto Rico issued similar stay-at-home orders. The White House has announced that physical distancing should continue until at least April 30. With the potential for an explosion of new cases that could overwhelm health-care resources, "business as usual" ceased to exist practically overnight.

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Nucala
(mepolizumab)

REAL PATIENTS. REAL LIFE.

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Real patient compensated by GSK for his time.

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The speed with which these events transpired, the demand to tailor response within days or even hours, the lack of robust data to support decision-making, the possibility of spread by asymptomatic carriers, and the potential risk for airborne, as well as droplet and fecal-oral spread, caused sleep medicine clinicians to rely on expert consensus and clinical judgment. The goal of such guidance has been to optimize care to patients with sleep disorders, while protecting the health and safety of all. Sleep medicine practices have had to balance efforts to reduce viral exposure and transmission, the need to triage health-care resources and personnel, and maintain access to care.

General clinical measures

From the outset, in areas of community spread, sleep medicine practices were called to adapt to now-standard measures, such as provider self-quarantine if ill or exposed, in-person clinic triage strategies for patients and staff prior to entrance to facilities to rapidly identify people with respiratory illness (eg, temperature monitoring), elimination of nonessential visitors, and infection control measures such as vigilant cleaning and appropriate use of personal protective equipment (PPE) during patient interactions. Typical issues facing sleep medicine practices include the need to prioritize urgent or emergency care, track canceled or postponed visits, and maintain access to communication with patients, the health-care team, payors, and employers.

Sleep medicine practices have had to balance efforts to reduce viral exposure and transmission, the need to triage health-care resources and personnel, and maintain access to care.

Infection mitigation recommendations: sleep laboratories and ambulatory practices

Diagnostic testing

By mid-March, relatively early in the course of the outbreak in the US, the American Academy of Sleep Medicine (AASM) released recommendations for sleep clinics and laboratories regarding continuation of in-lab diagnostic, split-night, and titration studies, as well as clinical interactions and telemedicine, taking into account the CDC mitigation strategies[3] which vary according to level of community transmission or impact of COVID-19.

Dr. Sullivan

This advisory was updated repeatedly over the ensuing weeks, most recently on April 8, as community-based spread increased. The AASM now strongly urges all sleep clinicians to postpone in-laboratory polysomnography (PSG) for adults and children, both diagnostic and positive airway pressure (PAP) titrations, except in emergencies. Data regarding adherence with these recommendations are lacking; anecdotal reports suggest that sleep medicine communities most heavily affected by the community spread are indeed following this practice.

The AASM guidance also advises use of home sleep apnea testing (HSAT) with consideration of single-use components or devices, use of mail-in recorders, and/or removal of reusable devices from service for 72 hours between patients.

Positive airway pressure (PAP) therapy

The potential for PAP devices to promote the aerosolization of viral particles, which could increase transmission to others on shared ventilation networks in homes and health-care settings, requires careful attention.

Generally, exhaled particle size depends on multiple characteristics, including the force and pressure at generation and environmental conditions (eg, temperature, relative humidity, and air flow). Large-size particles remain suspended in the air only briefly and settle within 1 meter from the source; these are usually mediated by breathing zones of individuals.[4] However, smaller particles can travel farther, with distance governed by airflow that is driven by many variables, including ventilation, human movement, and temperature gradients. While droplets tend to evaporate rapidly, dry residues can remain suspended in the air.[5] Infectious respiratory aerosols can occur as droplets >5 mcm diameter, or droplet nuclei (<5 mcm diameter).[6] Present evidence indicates that SARS-CoV-2 transmission occurs primarily through droplet spread in settings with normal breathing. However, the World Health Organization (WHO) advises more stringent, airborne precautions for aerosol-generating procedures with COVID-19. Such procedures include intubation, extubation, noninvasive ventilation, high-flow nasal cannula, and cardiopulmonary resuscitation before intubation.[7] Some evidence indicates that SARS-CoV-2 can linger in aerosol form for hours,[8] and aerosol transmission is therefore plausible. Non-peer reviewed data in real-world settings indicate the presence of SARS-CoV-2 in air samples from hallways outside and in rooms adjacent to COVID-19-containing patients.[9]

These findings raised some concerns about use of PAP in medical and home environments, leading to the recommendation that the decision to continue or withhold PAP temporarily be made based on a risk-benefit evaluation. Scant data hint that PAP therapy may be safe to use in rooms that support appropriate ventilation (eg, negative pressure rooms). Regarding mask type, recently, a group reported the possibility that oronasal masks have a better aerosol dispersal profile.5 However, this conclusion was based on a single study of a specific model of oronasal mask, which demonstrated an absence of ability to measure a dispersion air jet, because the exhalation ports on the mask caused diffuse rather than directed dispersion of air.[10] The same study found, that when the jet could be measured (with nasal pillows or with leak from any interface), greater dispersion was indeed evident. While anecdotal practical methods to filter exhaled air from PAP devices to reduce aerosol transmission have been proposed, data regarding successful reduction in transmission are still lacking, and such methods are not endorsed by mask manufacturers.

As the spread of COVID-19 accelerated, the AASM recommended that sleep medicine practices postpone and reschedule all nonemergency, in-person appointments, and conduct as many visits as possible by telemedicine.

Ambulatory clinics: role of telemedicine

As the spread of COVID-19 disease accelerated, the AASM recommended that sleep medicine practices postpone and reschedule all non-

EDITOR'S PERSPECTIVE

Drs. Sullivan and Gurubhagavatula, co-chairs of the American Academy of Sleep Medicine Public Safety Committee, contributed an excellent and timely overview of the impact of COVID-19 on sleep medicine practices nationally. The speed of change to current practices came like a sudden storm on March 18, 2020, when CMS announced its recommendation of halting all nonessential medical, surgical, and dental procedures in order to preserve medical equipment, free up the health-care workforce, and minimize infection risks to patients and health-care providers.

With this pivotal announcement, the medical community was forced to mobilize in ways that were never expected before. CMS followed up with recommendations for new models of care and billing practices with a specific focus on telemedicine. With technologic advances in remote monitoring for evaluation and treatment of sleep-disordered breathing and other sleep disorders, the field of sleep medicine is poised to be an ideal model for telemedicine. Although telemedicine is not new to the practice of sleep medicine, it has not been widely embraced.

The COVID-19 pandemic will undoubtedly force a "new normal" for medicine worldwide, and we can be sure to embrace certain aspects of this change, including implementation of telemedicine into existing models of care. It remains to be seen how the medical community will be able to successfully adapt and will heavily depend on how CMS implements its policies to this "new normal."

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emergency, in-person appointments, and conduct as many visits as possible by telemedicine.

This rapid transition posed many layers of logistical complexity, including how to quickly initiate or scale up an often fledging telemedicine presence; scheduling and instructing patients for telemedicine encounters; problem-solving in situations with limited device and Internet availability; triaging patients based on risk; and tracking postponed appointments. Administrators, medical assistants, nurses, advanced practitioners, respiratory therapists, technologists, and physicians have learned new ways of doing things, and laboratory personnel have undergone training and transitioned to new roles and responsibilities during postponement of lab studies. Training programs, in particular, have had to be nimble in finding ways to meet the educational needs of sleep medicine fellows that leveraged telemedicine opportunities.

AASM has recommended avoidance of PAP or noninvasive ventilation for those with presumed or confirmed COVID-19 who cannot self-isolate according to CDC guidance.

Economic implications of transformed sleep medicine practices

While deploying such systematic change costs both time and money, sleep practices are also confronted with questions around lost revenue from drops in laboratory and clinic volumes. Many additional questions around reimbursement and revenue shortfalls are present, and short-term, furloughed employees may not be able to sustain income loss, which could result in difficulty in resuming services when the COVID-19 threat has been reduced.

Helpfully, during this public health emergency, CMS has expanded coverage for telemedicine services and waived requirements for face-to-face or in-person encounters,[11] and some private payers have followed. Additionally, for the duration of the public health emergency, Medicare will cover PAP devices based on the clinician's assessment of the patient without requiring PSG or a home sleep apnea test (HSAT). However, CMS has not clarified what follow-up testing, if any, may be required after this public health emergency is over. The duration of these new payment models remains uncertain.

Recommendations for PAP users

Patients and families, practitioners, and group living facilities have all expressed concerns about use of PAP during the epidemic given presumed increased risk of viral spread. In many hospital protocols, the use of PAP is restricted or disallowed for patients with suspected or confirmed COVID-19. Guidance regarding out-of-hospital use of PAP has been sparse.

AASM has recommended avoid-

Continued on following page

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tion (NIV) for those with presumed or confirmed COVID-19 who cannot self-isolate according to CDC guidance. Risk-benefit assessment is recommended for those who perform safety-sensitive activities or have higher-risk medical conditions. During the period that PAP is withheld, alternative or modifying therapies can be considered, such as positional therapy or oral appliance.

Cleaning device components and washing and replacing filters as recommended by the manufacturer, as well as simple but important interventions like handwashing before and after touching the face or airway gear is thought to be especially important during this time.

Conclusions

The COVID-19 pandemic has fueled unprecedented, rapid changes in the way sleep medicine practices deliver care to millions of patients. These changes have been propelled by practitioners and staff who have embraced adaptability, creativity, resourcefulness, and attention to safety and effectiveness.

Widespread use of telemedicine services, greater reliance on ambulatory testing, ongoing risk-benefit stratification, leveraging technology and teamwork, and sharing knowledge as it becomes available has resulted in care that is more accessible and convenient for some vulnerable patients, and, yet, challenges persist in accessing needed care. Necessity has been the mother of invention, and we expect the field will need to continue to rebalance as the situation evolves. The ultimate test of these rapid innovations will be how sleep medicine patients fare in the long run, in terms of their health, safety, mortality, and overall quality of life. Future research must address these questions, and the resulting information may yet inform the way sleep medicine is practiced in the years to come.

Dr. Shannon is Medical Director, EVAL Research Institute, Palo Alto, CA; Dr. Gurubhagavatula is Associate Professor, Perelman School of Medicine, University of Pennsylvania, and with Crescenz VA Medical Center, Philadelphia, PA.

References

1. Worldometer. COVID-19 coronavirus pandemic.

2. Centers for Medicare & Medicaid Services. CMS releases recommendations on adult elective surgeries, non-essential medical, surgical, and dental procedures during COVID-19 response. 2020 Mar 18.

3. Centers for Medicare & Medicaid Services. Implementation of mitigation strategies for communities with local COVID-19 transmission.

4. Tang JW et al. Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises. *J Hosp Infect*. 2006;64(2):100-14.

5. Martina Ferioli et al. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. *European Respiratory Review* 2020;29:200068. doi: 10.1183/16000617.0068-2020.

6. World Health Organization. 2014 Apr. Infection prevention and control of epidemic and pandemic-prone acute respiratory infections in health care.

7. World Health Organization. 2020 Feb 27. Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19) Interim guidance.

8. Van Doremalen N et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020 Apr 16;382(16):1564-7. doi: 10.1056/NEJMc2004973.

9. Joshua L Santarpia et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center. *MedRxiv*. 2020 Mar 26. doi: 10.1101/2020.03.23.20039446.

10. David S. Hui et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. *Eur Respir J.* 2019 Apr 11.53(4):pii: 1802339. doi: 10.1183/13993003.02339-2018.

11. Worldometer. COVID-19 coronavirus pandemic.

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Meet the FISH Bowl finalists

CHEST 2019 marked the inaugural FISH Bowl competition for attendees. Inspired by Shark Tank, our kinder, gentler, yet still competitive and cutting-edge FISH Bowl (Furthering Innovation and Science for Health) featured CHEST members disrupting our beliefs about how clinical care and education are performed. As health-care providers, they presented innovative ideas pertaining to education and clinical disease for pulmonary, critical care, and sleep medicine. Six finalists were chosen from dozens of submissions, and three emerged winners. In this new Meet the FISH Bowl Finalists series, CHEST introduces you to many of them – including the People's Choice Award winning team that includes Dr. Russ Acevedo, Wendy Fascia, and Jennifer Pedley.

Names: Russ Acevedo, MD, FCCP; Wendy Fascia MA, RRT; Jennifer Pedley, RRT
Institutional Affiliation: Crouse Health
Title: Crouse Lung PaRTners
Brief Summary of Submission: The goal of our program is to improve the quality of life for patients with COPD by establishing a primary life-long relationship with a respiratory therapist who ensures that they and their caretakers have a thorough understanding of the disease process, as well as the ability to carry out prescribed therapy, obtain resources, and reach out for help once they leave the hospital.

Meet the FISH Bowl competition People's Choice Award winning team that includes Dr. Russ Acevedo, Wendy Fascia, and Jennifer Pedley.

Once enrolled in the Lung Partners Program, patients receive an in-depth initial assessment and daily assessments by a team of specially trained, primary respiratory therapists who will screen them for health literacy, physical functionality, anxiety, depression, sleep disorders, nutrition, and medication management.

Clinical protocols are in place to allow for optimal treatment plans in an efficient timeframe and to assist in timely referral of patients to specialists for further assessment and follow-up.

1. What inspired your innovation? By maximizing the Respiratory Care department efficiency, this allowed for the ability of a primary respiratory care inpatient disease management program. This allows us to use our respiratory therapists to the full extent of their licensure.

2. Who do you think can benefit most from it, and why? We feel this will most benefit the patients, the respiratory therapists, and our physician partners. In the end, the major benefit is to decrease healthcare fractionation.

3. What do you see as challenges to your innovation gaining widespread acceptance? How can they be overcome? To be successful, there needs to be very strong direction from the medical director. We do a poor job in training our fellows to be strong medical directors. Increasing attention to training our fellows in the science of respiratory care will help to overcome this challenge.

Getting the word out is also a challenge that can be overcome by increased exposure of our program like we are receiving from the Fish Bowl Competition and presentations at national meetings.

4. What impact has winning Fish Bowl 2019 had on your vision for the innovation? The positive feedback and networking from our winning has confirmed the value of our program. We have received many requests for our Lung Partner Handbook.

5. How do you think your success at Fish Bowl 2019 will continue to impact your career overall in the months and years to come? We would like to grow our involvement in state and national leadership. In all that we have learned in the development and implementation of Lung PaRTners, we can help support other local and national COPD initiatives.

President's report

BY STEPHANIE M. LEVINE, MD, FCCP

As I write, I must admit this message is different than the one I'd envisioned sharing with you weeks ago. I anticipated updating you on meetings and collaborations with sister societies, new educational offerings, and how the Bologna World Congress and Annual Meeting plans were progressing, but activities at CHEST – and our sense of priority – have evolved along with those of our global community.

Pulmonary and critical care providers are now at the forefront of health care. Our patients, and now the greater public, are relying on our efforts and those of our teams. Amid this crisis, there is a renewed appreciation for the work all of you do; and with it, an opportunity for CHEST to lead and help ensure that the profession and our systems emerge stronger.

Back in February, we held the program committee meeting for the Annual Meeting with over 1,000 submissions. It is astounding how the program came together over just a few days thanks to the preemptive work done by Chair, Dr. Victor Test, and, Co-Chair, Dr. Christopher Carroll, and all of the curricular groups, program committee members, and staff putting in so much work prior to the face-to-face meeting. Also during February, CHEST leadership held the Forum of International Respiratory Societies' (FIRS) strategic planning meeting. The main outcome is a plan to engage a lobbyist to represent the worldwide respiratory societies in the WHO in Geneva on universal topics such as air pollution and now, unfortunately, COVID-19. CHEST was represented at the Society of Critical Care Medicine (SCCM) Congress where we heard late-breaking information as the pandemic was beginning to unfold. We met with the Critical Care Societies Collaborative (CCSC), which is composed of representatives from CHEST, SCCM, the American Thoracic Society (ATS), and the American Association of Critical-Care Nurses (AACN). We had an opportunity to meet with the European Society of Intensive Care Medicine (ESICM) and initiate discussions toward future collaboration.

In early March, as COVID-19 began to interfere with in-person meetings, we participated virtually in the NAMDRC meeting, and finalized our commitment to formally joining forces under the umbrella of CHEST to better serve our members in the area of advocacy. To this end, a new standing CHEST committee was founded, consisting of members from the former NAMRDC Board and members from the CHEST Board of Regents and Board of Trustees and chaired by Dr. Neil Freedman and Dr. Jim Lamberti. We look forward to hosting advocacy sessions during our October meeting, and going forward, our Spring Leadership Meeting will be combined with the former NAMDRC meeting to allow our leaders to participate in advocacy efforts. We will continue to publish the Washington Watchline, bringing important news on efforts to enhance access to care and our ability to deliver it effectively. Our spring leadership meetings, board meetings, and committee meetings in early April were held virtually in light of the pandemic.

Since March, CHEST has been heavily immersed in COVID-19 preparation with new plans for alternate methods of educational delivery, new business models, and curtailment of travel on both our home fronts and on the CHEST front. Zoom and like platforms are now my best friend! Our daily vocabulary now includes an abundance of caution, surge, sheltering in place, quarantine, social distancing, flattening the curve, telemedicine, and don and doff, and we close e-mails, texts, and phone calls with Stay Safe! I established a COVID task force led by Dr. Steve Simpson (CHEST President-Elect) and with representation from the Critical Care, Chest Infections, and Disaster Response and Global Health NetWorks. They have been meeting weekly with the goals of disseminating and distilling COVID-related materials for the busy practitioner with links to the specific article or statement along with the BLUF (Bottom Line Up Front). I'm sure you were able to see and hear some of the reports by Dr. Mangala Narasimhan and others on the front lines in New York, on the CHEST website, *60 Minutes*, and *CNN*. CHEST held a two-part webinar with our Chinese colleagues who shared their COVID experiences with us. These relationships were, in part, built from the PCCM Fellowship Training program we conducted with Chinese physicians, led by Dr. Darcy Marciniuk and Dr. Chen Wang under the guidance of Dr. Renli Qiao, and with the help of the late Dr. Mark Rosen, Dr. Jack Buckley, and myself. CHEST has posted a webinar on point of care ultrasound testing in the setting of COVID since many units are now using more POCUS instead of standard imaging for the critically ill. We have also posted some of our board review lectures on demand for those who want to brush up on their critical care skills and knowledge.

Dr. Stephanie M. Levine

Pulmonary and critical care providers are now at the forefront of health care. Our patients, and now the greater public, are relying on our efforts and those of our teams. Amid this crisis, there is a renewed appreciation for the work all of you do; and with it, an opportunity for CHEST to lead and help ensure that the profession and our systems emerge stronger.

CHEST, unfortunately, had to reschedule the Bologna meeting due to the tragic situation in Italy and plans to reconvene the meeting June 24-26 of 2021. As of now, CHEST 2020 in Chicago is a go, but, of course, we will monitor that situation carefully. We have extended the deadline for abstracts and case reports to June 1, 2020, given the ongoing crisis. The team is busy planning for standalone and complementary online offerings to ensure seamless delivery of critical education in formats that cater easily to our newly formed habits.

CHEST staff have been working from home due to the Illinois shelter in place order but continue to work tremendously hard. They are implementing new areas to the website in an effort to improve the user experience by making information easier to find and more timely. In the publishing space, Dr. Peter Mazzone and the journal team have been receiving hundreds of COVID-related publications, which they have been reviewing and expediting for publication where appropriate. There will also be additional podcasts coming from our journal. The guidelines group has been working on shorter expert panel statements in the setting of rapidly changing evidence. And, to keep us all well, there are opportunities to share our personal feelings and experiences with treating those with COVID in video format on the website and across CHEST social media channels. The CHEST and the CHEST Foundation have initiated a new microgrants program and have reached out to over 150 ILD and COPD support groups across the country to offer them the opportunity to apply for a max $2,500 grant. So far, 7seven groups have requested support. These grants go directly to patients and caregivers and provide needed relief through provision of:

1. Groceries
2. Gift cards
3. Medical supplies (including PPE for patients)
4. Technology needed to communicate with their community and HCPs
5. Household supplies, cleaning supplies

In an attempt to assist our colleagues in New York City, a call went out for volunteers at the end of March and has resulted in over 200 volunteers and more than 400 inquiries from our members. Bravo!!! We want to thank our sister societies for joining our efforts during this time to help all of our respective members and, ultimately, those patients stricken with this terrible illness. As I don and doff my COVID gear, I hope you are all safe and well in this time of unprecedented change in our lives. I look forward to my next report in a few months, hopefully on a happier note.

Stay safe!
Stephanie

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.

POWER TO PREVENT EXACERBATIONS

CLINICAL CHARACTERISTICS TO HELP IDENTIFY SEVERE EOSINOPHILIC ASTHMA:

≥2 exacerbations annually despite maximum doses of ICS/LABA with or without systemic steroids[1-4]

Responsiveness to OCS[1,2]

Elevated blood eosinophils (≥150 cells/µL)*[5,6]

Consider that blood eosinophils can be affected by recent corticosteroid use and can naturally vary throughout the day.[7,8]

*Although not defined by clinical guidelines, one characterization of eosinophilic asthma can be a blood eosinophil count ≥150 cells/µL.[5,6]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

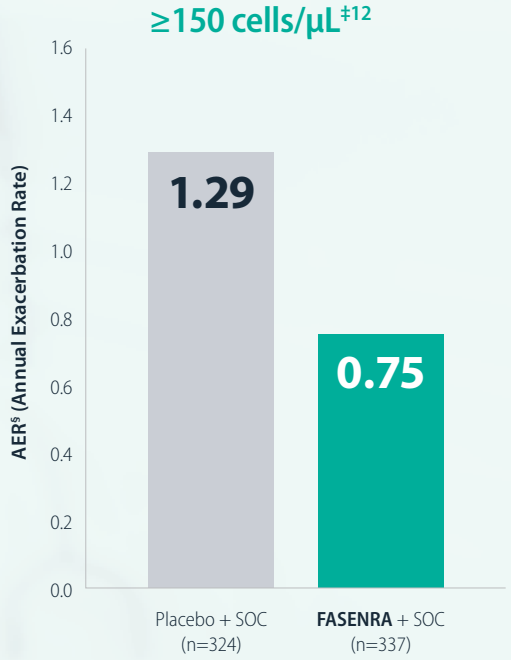
CONSISTENT ANNUAL ASTHMA EXACERBATION RATE DATA

LESS THAN 1

ACROSS BLOOD EOSINOPHIL COUNTS ≥150 AND ≥300 CELLS/µL[9-12]

SIROCCO (48 WEEKS)

≥150 cells/µL[‡12]

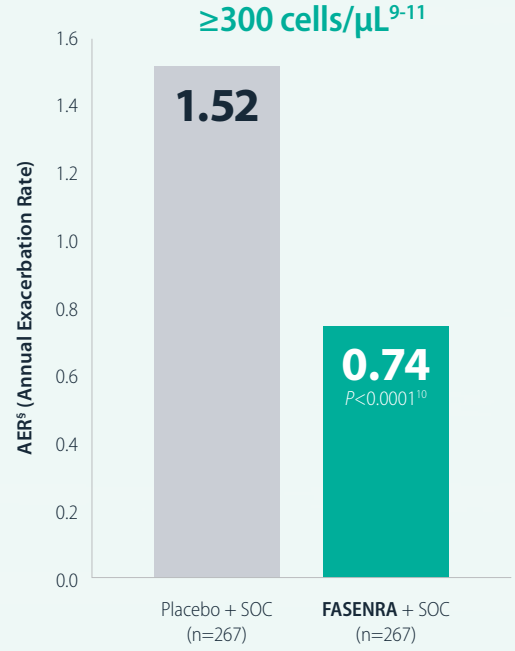


AER§ with **FASENRA** was 0.65 vs 0.98 with placebo + SOC in CALIMA (56 weeks)[‡12]

FASENRA (n=309); Placebo (n=324)

‡The analyses of these endpoints were not multiplicity protected. Results are descriptive only.

≥300 cells/µL[9-11]



AER§ with **FASENRA** was 0.73 vs 1.01 with placebo + SOC in CALIMA (56 weeks, *P*=0.019)[9,11]

FASENRA (n=239); Placebo (n=248)

In SIROCCO and CALIMA, FASENRA and placebo were administered plus standard of care (SOC), which is defined as high-dose ICS/LABA (inhaled corticosteroids/long-acting ß$_2$-agonist) with or without other controllers, including systemic steroids. In SIROCCO and CALIMA, the primary endpoint was the rate of asthma exacerbations in patients with baseline blood eosinophil counts ≥300 cells/µL who were taking high-dose ICS and LABA.[9]

The most common adverse reactions (incidence greater than or equal to 3%) associated with the use of **FASENRA** (and placebo) included headache 8% (6%); pharyngitis 5% (3%); pyrexia 3% (2%); and hypersensitivity reactions 3% (3%).[9]

§Annual exacerbation rate (AER) was defined as the total number of exacerbations multiplied by 365.25, divided by the total duration of follow-up (days) within the treatment group.

MAKE FASENRA YOUR FIRST CHOICE RESPIRATORY BIOLOGIC

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate,

Please see additional Important Safety Information on next page and Brief Summary of Prescribing Information on adjacent pages.

Fasenra®
(benralizumab) Subcutaneous Injection 30 mg
FROM THE START

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.

STUDY DESIGNS

SIROCCO and CALIMA (Trials 1 and 2)

SIROCCO (48-week) and CALIMA (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (SIROCCO) and 1306 (CALIMA) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (SIROCCO) and medium- to high-dose ICS (CALIMA) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. Patients were stratified by geography, age, and blood eosinophil counts (≥300 cells/µL and <300 cells/µL). The primary endpoint was annual exacerbation rate ratio vs placebo in patients with blood eosinophil counts of ≥300 cells/µL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (SIROCCO) and Week 56 (CALIMA) in the same population.[10,11]

References: 1. de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res*. 2016:2(2):00100-2015. **2.** de Groot JC, ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res*. 2015;1(1):00024-2015. **3.** Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med*. 2015;3:849-858. **4.** Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf. Accessed August 12, 2019. **5.** Tran TN, Zeiger RS, Peters SP, et al. Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol*. 2016;116(1):37-42. **6.** Skolnik NS, Carnahan SP. Primary care of asthma: new options for severe eosinophilic asthma. *Curr Med Res Opin*. 2019;35(7):1309-1318. **7.** Carr TF, Berdnikovs S, Simon H-U, et al. Eosinophilic bioactivities in severe asthma. *World Allergy Organ J*. 2016;9:21. **8.** Ortega H, Llanos JP, Lafeuille MH, et al. Effects of systemic corticosteroids on blood eosinophil counts in asthma: real-world data. *J Asthma*. 2019;56(8):808-815. **9.** FASENRA [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. **10.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127. **11.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141. **12.** Data on File, REF-60828, AZPLP.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Reduction of Corticosteroid Dosage (cont'd)

should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

It is unknown if FASENRA will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/fasenra.

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

- FASENRA is not indicated for treatment of other eosinophilic conditions
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus

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****.*

AstraZeneca

Fasenra®
(benralizumab) Subcutaneous Injection 30 mg
FROM THE START

FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

General Administration Instructions

FASENRA is intended for use under the guidance of a healthcare provider. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Administer FASENRA into the thigh or abdomen. The upper arm can also be used if a healthcare provider or caregiver administers the injection. Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter.

Prefilled Syringe

The prefilled syringe is for administration by a healthcare provider.

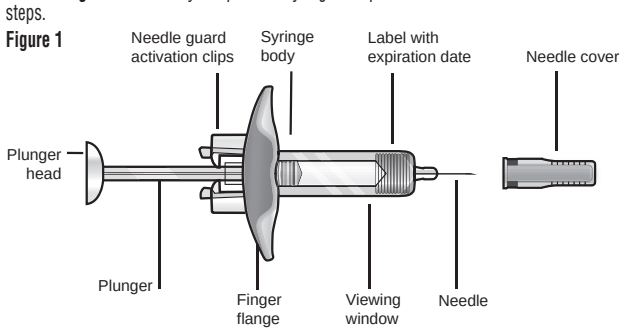
Autoinjector (FASENRA PEN™)

FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.

Instructions for Administration of FASENRA Prefilled Syringe (Healthcare Providers)

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

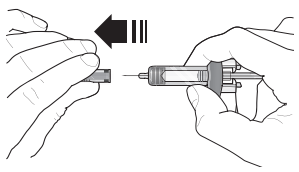
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

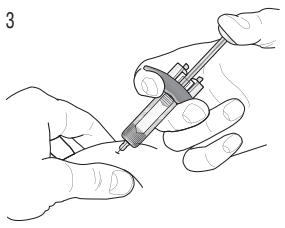
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. **Do not** expel the air bubbles prior to administration.

2



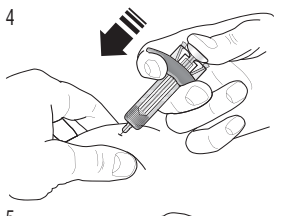
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3



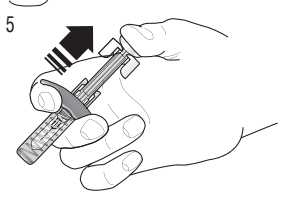
Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4



Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5



After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

Instructions for Administration of FASENRA PEN

Refer to the FASENRA PEN 'Instructions for Use' for more detailed instructions on the preparation and administration of FASENRA PEN *[See Instructions for Use in the full Prescribing Information]*. A patient may self-inject or the patient caregiver may administer FASENRA PEN subcutaneously after the healthcare provider determines it is appropriate.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued *[see Contraindications (4) in the full Prescribing Information]*.

Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two Phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n=841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n=822), and placebo (n=847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N=822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions†	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

† Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n=73) or placebo (n=75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of FASENRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to FASENRA or a combination of these factors.

Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting mothertobaby.org/Fasenra.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see *Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n=320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use for FASENRA PEN) before the patient starts using FASENRA and each time the prescription is renewed as there may be new information they need to know.

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique using the FASENRA PEN, including aseptic technique, and the preparation and administration of FASENRA PEN prior to use. Advise patients to follow sharps disposal recommendations [*see Instructions for Use in the full Prescribing Information*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting mothertobaby.org/Fasenra *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

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CHEST NETWORKS

3D printing. COVID-19 and pediatrics. Lung volume measurements. PAH and atrial septal defect.

Interventional and Chest Diagnostic Procedures

3D printing and pulmonology

Recent advances in 3D printing have enabled physicians to apply this technology in medical education, procedural planning, tissue modeling, and implantable device manufacturing. This is especially true in the field of pulmonology. Advancements in 3D printing have made personalized airway stents a reality, both by 3D printing-assisted injection molding or direct 3D printing.

Dr. Cheng

Airway stents have significantly evolved over the last half century. With use of silicone, bare metallic, and hybrid stents, pulmonologists have an ever-expanding option to address airway stenosis due to both benign and malignancy etiologies. Personalized airway stents hold the potential for advanced customization, minimizing pressure points, and improving airflow dynamics to increase mucus clearance. In January 2020, the US Food and Drug Administration (FDA) cleared patient-specific airway stents developed by Dr. Thomas Gildea of Cleveland Clinic. The patient-specific silicone stents are created using CT scans and 3D visualization software to generate a 3D-printed mold that was subsequently used to inject with medical-grade silicone. Two years earlier, a Duke University startup known as restor3D created the first direct 3D printed airway stent using a compressible biocompatible material with properties similar to that of silicone. Both of these stents have been used in patients with promising response.

As we look into the future, the field of pulmonology will experience significant changes with more adoption of 3D printing (ie, additive manufacturing). We may soon be able to create personalized airway prosthesis of any type (stents, spigots, valves, tracheostomies, t-tubes) for the benefit of our patients.

Disclosure: Dr. George Cheng is a cofounder of restor3D.

George Cheng, MD, PhD, FCCP
Steering Committee Member

Pediatric Chest Medicine

COVID-19: Pediatric story of a new pandemic

In December 2019, an outbreak of pneumonia identified to be caused by 2019 novel coronavirus (2019-nCoV) emerged in Wuhan, China, possibly originating from the local wet market selling many species of live animals. A novel member of enveloped RNA coronavirus was identified in samples of BAL fluid from a patient in Wuhan.

It has since rapidly spread globally to countries across six continents. As of early April, 1,286,409 cases have been reported worldwide with 337,933 cases (9,600 deaths) in the US (https://coronavirus.jhu.edu/map.html) with more cases and deaths every day. Most of these initial reports of COVID-19 (COronaVIrusDisease) in children are from China. Fever (60%) and cough (65%) were the most common symptoms. Procalcitonin elevation (80% and co-infection (80%) were prominent clinical findings. Consolidation with surrounding halo sign (50%) and ground-glass opacities (60%) on CT scan were typical radiologic findings. Almost all children recovered with-

Dr. Rao

out needing intensive care support.

Increased IgM COVID-19 antibody levels observed in three neonates raise questions of potential in-utero transmission (Kimberlin et al. *JAMA* 2020 Mar 26. doi: 10.1001/jama.2020.4868). One study provided evidence for persistent fecal shedding and possibility of fecal-oral transmission (Xu et al. *Nat Med* 2020 Mar 13. doi: 10.1038/s41591-020-0817-4).

Initial reports show that children appear to be at similar risk of infection as adults, though less likely to have severe symptoms. Young children, particularly infants, are more vulnerable to infection (Dong et al. *Pediatrics*. 2020 Apr. doi: 10.1542/peds.2020-0702); (Bi et al. *medRxiv* 2020 Mar 27. doi: 10.1101/2020.03.03.20028423v3). Thus far, few deaths have been reported in the pediatric age group. Trials are being conducted on a war footing to find a cure and a vaccine.

Harish Rao, MD, MBBS
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Controversies and the clinical value of lung volume measurements

Lung volumes are often measured by body plethysmography or gas dilution. Their clinic importance in decision making is unclear. Though measured differently, predicted sets obtained by plethysmography from Caucasian populations are often used for gas dilution measurements (Ruppel GL. *Respir Care*. 2012 Jan;57[1]:26). Recently the Global Function Lung Initiative (GLI) felt lung volume data were insufficient to develop universal reference equations (Cooper B, et al. *Breathe* (Sheff). 2017 Sep;13[3]:e56-e64). ERS/ATS guidelines recommend adjusting Caucasian predicted values depending on race, without advising how to adjust the confidence limits. Their algorithms show if the VC is normal, lung volumes are unnecessary, though it is not unusual to see a normal VC with reduced TLC. Does this suggest the VC is more important than the TLC, even if lacking predicted volume equations for non-Caucasians? Because combined obstructive and restrictive abnormalities occur simultaneously, recommendations state severity of impairment be determined by the FEV_1 percent of predicted rather than TLC (Pellegrino R, et al. *Eur Respir J*. 2005;26:948). The value of quantifying other volumes such as FRC and ERV in conditions such as obesity and musculoskeletal defects is also not clear. In obstruction, volumes can indicate air trapping or hyperinflation measuring RV and RV/TLC. Though cutoffs of <80% and >120% of predicted are often used, guidelines discourage this practice, recommending using predicted equations based on age, race, height, and sex, with statistical limits of normal (Ruppel GL. *Respir Care*. 2012 Jan;57(1):26).


Dr. Chaaban


Dr. Morris

Further research is needed to define comprehensive racially appropriate predicted equations for lung volumes to support their clinical applicability in decision making, as well as if predicted values by plethysmography are applicable to values obtained from gas dilution.

Said A. Chaaban, MD
Steering Committee Member
Zachary Q. Morris, MD
NetWork Member

Pulmonary Vascular Disease

Pulmonary hypertension associated with atrial septal defect in adults: Closing time?

Up to 10% of adults with atrial septal defects (ASDs) can develop pulmonary arterial hypertension (PAH) according to European Guidelines on pulmonary hypertension (PH) (Galie, et al. *Eur Heart J*. 2016;37[1]:67). If ASD closure is considered, they propose a pulmonary vascular resistance index (PVRi) <4 Wood units (WU) m^2 as a safe cutoff. Higher PVRi carries a higher operative risk, warranting evaluation in specialized PH centers.

American guidelines (Stout, et al. *Circulation*. 2019 Apr 2;139[14]:e698) recommend closure in symptomatic patients with a net shunt (Qp/Qs) of >1.5:1. Closure appears safe if pulmonary artery (PA) systolic pressure is <1/2 systemic blood pressure, and PVR / systemic vascular resistance is <0.3. They recommend specialized evaluation for higher pressures and to avoid closure once a net right to left shunt is present (Qp/Qs <1.0).

However, in severe cases, experienced centers have reported some success with a "treat-and-close" approach if post-therapy PVR reaches <6.5 WU (Bradley, et al. *Int J Cardiol.* 2019;291:127).

Finally, consider the following when evaluating ASD-associated PAH: 1. A thermodilution cardiac output method should not be used to calculate PVR/PVRi because of confounding recirculation from the intracardiac shunt (Kwan, et al. *Clin Cardiol.* 2019;42[3]:334). Qp is used instead and is calculated using Fick equation, requiring accurate oxygen saturation measurements. 2. Mixed venous saturation (MvO_2) is needed to determine Qs, and PA saturation cannot be used as MvO_2 surrogate. MvO_2 must be calculated using superior and inferior vena cava saturations. 3. Some patients with idiopathic PAH may have a small coexisting ASD that is not responsible for the abnormal hemodynamics. Closing the ASD in those cases would be contraindicated. 4. Patients may have more than one type of coexistent congenital heart defect.


Dr. Soto

Francisco J. Soto, MD, MS, FCCP
Steering Committee Member

This month in the journal *CHEST*®

Editor's Picks

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

Fighting the novel coronavirus together with you.
By Dr. J. Li.

The Evolving Landscape of e-Cigarettes: A Systematic Review of Recent Evidence.
By Dr. J. Bozier, et al

Comparative Safety and Effectiveness of Inhaled Corticosteroid and Long-Acting Beta2-Agonist Combinations in Patients With COPD.
By Dr. T-U Chang, et al.

Sharing your philanthropic dollars

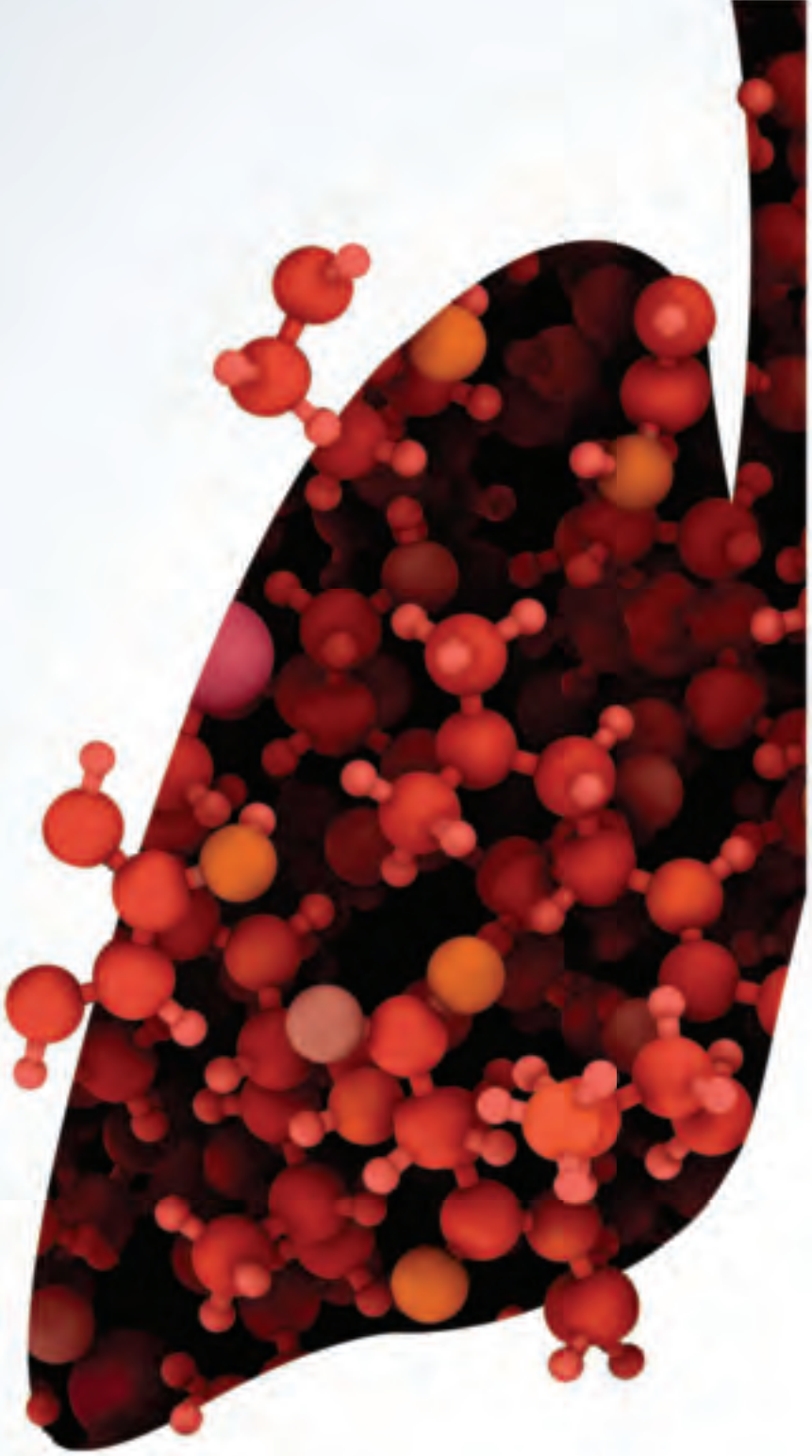
Amid the COVID-19 pandemic, we are filled with gratitude because of the support you have provided the CHEST Foundation. Along with our sincere thanks, we wanted to share how your philanthropic dollars are being put to use fulfilling the urgent needs of our community during this crisis. Specifically, the CHEST Foundation is:

1. Continuing to provide reliable educational materials and resources that support our clinicians, their patients, and caregivers;
2. Actively working with manufacturers and vendors from around the globe to secure life-saving equipment for US hospitals; and
3. Partnering with other leading health-care organizations to increase our impact in vulnerable and at-risk communities.

These are just some of the ways the CHEST Foundation and CHEST are rallying to support the fight against COVID-19. To see more of what we are doing, and to keep an eye out for future resources, please visit us here: https://bit.ly/3bKAGI2. We will continue to identify new ways in which we can support the efforts of our health-care providers and serve as a leading resource for patients, caregivers, and those we consider "at-risk, noninfected" populations.

Additionally, the CHEST Foundation's redesigned website will be launching May 1! Be sure to visit us at chestfoundation.org to view and share our clinician-authored patient education guides with anyone who needs them.

Thank you for providing your generous support, which has allowed us to develop these much-needed resources. We would not be able to do it without you.



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