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

PULMONOLOGY
COVID-19 survivors have symptoms of depression and insomnia // **22**

CARDIOLOGY
A history of heart failure is a risk factor for severe COVID-19 // **25**

LUNG CANCER
Screening misses young at-risk African Americans // **49**

VOL. 15 • NO. 12 • DECEMBER 2020

CHEST Physician®

Tempura/Getty Images

Insufficient dialysis treatment time, staff shortages, and routine supply scarcity are examples "for which there was not an established plan or approach for appropriate allocation."

Moral distress: COVID-19 crisis means tough triage decisions

BY DAMIAN MCNAMARA

Choosing which hospitalized COVID-19 patients receive potentially lifesaving care, making urgent calls for ventilators and other equipment, and triaging care based on patient age and comorbidities were among the challenges revealed in new feedback from health care leaders and frontline workers.

Even though many hospitals have contingency plans for how to allocate resources and triage patient care during crisis capacity, for many providers during the real-world COVID-19 trial of these protocols, they fell short.

Many hospital crisis capacity plans, for example, were too general to address all the specific challenges arising during the pandemic, investigators report in a study published online Nov. 6 in JAMA Network Open (2020. doi: 10.1001/jamanetworkopen.2020.27315).

"Our research shows that the types of challenges and approaches to resource limitation in real-world clinical settings during the pandemic differed in practice from how we had prepared in theory," lead author Catherine Butler, MD, told this news organization. Insufficient dialysis treatment time, staff shortages, and routine supply scarcity are examples "for which there was not an established plan or approach for appropriate allocation."

"This left frontline clinicians to determine what

DISTRESS // *continued on page 7*

Readmissions of COVID-19 patients estimated at 10%

BY LAIRD HARRISON

About 1 in 11 patients discharged after COVID-19 treatment is readmitted to the same hospital, according to researchers from the Centers for Disease Control and Prevention.

Older age and chronic diseases are associated with increased risk, said senior author Adi V. Gundlapalli, MD, PhD, chief public health informatics officer of the CDC's Center for Surveillance, Epidemiology, and Laboratory Services.

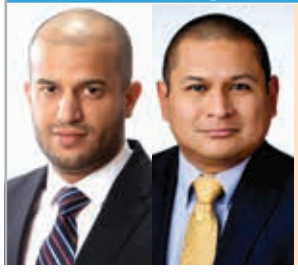
Dr. Gundlapalli and colleagues published the finding in Morbidity and Mortality Weekly Report.

To get a picture of readmission after COVID-19 hospitalization, the researchers analyzed records of 126,137 patients hospitalized with COVID-19 between March and July and included in the Premier Healthcare Database, which covers discharge records from 865 nongovernmental, community, and teaching hospitals.

Overall, 15% of the patients died during hospitalization. Of those who survived to discharge, 9% were readmitted to the same hospital within 2 months of discharge; 1.6% of patients were readmitted more than once. The median interval from discharge to first readmission was 8 days (interquartile range, 3-20 days). This short

READMISSIONS // *continued on page 6*

INSIDE HIGHLIGHT



NEWS FROM CHEST

Critical Care Commentary

COVID-19: Choosing the proper treatment at the proper time

Page 65

CHEST Physician
10255 W Higgins Road,
Suite 280
Rosemont, IL 60018

CHANGE SERVICE REQUESTED

PRSRT STD
U.S. POSTAGE
PAID
HARRISBURG PA
PERMIT 500

Rx

Why we write Esbriet

Your patients trust you. That's why you trust Esbriet for efficacy, safety, and tolerability.

INDICATION

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

SELECT IMPORTANT SAFETY INFORMATION

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

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

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

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

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

Drug Interactions:

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

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

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

Genentech
A Member of the Roche Group

ESBRIET OFFERS ESTABLISHED SAFETY BUILT ON MULTIPLE CLINICAL STUDIES

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

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

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

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

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

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

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

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

Demonstrated efficacy

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

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

Learn more at **EsbrietHCP.com**

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

Specific Populations:

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

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

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

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

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

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

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

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

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

Esbriet® (pirfenidone) tablets 267 mg 801 mg

AMA reports a drop in physician revenues during 2020

BY KEN TERRY

Physician practices nationwide lost 32% of their revenue, on average, from February to the summer, according to a new American Medical Association survey of 3,500 physicians, conducted from mid-July to August. That period coincided with the second wave of the coronavirus pandemic in the United States.

A third of practices reported a revenue drop of 25%-49%; 15% said their volume had fallen by 50%-74%, and 4% saw a decrease of 75% or more.

Because of the pandemic, 81% of physicians were providing fewer in-person visits than in February. In-person visits dropped by 50% or more for more than one-third of physicians. The average in-person visits fell from 95 to 57 per week.

Physicians who responded to the

survey held an average of 6 weekly telehealth visits before the pandemic, 29 at the height of the pandemic in the spring, and 16 the week they were surveyed. About 20% of respondents with any telehealth visits had conducted them before the pandemic, 77% at the height of the crisis, and 68% in the survey week.

Despite the telehealth increase, almost 70% of physicians were providing fewer total visits, including in-person and virtual encounters, than before the pandemic, the survey showed. About 21% saw a decrease of 25%-49%; 11%, a drop of 50%-74%; and 10%, a falloff of at least 75%. On average, total visits fell from 101 to 72 per week.

Other surveys more upbeat

A larger survey by Harvard University, the Commonwealth Fund, and the technology company Phreesia found that total outpatient visits in early October had rebounded to the level of March 1. This was a major turnaround from late March, when visits had plunged by nearly 60%.

According to the Harvard/Commonwealth Fund's ongoing survey, visits started recovering in late June, although they were still off by 10%. They began rising further around Labor Day. The AMA began conducting their survey in mid-June. The summertime surge in COVID-19 likely accounted for their finding that practice revenues were off by a third from the February baseline.

If so, the return to normalcy early this month may not represent the current situation as the virus sweeps across the country for a third time.

DOOMU/THINKSTOCK

In any case, even if patient visits and revenues have recovered more than the AMA data indicate, most practices will not have recovered from their losses earlier in the year.

A third survey more closely mirrors the AMA results. At the end of June, according to data from the Medical Group Management Association, revenues for the association's members were 76% of what they had been in June 2019, and patient volume was 78% of that in the previous year.

Practice expenses rise

The AMA survey also found that, since February, practice spending on personal protective equipment (PPE) had increased by 57% or more, on average. About 64% of practice owners said their PPE expenditures were up from what they had been before the pandemic. For nearly 40% of practice owners, this expense had increased by 50% or more.

About 36% of the respondents said that acquiring PPE was very or extremely difficult. This was an especially big challenge for smaller practices, which do not have the purchasing power to compete with big health care systems for masks, gowns, and gloves.

AMA President Susan R. Bailey, MD, said in a news release, "More economic relief is needed now from Congress as some medical practices contemplate the brink of viability, particularly smaller practices that are facing a difficult road to recovery."

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

FDA approves first at-home COVID-19 test kit

BY CAROLYN CRIST

The Food and Drug Administration issued an emergency-use authorization Tuesday for the first self-testing COVID-19 kit to use at home, which provides results in about 30 minutes.

The Lucira COVID-19 All-In-One Test-Kit is a single-use test that has a nasal swab to collect samples for people ages 14 and older. It's available only by prescription, which can be given by a doctor who suspects a patient may have contracted the coronavirus.

"While COVID-19 diagnostic tests have been authorized for at-home collection, this is the first that can be fully self-administered and provide results at home," FDA Commissioner Stephen Hahn, MD, said in the statement.

The test kit can also be used in doctor's offices, hospitals, urgent care centers, and emergency rooms for all ages, but samples must be collected by a health care professional if the patient is under age 14.

After using the nasal swab, the test works by swirling the sample in a vial and then placing it in the provided test unit, according to the FDA. Within 30 minutes, the results appear on the unit's light-up display. People who receive a positive result should self-isolate and seek care from their doctor. Those who test negative but have COVID-like symptoms should follow up with their doctor, since a negative result doesn't necessarily mean they don't have the coronavirus.

Testing is still a key part of controlling the spread of the coronavirus, Reuters reports. The United States surpassed 11 million infections Sunday, only 8 days after passing 10 million cases.

With the at-home testing kit, public health officials still need to track and monitor results. As part of the emergency-use authorization, the FDA requires doctors who prescribe the tests to report all results to public health authorities based on local, state, and federal requirements. Lucira Health, the test maker, also created box labeling and instructions to help doctors to report results.

"Now, more Americans who may have COVID-19 will be able to take immediate action, based on their results, to protect themselves and those around them," Jeff Shuren, MD, director of the FDA's Center for Devices and Radiological Health, said in the statement.

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

Age a risk factor for readmission

// continued from page 1

interval suggests that patients are probably not suffering a relapse, Dr. Gundlapalli said in an interview. More likely they experienced some adverse event, such as difficulty breathing, that led their caretakers to send them back to the hospital.

Forty-five percent of the primary discharge diagnoses after readmission were infectious and parasitic diseases, primarily COVID-19. The next most common were circulatory system symptoms (11%) and digestive symptoms (7%).

After controlling for covariates, the researchers found that patients were more likely to be readmitted if they had chronic obstructive pulmonary disease (odds ratio, 1.4), heart failure (OR, 1.6), diabetes (OR, 1.2), or chronic kidney disease (OR, 1.6).

They also found increased odds among patients discharged from the index hospitalization to a skilled nursing facility (OR, 1.4) or with home health organization support (OR, 1.3), compared with being discharged to home or self-care. Looked at another way, the rate of readmission was 15% among those discharged to a skilled nursing facility, 12% among those needing home health care, and 7% of those discharged to home or self-care.

The researchers also found that people who had been hospitalized within 3 months prior to the index hospitalization were 2.6 times more likely to be readmitted than were those without prior inpatient care.

Further, the odds of readmission increased significantly among people over 65 years of age, compared with people aged 18-39 years.

"The results are not surprising," Dr. Gundlapalli said. "We have known from before that elderly pa-

Continued on following page

***CHEST PHYSICIAN* IS ONLINE**

CHEST Physician is available at chestphysician.org.

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

CHEST Physician®

American College of Chest Physicians (CHEST)

EDITOR IN CHIEF
David A. Schulman, MD, FCCP
PRESIDENT
Steven Q. Simpson, MD, FCCP
EXECUTIVE VICE PRESIDENT & CEO
Robert Musacchio
PUBLISHER, CHEST
Nicki Augustyn
MANAGER, EDITORIAL RESOURCES
Pamela L. Goorsky
PUBS & DIGITAL CONTENT EDITOR
Martha Zaborowski
SECTION EDITORS
Corey Kershaw, MD
Pulmonary Perspectives®
Angel Coz, MD, FCCP
Critical Care Commentary
Michelle Cao, DO, FCCP
Sleep Strategies

E-mail: chestphysiciannews@chestnet.org

CHEST Physician, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST Physician** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

POSTMASTER: Send change of address (with old mailing label) to CHEST Physician, Subscription Services, 10255 W Higgins Road, Suite 280, Rosemont, IL 60018-9914.

RECIPIENT: To change your address, contact Subscription Services at 1-800-430-5450. For paid subscriptions, single issue purchases, and missing issue claims, call Customer Service at 1-833-836-2705 or e-mail custsvc.chph@fulcoinc.com

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

EDITORIAL OFFICES 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

ADVERTISING OFFICES 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378

FRONTLINE MEDICAL COMMUNICATIONS

Frontline Medical Communications Society Partners

EXECUTIVE EDITOR Kathy Scarbeck, MA
EDITOR Therese Borden, PhD
CREATIVE DIRECTOR Louise A. Koenig

DIRECTOR, PRODUCTION/MANUFACTURING
Rebecca Slebodnik

DIRECTOR, BUSINESS DEVELOPMENT
Monique Michowski,
973-206-8015, cell 732-278-4549,
mmichowski@mdedge.com

CLASSIFIED SALES REPRESENTATIVE
Linda Wilson 973-290-8243,
lwilson@mdedge.com
SENIOR DIRECTOR OF CLASSIFIED SALES
Tim LaPella, 484-921-5001,
tlapella@mdedge.com

FRONTLINE
MEDICAL COMMUNICATIONS

Corporate
VP, SALES Mike Guire
VP, MEMBER MARKETING & DIGITAL PRODUCTION Amy Pfeiffer
PRESIDENT, CUSTOM SOLUTIONS JoAnn Wahl
CIRCULATION DIRECTOR Jared Sonners
DIRECTOR, CUSTOM PROGRAMS Patrick Finnegan

In affiliation with Global Academy for Medical Education, LLC
PRESIDENT David J. Small, MBA

Triage decisions and resource shortages can cause moral distress

// continued from page 1

constituted an acceptable standard of care and to make difficult allocation decisions at the bedside," added Dr. Butler, acting instructor in the Division of Nephrology at the University of Washington in Seattle and a research fellow at the VA Health Services Research and Development Seattle–Denver Center of Innovation.

The investigators conducted semi-structured interviews in April and May with 61 clinicians and health leaders. Mean age was 46 years, 63% were women, and participants practiced in 15 states. Most participants hailed from locations hard-hit by the pandemic at the time, including Seattle, New York City, and New Orleans.

Triage tribulations

The qualitative study included comments from respondents on three major themes that emerged: planning for crisis capacity, adapting to resource limitation, and experiencing multiple unprecedented barriers to care delivery.

Overall, planning and support from institutional leaders varied. One provider said, "Talking to administration, and they just seemed really disengaged with the problem. We asked multiple times if there was a triage command center or a plan for what would occur if we got to the point where we had to triage resources. They said there was, but they wouldn't provide it to us."

Another had a more positive experience. "The biggest deal in the ethics world in the last 2 months has been preparing in case we need to triage. So, we have a very detailed, elaborate, well thought–out triage policy … that was done at the highest levels of the system."

Clinicians said they participate on triage teams – despite the moral weight and likely emotional burden – out of a sense of duty.

Interestingly, some providers on these teams also reported a reluctance to reveal their participation to colleagues. "I didn't feel like I should tell anybody … even some of my close friends who are physicians and nurses here … that I've been asked to be on this [triage team]," one respondent said. "I didn't feel like I should make it known."

ANDREI MALOV/THINKSTOCK

"The biggest deal in the ethics world in the last 2 months has been preparing in case we need to triage. So, we have a very detailed, elaborate, well thought–out triage policy … that was done at the highest levels of the system."

Allocation of scarce resources

Multiple providers said they faced difficult care decisions because of limited dialysis or supply shortages. "They felt that this patient had the greatest likelihood of benefiting from most aggressive therapy. … I think there was probably like 5 or 6 patients in the ICU … and then you had this 35-year-old with no comorbidities," one respondent said. "That's who the ICU dialyzed, and I couldn't really disagree."

"I emailed all of [my colleagues], and I said 'Help! We need X, we need CRRT [continuous renal replacement therapy] machines, we need dialysates,'" another responded.

"One of the attendings had a tweet when we were running out of CRRT. He had a tweet about, 'Can anybody give us supplies for CRRT?' So, it got to that. You do anything. You get really desperate," the clinician said.

Other providers reported getting innovative under the circumstances. "My partner's son, he actually borrowed a couple of 3D printers. He printed some of these face shields, and then they got the formula, or the specifics as to how to make this particular connection to connect to a dialysis machine to generate dialysate. So, he also printed some of those from the 3D printer."

Dire situations with dialysis

Another respondent understood the focus on ventilators and ICU beds throughout the crisis, but said "no one has acknowledged that dialysis has been one of the most, if not the most, limited resource."

Another clinician expressed surprise at a decision made in the face of limited availability of traditional dialysis. "A month ago, people said we were going to do acute peritoneal dialysis [PD]. And I said, 'No, we're not going to do acute PD. PD, it's not that great for acute patients, sick people in the ICUs. I don't think we're going to do PD.'

"Three days later we were doing acute PD. I mean, that was unbelievable!"

Some institutions rationed dialysis therapy. "We went through the entire list at the beginning of the week and [said], this person has to dialyze these days, this person would probably benefit from a dialysis session, a third group person we could probably just string along and medically manage if we needed to," one provider said.

Another respondent reported a different strategy. "No one was not getting dialysis, but there were a lot of people getting minimal dialysis. Even though people were getting treated, resources were very stretched."

Change in family dynamics

COVID-19 has naturally changed how clinicians speak with families. One respondent recalled looking at the ICU physician and being like, 'Have you talked to the son this week?' And she's like, 'Oh my God, no. … Did you talk to the son?' I'm like, 'Oh my God, no.'"

They realized, the respondent added, "that none of us had called the family because it's just not in your workflow. You're so used to the family being there."

Multiple providers also feared a conversation with family regarding necessary changes to care given the limitation of resources during the pandemic.

"Most families have been actually very understanding. This is a crisis, and we're in a pandemic, and we're all doing things we wouldn't normally do."

Many clinicians facing these challenges experience moral distress, the researchers noted.

"Early in the pandemic, it became quickly apparent that possible resource limitation, such as scarce ventilators, was a major ethical concern. There was robust debate and discussion published in medical journals and the popular press about how to appropriately allocate health care resources," the University of Washington's Dr. Butler said.

"Transparency, accountability, and standardized processes for rationing these resources in 'crisis capacity' settings were seen as key to avoiding the impact of implicit bias and moral distress for clinicians," she added.

Learned lesson

In terms of potential solutions that could mitigate these challenges in the future, health care leaders "could develop standardized protocols or guidelines for allocating a broader range of potentially scarce health care resources even before 'crisis capacity' is declared," Dr. Butler said.

Furthermore, no frontline worker should have to go it alone. "Medical ethicists and/or other clinicians familiar with ethical considerations in settings of scarce health care resources might provide bedside consultation and collaborate with frontline providers who must grapple with the impact of more subtle forms of resource limitation on clinical decision-making."

The study was partially funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases and a COVID-19 Research Award from the University of Washington Institute of Translational Health Sciences given to Dr. Butler.

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

Continued from previous page

tients, especially with chronic conditions, certain clinical conditions, and those who have been hospitalized before, are at risk for readmission."

But admitting COVID-19 patients requires special planning because they must be isolated and because more personal protective equipment is required, he pointed out.

One unexpected finding from the report is that non-Hispanic White people were more likely to be readmitted than were people of other racial or ethnic groups. This contrasts with other research showing Hispanic and Black individuals are more severely affected by COVID-19 than White people. More research is needed to explain this result, Dr. Gundlapalli said.

The authors have disclosed no relevant financial relationships.

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

COVID-19 burdens follow patients after discharge

BY RICHARD MARK KIRKNER
MDedge News

PAOLO_TOFFANIN/GETTY IMAGES

COVID-19 patients who survive their hospitalization don't leave the disease behind upon discharge, as a significant percentage died within 60 days of discharge, with an ICU admission heightening the risk, according to an observational study of 38 Michigan hospitals. What's more, many of them were burdened with health and emotional challenges ranging from hospital readmission to job loss and financial problems.

"These data confirm that the toll of COVID-19 extends well beyond hospitalization, a finding consistent with long-term sequelae from sepsis and other severe respiratory viral illnesses," wrote lead author Vineet Chopra, MBBS, of the University of Michigan, Ann Arbor, and colleagues (Ann Intern Med. 2020 Nov 11: doi: 10.7326/M20-5661)

The researchers found that 29.2% of all patients hospitalized for COVID-19 from March 16 to July 1 died. The observational cohort study included 1,648 COVID-19 patients hospitalized at 38 Michigan hospitals participating in a statewide collaborative.

The bulk of those deaths occurred during hospitalization: 24.2% of patients (n = 398). Of the 1,250 patients discharged, 78% (n = 975) went home and 12.6% (n = 158) went to a skilled nursing facility, with the remainder unaccounted for. Within 60 days of discharge, 6.7% (n = 84) of hospitalized survivors had died and 15.2% (n = 189) were readmitted. The researchers gathered 60-day postdischarge data via a telephone survey, contacting 41.8% (n = 488) of discharged patients.

Dr. Farmer

Outcomes were even worse for discharged patients who spent time in the ICU. The death rate among this group was 10.4% (17 of 165) after discharge. That resulted in an overall study death rate of 63.5% (n = 257) for the 405 patients who were in the ICU.

While the study data were in the first wave of the novel coronavirus, the findings have relevance today, said Mary Jo Farmer, MD, FCCP, directory of pulmonary hypertension services at Baystate Health in Springfield, Mass.

"This is the best information we have to date," she said. "We have to continue to have an open mind and expect that this information may change as the virus possibly mutates as it spreads, and we should continue doing these types of outcomes studies at 90 days, 120 days, etc."

The median age of study patients was 62, with a range of 50-72. The three leading comorbidities among discharged patients were hypertension (n = 800, 64%), diabetes (34.9%, n = 436), and cardiovascular disease (24.1%, n = 301).

Poor postdischarge outcomes weren't limited to mortality and readmission. Almost 19% (n = 92) reported new or worsening cardiopulmonary symptoms such as cough and dyspnea, 13.3% had a persistent loss of taste or smell, and 12% (n = 58) reported more difficulty with daily living tasks.

Dr. Gupta

The aftereffects were not only physical. Nearly half of discharged patients (48.7%, n = 238) reported emotional effects and almost 6% (n = 28) sought mental health care. Among the 40% (n = 195) employed before they were hospitalized, 36% (n = 78) couldn't return to work because of health issues or layoffs. Sixty percent (n = 117) of the pre-employed discharged patients did return to work, but 25% (n = 30) did so with reduced hours or modified job duties because of health problems.

Financial problems were also a burden. More than a third, 36.7% (n = 179), reported some financial impact from their hospitalization. About 10% (n = 47) said they used most or all of their savings, and 7% (n = 35) said they resorted to rationing necessities such as food or medications.

The researchers noted that one in five patients had no primary care follow-up at 2 months post discharge. "Collectively, these findings suggest that better models to support COVID-19 survivors are necessary," said Dr. Chopra and colleagues.

The clinical course for hospitalized patients involves two humps, said Sachin Gupta, MD, FCCP a pulmonary and critical care specialist at Alameda Health System in Oakland, Calif.: getting over the hospitalization itself and starting the recovery phase. "As you look at the median age of the survivors, elderly patients who survive a hospital stay are still going to have a period of recovery, and like any viral illness that leads to someone being hospitalized, when you have an elderly patient with comorbidities, not all of them can make it over that final hump."

He echoed the study authors' call for better postdischarge support for COVID-19 patients. "There's typically, although not at every hospital, a one-size-fits-all discharge planning process," Dr. Gupta said. "For older patients, particularly with comorbid conditions, close follow-up after discharge is important."

Dr. Farmer noted that one challenge in discharge support may be a matter of personnel. "The providers of this care might be fearful of patients who have had COVID-19 – Do the patients remain contagious? What if symptoms of COVID-19 return such as dry cough, fever? – and of contracting the disease themselves," she said.

The findings regarding the emotional status of discharged patients should factor into discharge planning, she added. "Providers of posthospital care need to be educated in the emotional impact of this disease (e.g., the patients may feel ostracized or that no one wants to be around them) to assist in their recovery."

Dr. Chopra and Dr. Farmer have no financial relationships to disclose. Dr. Gupta is an employee and shareholder of Genentech.

chestphysiciannews@chestnet.org

SOURCE: Chopra V et al. Ann Intern Med. 2020 Nov 11. doi: 10.7326/M20-5661.

Critical illness survivors can emerge with debility

BY WILL PASS
MDedge News

More patients are surviving critical illnesses requiring ICU care but many emerge with physical debility that may or may not eventually resolve.

Over the past decade, functional-status deterioration after critical illness has become more common and of greater magnitude, despite concurrent efforts to reduce post–intensive care syndrome, based on a retrospective analysis of more than 100,000 patients.

Almost one-third of patients who survived nonsurgical ICU admission had evidence of functional status decline, reported lead author Nicholas E. Ingraham, MD, of the University of Minnesota, Minneapolis, and colleagues.

"Increasing capacity and decreasing mortality have created an evolving and diverse population of ICU survivors," the investigators wrote in Critical Care Medicine. "Today's survivors of critical illness are increasingly burdened by extensive physical and psychological comorbidities, often resulting in reduced quality of life."

To determine trends in post–intensive care syndrome from 2008 to 2016, Dr. Ingraham and colleagues analyzed data from the Cerner Acute Physiology and Chronic Health Evaluation outcomes database, a national prospective cohort. Out of 202,786 adult patients admitted to the ICU, 129,917 were eligible for the study. Patients were excluded because of surgical admission, death, lack of functional status documentation, or inadequate hospital size or duration of participation. The final dataset had a median age of 63 years, with a slight predominance of male patients (54.0%). Most patients (80.9%) were White.

The primary outcome was defined as presence or absence of functional-status deterioration, based on functional status at admission versus time of discharge. The secondary outcome was magnitude of deterioration over time.

The analysis, which controlled for age and severity of illness, revealed concerning trends for both outcomes.

Across the entire cohort 38,116 patients (29.3%) had functional-status deterioration, with a 15% increase in prevalence over the course of the decade that spanned all disease categories (prevalence rate ratio, 1.15; 95% confidence interval, 1.13-1.17; $P < .001$). The magnitude of functional-status decline also increased by 4% (odds ratio, 1.04; $P < .001$), with all but nonsurgical trauma patients showing greater deterioration over time.

Dr. Bowton

"Early mobility and patient and family diaries appear to improve functional status at discharge and postdischarge anxiety and depression, though the evidence supporting this is thin."

"However, despite the decreasing magnitude of functional status deterioration in nonsurgical trauma, many admission diagnoses in this category remain in the top quartile of higher risk for functional status deterioration," the investigators noted.

Functional-status decline was most common among patients with head and polytrauma (OR, 3.39), followed closely by chest and spine trauma (OR, 3.38), and spine trauma (OR, 3.19). The top quartile of categories for prevalence of deterioration included nonsurgical trauma, neurologic, pulmonary, and gastrointestinal diseases.

Functional-status decline was least common among patients diagnosed with diabetic ketoacidosis (OR, 0.27) or asthma (OR, 0.35).

"We believe our study provides important information that can be used in beginning to identify patients at high risk of functional status decline," the investigators concluded. "Improving the identification of these patients and targeting appropriate interventions to mitigate this decline will be important directions for future studies in this area."

According to David L. Bowton, MD, FCCP, professor emeritus, section on critical care, Wake Forest Baptist Health, Winston-Salem, N.C., the findings show just how common functional decline is after critical illness, and may actually underestimate prevalence.

"Because the authors employed a course evaluation tool employing only three categories of ability/disability and abstracted the level of disability from the medical record, they likely underestimated the frequency of clinically important, though not detected, disability at the time of hospital discharge," Dr. Bowton said. "The study did not address cognitive impairment which can be detected in half of patients at 3 months following critical illness, and which significantly affects patients' quality of life (Am J Respir Crit Care Med. 2020;202[2]:193-201)."

Dr. Bowton suggested that evidence-based methods of preventing post–intensive care syndrome are limited.

"Current efforts to improve post-ICU functional and cognitive outcomes suffer from the lack of proven effective interventions (Crit Care Med. 2019;47[11]:1607-18)," he said. "Observational data indicates that compliance with the ABCDEF bundle decreases the duration and incidence of delirium, ICU length of stay, duration of mechanical ventilation, and mortality (Crit Care Med. 2019;47[1]:3-14). However, the implications of these improvements on postdischarge functional outcomes are unknown as area the relative importance of individual elements of the bundle. Early mobility and patient and family diaries appear to improve functional status at discharge and postdischarge anxiety and depression, though the evidence supporting this is thin."

Dr. Mikkelsen

"As part of a standard ICU and then hospital discharge, we need to engage, educate, and inform our patients and their loved ones about life after critical illness. We also need to coordinate their care more effectively."

Appropriate intervention may be especially challenging during the COVID-19 pandemic, he added.

"The impact of COVID on ICU staffing adequacy and stress is significant and the impact on quality bundle compliance and the availability of support services is currently not clear, but likely to be detrimental, especially to support services such as physical therapy that are already commonly understaffed," Dr. Bowton said.

Mark E. Mikkelsen, MD, chief, section of medical critical care and director, Medical Intensive Care Unit, Penn Presbyterian Medical Center, Philadelphia, found this study valuable. "First, it emphasizes that impairments after critical illness are common, and becoming more common over time (likely a result of improved survival, aging, and illness severity). Second, although the assessments were conducted at hospital discharge, it's likely that they served as a prelude to long-term impairments, known as Post–Intensive Care Syndrome or PICS. This work also provides further evidence for why we need to serially screen for impairments post discharge, to ensure that patients receive rehabilitation. Sadly, most patients are not informed about what life is like after critical illness. As part of a standard ICU and then hospital discharge, we need to engage, educate, and inform our patients and their loved ones about life after critical illness. We also need to coordinate their care more effectively. By partnering with outpatient providers, we can ensure that patients are screened for long-term impairments, so that they get the services and care they need to get back on their feet and get back to their lives."

The study was supported by grants from the University of Minnesota's Critical Care Research and Programmatic Development Program; the National Heart, Lung, and Blood Institute; and the University of Minnesota Clinical and Translational Science via the National Center for Advancing Translational Sciences.

chestphysiciannews@chestnet.org

SOURCE: Ingraham NE et al. Crit Care Med. 2020 Nov. doi: 10.1097/CCM.0000000000004524.

Painful ethical choices in 2020 vs. 2010

BY MARCIA FRELLICK

Much has changed in the 10 years since Medscape's first survey on what physicians would do when faced with painful choices in patient care.

A new report, Ethics 2020: Life, Death, and Painful Dilemmas, shows that physicians' value judgments have shifted in many respects, sometimes as a result of increased regulations and fears of litigation.

End-of-life decisions

Several of the questions in the survey revolved around end-of-life decisions, and in some cases, the differences seen in just a decade were striking. One example concerned life-support decisions in the context of a family's choices.

Age also seemed to play a role in the 2020 answers to that question: Physicians younger than 45 were more likely (28%) to answer "yes" (that they would withdraw life support in that instance) than were those 45 and older (16%).

A critical care physician said, "If the family appears to have an underlying motivation that may not be in the patient's best interest, I might be inclined to pursue a legal decision prior to withdrawing support."

A cardiologist had a more pointed response to the question: "To me, that would be murder."

Another example of how perspectives have changed over the past 10 years concerns whether physician-aided dying should be legal for terminally ill patients. The practice is now mandated by law in eight states and the District of Columbia, and it is mandated by court ruling in two additional states.

In 2010, 41% said "no." That number dropped to 28% in 2020.

On legalization, a psychiatrist said, "Yes, when there is truly no hope and the quality of remaining life is too poor. We show more compassion to our sick animals than we do to our human population."

Conversely, a neurologist answered, "No, I see younger physicians already becoming comfortable with the idea of deciding ASAP whether there is a reasonable chance of survival and then pressing for the right code status. This change would make things worse."

Assisted death and incurable suffering

Far fewer physicians supported physician-assisted death for those who had years to live but faced incurable suffering: Thirty-seven percent said "yes," 34% said "no," and 29% said "it depends."

However, support was significantly higher than it was just 2 years ago, in 2018, when only 27% supported the concept, the report authors noted.

"The shift reflects movements by many states to legalize assisted dying for the terminally ill," Arthur Caplan, PhD, director of the division of medical ethics, New York University, said. "Legalization has not been abused, so some doctors are more willing to press further beyond terminal illness as a trigger to suffering."

Conversely, many more physicians (44% vs. 24% a decade ago) said they would provide life-sustaining therapy if the family requested it, even if the physician thought it was futile.

"Concerns over a malpractice lawsuit and potential negative patient/family online reviews are factors that play into this change," the survey authors wrote.

Shared decision-making also increased in the past decade.

Undertreatment of pain

Primary care physicians fear the consequences of what they consider adequate pain management more than specialists do (24% vs. 17%), the survey authors noted.

Ten years ago, Medscape asked physicians whether they would undertreat a patient's pain because of fear of repercussions or the patient's becoming addicted: Eighty-four percent said "no," and 6% said "yes." The rest said "it depends."

In 2020, the question was asked slightly differently: "Would you undertreat a patient's pain for fear of addiction or Drug Enforcement Administration or medical board scrutiny?" This year, three times as many said "yes" (18%); 63% said "no."

"Respondents this year talked about investigations and reprimands by medical boards, and how much they wanted to avoid that," the survey authors wrote.

Required treatment for COVID-19 patients

Some questions were new this year, including one on whether physicians should be required to treat COVID-19 patients. Fewer than half (47%) answered "yes," 24% said "no," and 29% answered "it depends."

Doctors' answers to this question differed slightly by gender: 50% of men and 43% of women said "yes." In their responses, many physicians said consideration should be given to risk factors, such as age, underlying conditions, risk of family members, and availability of personal protective equipment (PPE).

Another pandemic-related question asked whether physicians felt they should correct physicians who post misinformation about the pandemic on social media. Half (50%) said "yes," 19% said "no," and 31% said "it depends."

Dissent against the workplace

This year, many physicians have felt betrayed when they didn't have adequate PPE during the pandemic. Asked, "Is it right to speak out against your hospital or workplace when they don't give you what you need?" 53% of physicians said "yes," 8% said "no," and 40% said "it depends."

A cardiologist made the value judgment this way: "Speaking out just because you had an argument with your boss is inappropriate. Bringing to the public repeated failures to correct situations that have been brought through the proper channels is necessary to incite change."

Random drug testing for physicians

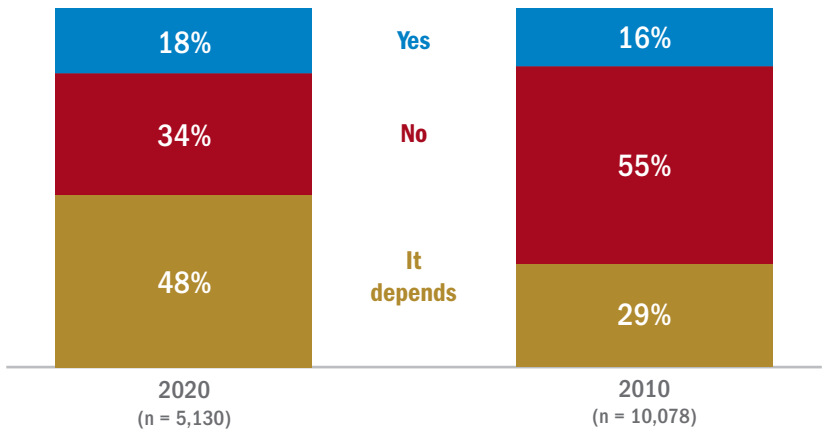
Another question in the survey asked whether physicians should be subjected to random drug testing for alcohol and drug abuse. About one-third (34%) said yes, 43% said no, and 23% said "it depends." A study found that between 10% and 15% of physicians have abused a substance at some point in their careers.

A family physician wrote, "This should not be done unless a particular physician had a problem with drug or alcohol abuse and shows signs of impairment."

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

Surveys highlight a decade of changes in physicians' attitudes

Should you withdraw a patient from life support at a family's request if you think the patient has a chance to survive?

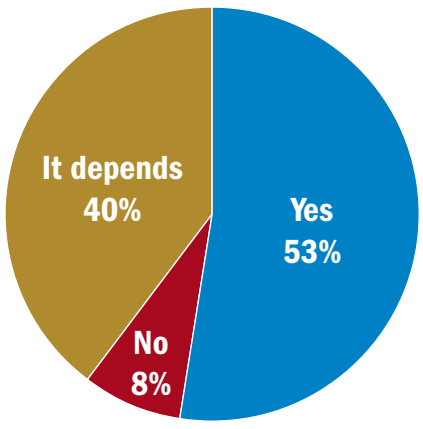


MDedge News

Source: Medscape

Survey: 'Ethics 2020: Life, Death, and Painful Dilemmas'

Is it right for physicians to speak out against their hospitals or workplaces when they are not given what they need?



MDedge News

Note: Based on data collected from 5,130 physicians between July 25 and Sept. 10, 2020.
Source: Medscape

FDA clears antibody COVID-19 therapy for emergency use

BY DAMIAN MCNAMARA

The U.S. Food and Drug Administration issued an emergency-use authorization (EUA) Nov. 9 for the investigational monoclonal antibody therapy bamlanivimab (Eli Lilly) to treat adults and children with mild to moderate COVID-19.

The monoclonal antibody therapy has emergency authorization for treating patients who have tested positive for SARS-CoV-2 infection and who are considered to be at high risk for progression to severe COVID-19 or hospitalization. To be eligible for treatment with bamlanivimab, patients must be at least 12 years of age and weigh at least 40 kg (approximately 88 lb). The agency notes that this includes patients aged 65 years and older or people with certain chronic conditions.

Bamlanivimab is not authorized for use in patients who are hospitalized or who require oxygen therapy because of COVID-19. The FDA's action comes less than 2 weeks after Eli Lilly halted the ACTIV-3 study of the therapy for severe, hospitalized COVID-19 patients after evidence showed that adding the antibody therapy to standard care did not improve outcomes over standard care alone for patients with advanced COVID-19.

The government contract with Eli Lilly involves the purchase of 300,000 doses through December, with the option to procure another 650,000 doses through June 2021.

Because of Operation Warp Speed, "we have supplies to distribute now. Product distribution will begin this week," U.S. Health & Human Services Secretary Alex Azar said at a news conference today.

"We talked about building the bridge to safe and effective vaccines" for COVID-19, Mr. Azar added. "With this therapeutic, the bridge is taking shape."

Bamlanivimab 700 mg will be administered as a 1-hour infusion followed by a 1-hour observation period for detecting any infusion-related side effects. The authorized dose is 700 mg, which was on the lower end of the dose range evaluated in studies.

During the press conference, a reporter asked whether the lower dose was chosen in order that more doses of the antibody could be made available. "The lower dose is a rational choice in this situation because we don't want to give more of a drug than you need," said Janet Woodcock, MD, the therapeutics lead for Operation Warp Speed. "I think we could probably go lower."

Bamlanivimab works by attaching to the virus and blocking its entry into the cells and possibly by helping the patients' immune system clear the virus, said Dr. Woodcock, who is also director of the FDA's Center for Drug Evaluation and Research.

"The goal is to treat high-risk people as soon as possible after they

Continued on following page

Continued from previous page

show symptoms and are diagnosed," she added.

Infusions may pose an initial challenge

There could be some logistic challenges at first because the antibody is administered via infusion. "We expect there will initially be a challenge in administering ... these infusions and setting up infusion centers," Dr. Woodcock said.

Outpatient intravenous infusions are normally performed at infusion centers for patients with cancer and immune disorders, she noted. "You really don't want them mixing with people who have COVID-19 disease, so we will need to set up separate sites."

Bamlanivimab will be provided free of cost to patients, Mr. Azar said. Patients should be aware that coinsurance may be required for the infusion.

"Fair and equitable" distribution planned

During phase 1 of distribution, the agent will first be allocated to hospitals and hospital-affiliated locations only, John Redd, MD, MPH, chief medical officer, Office of the Assistant Secretary for Preparedness and Response at HHS, said at the press conference.

During phase 2, "there will be expanded distribution to outpatient sites," he said. In an effort to keep the process transparent, a new website features the latest updates on the

To be eligible for treatment with bamlanivimab, patients must be at least 12 years of age and weigh at least 40 kg. The agency notes that this includes patients aged 65 years and older or people with certain chronic conditions.

distribution of bamlanivimab.

Allocation will be based on two factors: the number of new cases reported in a state or territory in the prior 7 days, and rates of COVID-19 hospitalization during the same period.

Asked why the government would determine distribution of the antibody on the basis of the number of hospitalized patients when the indication includes prevention of admission, Dr. Woodcock replied that hospitalization is a surrogate measure that can reflect risk factors in a particular state population, such as obesity, diabetes, or the proportion of older people.

Furthermore, the confirmed cases are a "leading indicator," she said, that can help identify a steep rise in COVID-19 cases that could indicate more hospitalizations are likely soon. "We don't want to miss that."

Data underlying the EUA decision presented

A decrease in hospitalizations or emergency department visits within

Continued on following page

Continued from previous page

28 days of treatment in preclinical studies was "the most important evidence that bamlanivimab may be effective," the agency noted in the press release announcing the EUA. Among patients at high risk for progression, 3% required such interventions, compared with 10% of placebo-treated patients.

Bamlanivimab will be provided free of cost to patients, said Sec. Azar. Patients should be aware that coinsurance may be required for the infusion.

Potential side effects of bamlanivimab include anaphylaxis, infusion-related reactions, nausea, diarrhea, dizziness, headache, itching, and vomiting.

"As illustrated by today's action, the FDA remains committed to expediting the development and availability of potential COVID-19 treatments and providing sick patients timely access to new therapies where appropriate," FDA Commissioner Stephen M. Hahn, MD, said in the news release.

Health care providers can download a detailed FDA fact sheet on the EUA for bamlanivimab, which includes dosing instructions.

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

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation use

The following is a brief summary only; see full prescribing information for complete product information.

1. INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

TRELEGY 100/62.5/25 mcg is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

1.2 Maintenance Treatment of Asthma

TRELEGY is indicated for the maintenance treatment of asthma in patients aged 18 years and older.

1.3 Limitations of Use

TRELEGY is NOT indicated for the relief of acute bronchospasm.

4 CONTRAINDICATIONS

TRELEGY is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When 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 with ICS alone *(see Serious Asthma-Related Events With Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists)*.

Serious Asthma-Related Events With Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists

Four (4) large, 26-week, randomized, double-blind, 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 with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma related.

The 3 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 margin 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 3 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 Subjects with Asthma Aged 12 Years and Older

	ICS/LABA (n = 17,537)[a]	ICS (n = 17,552)[a]	ICS/LABA vs. ICS Hazard Ratio (95% CI)[b]
Serious asthma-related event[c]	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.

[a] Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

[b] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

[c] Number of subjects 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. Subjects can have 1 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 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects 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 with 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). TRELEGY is not indicated for use in pediatric patients aged 17 years and younger.

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 subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects 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.

5.2 Deterioration of Disease and Acute Episodes

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

If TRELEGY 100/62.5/25 mcg no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. For COPD, the daily dose of TRELEGY 100/62.5/25 mcg should not be increased.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the need for additional therapeutic options. Patients should not use more than 1 inhalation once daily of TRELEGY.

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

When beginning treatment with TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing TRELEGY, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

Continued on next page

Blood glucose on admission can predict COVID-19 severity

BY MIRIAM E. TUCKER

Hyperglycemia at hospital admission – regardless of diabetes status – is a key predictor of COVID-19–related death and severity among noncritical patients, new research from Spain finds.

The observational study, the largest to date to investigate this association, was published online Nov. 23 in Annals of Medicine by Francisco Javier Carrasco-Sánchez, MD, PhD, and colleagues (doi: 10.1080/07853890.2020.1836566).

Among more than 11,000 patients with confirmed COVID-19 from March to May 2020 in a nationwide Spanish registry of 109 hospitals, admission hyperglycemia independently predicted progression from noncritical to critical condition

Continued on following page

Continued on next page

Continued from previous page

and death, regardless of prior diabetes history.

Those with abnormally high glucose levels were more than twice as likely to die from the virus than those with normal readings (41.4% vs. 15.7%). They also had an increased need for a ventilator and ICU admission.

"These results provided a simple and practical way to stratify risk of death in hospitalized patients with COVID-19. Hence, admission hyperglycemia should not be overlooked, but rather detected and appropriately treated to improve the outcomes of COVID-19 patients with and without diabetes," Dr. Carrasco-Sánchez and colleagues wrote.

The findings confirm those of previous retrospective observational studies, but the current study "has, by far, the biggest number of patients involved in this kind of study [to date]. All conclusions are consistent to other studies," Dr. Carrasco-Sánchez, of University Hospital Juan Ramón Jiménez, Huelva, Spain, said in an interview.

However, a surprising finding, he said, "was how hyperglycemia works in the nondiabetic population and [that] glucose levels over 140 [mg/dL] ... increase the risk of death."

Pay attention to even mild hyperglycemia from admission

The study also differs from some of the prior observational ones in that

Continued on next page

it examines outcome by admission glycemia rather than during the hospital stay, therefore eliminating the effect of any inpatient treatment, such as dexamethasone, he noted.

Although blood glucose measurement at admission is routine for all patients in Spain, as it is in the United States, a mildly elevated level in a person without a diagnosis of diabetes may not be recognized as important.

"In patients with diabetes we start the protocol to control and treat hyperglycemia during hospitalization. However, in nondiabetic patients blood glucose levels under 180 [mg/dL], and even greater, are usually overlooked. "After this study we learned that we need to pay attention to this population ... who develop hyperglycemia from the beginning," he said.

The study was limited in that patients who had previously undiagnosed diabetes couldn't always be distinguished from those with acute "stress hyperglycemia."

However, both need to be managed during hospitalization, he said.

All-cause death, progress to critical care

The retrospective, multicenter study was based on data from 11,312 adult patients with confirmed COVID-19 in 109 hospitals participating in Spain's SEMI-COVID-19 registry as of May 29, 2020. They had a mean age of 67 years, 57% were male, and

Continued on following page

BRIEF SUMMARY

TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation *(cont'd)*

fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100/25 mcg or placebo + fluticasone furoate/vilanterol 100/25 mcg administered once daily (mean age: 64 years; 92% White, 66% male across all treatments) *[see Clinical Studies (14.1) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100/25 mcg presented in Table 2 (on preceding page) is based on the two 12-week trials.

Trial 3 - Long-term Safety Data

A 52-week trial (Trial 3, NCT #02164513) evaluated the long-term safety of TRELEGY 100/62.5/25 mcg compared with the fixed-dose combinations of fluticasone furoate/vilanterol 100/25 mcg and umeclidinium/vilanterol 62.5/25 mcg. A total of 10,355 subjects with COPD with a history of moderate or severe exacerbations within the prior 12 months were randomized (2:2:1) to receive TRELEGY 100/62.5/25 mcg, fluticasone furoate/vilanterol, or umeclidinium/vilanterol administered once daily in a double-blind clinical trial (mean age: 65 years, 77% White, 66% male across all treatments) *[see Clinical Studies (14.1) of full prescribing information]*.

The incidence of adverse reactions in the long-term trial were consistent with those in Trials 1 and 2. However, in addition to the adverse reactions shown in Table 2, adverse reactions occurring in ≥1% of the subjects treated with TRELEGY 100/62.5/25 mcg (n = 4,151) for up to 52 weeks also included upper respiratory tract infection, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, oral candidiasis *[see Warnings and Precautions (5.4)]*, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

6.2 Clinical Trials Experience in Asthma

The safety of TRELEGY in asthma is based on a randomized, double-blind, parallel-group, active-controlled trial of 24 to 52 weeks' duration (Trial 4, NCT #02924688) that enrolled 2,436 adult subjects inadequately controlled on their current treatment of combination therapy (ICS plus a LABA) *[see Clinical Studies (14.2) of full prescribing information]*. In the overall population, 62% were female and 80% were White; mean age was 53 years. The incidence of adverse reactions occurring in ≥1% of the subjects treated with TRELEGY 100/62.5/25 mcg or TRELEGY 200/62.5/25 mcg is shown in Table 3 below. Adverse reactions observed for the groups treated with TRELEGY were similar to those observed for the fluticasone furoate/vilanterol arms.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of TRELEGY. 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 TRELEGY or a combination of these factors.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, and QTc Prolonging Drugs

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or 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 for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic 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

Table 3. Adverse Reactions With TRELEGY With ≥1% Incidence in Subjects With Asthma (Trial 4)

Adverse Reaction	TRELEGY 200/62.5/25 mcg (n = 408) %	TRELEGY 100/62.5/25 mcg (n =406) %	FF/VI 200/25 mcg (n = 406) %	FF/VI 100/25 mcg (n = 407) %
Infections and infestations				
Pharyngitis/nasopharyngitis	15	17	16	16
Upper respiratory tract infection/viral upper respiratory tract infection	7	5	6	7
Bronchitis	5	4	5	3
Respiratory tract infection/viral respiratory tract infection	3	4	2	4
Sinusitis/acute sinusitis	3	2	2	3
Urinary tract infection	2	<1	<1	1
Rhinitis	1	2	2	3
Influenza	1	4	2	3
Pneumonia	<1	1	2	2
Nervous system disorders				
Headache	5	9	6	7
Musculoskeletal and connective tissue disorders				
Back pain	2	3	1	4
Respiratory, thoracic, and mediastinal disorders				
Dysphonia	1	1	2	1
Oropharyngeal pain	1	1	<1	<1
Cough	1	<1	1	1

FF/VI = Fluticasone Furoate/Vilanterol.

Continued on next page

Continued from previous page

19% had a diagnosis of diabetes. A total of 20% (n = 2,289) died during hospitalization.

Overall all-cause mortality was 41.1% among those with admission blood glucose levels above 180 mg/dL, 33.0% for those with glucose levels 140-180 mg/dL, and 15.7% for levels below 140 mg/dL. All differences were significant ($P < .0001$), but there were no differences in mortality rates within each blood glucose category between patients with or without a previous diagnosis of diabetes.

After adjustment for confounding factors, elevated admission blood glucose level remained a significant predictor of death. Compared to <140 mg/dL, the hazard ratios for 140-180 mg/dL and >180 mg/dL were 1.48 and 1.50, respectively (both $P < .001$). Adjustments included age, gender, hypertension, diabetes, chronic obstructive pulmonary disease, lymphopenia, anemia (hemoglobin <10 g/dL), serum creatinine, C-reactive protein >60 mg/L, lactate dehydrogenase > 400 U/L and D-dimer >1000 ng/mL.

The study was supported by the Spanish Federation of Internal Medicine. The authors have reported no relevant financial relationships.

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

Continued on next page

FDA authorizes baricitinib combo for COVID-19

BY MARCIA FRELLICK

The Food and Drug Administration Nov. 19 issued an emergency use authorization (EUA) for the Janus kinase inhibitor baricitinib (Olumiant, Eli Lilly) in combination with remdesivir (Veklury, Gilead) for treating hospitalized adults and children at least 2 years old with suspected or confirmed COVID-19.

The combination treatment is meant for patients who need supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Baricitinib/remdesivir was shown in a clinical trial to reduce time to recovery within 29 days of starting the treatment compared to control who received placebo/remdesivir.

The median time to recovery from COVID-19 was 7 days for the combination group vs. 8 days for those in the placebo/remdesivir group. Recovery was defined as either discharge from the hospital or "being hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care," the FDA stated.

The odds of a patient dying or being ventilated at day 29 was lower in the combination group compared with those taking placebo/remdesivir, the press release said without providing specific data. "For all of these endpoints, the effects were statistically significant," the FDA said. Safety and efficacy continues to be evaluated. Baricitinib alone is not approved as a treatment for COVID-19.

"The FDA's emergency authorization of this combination therapy represents an incremental step forward in the treatment of COVID-19 in hospitalized patients, and FDA's first authorization of a drug that acts on the inflammation pathway," said Patrizia Cavazzoni, MD, acting director of the FDA's Center for Drug Evaluation and Research.

"Despite advances in the management of COVID-19 infection since the onset of the pandemic, we need more therapies to accelerate recovery and additional clinical research will be essential to identifying therapies that slow disease progression and lower mortality in the sicker patients," she said.

As a JAK inhibitor, baricitinib interferes with a pathway that leads to inflammation. Baricitinib is already prescribed as an oral medication and is FDA-approved for treating moderate to severe rheumatoid arthritis. The data supporting the EUA for the combination treatment are based on a randomized, double-blind, placebo-controlled clinical trial (ACTT-2), conducted by the National Institute of Allergy and Infectious Diseases.

The trial followed patients for 29 days and included 1,033 patients with moderate to severe COVID-19; 515 patients received baricitinib/remdesivir, and 518 patients received placebo/remdesivir.

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

Moderna COVID-19 vax: Early data yield 94.5% efficacy

BY DAMIAN MCNAMARA

The Moderna mRNA-1273 vaccine, in development to prevent COVID-19, yielded 94.5% efficacy in early results and is generally well tolerated, the company announced early Monday. The product can be stored at refrigeration temperatures common to many physician offices, pharmacies, and hospitals.

The first interim results of the phase 3 COVE trial included 95 participants with confirmed COVID-19. An independent data safety monitoring board (DSMB), which was appointed by the National Institutes of Health, informed Moderna that 90 of the patients who were positive for COVID-19 were in a placebo group and that 5 patients were in the mRNA-1273 vaccine group, resulting in a vaccine efficacy of 94.5% ($P < .0001$).

Interim data included 11 patients with severe COVID-19, all of whom were in the placebo group.

The vaccine met its primary study endpoint, which was based on adjudicated data that were collected starting 2 weeks after the second dose of mRNA-1273. The interim study population included people who could be at higher risk for COVID-19, including 15 adults aged 65 years and older and 20 participants from diverse communities.

Safety data

The DSMB also reviewed safety data for the COVE study interim results. The vaccine was generally safe and well tolerated, as determined on the basis of solicited adverse events.

Injection-site pain was reported in 2.7% of participants after the first dose. After the second dose, 9.7% of participants reported fatigue, 8.9% myalgia, 5.2% arthralgia, 4.5% headache, 4.1% pain, and 2.0% erythema or redness at the injection site.

Moderna plans to request emergency-use authorization (EUA) from the Food and Drug Administration in the coming weeks. The company expects that the EUA will be based on more data from the COVE study, including a final analysis of 151 patients with a median follow-up of more than 2 months. The company expects to have approximately 20 million doses of mRNA-1273 ready to ship in the United States by the end of the year. In addition, the company says it remains on track to manufacture between 500 million and 1 billion doses globally in 2021.

Moderna is developing distribution plans in conjunction with the Centers for Disease Control and Prevention, the federal government's Operation Warp Speed, and McKesson, a COVID-19 vaccine distributor contracted by the U.S. government.

The mRNA-1273 vaccine can be shipped and stored for up to 6 months at –20° C (about –4° F), a temperature maintained in most home or medical freezers, according to Moderna. After the product thaws, it will remain stable at standard refrigerator temperatures of 2°-8° C (36°-46° F) for up to 30 days within the 6-month shelf life.

Refrigeration requirements

The mRNA-1273 vaccine can be shipped and stored for up to 6 months at –20° C (about –4° F), a temperature maintained in most home or medical freezers, according to Moderna. The company expects that, after the product thaws, it will remain stable at standard refrigerator temperatures of 2°-8° C (36°-46° F) for up to 30 days within the 6-month shelf life.

Because the mRNA-1273 vaccine is stable at these refrigerator temperatures, it can be stored at most physicians' offices, pharmacies, and hospitals, the company noted. In contrast, the similar Pfizer BT-N162b2 vaccine – early results for which showed a 90% efficacy rate – requires shipment and storage at "deep-freeze" conditions of –70° C or –80° C, which is more challenging from a logistic point of view.

Moderna's mRNA-1273 can be kept at room temperature for up to 12 hours after removal from a refrigerator for patient administration. The research is being conducted with the National Institute of Allergy and Infectious Diseases and the Biomedical Advanced Research and Development Authority, part of the Office of the Assistant Secretary for Preparedness and Response at the Department of Health & Human Services.

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

CPT codes created for initial COVID-19 vaccines

BY KERRY DOOLEY YOUNG

The largest U.S. physician organization on Tuesday took a step to prepare for future payments for administration of two leading COVID-19 vaccine candidates, publishing new billing codes tailored to track each use of these medications.

The American Medical Association updated its CPT code set to reflect the expected future availability of COVID-19 vaccines. The new codes apply to the experimental vaccine being developed by Pfizer, in collaboration with a smaller German firm BioNTech, and to the similar product expected from Moderna, according to an AMA press release.

Positive news has emerged this week about both of these vaccines, which were developed using a newer – and as-yet unproven – approach. They seek to use messenger RNA to instruct cells to produce a target protein for SARS-CoV-2.

The severity of the global pandemic has put the Food and Drug Administration under pressure to move quickly on approval of COVID-19 vaccines, based on limited data, while also working to make sure these products are safe. The creation of CPT codes for each of two coronavirus vaccines, as well as accompanying administration codes, will set up a way to keep tabs on each dose of each of these shots, the AMA said.

"Correlating each coronavirus vaccine with its own unique CPT code provides analytical advantages to help track, allocate and optimize resources as an immunization program ramps up in the United States," AMA President Susan R. Bailey, MD, said in the release.

AMA plans to introduce more vaccine-specific CPT codes as more vaccine candidates approach FDA review. These vaccine-specific CPT codes can go into effect only after the FDA grants a clearance.

The newly created Category I CPT codes and long descriptors for the vaccine products are:

- 91300; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted, for intramuscular use (Pfizer/BioNTech)
- 91301; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage, for intramuscular use (Moderna)

These two administrative codes would apply to the Pfizer-BioNTech shot:

- 0001A; Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; first dose.
- 0002A; Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 30 mcg/0.3 mL dosage, diluent reconstituted; second dose.

And these two administrative codes would apply to the Moderna shot:

- 0011A; Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage; first dose.
- 0012A; Immunization administration by intramuscular injection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA-LNP, spike protein, preservative free, 100 mcg/0.5 mL dosage; second dose.

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

‘Hospital at home’ increases COVID-19 care capacity

BY KEN TERRY

A “hospital at home” (HaH) program at Atrium Health, a large integrated delivery system in the Southeast, expanded its hospital capacity during the early phase of the COVID-19 pandemic by providing hospital-level acute care to COVID-19 patients at home, according to a new study in Annals of Internal Medicine.

“Virtual hospital programs have the potential to provide health systems with additional inpatient capacity during the COVID-19 pandemic and beyond,” wrote Kranthi Sitammagari, MD, from the Atrium Health Hospitalist Group, Monroe, N.C., and colleagues.

Whereas most previous HaH programs have relied on visiting nurses and physicians, the new study uses telemedicine to connect with patients. Advocate Health Care researchers published the only other study using the telemedicine-powered model in 2015.

The new Atrium Health study evaluated 1,477 patients who received care in the HaH program between March 23 and May 7 of this year after having been diagnosed with COVID-19. The program provided home monitoring and hospital-level care in a home-based virtual observation unit (VOU) and a virtual acute care unit (VACU).

Patients were tested for the virus in Atrium emergency departments, primary care clinics, urgent care centers, and external testing sites. Those who tested positive were invited to be cared for either in the VOU, if they had mild to moderate symptoms, or in the VACU, if they were sick enough to be admitted to the hospital.

Patients hop onboard

Nearly all COVID-positive patients tested in these sites agreed to be admitted to the hospital at home, coauthor Stephanie Murphy, DO, medical director of the Atrium Health HaH program, said in an interview.

Patients with moderate symptoms were glad to be monitored at home, she said. When they got to the point where the nurse supervising their care felt they needed escalation to acute care, they were asked whether they wanted to continue to be cared for at home. Most opted to stay home rather than be admitted to the hospital, where their loved ones couldn’t visit them.

Low-acuity patients in the VOU received daily telemonitoring by a nurse to identify disease progression and escalate care as needed. For those who required more care and were admitted to the VACU, a team of paramedics and registered nurses (RNs; mobile clinicians) visited the patient’s home within 24 hours, setting up a hospital bed, other necessary medical equipment, videoconferencing gear, and a remote-monitoring kit that included a blood pressure cuff, a pulse oximeter, and a thermometer.

Dr. Sitammagari

Dedicated hospitalists and nurses managed patients with 24/7 coverage and monitoring, bringing in other specialties as needed for virtual consults. Mobile clinician and virtual provider visits continued daily until a patient’s condition improved to the point where they could be deescalated back to the VOU. After that, patients received mobile app–driven symptom monitoring and telephone follow-up with a nurse until they got better.

Few patients go to hospital

Overall, patients had a median length of stay of 11 days in the VOU or the VACU or both. The vast majority, 1,293 patients (88%), received care in the VOU only. In that cohort, just 40 patients (3%) required hospitalization in an Atrium facility. Sixteen of those patients spent time in an ICU, seven required ventilator support, and two died in the hospital.

A total of 184 patients (12%) were admitted to the VACU. Twenty-one (11%) required intravenous fluids, 16 (9%) received antibiotics, 40 (22%) required inhaler or nebulizer treatments, 41 (22%) used supplemental oxygen, and 24 (13%) were admitted to a conventional hospital. Of the latter patients, 10 were admitted to an ICU, 1 required a ventilator, and none died in the hospital.

Dr. Sitammagari, a hospitalist and comedical director for quality at Atrium Health, told this news organization that, overall, the outcomes for patients in the system’s HaH were comparable to those seen in the literature among other COVID-19 cohorts.

Hospital capacity adjusted

The authors note that treating the 160 VACU patients within the HaH saved hospital beds for other patients. The HaH maintained a consistent census of between 20 and 30 patients for the first 6 weeks as COVID-19 cases spread.

Since last spring, Dr. Murphy said, the Atrium HaH’s daily census has grown to between 30 and 45 patients. “We could absorb 50 patients if our hospitals required it.”

“Virtual hospital programs have the potential to provide health systems with additional inpatient capacity during the COVID-19 pandemic and beyond.”

How much capacity does that add to Atrium Health? While there are 50 hospitals in the health system, the HaH was set up mainly to care for COVID-19 patients who would otherwise have been admitted to the 10 acute-care hospitals in the Charlotte, N.C., area. In the 4 weeks ending Nov. 16, these facilities carried an average daily census of around 160 COVID-19 patients, Dr. Murphy noted. “During that time, the Atrium Health HaH has carried, on average, about 20%-25% of that census.”

If the pandemic were to overwhelm area hospitals, she added, “the structure would support flexing up our staffing and supplies to expand to crisis capacity,” which could be up to 200 patients a day.

For the nurses who make most of the phone calls to patients, patients average about 12-15 per RN, Dr. Murphy said, and there’s one mobile clinician for every 6-9 patients. That’s pretty consistent with the staffing on med-surg floors in hospitals, she said.

The physicians in the program include hospitalists dedicated to telemedicine and some doctors who can’t work in the regular hospital because they’re immunocompromised. The physicians round virtually, covering 12-17 HaH patients per day, according to Dr. Murphy.

Prior planning paid off

Unlike some other health care systems that have launched HaH programs with the aid of outside vendors, Atrium Health developed its own HaH and brought it online just 2 weeks after deciding to launch the program. Atrium was able to do this, Dr. Sitammagari explained, because before the pandemic its hospitalist program was already developing an HaH model to improve the care of high-risk patients after hospital discharge to prevent readmission.

While Atrium’s electronic health record system wasn’t designed for hospital at home, its health information technology department and clinicians collaborated in rewriting some of the workflows and order sets in the EHR. For example, they set up a nursing questionnaire to administer after VACU admission, and they created another form for automatic admission to the HaH after a patient tested positive for COVID-19. Atrium staff also modified a patient-doctor communications app to help clinicians monitor HaH patients, Dr. Murphy noted.

COVID and non-COVID patients compared

Atrium’s decision to focus its HaH effort on COVID-19 patients is unusual among the small but growing number of health systems that have adopted the HaH model to increase their capacity. (Atrium is now transferring some hospitalized patients with other conditions to its HaH, but is still focusing mainly on COVID-19 in its HaH program.)

Bruce Leff, MD, a professor of health policy and management at Johns Hopkins Bloomberg School of Public Health, Baltimore, a leading expert on the HaH model, agrees that it can increase hospital capacity significantly.

Dr. Leff praised the Atrium Health study. “It proves that within an integrated delivery system you can quickly deploy and implement a virtual hospital in the specific-use case of COVID, and help patients and help the system at scale,” he said. “They took a bunch of people into the virtual observation unit and thereby kept people from overwhelming their [emergency department] and treated those people safely at home.”

Most of the authors are employees of Atrium Health. In addition, one coauthor reports being the cofounder of a digital health company, iEnroll, and receiving grants from The Heineman Foundation. Dr. Leff is an adviser to Medically Home, which provides support to hospital at home programs.

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

COVID-19 aftermath: Depression, insomnia

BY MEGAN BROOKS

One in five COVID-19 patients are diagnosed with a psychiatric disorder such as anxiety or depression within 3 months of testing positive for the virus, new research suggests.

"People have been worried that COVID-19 survivors will be at greater risk of psychiatric disorders, and our findings in a large and detailed study show this to be true," principal investigator Paul Harrison, BM, DM, professor of psychiatry, University of Oxford (England), said in a statement.

Health services "need to be ready to provide care, especially since our results are likely to be underestimates of the actual number of cases," said Dr. Harrison.

The study also showed that having a psychiatric disorder independently increases the risk of getting COVID-19 – a finding that's in line with research published earlier this month.

"Having a psychiatric illness should be added to the list of risk factors for COVID-19," study coauthor Maxime Taquet, PhD, University of Oxford, said in the release.

Older COVID-19 patients had a two- to threefold increased risk for a first dementia diagnosis, a finding that supports an earlier U.K. study. Some of this excess risk could reflect misdiagnosed cases of delirium or transient cognitive impairment due to reversible cerebral events.

The study was published online Nov. 9 in The Lancet Psychiatry (doi: 10.1016/S2215-0366[20]30462-4).

Double the risk

The investigators took advantage of the TriNetX analytics network, which captured deidentified data from electronic health records of a total of 69.8 million patients from 54 health care organizations in the United States.

Of those patients, 62,354 adults were diagnosed with COVID-19 between Jan. 20 and Aug. 1, 2020.

To assess the psychiatric sequelae of COVID-19, the investigators created propensity score–matched cohorts of patients who had received a diagnosis of other conditions that represented a range of common acute presentations.

In 14-90 days after being diagnosed with COVID-19, 5.8% of patients received a first recorded diagnosis of psychiatric illness. Among patients with health problems other than COVID, 2.5%-3.4% of patients received a psychiatric diagnosis, the authors report. The risk was greatest for anxiety disorders, depression, and insomnia.

Older COVID-19 patients had a two- to threefold increased risk for a first dementia diagnosis, a finding that supports an earlier U.K. study.

Some of this excess risk could reflect misdiagnosed cases of delirium or transient cognitive impairment due to reversible cerebral events, the authors noted.

The study also revealed a bidirectional relationship between mental illness and COVID-19. Individuals with a psychiatric diagnosis were about 65% more likely to be diagnosed with COVID-19 in comparison with their counterparts who did not have mental illness, independently of known physical health risk factors for COVID-19.

"We did not anticipate that psychiatric history would be an independent risk factor for COVID-19. This finding appears robust, being observed in all age strata and in both sexes, and was substantial," the authors write.

At present, "we don't understand what the explanation is for the associations between COVID and mental illness. We are looking into this in more detail to try and understand better what subgroups are particularly vulnerable in this regard," Dr. Harrison said in an interview.

"Ambitious" research

Commenting on the findings, Roy H. Perlis, MD, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, said this is "an ambitious effort to understand the short-term consequences of COVID in terms of brain diseases."

Dr. Harrison

Dr. Perlis said he's not particularly surprised by the increase in psychiatric diagnoses among COVID-19 patients.

"After COVID infection, people are more likely to get close medical follow-up than usual. They're more likely to be accessing the health care system; after all, they've already had COVID, so they're probably less fearful of seeing their doctor. But, that probably also means they're more likely to get a new diagnosis of something like depression," he said.

Dementia may be the clearest illustration of this, Dr. Perlis said. "It seems less likely that dementia develops a month after COVID; more likely, something that happens during the illness leads someone to be more likely to diagnose dementia later on," he noted.

Dr. Perlis cautioned against being "unnecessarily alarmed" by the findings in this study.

"We know that rates of depression in the U.K. and the U.S., as in much of the world, are substantially elevated right now. Much of this is likely a consequence of the stress and disruption that accompanies the pandemic," said Dr. Perlis.

The study was funded by the National Institute for Health Research. Dr. Harrison has disclosed no relevant financial relationships. One author is an employee of TriNetX. Dr. Perlis has received consulting fees for service on scientific advisory boards of Belle Artificial Intelligence, Burrage Capital, Genomind, Psy Therapeutics, Outermost Therapeutics, RID Ventures, and Takeda. He holds equity in Psy Therapeutics and Outermost Therapeutics.

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

DEMAERRE/GETTY IMAGES

VIEW ON THE NEWS

Sachin Gupta, MD, FCCP, comments: Long-haul, post-COVID manifestations are not limited to those picked up in the usual history and physical exam. Many of these patients have symptoms of mental distress which will add to the burden of recovery from COVID-19.

One of my patients experienced survivor's guilt and associated depressive symptoms during her recovery from COVID-19 ARDS. Tragically, her elderly father (diagnosed and hospitalized a few days earlier) was unable to overcome the disease. Financial distress related to economic hardship and generalized fear of infecting others at home contribute to anxiety, depression, and insomnia in our patients. Postinfectious delirium or depression, masquerading as newly diagnosed dementia, may affect our seniors who are cut off from vital sources of social connection during shelter-in-place, particularly painfully during birthdays and holidays. Perhaps in some cases, though yet to be defined, the post-COVID long-hauler physical symptoms of fatigue, body-aches, dizziness, and chest pain are in part attributable to anxiety, depression, and/or insomnia. Even as we eventually turn the corner in this pandemic, the long-term mental health effects of the pandemic will continue to be an issue for many of our patients. Chest physicians, working with primary care providers, social workers, and psychiatrists should remain vigilant in both short- and long-term patient follow-up to this critical pillar in our patients' health. This small slice of data should serve as a clarion call for further attention and resources by health care systems to the challenges patients face after a COVID infection.

About 17% of COVID-19 survivors retest positive

BY DAMIAN MCNAMARA

For reasons unknown, about one in six people who recovered from COVID-19 subsequently retested positive at least 2 weeks later, researchers reported in a study in Italy.

Sore throat and rhinitis were the only symptoms associated with a positive result. "Patients who continued to have respiratory symptoms, especially, were more likely to have a new positive test result," lead author Francesco Landi, MD, PhD, said in an interview

"This suggests the persistence of respiratory symptoms should not be underestimated and should be adequately assessed in all patients considered recovered from COVID-19," he said.

"The study results are interesting," Akiko Iwasaki, PhD, an immunobiologist at Yale University and the Howard Hughes Medical Institute, both in New Haven, Conn., said in an interview. "There are other reports of RNA detection postdischarge, but this study ... found that only two symptoms out of many – sore throat and rhinitis – were higher in those with PCR [polymerase chain reaction]–positive status."

The study was published online Sept. 18 in the American Journal of Preventive Medicine (doi: 10.1016/j.amepre.2020.08.014).

The findings could carry important implications for people who continue to be symptomatic. "It is reasonable to be cautious and avoid close contact with others, wear a face mask, and possibly undergo an additional nasopharyngeal swab," said Dr. Landi, associate professor of internal medicine at Catholic University of the Sacred Heart in Rome.

"One of most interesting findings is that persistent symptoms do not correlate with PCR positivity, suggesting that symptoms are in many cases not due to ongoing viral replication," Jonathan Karn, PhD, professor and chair of the department of molecular biology and microbiology at Case Western Reserve University, Cleveland, said in an interview.

"The key technical problem, which they have discussed, is that a viral RNA signal in the PCR assay does not necessarily mean that infectious virus is present," Dr. Karn said. He added that new comprehensive viral RNA analyses would be needed to answer this question.

Official COVID-19 recovery

To identify risk factors and COVID-19 survivors more likely to retest positive, Dr. Landi and members of the Gemelli Against COVID-19 Post-Acute Care Study Group evaluated 131 people after hospital discharge.

All participants met World Health Organization criteria for release from isolation, including two negative test results at least 24 hours apart, and were studied between April 21 and May 21. Mean age was 56 and 39% were women. Although 51% of survivors reported fatigue, 44% had dyspnea, and 17% were coughing, the rates did not differ significantly between groups. In contrast, 18% of positive survivors and 4% of negative survivors had a sore throat ($P = .04$), and 27% versus 12%, respectively, reported rhinitis ($P = .05$).

People returned for follow-up visits a mean 17 days after the second negative swab test.

Continued on following page

SENIOR AIRMAN PEDRO TENORIO/U.S. AIR FORCE

Tech. Sgt. Jonisha Gibson, 82nd Medical Group clinical laboratory noncommissioned officer in charge, inspects a FilmArray pouch.

FDA-approved peanut immunotherapy protocol comes with a cost

BY INGRID HEIN

Peanut allergy immunotherapy now comes with approval from the U.S. Food and Drug Administration, but it also comes with protocols, standards, and paperwork. Whether it will be widely adopted has yet to be determined.

A few dozen allergists around the world have been offering food allergy immunotherapy for many years, having developed their own measuring techniques using store-bought food.

But the vast majority of doctors are not interested in developing home-grown treatments, not only because it involves research and development, but also because it comes with legal risks.

"Finally we have another treatment option," said Edwin Kim, MD, from the UNC Allergy and Immunology Clinic in Chapel Hill, N.C. "This is what we were waiting for. It's not cowboy stuff; this works."

In January, the FDA approved peanut allergen powder (Palforzia) for patients 4-17 years of age, as reported by Medscape Medical News.

The pill contains measured doses of peanut flour and comes with a protocol that will allow allergists to bring patients to a peanut tolerance of 300 mg (about one peanut) and a black-box warning about anaphylaxis risk.

And before allergists can prescribe it, they must take a Risk Evaluation and Mitigation Strategy course to learn about dosing and the allergic reaction protocol.

"That may scare some away," said Dr. Kim, who discussed the FDA-approved option during his presentation at the American College of Allergy, Asthma & Immunology 2020 Annual Scientific Meeting.

Allergic reaction, including the potential for anaphylaxis, has always been an issue with immunotherapy.

"People make the argument that there is a difference" between an expected allergic reaction – such as one that occurs after the administration of immunotherapy – and an unexpected reaction, he said. Because an expected reaction can be treated quickly, "some feel these expected reactions don't matter so much."

"Others say a reaction is a reaction" and argue that, if a treatment causes reaction, then it doesn't make sense, he explained.

It comes down to patients – they must be willing to take a risk to develop tolerance and improve their quality of life – and the allergists willing to treat them.

The peanut powder involves paperwork, preauthorization forms, denials of care, a higher price tag, regimented procedures, and a prerequisite number of visits with patients. "Not everyone will want to do this," said Dr. Kim.

The regimen involves three phases. During initial dose escalation, five doses are administered in the office on day 1. Then, over the next 6 months, updoses are administered during 11 in-office sessions and a 300-mg tolerance is achieved. Finally, to maintain tolerance to one peanut, daily doses are administered at home.

The drug cost alone is about $4,200 a year, according to Institute for Clinical and Economic Review. Peanut flour from the grocery store is cheaper, but comes with the risk of bacteria or other contamination.

The drug cost alone is about $4,200 a year, according to Institute for Clinical and Economic Review. Peanut flour from the grocery store is cheaper, but comes with the risk of bacteria or other contamination.

"This product offers some reassurance, and that matters," Dr. Kim said.

It's good to have more options for food allergy treatment. "We need a more proactive way to treat food allergy; avoidance is not good enough," he explained. "And presumably, at some point, the patient will be able to eat a grocery-store peanut instead of buying the pills."

The art of medicine

But not all allergists will be able to make the protocol work. And it's not clear whether there is room to alter treatment and offer patients with a higher tolerance a higher starting dose. What we do know, though, is that "the product leaves little room for 'the art of medicine,'" Kim said.

That art is practiced by Arnon Elizur, MD, from the Shamir Medical Center in Tzrifin, Israel, but it's backed by a rigid home-grown protocol.

Since 2010, he has treated 1,800 patients for peanut allergy, updosing slowly to a tolerance of 3,000 mg of peanut, the equivalent of 10 peanuts. He keeps the maintenance dose at four peanuts (1,200 mg). His center takes a personalized approach, starting patients on the highest dose they can tolerate and working up, with daily patient check-ins from home and a staff available around the clock to answer questions and deal with reactions.

"We aim for full sensitization," Dr. Elizur said in an interview.

The peanut pill is "a big step forward" for immunotherapy, he said. It is "a standardized product, checked for bacteria and allergen content, which is available to a wide community of physicians."

But, he pointed out, "it's expensive." And it's only for peanut. "There are millions of food-allergic patients around the world dying from adverse reactions to many different kinds of food. We don't want to wait for years for a product for all of them. We can use the actual food."

He questions the lifelong maintenance protocol with a daily 300-mg pill. "If you can't eat a peanut, why would you buy a drug that's a peanut?" he asked. He also said he's disappointed that the product is not indicated for adults.

At the Shamir clinic, reactions are closely monitored. "Some are mild, others we treat with autoinjectors, epinephrine," he reported. "Those are the most undesirable."

Data from his center show that reactions occur in about 15% of patients. But his treatment success rates are good. In an average of 8 months, he is able to get 80% of his adult patients to full sensitization.

But it's not for all patients or for all clinics, he acknowledged. "We continue to look at this balance in quality of life throughout the process. Our goal is to improve the quality of life threshold."

Dr. Kim reports receiving consulting honorarium from Aimmune, the maker of Palforzia; being on the clinical medical advisory board for DBV Technologies; and consulting for Aimmune, Allakos, Allergenis, DBV, Duke Clinical Research Institute, Ukko Incorporated, Vibrant America, and Kenota Health. Dr. Elizur has disclosed no relevant financial relationships.

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

Continued from previous page

Asymptomatic COVID-19 carriers

"These findings indicate that a noteworthy rate of recovered patients with COVID-19 could still be asymptomatic carriers of the virus," the researchers noted in the paper. "Even in the absence of specific guidelines, the 22 patients who tested positive for COVID-19 again were suggested to quarantine for a second time."

No family member or close contact of the positive survivors reported SARS-CoV-2 infection. All patients continued to wear masks and observe social-distancing recommendations, which makes it "very difficult to affirm whether these patients were really contagious," the researchers noted.

Next steps

Evaluating all COVID-19 survivors to identify any who retest positive "will be a crucial contribution to a better understanding of both the natural history of COVID-19 as well as the public health implications of viral shedding," the authors wrote.

One study limitation is that the reverse transcriptase–PCR test reveals genetic sequences specific to COVID-19. "It is important to underline that this is not a viral culture and cannot determine whether the virus is viable and transmissible," the researchers noted.

Dr. Landi and Dr. Karn disclosed no relevant financial relationships. Dr. Iwasaki disclosed a research grant from Condair, a 5% or greater equity interest in RIGImmune, and income of $250 or more from PureTec.

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

HF an added risk in COVID-19, regardless of etiology

BY PATRICE WENDLING

People with a history of heart failure – regardless of the etiology or ejection fraction – face more complications and death than their peers without HF once hospitalized with COVID-19, a new observational study shows.

A history of HF was associated with a near doubling risk of in-hospital mortality and ICU care and more than a tripling risk of mechanical ventilation despite adjustment for 18 factors including race, obesity, diabetes, previous treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors, and severity of illness.

Adverse outcomes were high regardless of whether patients had HF with a preserved, mid-range, or reduced left ventricular ejection fraction (HFpEF/HFmrEF/HFrEF).

"That for me was the real zinger," senior author Anuradha Lala, MD, said in an interview . "Because as clinicians, oftentimes, and wrongly so, we think this person has preserved ejection fraction, so they're not needing my heart failure expertise as much as someone with heart failure with reduced ejection fraction."

In the peak of the pandemic, that may have meant triaging patients with HFpEF to a regular floor, whereas those with HFrEF were seen by the specialist team.

"What this alerted me to is to take heart failure as a diagnosis very seriously, regardless of ejection fraction, and that is very much in line with all of the emerging data about heart failure with preserved ejection fraction," said Dr. Lala, from the Icahn School of Medicine at Mount Sinai, New York.

"Now when I see patients in the clinic, I incorporate part of our visit to talking about what they are doing to prevent COVID, which I really wasn't doing before. It was like 'Oh yeah, what crazy times we're dealing with' and then addressing their heart failure as I normally would," she said. "But now, interwoven into every visit is: Are you wearing a mask, what's your social-distancing policy, who are you living with at home, has anyone at home or who you've interacted with been sick? I'm asking those questions just as a knee-jerk reaction for these patients because I know the repercussions. We have to keep in mind these are observational studies, so I can't prove causality but these are observations that are, nonetheless, quite robust."

Although cardiovascular disease, including HF, is recognized as a risk factor for worse outcomes in COVID-19 patients, data are sparse on the clinical course and prognosis of patients with preexisting HF.

"I would have expected that there would have been a gradation of risk from the people with very low ejection fractions up into the normal range, but here it didn't seem to matter at all. So that's an important point that bad outcomes were independent of ejection fraction," commented Lee Goldberg, MD, professor of medicine and chief of advanced heart failure and cardiac transplant at the University of Pennsylvania, Philadelphia.

The study also validated that there is no association between use of RAAS inhibitors and bad outcomes in patients with COVID-19, he said.

Although this has been demonstrated in several studies, concerns were raised early in the pandemic that ACE inhibitors and angiotensin receptor blockers could facilitate infection with SARS-CoV-2 and increase the risk of severe or lethal COVID-19.

"For most clinicians that question has been put to bed, but we're still getting patients that will ask during office visits 'Is it safe for me to stay on?' They still have that doubt [about] 'Are we doing the right thing?'" Dr. Goldberg said.

"We can reassure them now. A lot of us are able to say there's nothing to that; we're very clear about this: Stay on the meds. If anything, there's data that suggest actually it may be better to be on an ACE inhibitor; that the hospitalizations were shorter and the outcomes were a little bit better."

VIEW ON THE NEWS

Jonathan Ludmir, MD, FCCP, comments: Patients with underlying cardiovascular disease who develop COVID-19 are at higher risk for poor outcomes. This study increases our knowledge about heart failure patients in particular. While heart failure patients need to be extra vigilant, this study should not prevent this patient population from seeking routine chronic care.

For the current study, published online Oct. 28 in the Journal of the American College of Cardiology, the investigators analyzed 6,439 patients admitted for COVID-19 at one of five Mount Sinai Health System hospitals in New York between Feb. 27 and June 26. Their mean age was 65.3 years, 45% were women, and one-third were treated with RAAS inhibitors before admission.

Through ICD-9/10 codes and individual chart review, HF was identified in 422 patients (6.6%), of which 250 patients had HFpEF (≥50%), 44 had HFmrEF (41%-49%), and 128 had HFrEF (≤40%).

Patients with HFpEF were older, more frequently women with a higher body mass index and history of lung disease than patients with HFrEF, whereas those with HFmrEF fell in between.

The HFpEF group was also treated with hydroxychloroquine or macrolides and noninvasive ventilation more frequently than the other two groups, whereas antiplatelet and neurohormonal therapies were more common in the HFrEF group.

Patients with a history of HF had significantly longer hospital stays than those without HF (8 days vs. 6 days), increased need for intubation (22.8% vs. 11.9%) and ICU care (23.2% vs. 16.6%), and worse in-hospital mortality (40% vs. 24.9%).

After multivariable regression adjustment, HF persisted as an independent risk factor for ICU care (odds ratio, 1.71; 95% confidence interval, 1.25-2.34), intubation and mechanical ventilation (OR, 3.64; 95% CI, 2.56-5.16), and in-hospital mortality (OR, 1.88; 95% CI, 1.27-2.78).

"I knew to expect higher rates of adverse outcomes but I didn't expect it to be nearly a twofold increase," Dr. Lala said. "I thought that was pretty powerful."

No significant differences were seen across left ventricular ejection fraction categories in length of stay, need for ICU care, intubation and mechanical ventilation, acute kidney injury, shock, thromboembolic events, arrhythmias, or 30-day readmission rates.

However, cardiogenic shock (7.8% vs. 2.3% vs. 2%) and HF-related causes for 30-day readmissions (47.1% vs. 0% vs. 8.6%) were significantly higher in patients with HFrEF than in those with HFmrEF or HFpEF.

Also, mortality was lower in those with HFmrEF (22.7%) than with HFrEF (38.3%) and HFpEF (44%). The group was small but the "results suggested that patients with HFmrEF could have a better prognosis, because they can represent a distinct and more favorable HF phenotype," the authors wrote.

The statistical testing didn't show much difference and the patient numbers were very small, noted Dr. Goldberg. "So they might be overreaching a little bit there."

"To me, the take-home message is that just having the phenotype of heart failure, regardless of EF, is associated with bad outcomes and we need to be vigilant on two fronts," he said. "We really need to be doing prevention in the folks with heart failure because if they get COVID their outcomes are not going to be as good. Second, as clinicians, if we see a patient presenting with COVID who has a history of heart failure we may want to be much more vigilant with that individual than we might otherwise be. So I think there's something to be said for kind of risk-stratifying people in that way."

Dr. Goldberg pointed out that the study had many "amazing strengths," including a large, racially diverse population, direct chart review to identify HF patients, and knowledge of a patient's specific HF phenotype.

Weaknesses are that it was a single-center study, so the biases of how these patients were treated are not easily controlled for, he said. "We also don't know when the hospital system was very strained as they were making some decisions: Were the older patients who had advanced heart and lung disease ultimately less aggressively treated because they felt they wouldn't survive?"

Dr. Lala has received personal fees from Zoll, outside the submitted work. Dr. Goldberg reported research funding with Respicardia and consulting fees from Abbott.

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

Updated heart failure measures add newer meds

BY RICHARD MARK KIRKNER
MDedge News

Safety measures for lab monitoring of mineralocorticoid receptor agonist therapy, performance measures for sacubitril/valsartan, cardiac resynchronization therapy and titration of medications, and quality measures based on patient-reported outcomes are among the updates the joint task force of the American College of Cardiology and the American Heart Association have made to performance and quality measures for managing adults with heart failure.


Dr. Fonarow

The revisions, published online Nov. 2 in the Journal of the American College of Cardiology (J Am Coll Card. 2020 Nov 2;76:2527-64), update the 2011 ACC/AHA heart failure measure set, writing committee vice chair Gregg C. Fonarow, MD, said in an interview. The 2011 measure set predates the 2015 approval of the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan for heart failure in adults.

Measures stress dosages, strength of evidence

"For the first time the heart failure performance measure sets also focus on not just the use of guideline-recommended medication at any dose, but on utilizing the doses that are evidence based and guideline recommended so long as they are well tolerated," said Dr. Fonarow, interim chief of cardiology at the University of California, Los Angeles. "The measure set now includes assessment of patients being treated with doses of medications at 50% or greater of target dose in the absence of contraindications or documented intolerance."

The update adds two performance measures for titration of medications based on dose, either reaching 50% of the recommended dose for a variety of medications or documenting that the dose wasn't tolerated.

The update includes seven new performance measures, two quality measures, and one structural measure. The performance measures come from the strongest recommendations – that is, a class of recommendation of 1 (strong) or 3 (no benefit or harmful, process to be avoided) – in the 2017 ACC/AHA/Heart Failure Society of American heart failure guideline update published in Circulation (Circulation. 2017 Apr 28;132:e137-61).

In addition to the 2017 update, the writing committee also reviewed existing performance measures. "Those management strategies, diagnostic testing, medications, and devices with the strongest evidence and highest level of guideline recommendations were further considered for inclusion in the performance measure set," Dr. Fonarow said. "The measures went through extensive review by peer reviewers and approval from the organizations represented."

Specifically, the update includes measures for monitoring serum potassium after starting mineralocorticoid receptor antagonists therapy, and cardiac resynchronization therapy for patients with heart failure with reduced ejection fraction already on guideline-directed therapy. "This therapy can significantly improve functional capacity and outcomes in appropriately selected patients," Dr. Fonarow said.

Measures added and retired

The update adds two performance measures for titration of medications based on dose, either reaching 50% of the recommended dose for a variety of medications, including ARNI, or documenting that the dose wasn't tolerated for other reason for not using the dose.

The new structural measure calls for facility participation in a heart failure registry. The revised measure set now consists of 18 measures in all.

The update retired one measure from the 2011 set: left ventricular ejection fraction assessment for inpatients. The committee cited its use above 97% as the reason, but LVEF in outpatients remains a measure.

The following three measures have been revised:

- Patient self-care education has moved from performance measure to quality measure because of concerns about the accuracy of self-care education documentation and limited evidence of improved outcomes with better documentation.
- ACE inhibitor or angiotensin receptor blocker therapy for left ventricular systolic dysfunction adds ARNI therapy to align with the 2017 ACC/AHA/HFSA update.
- Postdischarge appointments shifts from performance to quality measure and include a 7-day limit.

Measures future research should focus on, noted Dr. Fonarow, include the use of sodium glucose cotransporter 2 (SGLT2) inhibitors for heart failure, including in patients without diabetes. "Since the ACC/AHA heart failure guidelines had not yet been updated to recommend these therapies they could not be included in this performance measure set," he said.

The update retired one measure from the 2011 set: left ventricular ejection fraction assessment for inpatients. The committee cited its use above 97% as the reason, but LVEF in outpatients remains a measure.

He also said "an urgent need" exists for further research into treatments for heart failure with preserved ejection fraction along with optimal implementation strategies.

"If these ACC/AHA heart failure performance measures were applied in all settings in which patients with heart failure in the United States are being cared for, and optimal and equitable conformity with each of these measures were achieved, over 100,000 lives a year of patients with heart failure could be saved," he said. "There's in an urgent need to measure and improve heart failure care quality."

Dr. Fonarow reported financial relationships with Abbott, Amgen, AstraZeneca, CHF Solutions, Janssen, Medtronic, Merck, and Novartis.

chestphysiciannews@chestnet.org

SOURCE: American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol. 2020 Nov 2;76:2527-64.

New ESC/EACTS guidelines on atrial fibrillation

BY PATRICE WENDLING

New atrial fibrillation (AFib) management guidelines from the European Society of Cardiology call for diagnostic confirmation and structured characterization of AFib and the need to streamline integrated care with the Atrial fibrillation Better Care (ABC) pathway.

"It's as simple as CC to ABC," quipped one task force member during the virtual unveiling of the guidelines at the ESC Congress 2020.

The guidelines were developed in collaboration with the European Association of Cardio-Thoracic Surgery and published simultaneously Aug. 29 in the European Heart Journal (2020. doi: 10.1093/eurheartj/ehaa612).

Acknowledging the slew of novel screening tools now available and their reported sensitivity and specificity rates, the document supports opportunistic screening for AFib by pulse taking or electrocardiogram (ECG) rhythm strip in patients at least 65 years of age, with a class 1 recommendation, evidence level B.

Systematic ECG screening should also be considered to detect AFib in individuals at least 75 years of age or in those at high risk for stroke (class IIa, level B).

Other new class I screening recommendations are to inform individuals undergoing screening about the significance and treatment implications of detecting AFib and to have a structured referral platform in place for further physician-led evaluation.

A definite diagnosis of clinical AFib is established only after confirmation by a conventional 12-lead ECG or single-lead ECG strip with at least 30 seconds of AFib.

In line with ESC's 2016 AFib guidelines, the new iteration classifies AFib as first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent. But it's also important to classify the clinical profile of AFib, task force member Giuseppe Boriani, MD, PhD, University of Modena (Italy), said in the first of five presentations.

VIEW ON THE NEWS

Jonathan Ludmir, MD, FCCP, comments: While amiodarone has many extra-cardiac adverse effects and should be avoided if possible, in stable outpatients with atrial fibrillation, it has a class 1A indication for perioperative use to prevent postoperative atrial fibrillation after cardiac surgery. However, caution should be taken about maintaining postoperative cardiac surgery patients on long-term amiodarone.

Perhaps one of the most critical highlights of the new ESC Afib guidelines addresses cardiovascular comorbidities. Lifestyle changes are fundamental to ensure successful treatment of atrial fibrillation. Without appropriate risk factor modification, ablation outcomes among other strategies to control afib, are unlikely to succeed in the long term.

"So the novelty of the 2020 guidelines is related to the proposal of the 4S-AF scheme for a structured characterization of atrial fibrillation that takes into account Stroke risk, severity of Symptoms, Severity of atrial fibrillation burden, and Substrate severity," he said.

This represents a paradigm shift from a single-domain conventional classification of AFib toward a structured characterization that streamlines assessment, informs treatment decision-making, and facilitates communication among physicians of various specialties, said Tatjana Potpara, MD, PhD, guideline co-chair and head of the Department for Intensive Arrhythmia Care, Clinical Centre of Serbia, Belgrade.

"The beauty of this approach is that, at present, the assessment of the 'S' components are performed using available tools, but in the future, the 4S-AF has a great potential to incorporate whatever becomes available for a more precision assessment of substrate or symptoms or arrhythmia burden and so forth," she said.

ABC pathway

The guidelines advocate the previously described ABC pathway for integrated care management, which includes 'A' for Anticoagulation/Avoid stroke, 'B' for Better symptom control, and 'C' for Comorbidity/Cardiovascular risk factor optimization.

The document strengthens support for formal risk score–based assessment of bleeding risk in all patients, including use of the HAS-BLED score to help address modifiable bleeding risk factors and to identify patients at high bleeding risk (HAS-BLED score ≥3) for early and more frequent follow-up.

These assessments should be done regularly, given that both stroke and bleeding risk are dynamic and change over time with aging and comorbidities, Dr. Potpara stressed. In patients with AFib initially at low risk for stroke, the next assessment should be optimally performed at 4-6 months.

The guideline also targets weight loss in patients who are obese and have AFib, particularly those being evaluated for ablation, and good blood pressure control in patients with AFib and hypertension to reduce AFib recurrences and risk for stroke and bleeding (both class I, up from IIa).

It's particularly important that these risk factors are addressed, and that modifiable risk factors that go along with increased AFib occurrence and persistence are addressed and communicated to patients, said Gerhard Hindricks, MD, PhD, guideline cochair and medical director of the Rhythmology Department, Heart Centre Leipzig (Germany).

"I have to confess, as an interventional electrophysiologist, there has been a time where I have not appreciated these risk factors intensely enough," he said. "But we have learned, also in the field of catheter ablation, that weight loss is an essential basis for a good procedure. If we can motivate patients to lose weight and then come to the intervention with better outcome, it's a true benefit for the patient and addresses patient values. So I'm particularly happy we have introduced that with such intensity in the guidelines."

Rate and rhythm control

The guidelines make no recommendation of one novel oral anticoagulant (NOAC) over another. However, in patients already receiving vitamin K antagonists with low time in the therapeutic range, they recommend switching to a different NOAC but ensuring good adherence and persistence with therapy (class I recommendation) or efforts to improve time in therapeutic range (class IIa).

Catheter ablation takes on a more prominent role for rhythm control and is now recommended after one antiarrhythmic drug therapy fails to improve symptoms of AF recurrence in patients with paroxysmal AFib, or persistent AFib with or without major risk factors for recurrence. The class I recommendation is based on results from the CAPTAF and CABANA trials, said task force member Carina Blomström-Lundqvist, MD, PhD, Uppsala (Sweden) University.

Catheter ablation is also now a first-line therapy for patients with AFib who have a high likelihood of tachycardia-induced cardiomyopathy, independent of symptom status. "In this subset of patients, catheter ablation may offer a lot with respect to restoration of left ventricular function," observed Dr. Hindricks.

Complete electrical isolation of the pulmonary veins is recommended during all AFib catheter ablation procedures (class I).

"Even as a medical conservative, I think it is totally reasonable to move to catheter ablation after a failed drug trial," commented John Mandrola, MD, Baptist Health, Louisville, Ky., who was not a part of the guideline development.

Although the chance of a second drug working after one failure is low, he noted that operators in the United States have dofetilide, which is not used much in Europe, and sometimes works surprisingly well.

"That said, the caveat is that moving to catheter ablation after drug failure is only appropriate if we have addressed all the pertinent risk factors: sleep apnea, weight loss, lack of fitness, blood pressure control, and alcohol excess," he said.

As for tachycardia-mediated cardiomyopathy, this too can be reasonable, Dr. Mandrola said. "I often get people 'out of a hole' with amiodarone plus cardioversion for a few months and then proceed to ablation."

Notably, the 2020 iteration sharpens its recommendation that amiodarone not be used first-line for long-term rhythm control in all patients with AFib, including those with heart failure with reduced ejection fraction, given its extracardiac toxicity (class I, up from IIa).

Disclosure information for all writing committee members is in the report. Dr. Mandrola is a writer and podcaster for Medscape.

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

Cardiologists study cardiac impact of COVID-19

BY DEBRA L. BECK

A new study using cardiac magnetic resonance (CMR) imaging to examine the effects of novel coronavirus infection on the heart showed signs suggestive of myocarditis in 4 out of 26 competitive athletes who recovered from asymptomatic or mild cases of COVID-19.

While these and other similar findings are concerning, commentators are saying the results are preliminary and do not indicate widespread CMR screening is appropriate.

Two of the four patients showing signs of myocarditis in this series had no symptoms of COVID-19 but tested positive on routine testing. An additional 12 student athletes (46%) showed late gadolinium enhancement (LGE), of whom 8 (30.8%) had LGE without T2 elevation suggestive of prior myocardial injury.

An additional 12 student athletes (46%) showed late gadolinium enhancement (LGE), of whom 8 (31%) had LGE without T2 elevation suggestive of prior myocardial injury.

This finding, said Saurabh Rajpal, MBBS, MD, the study's lead author, "could suggest prior myocardial injury or it could suggest athletic myocardial adaptation."

Dr. Mandrola

In a research letter published in JAMA Cardiology, Dr. Rajpal and colleagues at Ohio State University in Columbus, described the findings of comprehensive CMR examinations in competitive athletes referred to the sport medicine clinic after testing positive for COVID-19 on reverse transcriptase–polymerase chain reaction between June and August 2020.

The university had made the decision in the spring to use CMR imaging as a screening tool for return to play, said Dr. Rajpal. While CMR is being used for research purposes, the American College of Cardiology's recent "consensus expert opinion" statement on resumption of sport and exercise after COVID-19 infection does not require CMR imaging for resumption of competitive activity (JAMA Cardiol. 2020 May 13. doi: 10.1001/jamacardio.2020.2136).

None of the athletes required hospitalization for their illness, and only 27% reported mild symptoms during the short-term infection, including sore throat, shortness of breath, myalgia, and fever.

On the day of CMR imaging, ECG and transthoracic echocardiography were performed, and serum troponin I was measured. There were no diagnostic ST/T-wave changes, ventricular function and volumes were normal, and no athletes showed elevated serum troponin levels.

The updated Lake Louise Criteria were used to assess CMR findings consistent with myocarditis.

"I don't think this is a COVID-specific issue. We have seen myocarditis after other viral infections; it's just that COVID-19 is the most studied thus far, and with strenuous activity, inflammation in the heart can be risky," Dr. Rajpal said in an interview. He added that more long-term and larger studies with control populations are needed.

His group is continuing to follow these athletes and has suggested that CMR "may provide an excellent risk-stratification assessment for myocarditis in athletes who have recovered from COVID-19 to guide safe competitive sports participation."

Significance still unknown

Matthew Martinez, MD, the director of sports cardiology at Atlantic Health – Morristown (N.J.) Medical Center and the Gagnon Cardiovascular Institute, urged caution in making too much of the findings of this small study.

"We know that viruses cause myocardial damage and myocarditis. What we don't know is how important these findings are. And in terms of risk, would we find the same phenomenon if we did this, say, in flu patients or in other age groups?" Dr. Martinez said in an interview.

There is concern in the medical community that the media has overstated the risks of heart damage, especially in athletes, and at the same time overstated the benefits of cardiac magnetic resonance.

"I haven't seen all the images, but what I'd want to know is are these very subtle findings? Are these overt findings? Is this part of an active individual with symptoms? I need to know a little more data before I can tell if this influences the increased risk of sudden cardiac death that we often associate with myocarditis. I'm not sure how this should influence making decisions with regards to return to play."

Dr. Martinez, who is the ACC's chair of Sports and Exercise but was not an author of their recent guidance on return to sport, said that he is not routinely using CMR to assess athletes post infection, as per the ACC's recommendations.

"My approach is to evaluate anybody with a history of COVID infection and, first, determine whether it was an important infection with significant symptoms or not. And then, if they're participating at a high level or are professional athletes, I would suggest an ECG, echo, and troponin. That's our recommendation for the last several months and is still an appropriate way to evaluate that group."

"In the presence of an abnormality or ongoing symptoms, I would ask for an MRI at that point," said Dr. Martinez. "We just don't have much data on athletes with no symptoms to use to interpret these CMR findings and the study didn't offer any controls. We don't even know if these findings are new findings or old findings that have just been identified now," he added.

New, updated recommendations from the ACC are coming soon, said Dr. Martinez. "I do not expect them to include CMR as first line."

Cardiologists concerned about misinformation

This is at least the fourth study showing myocardial damage post–COVID-19 infection and there is concern in the medical community that the media has overstated the risks of heart damage, especially in athletes, and at the same time overstated the benefits of CMR.

In particular, Puntmann et al. reported in July a 100-patient study that showed evidence of myocardial inflammation by CMR in 78% of patients recently recovered from a bout of COVID-19 (JAMA Cardiol. 2020 Jul 27; doi:10.1001/jamacardio.2020.3557).

"That paper is completely problematic," John Mandrola, MD, of Baptists Medical Associates, Louisville, Ky., said in an interview. "It has the same overarching weaknesses [of other studies] that it's observational and retrospective, but there were also numerical issues. So to me that paper is an interesting observation, but utterly unconvincing and preliminary," said Dr. Mandrola.

Those limitations didn't stop the study from garnering media attention, however. The Altmetric score (an attention score that tracks all mentions of an article in the media and on social media) for the Puntmann et al. paper is approaching 13,000, including coverage from 276 news outlets and more than 19,000 tweets, putting it in the 99th percentile of all research outputs tracked by Altmetric to date.

To counter this, an "open letter" posted online just days before Dr. Rajpal's study published urging professional societies to "offer clear guidance discouraging CMR screening for COVID-19 related heart abnormalities in asymptomatic members of the general public." The letter was signed by 51 clinicians, researchers, and imaging specialists from around the world.

"I understand that the current guidelines may be clear that CMR is not a first-line test for this indication, but when the media coverage is so extensive and so overblown, I wonder how much impact the guidelines will have in countering this fear that's in the community," he added.

Asked to comment on the letter, Dr. Rajpal said he agrees with the signatories that asymptomatic people from general population do not need routine cardiac MRI. "However, competitive athletes are a different story. Testing depends on risk assessment in specific population and competitive athletes as per our protocol will get enhanced cardiac work-up including CMR for responsible and safe start of competitive sports. ... In the present scenario, while we get more data including control data, we will continue with our current protocol."

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

In the crime of severe asthma inflammation...

"TSLP MADE US DO IT"

TSLP is a key epithelial cytokine that sits at the top of the inflammatory cascade and offers a new way to think about severe asthma.[1-3]

For patients with severe asthma, TSLP may drive an immune response that overreacts to various epithelial insults or injury, regardless of the type of inflammation.[1-3]

TO LEARN MORE ABOUT TSLP, VISIT
TSLPINFLAMMATION.COM

AMGEN® AstraZeneca

References: 1. Corren J. *J Allergy Clin Immunol Pract*. 2019;7(5):1394-1403. **2.** Lambrecht BN, Hammad H, Fahy JV. *Immunity*. 2019;50(4):975-991. **3.** Lambrecht BN, Hammad H. *Nat Immunol*. 2015;16(1):45-56.

EMPEROR-Reduced affirms empagliflozin benefit

BY MITCHEL L. ZOLER, PHD
MDedge News

The SGLT2-inhibitor drug class solidified its role as a major, new treatment for patients with heart failure with reduced ejection fraction and no diabetes, with results from a second large, controlled trial showing clear efficacy and safety in this population.


Dr. Packer

Patients with heart failure with reduced ejection fraction (HFrEF) treated with the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (Jardiance) had a statistically significant 25% relative cut in their incidence of cardiovascular death or first heart failure hospitalization, compared with placebo-treated controls when added on top of standard HFrEF treatment, and this benefit was consistent regardless of whether the treated patients also had type 2 diabetes, Milton Packer, MD, reported at the virtual annual congress of the European Society of Cardiology.

This 25% drop in the primary endpoint with empagliflozin treatment in the EMPEROR-Reduced trial exactly matched the cut in incidence of cardiovascular death or heart failure hospitalization produced by treatment with a another SGLT2 inhibitor, dapagliflozin (Farxiga), in the DAPA-HF trial (N Engl J Med. 2019 Nov 21;381[21]:1995-2008).

The performance of these two SGLT2 inhibitors was "incredibly consistent" across the their respective trials run in HFrEF patients with and without type 2 diabetes, and the combined evidence base of the two trials makes for "really compelling evidence" of both safety and efficacy that should prompt a change to U.S. practice, with both of these drugs forming a new cornerstone of HFrEF treatment, Dr. Packer said.

Results plant drug class firmly as HFrEF treatment

Dr. Packer stressed in his presentation that optimal treatment of patients with HFrEF now demands use of one of these two SGLT2 inhibitors, as well as sacubitril plus valsartan (Entresto), a beta-blocker, and a mineralocorticoid receptor antagonist, plus a diuretic as a fifth drug class for the many HFrEF patients who also need treatment for fluid overload. He further advocated for rapid introduction of these four cornerstone agents with proven survival benefits once a patient receives a HFrEF diagnosis, suggesting that sacubitril plus valsartan, an SGLT2 inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist could all be initiated within 6 weeks or less while acknowledging that optimal up-titration of the beta-blocker would likely take longer.

The order in which a patient starts these drugs shouldn't matter, and there currently seems to be no evidence that clearly points toward using either dapagliflozin or empagliflozin over the other, Dr. Packer added.

In recognition of the importance of sending a message to heart failure clinicians about the newly proven efficacy of SGLT2 inhibitors in HFrEF patients, the American College of Cardiology and American Heart Association are now drafting an "expert decision pathway" to help clinicians as they enter this new prescribing space. This interim guidance should come out before the end of 2020, prior to release of fully revised HFrEF management guidelines in 2021, said Athena Poppas, MD, president of the ACC, in an interview.


Dr. Poppas

"There is clearly need for education" that can help guide physicians who care for HFrEF patients on how to introduce an SGLT2 inhibitor along with the additional, lengthy list of drug classes proven to benefit these patients, noted Dr. Poppas, who is also a professor and chief of cardiology at the Brown University in Providence, R.I. Physicians may find that they need extra backup for successfully starting both sacubitril plus valsartan and an SGLT2 inhibitor in HFrEF patients because recent history has shown substantial pushback from third-party payers in reimbursing for these relatively expensive drugs, Dr. Poppas noted. She added that this is a problem that may be compounded when patients should ideally get both drug classes.


Dr. O'Connor

Physicians who care for heart failure patients have their own history of dragging their feet when adding new drugs to the regimens HFrEF patients receive. The angiotensin-converting enzyme inhibitors and beta-blockers took about 17 years each to start reaching a majority of U.S. HFrEF patients, and sacubitril plus valsartan is now used on perhaps a quarter to a third of HFrEF patients despite receiving Food and Drug Administration approval for these patients in mid-2015, noted Christopher M. O'Connor, MD, a heart failure specialist and president of the Inova Heart and Vascular Institute in Fairfax, Va.

Despite dapagliflozin receiving FDA approval in May 2020 for treating HFrEF in patients without diabetes, early uptake in U.S. practice has been very slow, with findings from large U.S. patient registries suggesting that perhaps 1% of suitable HFrEF patients currently get the drug, estimated Dr. O'Connor in an interview.

Given how strong the evidence now is for benefit and safety from dapagliflozin and empagliflozin, it may take as little as 5 years to reach greater than 50% penetration of one of these drugs into U.S. HFrEF patient populations, suggested Dr. Packer, a distinguished scholar in cardiovascular science at Baylor University Medical Center in Dallas.

EMPEROR-Reduced outcomes impressive

The road to routine use of these SGLT2-inhibitor drugs should be hastened by empagliflozin's impressive performance in EMPEROR-Reduced, in which the drug scored highly significant benefits over placebo for the prespecified primary and two major secondary endpoints, one of which was a measure of preserved renal function.

The trial randomized 3,730 patients at 520 sites in 20 countries during 2017-2019 and followed them on treatment for a median of 16 months. All patients had a left ventricular ejection fraction of 40% or less, and roughly three-quarters had New York Heart Association (NYHA) class II function, nearly one-quarter had class III function, and fewer than 1% of patients fell into the class IV category.

The primary endpoint occurred in 19% of the empagliflozin-treated patients and in 25% of those who received placebo. Among the half of patients with diabetes in the trial, the relative risk reduction by empagliflozin compared with placebo was a statistically significant 28%; among those without diabetes, it was a statistically significant 22%. Concurrently with Dr. Packer's report, the results appeared in an article posted online (N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190).

The study also had two main prespecified secondary endpoints: the incidence of total hospitalizations for heart failure, both first and recurrent, which fell by 30% in the empagliflozin-treated patients, compared with placebo, and the rate of declining renal function during the 16 months of the study as measured by estimated glomerular filtration rate, which dropped by roughly 1 mL/min per 1.73 m^2 among the empagliflozin recipients and by about 4 mL/min/ per 1.73 m^2 in the placebo patients.

Treatment with empagliflozin also achieved a notable, statistically significant 50% drop in major adverse renal events, consistent with the performance of other drugs in the class.

"Renal protection is a big plus" of empagliflozin in this trial and from the other SGLT2 inhibitors in prior studies, noted Dr. O'Connor.

The EMPEROR-Reduced results also showed an important benefit for HFrEF patients from empagliflozin not previously seen as quickly with any other drug class, noted Dr. Packer. The SGLT2 inhibitor led to statistically a significant slowing in the progression of patients from NYHA class II function to class III, compared with placebo, and it also significantly promoted the recovery of patients from NYHA class III to class II, an effect that became apparent within the first month on treatment and a benefit that is a "big deal" for patients because it represents a "significant change in functional capacity." This additional dimension of empagliflozin's benefit "really impressed me," Dr. Packer said.

EMPEROR-Reduced was funded by Boehringer Ingelheim and Eli Lilly, the companies that market empagliflozin. Dr. Packer has received personal fees from Boehringer Ingelheim and Eli Lilly and from several other companies. Dr. Poppas and Dr. O'Connor had no relevant disclosures.

mzoler@mdedge.com

SOURCE: Packer M. ESC 2020. N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190.

Dripping, dabbing, and bongs: Get the facts on 'alternate aerosol inhalation'

BY RICHARD FRANKI
MDedge News

E-cigarettes may be synonymous with vaping to most physicians, but there are other ways for patients to inhale nicotine or tetrahydrocannabinol-containing aerosols, according to investigators at the Cleveland Clinic.

Devices such as water pipes and techniques like dipping and dabbing "are increasingly popular, and use may not be recognized through a traditional substance use history," Humberto Choi, MD, and associates wrote in the Annals of the American Thoracic Society.

These "alternate aerosol inhalation methods" have been poorly described thus far, so little is known about their scope of use and potential health impact, they noted.

Dripping involves an e-cigarette modified to expose the heating coil. The e-cigarette liquid is dripped directly onto the hot coil, which produces immediate aerosolization and results in a thicker cloud.

Dripping "may expose users to higher levels of nicotine compared to e-cigarette inhalation" and lead to "increased release of volatile aldehydes as a result of the higher heating potential of direct atomizer exposure," the investigators suggested.

Water pipes, or bongs, produce both smoke and vapor, although an electronic vaporizer can be attached to create a "vape bong." About 21% of daily cannabis users report using a bong, but tobacco inhalation is less common. Cases of severe pulmonary infections have been associated with bong use, along with a couple of tuberculosis clusters, Dr. Choi and associates said.

Dabbing uses butane-extracted, concentrated cannabis oil inhaled through a modified water pipe or bong or a smaller device called a "dab pen." A small amount, or "dab," of the product is placed on the "nail," which replaces the bowl of the water pipe, heated with a blowtorch, and inhaled through the pipe, the researchers explained.

The prevalence of dabbing is unknown, but "the most recent Monitoring the Future survey of high school seniors shows that 11.9% of students have used a marijuana vaporizer at some point in their life," they said.

Inhalation of residual butane vapors could lead to vomiting, cardiac arrhythmias, acute encephalopathy, and respiratory depression. "Patients presenting with prolonged and severe vomiting, psychotic symptoms, or other acute neuropsychiatric symptoms should raise the suspicion of [tetrahydrocannabinol]-containing products especially synthetic cannabinoids," they wrote.

rfranki@mdedge.com

SOURCE: Choi H et al. Ann Am Thorac Soc. 2020 Oct 14. doi: 10.1513/AnnalsATS.202005-511CME.

Vaping is more than just e-cigarettes

A number of devices and methods can be used to inhale nicotine or tetrahydrocannabinol-containing aerosols.


HAZEMMKAMAL/iStock/Getty Images Plus

Dripping

E-liquid is dripped directly onto an exposed heating coil, producing a thicker aerosol cloud that intensifies flavors. In one cohort of high school e-cigarette users, 26.1% reported dripping.


Bubba-Z/iStock/Getty Images Plus

Dabbing

A small amount of butane-extracted cannabis oil, called a dab, is placed on the heated end of a cylinder, which aerosolizes the product and allows for inhalation through the pipe.

E-cigarettes

The most common form of vaping aerosolizes, or vaporizes, a liquid mixture of nicotine, vegetable glycerin, and polyethylene glycol. THC, cannabidiol, and synthetic cannabinoids are also used.


HAZEMMKAMAL/iStock/Getty Images Plus

Water pipe/bong

The user inhales cooled smoke and vapor from burning cannabis or tobacco through a chamber that is partially filled with water. An electronic vaporizer can be added to create a "vape bong."


rgbspace/iStock/Getty Images Plus

Source: Ann Am Thorac Soc. 2020 Oct 14. doi: 10.1513/AnnalsATS.202005-511CME

MDedge News

High schoolers prefer tobacco as vapor, not smoke

BY RICHARD FRANKI
MDedge News

In 2019, more than five times as many high school students were using tobacco electronically than smoking actual cigarettes, according to the Centers for Disease Control and Prevention.

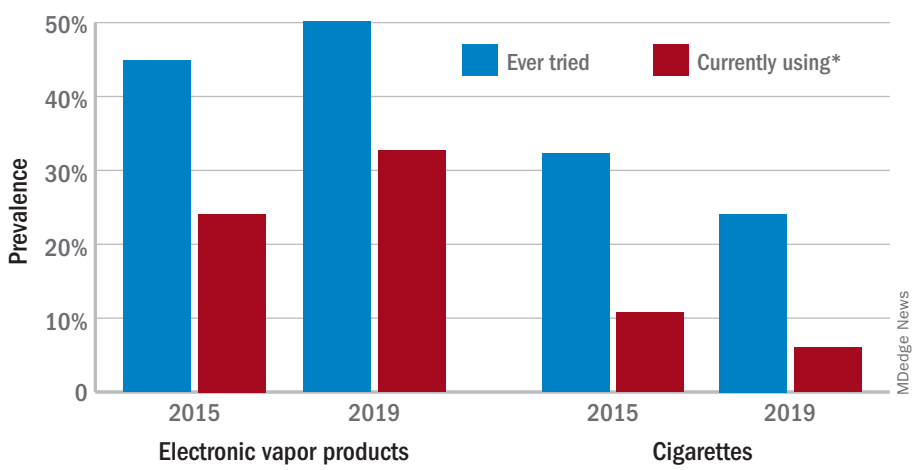
From 2015 to 2019, current use of electronic vapor products among students in grades 9-12 rose from 24.1% to 32.7%, while the same level of cigarette use – on 1 or more days in the previous 30 – dropped from 10.8% to 6.0%, based on data from the Youth Risk Behavior Survey.

Among the survey respondents, 50.1% had at least tried an electronic vapor product by 2019, up from 44.9% in 2015. Cigarettes again showed a decline, as ever use fell from 32.3% to 24.1%, or less than half of the e-product prevalence. Everyday use of vaping products was 7.2% in 2019 (up from 2.0% in 2015), compared with 1.1% for cigarettes (down from 2.3%), the YRBS data show.

"The dramatic increase in electronic vapor product use among high school students has led to increases in overall tobacco product use among U.S. youths, erasing gains made in previous years and leading the U.S. Surgeon General to declare youth e-cigarette use an epidemic in the United States," MeLisa R. Creamer, PhD, and associates at the CDC wrote in the MMWR.

rfranki@mdedge.com

High school students: More vaping, less cigarette smoking



MDedge News

*Use on 1 or more days during the previous 30 days before the survey.
Note: Based on data from the Youth Risk Behavior Survey.
Source: Centers for Disease Control and Prevention

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

RELEASE THE POWER OF PROTECTION WITH BREZTRI[1]

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

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

BREZTRI IS NOW AVAILABLE

LEARN MORE AT BREZTRIHCP.COM

IMPORTANT SAFETY INFORMATION

- BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients
- BREZTRI is not indicated for treatment of asthma. Long-acting $beta_2$-adrenergic agonist (LABA) monotherapy for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD
- BREZTRI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BREZTRI is NOT a rescue inhaler. Do NOT use to relieve acute symptoms; treat with an inhaled short-acting $beta_2$-agonist
- BREZTRI should not be used more often than recommended; at higher doses than recommended; or in combination with LABA-containing medicines, due to risk of overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation
- Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap
- Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients
- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI
- Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy
- Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur
- If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy
- Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider alternative therapy
- Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles

ICS=inhaled corticosteroids; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.
*Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in hospitalization or death.

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

BREZTRI is administered as 2 inhalations twice daily.

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

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

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

Please see Brief Summary of Prescribing Information on adjacent pages.

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

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

AstraZeneca

BREZTRI AEROSPHERE™

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

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

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations, Death

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

Use of long-acting $beta_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

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

Deterioration of Disease and Acute Episodes

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

BREZTRI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREZTRI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

When beginning treatment with BREZTRI AEROSPHERE, patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREZTRI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short-acting $beta_2$-agonist and instruct the patient on how it should be used. Increasing inhaled $beta_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREZTRI AEROSPHERE no longer controls symptoms, or the patient's inhaled, short-acting $beta_2$-agonist becomes less effective or the patient needs more inhalations of short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. The daily dosage of BREZTRI AEROSPHERE should not be increased beyond the recommended dose.

Avoid Excessive Use of BREZTRI AEROSPHERE and Avoid Use with other Long-Acting $Beta_2$-Agonists

As with other inhaled drugs containing $beta_2$-adrenergic agents, BREZTRI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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

Oropharyngeal Candidiasis

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

Pneumonia

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

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

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

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

Immunosuppression and Risk of Infections

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

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

Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

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

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

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

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

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

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

Corticosteroid Withdrawal Symptoms

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

Hypercorticism and Adrenal Suppression

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

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

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

Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm

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

Hypersensitivity Reactions including Anaphylaxis

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

Cardiovascular Effects

Formoterol fumarate, like other $beta_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*.

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

Reduction in Bone Mineral Density

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

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

Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

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

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

Worsening of Urinary Retention

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

Coexisting Conditions

BREZTRI AEROSPHERE, like all therapies containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonists may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. $Beta_2$-agonist therapies may produce transient hyperglycemia in some patients.

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

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

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

Additional Adverse Reactions

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

DRUG INTERACTIONS

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

Inhibitors of Cytochrome P450 3A4

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of $beta_2$-adrenergic agonists such as formoterol, a component of BREZTRI AEROSPHERE.

Non-Potassium Sparing Diuretics

The hypokalemia and/or ECG changes that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BREZTRI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-adrenergic Receptor Blocking Agents

Beta-adrenergic receptor antagonists (beta-blockers) and BREZTRI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

OVERDOSAGE

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

Budesonide

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

Glycopyrrolate

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

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest, and even death may be associated with overdosage of formoterol fumarate.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured by: AstraZeneca Dunkerque Production (AZDP), Dunkerque, France

Issued: 07/20 US-42033 7/20

Cystic fibrosis treatment: Triple combination benefits patients with advanced disease

BY JIM KLING
MDedge News

New cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies can offer life-altering benefits to some patients with cystic fibrosis, even those with advanced disease.

Triple-combination therapy in cystic fibrosis patients with advanced lung disease appears to improve lung function, and may delay the need for lung transplantation, according to a multicenter analysis of patients taking elexacaftor, tezacaftor, and ivacaftor.

The study participants had a percent predicted forced expiratory volume in 1 second ($ppFEV_1$) of 40% or below, or other high-risk factors. Researchers compared them to control patients who were genetically ineligible for triple-combination therapy.

Previous studies of such patients on individual drugs or previous combinations showed increases in lung function in patients with advanced disease, though the magnitude of improvement varied across regimens. "With this improvement, it's unclear how CFTR modulators should affect lung transplant referral timing," Brent Bermingham, MD, said at the virtual North American Cystic Fibrosis Conference.

"The rationale for our study was that, despite patients with advanced lung disease being excluded from phase III trials [of elexacaftor, tezacaftor, and ivacaftor], they are receiving a therapy with an unknown clinical efficacy and safety profile," said Dr. Bermingham, a pulmonary and critical care fellow at the Medical University of South Carolina, Charleston.

Lung transplant referral guidelines recommend that physicians initiate discussions about the potential benefit of lung transplant when FEV_1 drops below 50% of the predicted value. Patients should be referred for a transplant when the value is below 50% and rapidly declining (>20% decline in the past 12 months), when it drops below 40% with accompanying predictors of shortened survival, or when it drops below 30%. The guidelines were published before approval of triple-combination therapy.

The researchers conducted an open-label retrospective analysis of 60 patients started on triple-combination therapy between September 2019 and February 2020 at three centers in the Southeast. They compared percent predicted $ppFEV_1$ values prior to initiation of therapy to $ppFEV_1$ values obtained 2-12 weeks after the start of therapy. Patients on therapy were compared with 10 genetically ineligible controls. The therapeutic group experienced a 7.8% increase in $ppFEV_1$ after starting therapy ($P < .001$), compared with a 0.5% decrease in controls ($P = .65$). Before initiation of therapy, 33% of the therapy group met the criteria for initiating a transplant discussion, while 67% had been recommended for transplant. After therapy, 55% met the criteria for discussion, 33% were recommended for transplant, and 12% no longer met the criteria for discussion of transplantation. Fifty percent of controls were in discussion, and this dropped to 40%, while 50% were referred for transplantation, and this increased to 60%. On therapy, transplant referral candidates had an increase of forced vital capacity from 48.9 to 59.16 ($P < .001$).


Dr. Giusti

The results are encouraging, said Robert J. Giusti, MD, clinical professor of pediatrics at the New York University and director of the Pediatric Cystic Fibrosis Center, New York. "We're all remarking how wonderful patients feel these days. It's really a disease-altering treatment. But for the high-risk group, whose FEV_1 is less than 40%, those are the patients we're more concerned about because we thought maybe they had too much lung disease, and that they wouldn't benefit from triple combination. But they seem to be improving, so that's very reassuring," said Dr. Giusti, who was not involved in the study.

The study received funding from the Cystic Fibrosis Foundation and Dartmouth College. Dr. Bermingham and Dr. Giusti have no relevant financial disclosures.

chestphysiciannews@chestnet.org

SOURCE: Bermingham B et al. NACFC 2020, Abstract 645.

Flu vaccine cuts pediatric hospitalizations by over 40%

BY JILL D. PIVOVAROV
MDedge News

Unlike previous studies focused on vaccine effectiveness (VE) in ambulatory care office visits, Angela P. Campbell, MD, MPH, and associates have uncovered evidence of the overall benefit influenza vaccines play in reducing hospitalizations and ED visits in pediatric influenza patients.

"Our data provide important VE estimates against severe influenza in children," the researchers noted in Pediatrics, adding that the findings "provide important evidence supporting the annual recommendation that all children 6 months and older should receive influenza vaccination."

Dr. Campbell and colleagues collected ongoing surveillance data from the New Vaccine Surveillance Network (NVSN), which is a network of pediatric hospitals across seven cities, including Kansas City, Mo.; Rochester, N.Y.; Cincinnati; Pittsburgh; Nashville, Tenn.; Houston; and Seattle. The influenza season encompassed the period Nov. 7, 2018 to June 21, 2019 (Pediatrics. 2020;146[5]:e20201368).

Vaccine efficacy in hospital, ED

A total of 2,748 hospitalized children and 2,676 children who had completed ED visits that did not lead to hospitalization were included. Once those under 6 months were excluded, 1,792 hospitalized children were included in the VE analysis; of these, 226 (13%) tested positive for influenza infection, including 211 (93%) with influenza A viruses and 15 (7%) with influenza B viruses. Fully 1,611 of the patients (90%), had verified vaccine status, while 181 (10%) had solely parent-reported vaccine status. The researchers reported 88 (5%) of the patients received mechanical ventilation and 7 (<1%) died.


YARINCA/ISTOCK

Most noteworthy, the researchers observed a significant reduction in laboratory-confirmed hospitalizations by 41% in children vaccinated against the flu. They further estimated a significant reduction in hospitalizations linked to A(H3N2) and A(H1N1)pdm09 viruses, even in the presence of circulating A(H3N2) viruses that differed from the A(H3N2) vaccine component.

Studies from other countries during the same time period showed that while "significant protection against influenza-associated ambulatory care visits and hospitalizations among children infected with A(H1N1)pdm09 viruses" was observed, the same could not be said for protection against A(H3N2) viruses, which varied among pediatric outpatients in the United States (24%), in England (17% outpatient; 31% inpatient), Europe (46%), and Canada (48%). They explained that such variation in vaccine protection is multifactorial, and includes virus-, host-, and environment-related factors. They also noted that regional variations in circulating viruses, host factors including age, imprinting, and previous vaccination could explain the study's finding of vaccine protection against both A(H1N1)pdm09 and A(H3N2) viruses.

When comparing VE estimates between ED visits and hospitalizations, the researchers observed one significant difference: that "hospitalized children likely represent more medically complex patients, with 58% having underlying medical conditions and 38% reporting at lease one hospitalization in the past year, compared with 28% and 14% respectively, among ED participants."

Continued on following page

Economic stress ups depression risk in cystic fibrosis

BY JIM KLING
MDedge News

People with chronic illnesses who are also under socioeconomic stress have greater difficulty managing their disease than do their better-off counterparts, and a new study confirms this reality for patients with cystic fibrosis.

Individuals with cystic fibrosis (CF) who have low socioeconomic status (SES) are more likely to have poor adherence to treatment and also experience depression and anxiety symptoms, according to a new cross-sectional study. The data were drawn from the Cystic Fibrosis Foundation's Success With Therapies Research Consortium.

"Assessing the special challenges that individuals with lower SES face, including financial barriers, is essential to understand how we can address the unique combinations of adherence barriers. In other chronic disorders, financial barriers or lower socioeconomic status are associated with nonadherence, but this relationship has not been well established in cystic fibrosis," said Kimberly Dickinson, MD, MPH, of Johns Hopkins University, Baltimore, during her presentation of the results at the virtual North American Cystic Fibrosis Conference.

"I've always thought that my patients in the poorer population were doing worse, and I think this demonstrates that that's true," said Robert J. Giusti, MD, in an interview. Dr. Giusti is a clinical professor of pediatrics at New York University and director of the Pediatric Cystic Fibrosis Center, New York. He was not involved in the study.

"These are very pertinent issues, especially if you think about the pandemic, and some of the issues related to mental health. It just highlights the importance of socioeconomic status and screening for some of the known risk factors so that we can develop interventions or programs to provide equitable care to all of our cystic fibrosis patients," said Ryan Perkins, MD, who moderated the session where the study was presented. He is a pediatric and adult pulmonary fellow at Boston Children's Hospital and Brigham and Women's Hospital, also in Boston.

The researchers looked retrospectively at 1 year's worth of pharmacy refill receipts and number of times prescriptions were refilled versus the number of times prescribed, then calculated medicinal possession ratios. This was cross-referenced with annual household income and insurance status of patients with CF at 12 pediatric and 9 adult CF care centers, for a total of 376 patients (128 pediatric and 248 adult).

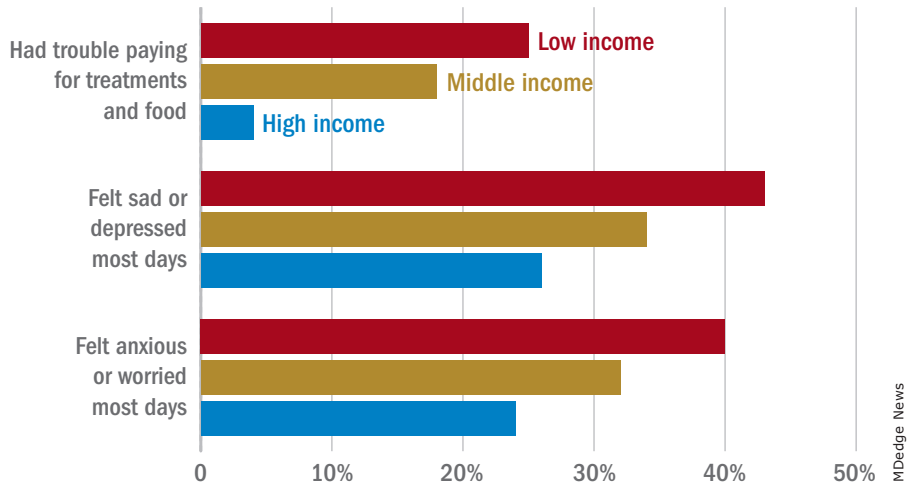
In this population, 32% of participants had public or no insurance, 68% had private or military insurance. The public/no insurance group was more likely than the private/military insurance group to report having trouble paying for treatments, food, or critical expenses related to CF care (23.3% vs. 12.1%, respectively); feeling symptoms on most days of depression (42.5% vs. 31.3%) or anxiety (40.0% vs. 28.5%); and experiencing conflict or stress with loved ones over treatments (30.0% vs. 20.3%) ($P < .05$ for all).

In all, 35% had a household income less than $40,000 per year, 33% between $44,000 and $100,000, and 32% higher than $100,000. The low-income group had a lower composite medication possession ratio (0.41) than the middle- (0.44) or high-income (0.52) groups; were more likely to have trouble paying for treatments, food, or treatment-related expenses (25%, 18%, 4%, respectively); were more likely most days to report symptoms of depression (43%, 34%, 26%) or anxiety (40%, 32%, 24%); and have concerns about whether treatments were effective (42%, 27%, 29%). They were more likely to not be able to maintain a daily schedule or routine for treatments (28%, 22%, 14%).

The study showed that adherence barriers and suboptimal adherence are issues that cross all socioeconomic categories, though they were more problematic in the lowest bracket. Greater anxiety and depression among lower income individuals and those with private or no insurance was a key finding, according to Dr. Dickinson. The study received funding from the Cystic Fibrosis Foundation. Dr. Dickinson, Dr. Giusti, and Dr. Perkins have no relevant financial disclosures.

chestphysiciannews@chestnet.org

Barriers to cystic fibrosis treatment adherence by income level



Note: Based on data from 376 patients (128 pediatric and 248 adult).
Source: Dr. Dickinson

VIEW ON THE NEWS

Mary Cataletto, MD, FCCP, comments: Adherence is a complex variable affected by a number of factors not the least of which is socioeconomic status (SES). For many Americans SES changed dramatically with the COVID-19 pandemic. In June of 2020 an estimated 15.9 million adults became unemployed because of to the COVID 19 pandemic. As a consequence, 14.6 million individuals either lost a job with employer-sponsored insurance or were the covered dependent of an individual who lost their job with employer-sponsored insurance. Psychosocial stressors associated with the pandemic, chronic disease, and poverty can all be expected to impact on both mental and physical health of our patients. Anxiety and depression have been well described in other chronic diseases, such as asthma. As physicians we must be cognizant of the many factors affecting adherence and ask patients and families about resource needs affecting both physical and mental health concerns (Source: https://bit.ly/334VSGq).

Continued from previous page

Strengths and limitations

Strengths of the study included the prospective multisite enrollment that provided data across diverse locations and representation from pediatric hospitalizations and ED care, which were not previously strongly represented in the literature. The single-season study with small sample size was considered a limitation, as was the inability to evaluate full and partial vaccine status. The investigators did caution that, while they consider their test-negative design optimal for evaluating both hospitalized and ED patients, they feel their results should not be "interpreted as VE against influenza-associated ambulatory care visits or infections that are not medically attended."

In a separate interview, Michael E. Pichichero, MD, director of the Rochester (N.Y.) General Hospital Research Institute and a clinical professor of pediatrics at the University of Rochester, observed: "A well-done contemporary study confirms again the benefits of annual influenza vaccinations for children. Viral coinfections involving SARS-CoV-2 and influenza have been reported from Australia to cause heightened illnesses. That observation provides further impetus for parents to have their children receive influenza vaccinations."

The researchers cited multiple sources of financial support for their ongoing work, including Sanofi, Quidel, Moderna, Karius, GlaxoSmithKline, Merck, AstraZeneca, and Pfizer. Funding for this study was supported by the Centers for Disease Control and Prevention. Dr. Pichichero said he had no relevant financial disclosures.

chestphysiciannews@chestnet.org

SOURCE: Campbell AP et al. Pediatrics. 2020. doi: 10.1542/peds.2020-1368.

Home spirometry improved monitoring of cystic fibrosis patients during COVID-19 pandemic

BY JIM KLING
MDedge News

Home spirometry has become increasingly used among cystic fibrosis patients during the COVID-19 pandemic, and new research suggests that home devices perform reasonably well. Forced expiratory volume in 1 second (FEV_1) values were a bit lower than values seen in clinical spirometry performed in the same patient at a nearby time point, but the procedure reliably picked up decreases in FEV_1, potentially helping patients and clinicians spot exacerbations early.

"Home spirometry was sort of a curiosity that was slowly working its way into cystic fibrosis research in 2019, and then all of a sudden in 2020 it became front and center as the only way to continue with clinical monitoring and research in many cases," Alexander Paynter, MS, a biostatistician at the Cystic Fibrosis Foundation's Therapeutic Development Network Coordinating Center, said during a talk at the virtual North American Cystic Fibrosis Conference.

To better determine how closely home spirometry matches clinical spirometry, Mr. Paynter and his colleagues analyzed data from the eICE study, which included 267 cystic fibrosis patients aged 14 and over at 14 cystic fibrosis centers. They were randomized to use home spirometry as an early intervention to detect exacerbations, or to continue usual clinic care with visits to the clinic every 3 months. The dataset includes twice-weekly home spirometry values, with a full year of follow-up data. The researchers compared the home spirometry data to the clinical data closest in time to it. Clinic spirometry data with no corresponding home data within 7 days were discarded.

> *"The clinic and home observations tend to track each other pretty well. At 6 months, for instance, it's about a change of three points decrease (in both). But the bad news is that the variability is much greater in home devices."*

There was an estimated difference of –2.01 mL between home and clinic tests, with home spirometry producing lower values (95% confidence interval, –3.56 to –0.45). "There is actually a bias in home spirometry as compared to clinic spirometry," concluded Mr. Paynter.

One explanation for lower values in home spirometry is that users are inexperienced with the device. If that's true, then agreement should improve over time, but the researchers didn't see strong evidence of that. Among 44 patients who completed five clinical visits, there was a difference of –2.97 (standard deviation, 0.51) at baseline, –1.66 at 3 months (SD, 13.49), –3.7 at 6 months (SD, 12.44), –0.86 at 9 months (SD, 13.73), and –0.53 at 12 months (SD, 13.35). Though there was improvement over time, "we don't find a lot of evidence that this bias completely res olves," said Mr. Paynter.

In fact, a more likely explanation is the presence of coaching by a technician during clinical spirometry, according to Robert J. Giusti, MD, clinical professor of pediatrics and director of the Pediatric Cystic Fibrosis Center at New York University. "When they're doing it at home, they don't do it with the same effort, so I think that coaching through telemedicine during the home spirometry would make that difference disappear," he said when asked to comment on the study.

The researchers found that change-based endpoints were similar between clinic and at-home spirometry. Compared to baseline, the two showed similar declines over time. "The clinic and home observations tend to track each other pretty well. At 6 months, for instance, it's about a change of three points decrease (in both). But the bad news is that the variability is much greater in home devices," said Mr. Paynter, noting larger confidence intervals and standard deviation values associated with home spirometry. That could influence future clinical designs that may rely on home spirometry, since a larger confidence interval means reduced power, which could double or even quadruple the number of participants needed to achieve the required power, he said.

But from a clinical standpoint, the ability of home spirometry to consistently detect a change from baseline could be quite valuable to future patient management, according to Dr. Giusti. "It looks like home spirometry will show that kind of a decrease, so that it's still sensitive to pick up the concern that a patient is getting worse at home," he said.

Mr. Paynter and Dr. Giusti have no relevant financial disclosures.

chestphysiciannews@chestnet.org

SOURCE: Alex Paynter et al. NACFC 2020, Poster 643.

Triple-combination CF therapy drove down hospitalizations

BY JIM KLING
MDedge News

New data show that new CFTR-modulator therapies for cystic fibrosis may be driving down hospitalizations in this patient population.

The triple-combination therapy elexacaftor/tezacaftor/ivacaftor was associated with a near elimination of hospital stays in one hospital in Oregon, according to a new report. The hospital savings still weren't nearly enough to pay for the cost of therapy, but the study underscores what many institutions have observed and adds a new layer to the view of quality of life improvements that the new therapy brings.

"After we started prescribing it, we noticed pretty quickly that hospitalizations appeared to be declining after patients started triple-combination therapy, and we were hearing [similar reports] from other centers as well. We wanted to quantify this," Eric C. Walter, MD, a pulmonologist at the Kaiser Permanente Cystic Fibrosis Clinic in Portland, Ore., said during a presentation of the results at the virtual North American Cystic Fibrosis Conference.

"We're seeing that across the board in real practice, the number of cystic fibrosis patients that have to be hospitalized since starting this triple combination has gone down," Robert J. Giusti, MD, said in an interview. "When they've had pulmonary exacerbations in the past, it was frequently because they failed outpatient antibiotics, but I think with triple-combination therapy, if they do get sick, the likelihood is they will respond to oral antibiotics, so they may not need that prolonged IV course in the hospital." Dr. Giusti is clinical professor of pediatrics and director of the Pediatric Cystic Fibrosis Center at New York University. He was not involved in the study.

The therapy gained Food and Drug Administration approval in 2019 for the treatment of individuals with CF who are aged 12 years and older, and who have at least one copy of the F508del mutation. Its cost is about $317,000 per year within the Kaiser Permanente system, according to Dr. Walter. His group compared hospitalization days for CF-related diagnoses from Jan. 1 through Aug. 31, 2020, before and after initiation of triple-combination therapy.

Of 47 eligible patients, 32 initiated therapy during the study period; 38% had severe lung disease, defined by forced expiratory volume in 1 second (FEV_1) value less than 40%. In 2020, before initiation of therapy, there were an average of 27 hospital days per month, all among patients with severe lung disease.

Among the therapy group, there were no hospitalizations after initiation of therapy through Aug. 31. Dr. Walter noted that the first hospitalization of a patient on triple-combination therapy didn't occur until early October.

At an average daily cost of $6,700, the researchers calculated that triple-combination therapy saved about $189,000 per month in this group of patients. Comparing numbers to previous years, in which some patients with FEV_1 greater than 40% were hospitalized, the researchers calculated that the therapy saved about $151,000 per month among individuals with severe lung disease

Dr. Walter and Dr. Giusti have no relevant financial disclosures.

chestphysiciannews@chestnet.org

SOURCE: Walter E et al. NACFC 2020, Abstract 795.

Nucala
(mepolizumab)

REAL PATIENTS. REAL LIFE.

See the data at
ThisIsNUCALA.com

Real patient compensated by GSK for his time.

Obstructive sleep apnea diagnoses often not noted in the inpatient setting

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL CHEST® ▪ Obstructive sleep apnea diagnoses may not be carried over to the inpatient setting, with potentially negative consequences for clinical outcomes, quality of life, and health care costs, an investigator said at the virtual meeting of the American College of Chest Physicians.

In a retrospective, single-center study, nearly 40% of patients with obstructive sleep apnea (OSA) diagnosed in the outpatient setting did not have a corresponding diagnosis during hospitalization, according to researcher Nitasa Sahu, MD.

The missed OSA diagnoses could have especially negative implications for patients who don't continue on positive airway pressure (PAP) therapy during the hospital stay, said Dr. Sahu, a fellow in pulmonary/critical care at St. Luke's University Health Network in Bethlehem, Pa.

The finding indicates a large-magnitude opportunity to improve health care through better communication and optimized care, according to the researcher.

"Obstructive sleep apnea is underrecognized, it's underdiagnosed, and it has a lot of implications for a patient's hospitalization," she said in interview

Clinical pathways should be set up to ensure that patients with OSA are properly identified and use their prescribed treatment, according to Dr. Sahu.

"I think that should, and would, reduce overall health care costs, with better outcomes as well," she said.

Pulmonologist Saadia A. Faiz, MD, FCCP, said she hoped this study, presented at a late-breaking abstract at the virtual meeting, would highlight the importance of OSA screening and call attention to barriers to screening that may be in place in the inpatient setting.

> *In a retrospective, single-center study, nearly 40% of patients with obstructive sleep apnea diagnosed in the outpatient setting did not have a corresponding diagnosis during hospitalization.*

That's especially important because, after admission, the focus is often on the cause of admission rather than underlying comorbidities such as OSA, said Dr. Faiz, professor in the department of pulmonary medicine at the University of Texas MD Anderson Cancer Center in Houston.

"Working in a cancer hospital, the focus is always on the cancer, so sometimes even the patient will dismiss issues with their sleep," Dr. Faiz said of her own experience in an interview.

"Often with sleep apnea, for people in the general population, the reason they seek medical attention is because their spouse notices that they're snoring, so it is something that is not as emphasized," added Dr. Faiz, who was not involved in the study.

In their study, Dr. Sahu and coauthors reviewed electronic health record data for adults hospitalized on the general internal medicine service at Penn State Hershey Medical Center from January 2017 through 2018. They restricted their search to first admissions.

The researchers looked for ICD-9 codes indicating an OSA diagnosis during their inpatient admission. They looked for the same codes in the preceding 5 years to see if the patients had a prior outpatient OSA diagnosis.

The inpatient cohort included 13,067 patients, of whom 53% were male, 87% were White, and 77% were over 50 years of age. Comorbidities included hypertension in 42%, atrial fibrillation in 21%, type 2 diabetes mellitus in 14%, congestive heart failure in 15%, and prior stroke in 0.5%.

A total of 991 individuals in the inpatient cohort had a prior outpatient OSA diagnosis. Of that group, 376 patients (38%) did not have an inpatient OSA diagnosis on inpatient record, according to the reported study data.

That large proportion of discordant diagnoses suggests a lot of missed opportunities to provide OSA therapy in the inpatient setting and to reinforce chronic disease state management, according to Dr. Sahu and colleagues.

How those discordant OSA diagnoses impact length of stay, cost of care, and readmissions are unanswered questions that deserve further study, Dr. Sahu said.

Among patients who did not have outpatient OSA diagnoses, another 804 patients, or about 6%, ended up with an inpatient diagnosis during their hospitalization, the researchers also reported.

While a number of those inpatient OSA diagnoses could have been coded in error, it's also possible that they were indeed cases of OSA that went unrecognized until the individuals were hospitalized, Dr. Sahu said.

Dr. Sahu had no relevant relationships to report related to the study. One of four study coauthors reported relationships with Boehringer-Ingelheim, Nitto Denko, and Galapagos.

chestphysiciannews@chestnet.org

SOURCE: Sahu N. CHEST 2020, Abstract.

FDA okays phone app to interrupt PTSD-related nightmares

BY MEGAN BROOKS

The Food and Drug Administration has cleared for marketing a smartphone app that can detect and interrupt nightmares in adults with posttraumatic stress disorder (PTSD).

The NightWare app, from Minneapolis-based NightWare, runs on the Apple Watch and Apple iPhone.

During sleep, Apple Watch sensors monitor heart rate and body movement. These data are used to create a unique sleep profile using a proprietary algorithm.

When the NightWare app detects that a patient is experiencing a nightmare based on changes in heart rate and movement, it provides slight vibrations through the Apple Watch to arouse the patient and interrupt the nightmare, without fully awakening the patient, the company notes.

NightWare is available by prescription only and is intended for use in adults aged 22 years and older with PTSD.

"Sleep is an essential part of a person's daily routine. However, certain adults who have a nightmare disorder or who experience nightmares from PTSD are not able to get the rest they need," Carlos Peña, PhD, director, Office of Neurological and Physical Medicine Devices, Center for Devices and Radiological Health at the FDA, said in a news release.

This authorization "offers a new, low-risk treatment option that uses digital technology in an effort to provide temporary relief from sleep disturbance related to nightmares," said Dr. Peña.

NightWare was tested in a 30-day randomized, sham-controlled trial of 70 patients. Patients in the sham group wore the device, but no vibrations were provided.

Both the sham and active groups showed improvement in sleep on standard sleep scales, with the active group showing greater improvement than sham. "The evidence demonstrated the probable benefits outweighed the probable risks," the FDA said in a statement.

NightWare is not a standalone therapy for PTSD and should be used in conjunction with prescribed medications for PTSD and other recommended therapies for PTSD-associated nightmares and nightmare disorder, the agency said.

NightWare was granted breakthrough device designation for the treatment of nightmares in patients with PTSD. The device reviewed through the de novo premarket pathway, a regulatory pathway for some low- to moderate-risk devices of a new type.

Along with this marketing authorization, the FDA is establishing "special controls" designed to provide a "reasonable assurance of safety and effectiveness for tests of this type," the agency said.

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

Biometric devices detect COVID-19–related sleep changes

BY DIANA SWIFT

A smartphone app that combines passively collected physiologic data from wearable devices, such as fitness trackers, and self-reported symptoms can discriminate between COVID-19–positive and –negative individuals among those who report symptoms, new data suggest.

After analyzing data from more than 30,000 participants, researchers from the Digital Engagement and Tracking for Early Control and Treatment (DETECT) study concluded that adding individual changes in sensor data improves models based on symptoms alone for differentiating symptomatic persons who are COVID-19 positive and symptomatic persons who are COVID-19 negative.

The combination can potentially identify infection clusters before wider community spread occurs, Giorgio Quer, PhD, and colleagues report in an article published online Oct. 29 in Nature Medicine (doi: 10.1038/s41591-020-1123-x). DETECT investigators note that marrying participant-reported symptoms with personal sensor data, such as deviation from normal sleep duration and resting heart rate, resulted in an area under the curve (AUC) of 0.80 (interquartile range, 0.73-0.86) for differentiating between symptomatic individuals who were positive and those who were negative for COVID-19.

"By better characterizing each individual's unique baseline, you can then identify changes that may indicate that someone has a viral illness," said Dr. Quer, director of artificial intelligence at Scripps Research Translational Institute in La Jolla, Calif. "In previous research, we found that the proportion of individuals with elevated resting heart rate and sleep duration compared with their normal could significantly improve real-time detection of influenza-like illness rates at the state level," he said in an interview.

Thus, continuous passively captured data may be a useful adjunct to bricks-and-mortar site testing, which is generally a one-off or infrequent sampling assay and is not always easily accessible, he added. Furthermore, traditional screening with temperature and symptom reporting is inadequate. An elevation in temperature is not as common as frequently believed for people who test positive for COVID-19, Dr. Quer continued. "Early identification via sensor variables of those who are presymptomatic or even asymptomatic would be especially valuable, as people may potentially be infectious during this period, and early detection is the ultimate goal," Dr. Quer said.

According to his group, adding these physiologic changes from baseline values significantly outperformed detection ($P < .01$) using a British model described in an earlier study by by Cristina Menni, PhD, and associates (Nat Med 2020;26:1037-40). That method, in which symptoms were considered

Continued on following page

Continued from previous page

alone, yielded an AUC of 0.71 (IQR, 0.63-0.79).

According to Dr. Quer, one in five Americans currently wear an electronic device. "If we could enroll even a small percentage of these individuals, we'd be able to potentially identify clusters before they have the opportunity to spread," he said.

DETECT study details

During the period March 15 to June 7, 2020, the study enrolled 30,529 participants from all 50 states. They ranged in age from younger than 35 years (23.1%) to older than 65 years (12.8%); the majority (63.5%) were aged 35-65 years, and 62% were women. Sensor devices in use by the cohort included Fitbit activity trackers (78.4%) and Apple HealthKit (31.2%).

Participants downloaded an app called MyDataHelps, which collects smartwatch and activity tracker information, including self-reported symptoms and diagnostic testing results. The app also monitors changes from baseline in resting heart rate, sleep duration, and physical activity, as measured by steps.

Overall, 3,811 participants reported having at least one symptom of some kind (e.g., fatigue, cough, dyspnea, loss of taste or smell). Of these, 54 reported testing positive for COVID-19, and 279 reported testing negative.

Sleep and activity were significantly different for the positive and negative groups, with an AUC of

0.68 (IQR, 0.57-0.79) for the sleep metric and 0.69 (IQR, 0.61-0.77) for the activity metric, suggesting that these parameters were more affected in COVID-19–positive participants.

When the investigators combined resting heart rate, sleep, and activity into a single metric, predictive performance improved to an AUC of 0.72 (IQR, 0.64-0.80).

The next step, Dr. Quer said, is to include an alert to notify users of possible infection.

Alerting users to possible COVID-19 infection

In a similar study, an alert feature was already incorporated. The study, led by Michael P. Snyder, PhD, director of the Center for Genomics and Personalized Medicine at Stanford (Calif.) University, will soon be published online in Nature Biomedical Engineering. In that study, presymptomatic detection of COVID-19 was achieved in more than 80% of participants using resting heart rate.

"The median is 4 days prior to symptom formation," Dr. Snyder said in an interview. "We have an alarm system to notify people when their heart rate is elevated. So a positive signal from a smartwatch can be used to follow up by polymerase chain reaction [testing]."

Dr. Snyder said these approaches offer a roadmap to containing widespread infections. "Public health authorities need to be open to these

Continued on following page

Continued from previous page

technologies and begin incorporating them into their tracking," he said. "Right now, people do temperature checks, which are of limited value. Resting heart rate is much better information."

Although the DETECT researchers have not yet received feedback on their results, they believe public health authorities could recommend the use of such apps. "These are devices that people routinely wear for tracking their fitness and sleep, so it would be relatively easy to use the data for viral illness tracking," said co–lead author Jennifer Radin, PhD, an epidemiologist at Scripps. "Testing resources are still limited and don't allow for routine serial testing of individuals who may be asymptomatic or presymptomatic. Wearables can offer a different way to routinely monitor and screen people for changes in their data that may indicate COVID-19."

The marshaling of data through consumer digital platforms to fight the coronavirus is gaining ground. New York State and New Jersey are already embracing smartphone apps to alert individuals to possible exposure to the virus.

More than 710,000 New Yorkers have downloaded the COVID NY Alert app, launched in October to help protect individuals and communities from COVID-19 by sending alerts without compromising privacy or personal information. "Upon

receiving a notification about a potential exposure, users are then able to self-quarantine, get tested, and reduce the potential exposure risk to family, friends, coworkers, and others," Jonah Bruno, a spokesperson for the New York State Department of Health, said in an interview.

And recently the Mayo Clinic and Safe Health Systems launched a platform to store COVID-19 testing and vaccination data.

Both the Scripps and Stanford platforms are part of a global technologic response to the COVID-19 pandemic. Prospective studies, led by device manufacturers and academic institutions, allow individuals to voluntarily share sensor and clinical data to address the crisis. Similar approaches have been used to track COVID-19 in large populations in Germany via the Corona Data Donation app.

The study by Dr. Quer and colleagues was funded by a grant from the National Center for Advancing Translational Sciences at the National Institutes of Health. One coauthor reported grants from Janssen and personal fees from Otsuka and Livongo outside of the submitted work. The other authors have disclosed no relevant financial relationships. Dr. Snyder has ties to Personalis, Qbio, January, SensOmics, Protos, Mirvie, and Oralome.

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

FDA okays immunotherapy for mesothelioma

BY ROXANNE NELSON, RN
MDedge News

The Food and Drug Administration has approved combination nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (*Yervoy*, Bristol-Myers Squibb) to be used as first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

This is the first drug regimen to receive regulatory approval for mesothelioma in 16 years and only the second systemic therapy to be approved for this indication.

"Today's approval of nivolumab plus ipilimumab provides a new treatment that has demonstrated an improvement in overall survival for patients with malignant pleural mesothelioma," Richard Pazdur, MD, director of the FDA's Oncolo-

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

gy Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research, said in a statement.

"In 2004, FDA approved pemetrexed in combination with cisplatin for this indication, and now patients have an important, additional treatment option after more than a decade with only one FDA-approved drug regimen," Dr. Pazdur added.

Improved overall survival

The approval is based on efficacy results from the CheckMate 743 trial, which compared immunotherapy with a chemotherapy regimen in a cohort of more than 600 treatment-naive patients (no systemic therapies) with unresectable mesothelioma.

Patients were randomized 1:1 to nivolumab and ipilimumab for up to 2 years (n = 303) or six cycles of combination chemotherapy with cisplatin or carboplatin plus pemetrexed (n = 302).

The study results were initially presented during the presidential symposium of the World Congress on Lung Cancer 2020.

The combined immunotherapy regimen was associated with a 26% improvement in overall survival. At 2 years, 41% of patients in the immunotherapy arm were still alive versus 27% in the chemotherapy group.

Overall, the trial demonstrated a statistically significant improvement in overall survival for patients who received nivolumab plus ipilimumab versus those treated with chemotherapy. Median overall survival was 18.1 months versus 14.1 months (hazard ratio, 0.74; $P = .002$).

Median progression-free survival per blinded independent central review was 6.8 months in the nivolumab plus ipilimumab arm and 7.2 months in the chemotherapy arm (HR, 1.0). The confirmed overall response rate was 40% versus 43% in the immunotherapy and chemotherapy arms, respectively.

Median response duration was 11.0 months in the nivolumab plus ipilimumab arm and 6.7 months in the chemotherapy arm. At 24 months, 32% of the immunotherapy patients were still experiencing a response, compared with 8% of those in the chemotherapy arm.

The recommended doses for unresectable malignant pleural mesothelioma are nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable toxicity, or up to 2 years in patients without disease progression.

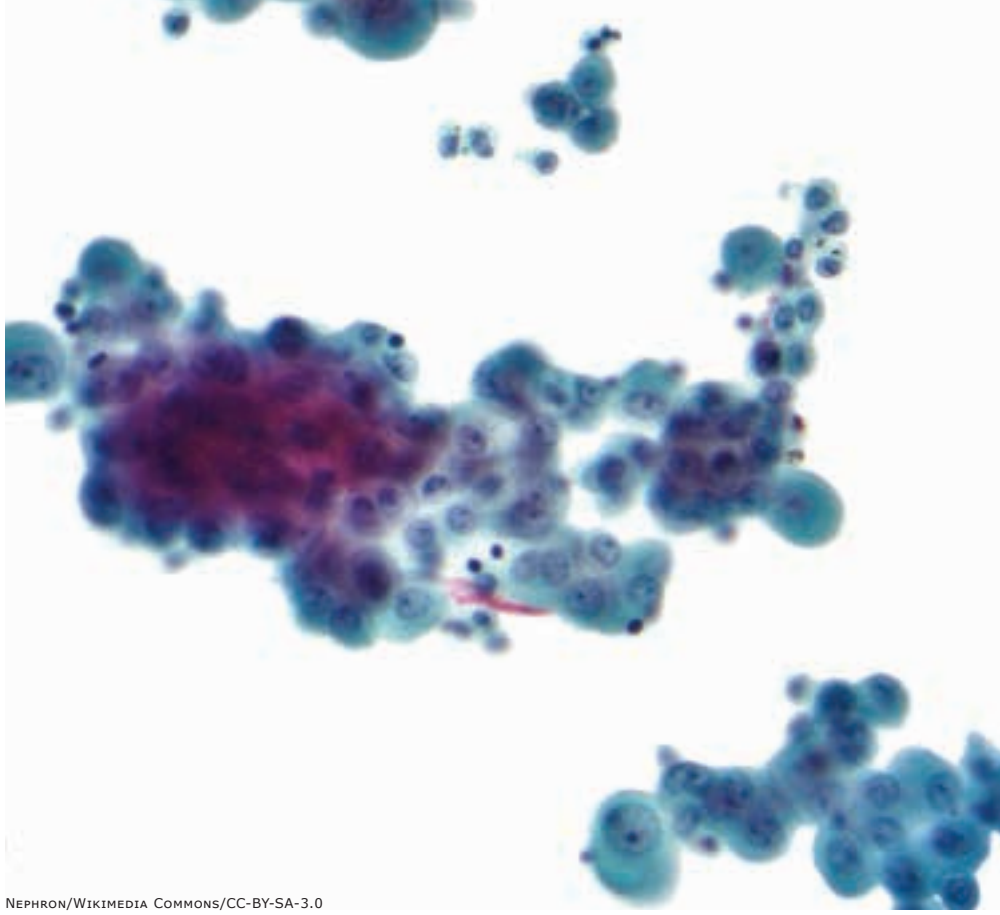
The most common adverse reactions (incidence ≥20%) in patients receiving combination immunotherapy were fatigue, musculoskeletal pain, rash, diarrhea, dyspnea, nausea, decreased appetite, cough, and pruritus.

Possible new standard of care

The CheckMate 743 trial "met its primary endpoint of statistically improving overall survival for the experimental arm vs. chemotherapy in a prespecified interim analysis," reported study author Paul Baas, MD, PhD, of the Netherlands Cancer Institute, Amsterdam, at the time of its presentation.

He suggested that combination nivolumab and ipilimumab should therefore "be considered as a new standard of care."

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



Nephron/Wikimedia Commons/CC-BY-SA-3.0

The approval is based on efficacy results from the CheckMate 743 trial, which compared immunotherapy with a chemotherapy regimen in a cohort of more than 600 treatment-naive patients (no systemic therapies) with unresectable mesothelioma.

Real-world results with checkpoint inhibitors found inferior to trial results

BY MARK L. FUERST
MDedge News

Real-world survival outcomes for cancer patients on immune checkpoint inhibitors (ICIs) are inferior to outcomes reported in patients on clinical trials of ICIs, according to research published in JCO Clinical Cancer Informatics.

However, the research also suggests that real-world patients who receive ICIs achieve longer survival than patients on standard-of-care medications.

"Patients receiving ICIs in real-world practice may differ from those enrolled in trials in a variety of ways, including age, race, performance status, and comorbidity burden," said study author Jerry S.H. Lee, PhD, of the University of Southern California, Los Angeles.

Dr. Lee noted that only 3%-4% of cancer patients participate in clinical trials. In fact, more than half of patients with melanoma and nearly three-quarters of those with non–small cell lung cancer (NSCLC) do not meet criteria for eligibility in clinical trials, he said.

To examine the discrepancies between real-world practice and clinical trials and to better understand which patients receive ICIs in clinical practice, Dr. Lee and colleagues conducted a retrospective analysis using EHR data from Veterans Administration facilities nationwide.

The researchers identified 11,888 cancer patients who were treated with ICIs. The cohort included patients who are underrepresented in pivotal clinical trials, including older, non-White, and/or higher disease-burdened patients.

The majority of patients were treated for NSCLC (51.1%), followed by melanoma (14.4%), renal cell carcinoma (RCC; 8.1%), squamous cell carcinoma of the head and neck (6.8%), urothelial cancer (6.4%), hepatocellular carcinoma (4.5%), and other less common cancer types (8.8%).

Overall survival by indication

In general, median overall survival (OS) in the VA cohort was inferior to median OS reported in clinical trials. However, patients treated with first-line nivolumab for melanoma and second-line pembrolizumab or nivolumab for NSCLC had similar OS in the real-world and trial data.

The researchers did not report exact OS numbers from clinical trials. However, they did report the exact numbers from the VA cohort and show OS differences between the VA cohort and clinical trials graphically.

Among patients in the VA cohort, the median OS was 25.5 months in melanoma patients on first-line nivolumab, 16.3 months in RCC patients receiving nivolumab in the second line or higher, 14 months in RCC patients on first-line ipilimumab and nivolumab, 10.6 months in NSCLC patients on first-line pembrolizumab, 9.9 months in NSCLC patients receiving pembrolizumab or nivolumab in the second line or higher, 9.1 months in NSCLC patients on first-line pembrolizumab and platinum-based chemotherapy, and 6.7 months in urothelial cancer patients receiving ICIs in the second line or higher.

A number of factors may have contributed to the shorter OS observed in the VA cohort, according to the researchers. The VA cohort is predominantly male, is older, and has a higher degree of comorbidity, compared with patients in clinical trials.

No data are available to determine the cause for discontinuation of therapy, and VA patients may have received ICIs after failing multiple lines of previous therapy, while clinical trials may limit patients to only one or two previous lines of therapy.

After stratification of VA patients by frailty status, the OS among non-frail patients was more similar to the OS reported in clinical trials.

"Real-world outcomes from the VA were more similar when adjusted for frailty, which shows the importance of patient diversity in clinical trials," Dr. Lee said. He added that the definition of frailty among VA patients included potential injury during combat and therefore differs from a generic frailty definition.

ICIs vs. standard care

The researchers also found that VA patients treated with ICIs had longer OS, compared with a cohort of VA patients receiving standard-of-care therapies.

The median OS was as follows:

- In melanoma patients on first-line treatment – 39.29 months with nivolumab and 5.75 months with chemotherapy ($P < .001$).
- In RCC patients on first-line treatment – 14.01 months with ipilimumab plus nivolumab and 8.63 months with targeted therapy ($P = .051$).
- In RCC patients on second-line or greater treatment – 12.43 months with nivolumab and 8.09 months with everolimus ($P < .001$).
- In NSCLC patients on first-line therapy – 8.88 months with pembrolizumab and 6.38 months with a platinum doublet ($P < .001$).
- In NSCLC patients on first-line combination therapy – 10.59 months with pembrolizumab plus platinum chemotherapy and 6.38 months with a platinum doublet ($P < .001$).
- In NSCLC patients on second-line or greater therapy – 10.06 months with pembrolizumab or nivolumab and 6.41 months with docetaxel ($P < .001$). In urothelial cancer patients on second-line or greater therapy – 7.66 months with an ICI and 6.31 months with chemotherapy ($P = .043$).

VIEW ON THE NEWS

A. Christine Argento, MD, FCCP, comments: This is a good first step in getting updated real-world data to clinicians on the front lines so that a wider array of patients will know what to expect. The next step would be a real-world population that is even more generalizable (more women, less smoking, less drinking, less Armed Forces–related comorbidities) than the VA population. This cohort does, however, demonstrate just how important information in a nonclinical trial–related cohort can be.

Help for treatment decisions

"The real-world survival outcomes not only indicate the breadth of indications but also represent patients who tend not to be eligible for immunotherapy trials, based on their health status," Dr. Lee said. "We hope this dataset of national-level experience provides practicing oncologists evidence to help patients and family members in the process of decision-making about therapy."

Real-world data can also inform oncologists who face decisions on whether to prescribe or withhold ICIs and patients who face the financial burden of paying for ICIs, he said.

This dataset will be continually updated. The researchers have already added another 10,000 VA patients who have received immunotherapies in the year since the trial began.

"In a longitudinal way, we plan to examine what causes differences in outcomes and continue to find ways to extend care to veterans with a balance of high quality of life," Dr. Lee said.

"Patients who participate in clinical trials are, on average, younger and healthier than the general population," said Bora Youn, PhD, a senior biostatistician at Biogen in Cambridge, Mass., who was not involved in this study.

"In the case of immunotherapies, those with poor performance status and autoimmune conditions are often excluded from trials," Dr. Youn added. "In the real world, these patients can also receive treatments, and clinicians often need to extrapolate the results from clinical trials. It is therefore important to collect real-world data to understand the effectiveness and safety of these therapies in patients with limited evidence."

Dr. Youn led a real-world study, published in Cancer (2020 Jan 14. doi: 10.1002/cncr.32624), of 1,256 Medicare recipients who were diagnosed with NSCLC and received ICI therapy.

"We found that factors associated with poor prognosis in general, such as squamous histology and failure of aggressive prior treatment, are also predictive of decreased survival among those who initiated immunotherapies. Yet, OS of older patients was relatively comparable to those observed in clinical trials," Dr. Youn said.

This study was supported by the VA Office of Research and Development Cooperative Studies Program. Dr. Lee and Dr. Youn had no disclosures.

chestphysiciannews@chestnet.org

SOURCE: La Jennifer et al. JCO Clinical Cancer Informatics. 2020;4:918-28.

Lung cancer screening guidelines miss some at-risk younger African Americans

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL CHEST® ▪ National guidelines failed to classify many younger African American lung cancer patients as being eligible for lung cancer screening in a recent retrospective study, the lead author reported at the annual meeting of the American College of Chest Physicians.

The finding highlights a health disparity issue that may be addressed through an update of those guidelines that is currently in the works, said Carol Velez Martinez, MD, a third-year internal medicine resident at Louisiana State University Health Sciences Center in Shreveport, La.

About one-third of the lung cancer patients in the retrospective cohort study were diagnosed before the age of 55 years, which means they would not have been recommended for screening with low-dose computed tomography (LDCT) based on the 2013 lung cancer guidelines from the United States Preventive Services Task Force, said Dr. Velez Martinez.

By contrast, 12.5% of screening-ineligible patients would have been counted as LDCT eligible based on guidelines from the National Comprehensive Cancer Network, Dr. Velez Martinez and coauthors found in their analysis.

VIEW ON THE NEWS

A. Christine Argento, MD, FCCP, comments: This is important news and a message that physicians really need to see and think about in order to consider individualized care for their patients. Guidelines are there for a reason and should be followed, but physicians need to know there are data coming out about lung cancer screening that will help to identify more young at-risk African Americans. We should keep an eye out for updated guidelines as a result.

In a draft recommendation statement posted July 7, the USPSTF said they would now recommend that screening at age 50 years, rather than 55, and that the pack-years of smoking history that would make an individual eligible for screening would be dropped from 30 pack-years to 20, changes that task force members said would be more inclusive of African Americans and women.

Dr. Velez Martinez said she is looking forward to a formal recommendation from USPSTF soon: "I'm hoping that's where they're heading," she said in an interview. "When I'm in practice as a resident, I actually bring it up to my patients, and if I have to call the insurance I don't have a problem – but I still have to call them because they're still going by the prior guidelines."

These findings suggest a need for further research to identify other gaps in lung cancer screening that may stem from race, ethnicity, or socioeconomic status, said Alberto Revelo, MD, an interventional pulmonologist at The Ohio State University Wexner Medical Center in Columbus.

"I think there are going to be a lot of other health disparities," Dr. Revelo said in an interview. "[Dr. Velez Martinez's] study was limited by the fact that she cared mostly for Caucasians and also African Americans, but maybe no Latinos or Hispanics that I'm sure would also be affected if we were looking to that in a bigger or national study."

The 2013 USPSTF guidelines were based on benefits observed in the National Lung Screening Trial (NLST), which indicated a 20% relative risk reduction in death from lung cancer; however, the generalizability of the study beyond White males has been questioned, said Dr. Velez Martinez in a presentation at the CHEST annual meeting.

About 90% of NSLT participants were White and 59% were male, according to results published in 2011.

Other studies have shown that African Americans are more likely to get lung cancer than Whites, despite comparable smoking rates between the races, and that African American men are more likely to die from lung cancer than White men, Dr. Velez Martinez said. Many African Americans live below the poverty line, which means they have limited resources for insurance and health providers, and they also participate less often in clinical trials, she added.

FOTOSMURF03/GETTY IMAGES

Dr. Revelo

These findings suggest a need for further research to identify other gaps in lung cancer screening that may stem from race, ethnicity, or socioeconomic status.

In their retrospective observational cohort study, Dr. Velez Martinez and coinvestigators reviewed 1,500 medical records of patients with newly diagnosed stage 1-4 lung cancers from the LSU Health Science Center Shreveport between 2011 and 2015.

They found that 33% of those lung cancer patients were diagnosed before the age of 55 years, meaning they did not meet the 2013 USPSTF screening guidelines, which recommend annual LDCT in adults aged 55-80 years with a 30–pack-year smoking history who currently smoke or have quit within the past 15 years.

Next, they sought to classify those screening-ineligible patients based on NCCN guidelines, which recommend LDCT in patients 50 years of age or older with at least a 20–pack-year smoking history and a 6-year risk of lung cancer of at least 1.3% based on the Tammemagi lung cancer risk calculator. The Tammemagi calculator considers factors such as age, education, body mass index, prior lung disease, familial cancer history, race and ethnicity, and smoking history.

After applying the risk stratification, the investigators found that 12.5% of these patients would have been categorized as high risk and therefore recommended for LDCT, and of that group, more than 65% were African American, Dr. Velez Martinez reported.

Dr. Revelo, who chaired the CHEST session where the findings were reported, said that shared decision-making will still be as important regardless of any changes to lung screening guidelines given the recognized potential harms of LDCT screening, such as false positives, radiation exposure, and psychological distress.

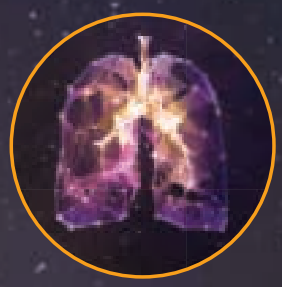
"I think we will continue to have a very personal conversation and make important decisions focused on what the patient wants," he said.

The study's authors reported no disclosures.

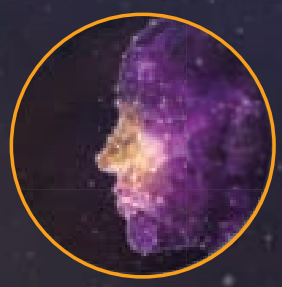
WHAT'S DRIVING INFLAMMATORY DISEASE IN YOUR PATIENTS?

IT COULD BE EOSINOPHILIC IMMUNE DYSFUNCTION

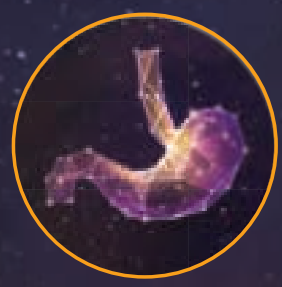
Eosinophils are key effector cells* in several debilitating inflammatory diseases[1-4]



Eosinophilic asthma (EA)

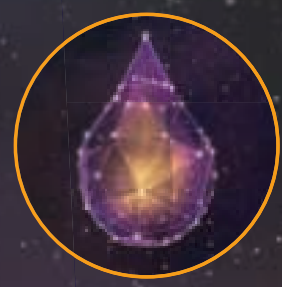


Chronic rhinosinusitis with nasal polyps (CRSwNP)



Eosinophilic esophagitis (EoE)

Eosinophilic granulomatosis polyangiitis (EGPA)



Hypereosinophilic syndrome (HES)

Millions of people are affected by these diseases[5-11]

Eosinophilic Immune Dysfunction (EID)

EID can be characterized as the dysregulation of biological processes involved with eosinophil recruitment and activation.[1]

Activated eosinophils can contribute to disease pathology through several mechanisms and play a key role in the self-perpetuating cycle of inflammatory damage in a range of diseases.[1-4]

*When activated, eosinophils modulate downstream immune and inflammatory signaling.[2]

Discover what may be driving your patient's inflammation at **explore-eid.com**

References: 1. Ramirez GA, Yacoub MR, Ripa M, et al. Eosinophils from physiology to disease: a comprehensive review. *Biomed Res Int*. 2018;2018:9095275. **2.** Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol*. 2006;24:147-174. **3.** Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. *Nat Rev Immunol*. 2013;13(1):9-22. **4.** Rosenberg HF, Dyer KD, Foster PS. Supplementary Appendix to: Eosinophils: changing perspectives in health and disease. *Nat Rev Immunol*. 2013;13(1):9-22. **5.** Global Asthma Report 2018. http://www.globalasthmareport.org/Global%20Asthma%20Report%202018.pdf. Accessed October 19, 2020. **6.** de Groot JC, Ten Brinke A, Bel EHD. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res.* 2015;1(1):00024-2015. **7.** Palmer JN, Messina JC, Biletch R, Grosel K, Mahmoud RA. A cross-sectional, population-based survey of U.S. adults with symptoms of chronic rhinosinusitis [published online ahead of print, 2018 Nov 14]. *Allergy Asthma Proc*. 2018;10.2500/aap.2018.39.4182. **8.** Fujieda S, Sakashita M, Tokunaga T, et al. [Eosinophilic chronic rhinosinusitis]. *Arerugi*. 2015;64(1):38-45. **9.** Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology*. 2018;154(2):319-332.e3. **10.** Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int*. 2019;68(4):430-436. **11.** Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. *J Allergy Clin Immunol*. 2010;126(1):179-181.

AstraZeneca

ESMO issues guideline on NGS for metastatic cancer

BY PAM HARRISON

Recommendations on the use of next-generation sequencing (NGS) tests for patients with metastatic cancer have been issued by the European Society for Medical Oncology, the first recommendations of their kind to be published by any medical society.

"Until now, there were no recommendations from scientific societies on how to use this technique in daily clinical practice to profile metastatic cancers," Fernanda Mosele, MD, medical oncologist, Gustave Roussy, Villejuif, France, said in a statement.

NGS testing is already used extensively in oncology, particularly in metastatic cancer, she noted. The technology is used to assess the sequence of DNA in genes from a tumor tissue sample. Numerous genes can be quickly sequenced at the same time at relatively low cost. The results provide information on mutations that are present, which, in turn, helps with deciding which treatments to use, including drugs targeting the identified mutations.

"Our intent is that they [the guidelines] will unify decision-making about how NGS should be used for patients with metastatic cancer," Dr. Mosele said.

The recommendations were published online in Annals of Oncology.

Overall, ESMO recommends the use of tumor multigene NGS for non–small cell lung cancer (NSCLC), prostate cancer, ovarian cancer, and cholangiocarcinoma.

For other cancers, the authors said that NGS is not recommended in clinical practice but could be used for research purposes.

However, patients should be informed that it is unlikely that test results would benefit them much personally.

Physicians and patients may decide together to subject the tumor to mutational testing using a large panel of genes, provided testing doesn't burden the health care system with additional costs.

"This recommendation acknowledges that a small number of patients could benefit from a drug because they have a rare mutation," Joaquin Mateo, MD, chair of the ESMO working group, said in a statement.

"So beyond the cancers in which everyone should receive NGS, there is room for physicians and patients to discuss the pros and cons of ordering these tests," he added.

ESMO also does not recommend the use of off-label drugs matched to any genomic alteration detected by NGS unless an access program and a decisional procedure have been developed, either regionally or nationally.

No need for NGS testing of other cancers

In contrast to NSCLC, "there is currently no need to perform tumor multigene NGS for patients with mBC [metastatic breast cancer] in the context of daily practice," ESMO stated.

This is largely because somatic sequencing cannot fully substitute for germline testing for BRCA status, and other mutations, such as HER2, can be detected using immunohistochemistry (IHC).

The same can be said for patients with metastatic gastric cancer, inasmuch as detection of alterations can and should be done using cheaper testing methods, ESMO pointed out.

However, ESMO members still emphasized that it's important to include patients with metastatic breast cancer in molecular screening programs as well as in clinical trials testing targeted agents.

Similarly, there is no need to test metastatic colorectal cancer (mCRC) using multigene NGS in daily practice, inasmuch as most level 1 alterations in mCRC can be determined by IHC or PCR.

However, NGS can be considered as an alternative to PCR-based tests in mCRC, provided NGS is not associated with additional cost.

ESMO again recommended that research centers include mCRC patients in molecular screening programs in order for them to have access to innovative clinical trial agents.

As for advanced prostate cancer, ESMO does recommend that clinicians perform NGS on tissue samples to assess the tumor's mutational status, at least for the presence of BRCA1 and BRCA2 mutations, when patients have access to the poly (ADP-ribose) polymerase inhibitors for treatment.

The authors cautioned, however, that this strategy is unlikely to be cost effective, so larger panels should be used only when there are specific agreements with payers.

Multigene NGS is also not recommended for patients with advanced pancreatic ductal adenocarcinoma (PDAC), although ESMO points out that it is the role of research centers to propose multigene sequencing for these patients in the context of molecular screening programs.

This is again to facilitate access to innovative drugs for these patients.

Similar to recommendations for patients with advanced PDAC, patients with advanced hepatocellular carcinoma (HCC) do not need to have tumor multigene NGS either.

Considering the high unmet needs of HCC patients, ESMO feels that research centers should propose multigene sequencing to patients with advanced HCC in the context of molecular screening programs.

In contrast, ESMO recommended that tumor multigene NGS be used to detect actionable alterations in patients with advanced cholangiocarcinoma. Again, they predict that this strategy is unlikely to be cost effective, so larger panels should be used only if a specific agreement is in place with payers.

ESMO also assessed the frequency of level 1 alterations in less frequent tumor types, including ovarian cancers. Because BRCA1 and BRCA2 somatic mutations in ovarian tumors have been associated with increased response to the PARP inhibitors, the use of multigene NGS is justified with this malignancy, ESMO states.

The authors also recommend that tumor mutational burden be determined in cervical cancer, moderately differentiated neuroendocrine tumors, salivary cancers, vulvar cancer, and thyroid cancers.

Dr. Mosele has disclosed no relevant financial relationships. Many coauthors have relationships with the pharmaceutical industry, as listed in the article.

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

Proton-beam radiotherapy may reduce CV events

BY SUSAN LONDON

Treating lung cancer with proton-beam radiotherapy instead of conventional photon radiotherapy almost halves the dose to the heart, reducing the risk of cardiovascular events over the next several years, a cohort study suggests.

The findings were reported at the American Society for Radiation Oncology Annual Meeting 2020.

Patients with lung cancer often have underlying cardiac risk factors, noted lead investigator Timothy P. Kegelman, MD, PhD, of University of Pennsylvania in Philadelphia.

"The dose to the heart correlates with adverse cardiovascular events following radiation therapy. One strategy to minimize dose to the heart is proton-beam radiation," Dr. Kegelman said.

He and his colleagues retrospectively studied consecutive patients with locally advanced non–small cell lung cancer (NSCLC) treated with chemotherapy plus either proton-beam radiotherapy or conventional photon radiotherapy.

The team used electronic health records to ascertain incidence of six cardiovascular events: MI, atrial fibrillation, coronary artery disease, heart failure, stroke, and transient ischemic attack. Patients who had previously experienced an event were not considered as part of the at-risk population for that specific event after radiotherapy.

Analyses were based on 98 patients who received proton-beam radiotherapy and 104 patients who received conventional photon radiotherapy.

At baseline, the proton cohort was older, had a heavier smoking history, and had a higher prevalence of previous cardiovascular events (46.9% vs. 31.7%; $P = .03$).

The total median radiation dose was identical for the proton and photon groups (66.6 Gy), but the former group had significantly lower measures of cardiac radiation dose, including roughly half the mean dose to the heart (6.9 vs. 13.3 Gy).

Outcomes and next steps

At a median follow-up of 29 months, the proton-beam radiotherapy group had a significantly lower

Continued on following page

Continued from previous page

incidence of transient ischemic attack, compared with the photon-radiotherapy group (1.1% vs. 8.2%; *P* = .04).

The proton group also had numerically lower incidences of MI (2.3% vs. 9.0%; *P* = .06) and stroke (3.2% vs. 6.1%; *P* = .50).

The proton and photon groups were similar as far as the incidence of total cardiovascular events (53.1% vs. 47.1%; *P* = .48) and the 3-year overall survival rate (38.8% vs. 42.1%; *P* = .99).

"Our future studies aim to examine the potential relationships between grade of cardiac event and type of radiotherapy and dose to cardiac substructures," Dr. Kegelman commented.

In addition, his institution is participating in RTOG 1308, a phase 3 trial comparing photon and proton-beam radiotherapy in patients with inoperable lung cancer that will better assess cardiac-related morbidity and mortality. The trial is expected to be completed by the end of 2025.

Dr. Kegelman

"The dose to the heart correlates with adverse cardiovascular events following radiation therapy. One strategy to minimize dose to the heart is proton-beam radiation."

Accumulating evidence

"This study adds to a growing body of evidence about the potential importance of heart dose in any radiation modality," said Daniel Gomez, MD, MBA, of Memorial Sloan Kettering Cancer Center in New York, who was not involved in the study.

The RTOG 0617 trial (Lancet Oncol. 2015;16:187-99) and the Lung ART trial (ESMO 2020, Abstract LBA3_PR) previously showed correlations between lower radiation dose to the heart and better survival in patients with lung cancer, Dr. Gomez noted.

"It's been well established that protons can improve heart dose, and therefore it's been inferred that they may improve outcomes, but the exact mechanisms remain unclear," Dr. Gomez said.

Proton-beam radiotherapy performed well in a single-arm, phase 2 trial among patients with unresectable NSCLC (JAMA Oncol. 2017;3:e172032).

"The ongoing phase 3 trial is using a more modern proton technique and has a larger population, with a randomized study design. It will be much more informative," Dr. Gomez predicted.

The current study did not receive specific funding. Dr. Kegelman disclosed no relevant conflicts of interest. Dr. Gomez disclosed honoraria from Varian.

chestphysiciannews@chestnet.org

SOURCE: Kegelman TP et al. ASTRO 2020, Abstract 1046.

Sotorasib is a 'triumph of drug discovery' in cancer

BY NEIL OSTERWEIL

KRAS, one of the most frequently mutated oncogenes in human cancer, has long been thought to be "undruggable," but early results from a clinical trial of the experimental KRAS inhibitor sotorasib (Amgen) suggest that at least one KRAS mutation common in non–small cell lung cancers (NSCLC) has a soft underbelly.

In the phase 1 CodeBreaK 100 trial, sotorasib, an investigational first-in-class inhibitor of the KRAS p.G12C mutation, showed encouraging activity against advanced NSCLC and other solid tumors.

Among patients with NSCLC, 19 (32.2%) of 59 had a confirmed objective response to sotorasib monotherapy, and 52 (88.1%) had disease control, reported David S. Hong, MD, from the University of Texas MD Anderson Cancer Center, Houston.

"Sotorasib also demonstrated durable disease control in heavily pretreated patients with non–small cell lung cancer," said Dr. Hong.

He presented secondary efficacy endpoint results from the trial in an online presentation during the European Society of Medical Oncology Virtual Congress 2020. The study was also published simultaneously online in the New England Journal of Medicine (N Engl J Med. 2020 Sep 20. doi: 10.1056/NEJMoa1917239).

The trial met its primary endpoint of safety of sotorasib, with no dose-limiting toxicities or treatment-related fatal adverse events, and treatment-emergent grade 3 or higher adverse events occurring in less than 20% of patients.

"The safety profile is more favorable than that of other targeted agents, and I think the reason why you have a quite safe compound here is that sotorasib is very specific in its binding to KRAS G12C, and KRAS G12C is only present in the tumor," coinvestigator Marwan G. Fakih, MD, a medical oncologist at City of Hope Comprehensive Cancer Center in Duarte, Calif., said in an interview. Dr. Fakih was co–lead author of the report in the New England Journal of Medicine.

A real "triumph"

Sotorasib is "a triumph of drug discovery," commented Colin Lindsay, MD, from the University of Manchester (England), the invited discussant.

"We know that KRAS, over many years, over 3 decades, has been very difficult to target," he said.

"The early development of KRAS G12C–targeted agents is just the beginning, lending hope that the ability to target not only other KRAS mutations but also other targets previously thought to be undruggable may be within reach," wrote Patricia M. LoRusso, DO, from the Yale Cancer Center in New Haven, Conn., and Judith S. Sebolt-Leopold, PhD, from the University of Michigan Rogel Cancer Center, Ann Arbor, in an accompanying editorial.

The KRAS, which stands for Kristen rat sarcoma viral oncogene homologue, p.G12C mutation is a glycine-to-cysteine substitution that results in the oncogene being switched on in its active form. The mutation has been identified in approximately 13% of NSCLC tumors, in 1%-7% of colorectal cancers, and in other solid tumors.

But the mutation has been considered too difficult to target because of KRAS's strong binding affinity for guanosine triphosphate (GTP), an essential building block of RNA synthesis, and by a lack of accessible drug-binding sites.

Sotorasib is a small-molecule, specific, and irreversible inhibitor of KRAS that interacts with a "pocket" on the gene's surface that is present only in an inactive conformation of KRAS. The drug inhibits oncogenic signaling and tumorigenesis by preventing cycling of the oncogene into its active form, Dr. Fakih explained.

Study details

The CodeBreaK 100 investigators enrolled patients with 13 different locally advanced or metastatic solid tumor types, all bearing the KRAS p.G12C mutation.

The trial began with a dose-escalation phase, with two to four patients per cohort assigned to receive daily oral sotorasib at doses of 180, 360, 720, or 960 mg. The 960-mg dose was selected for expansion cohorts and for planned phase 2 studies, based on the safety profile and the lack of dose-limiting toxicities.

Dr. Hong and colleagues reported results for 129 patients treated in the dose-escalation and expansion cohorts, including 59 with NSCLC, 42 with colorectal cancer, and 28 with other tumor types, but focused primarily on patients with NSCLC.

After a median follow-up of 11.7 months, 59 patients with NSCLC had been treated, 3 at the 180-mg dose, 16 at 360 mg, 6 at 720 mg, and 34 at 960 mg. At the time of data cutoff in June of this year, 14 patients were still on treatment and 45 had discontinued, either from disease progression (35 patients), death (5), patient request (4) or adverse events (1).

As noted, there were no dose-limiting toxicities or treatment-related fatalities reported.

Grade 3-4 treatment-related adverse events were reported in 18.6% of patients. The only grade 4 treatment-related event was diarrhea, in one patient. Grade 3 events included elevated liver transaminases in nine patients, increased alkaline phosphatase in two, anemia in one, and increased gamma-glutamyl transferase levels, decreased lymphocyte count, hepatitis, and hyponatremia in one patient each.

Dr. Fakih said that, given sotorasib's high degree of specificity, it's unclear what might be causing the observed adverse events.

Responses at all dose levels

The confirmed partial response rate was 32.2% for patients with NSCLC treated at all dose levels, and 35.3% for patients who received the 960 mg dose.

Among all NSCLC patients, and all treated at the highest 960-mg dose level, the stable disease rates were 55.9%. The respective disease control rates were 88.1% and 91.2%.

Tumor reductions occurred across all dose levels in patients with NSCLC. The median progression-free survival was 6.3 months.

Hong reported results for one patient, a 59-year-old man with the mutation who had experienced disease progression on five prior therapies including targeted agents, chemotherapy, and a checkpoint inhibitor, and had gamma-knife surgery for brain lesions.

This patient had a complete response in target lesions and a partial response overall, which included shrinkage of central nervous system metastases. He recently had progression in non-target lesions, after 1.5 years in response, Dr. Hong said.

The median duration of response was 10.9 months for patients with partial responses and 4 months for patients with stable disease.

Dr. Hong noted that response to sotorasib was seen across a range of co-mutational profiles, including several patients with four mutations in addition to KRAS p.G12C.

Other tumors, possible combinations

Among 42 patients with colorectal cancers bearing the KRAS p.G12C mutation, 3 (7.1%) had a partial response. There were also partial responses seen in one patient each with melanoma and with appendiceal, endometrial, and pancreatic tumors.

"Overall, the results of this trial are very encouraging, showing the first step in 'drugging the undruggable,'" Dr. LoRusso and Dr. Sebolt-Leopold wrote in their editorial.

"A recent study showed that KRAS G12C colorectal cancer cells have higher basal epidermal growth factor receptor (EGFR) activity than NSCLC cells, leading to a rapid rebound in mitogen-activated protein (MAP) kinase signaling and resistance to KRAS G12C inhibition," the editorialists wrote. "This observation is consistent with the weaker observed clinical activity of sotorasib in patients with colorectal cancer, a problem that may be addressed by combining it with an EGFR inhibitor [e.g., cetuximab], as seen preclinically."

The study was sponsored by Amgen and by grants from the National Institutes of Health. Dr. Hong disclosed research/grant funding and an advisory/consulting role with Amgen and others. Dr. Fakih disclosed a speaking engagement for Amgen and consulting for and grant support from others. Dr. Lindsay disclosed consulting for Amgen and institutional research funding from the company and others. Dr. LoRusso disclosed fees from multiple companies, not including Amgen. Dr. Sebolt-Leopold disclosed no relevant financial relationships.

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

VIEW ON THE NEWS

A. Christine Argento, MD, FCCP, comments: This could be a game-changer. The one mutation that we always hope to not see on the report, one that is synonymous with a poor prognosis and poor response to therapy. Having a target for therapy is a significant step forward and offers hope to patients who either have a discouraging molecular profile or who have tried and progressed despite multiple treatment strategies.

Risk factors for severe immune-related AEs identified

BY SUSAN LONDON
MDedge News

The first nationwide study of severe immune-related adverse events among cancer patients treated with immune checkpoint inhibitors helps identify those at elevated risk. The findings were reported at the Society for Immunotherapy of Cancer's 35th Anniversary Annual Meeting.

"Immune-related adverse events are a very serious side effect of immune checkpoint inhibitor therapy,

Mr. William Murphy

"Most of the current literature around the incidence of immune-related adverse events and factors that are predictive of incidence are based on clinical trials and small studies."

and as this therapy has become more common for treating advanced cancers, the incidence of immune-related adverse events has increased as well," said presenting author William Murphy, a dual MD and MBA student at Harvard Medical School and Harvard Business School, both in Boston.

"However, because there is no ICD code for immune-related adverse events, it's very difficult to study them at a population level. Most of the current literature around the incidence of immune-related adverse events and factors that are predictive of incidence are based on clinical trials and small studies," Mr. Murphy noted.

He and his colleagues analyzed claims data from a U.S. nationwide health insurance plan for 14,378 patients who had a primary cancer and received at least one administration of an immune checkpoint inhibitor – an inhibitor of programmed death–1, PD–ligand 1, or CTLA4 – during 2011-2019.

Over 19,117 patient-years of follow-up, 504 patients (3.5%) developed a severe immune-related adverse event (irAE), defined as one occurring within 2 years of their treatment and requiring inpatient hospitalization and new immunosuppression.

The incidence of severe irAEs per patient treatment year was 2.6% overall, rising from 0% in 2011 to 3.7% in 2016.

In multivariate analysis, patients had an elevated risk of severe irAEs if they received combination immunotherapy as compared with monotherapy (odds ratio, 2.44; $P < .001$).

On the other hand, risk fell with advancing age (OR, 0.98 per additional year; $P < .001$). And risk was lower for patients with melanoma (OR, 0.70; $P = .01$), renal cell carcinoma (OR, 0.71; $P = .03$), and other cancers (OR, 0.50; $P < .001$), compared with lung cancer.

Sex, geographic region, income, employment status, and comorbidity were not significantly associated with the risk of severe irAEs.

"We hope that patients and providers can use this evidence from a nationwide study of severe irAEs to guide treatment and management decisions," Mr. Murphy concluded.

Real-world evidence

"As the use of immune checkpoint inhibitors increases for patients with a variety of different tumor types, there is increasing need for population-level evidence for patients treated outside of clinical trials," said Allison Betof Warner, MD, PhD, an assistant attending physician with the melanoma service at Memorial Sloan Kettering Cancer Center in New York.

"This is a well-conducted study with an innovative approach to using real-world evidence to examine immune-related adverse events," she added.

To her knowledge, it is the first study to look at multiple cancers for which immunotherapy is approved, Dr. Betof Warner said. This approach resulted in a large patient sample, giving power to detect differences between groups.

"The authors' finding that combination immunotherapy is associated with more severe irAEs is in line with our clinical experience and other data sets, and the data regarding increased odds of severe irAEs in younger patients and those with lung cancer raise interesting biological questions about the etiology of

Dr. Allison Betof Warner

"The authors' finding that combination immunotherapy is associated with more severe irAEs is in line with our clinical experience and other data sets."

irAEs," Dr. Betof Warner noted.

However, certain factors complicate interpretation of the study's findings, she cautioned. One such factor is requiring hospitalization to define an irAE.

"Practice patterns regarding hospitalization vary quite widely from center to center. For example, in some centers, all patients with immune-mediated colitis are hospitalized, whereas in others, these patients are managed predominantly in the outpatient setting, even in cases of high-grade toxicity," she explained. "Practice patterns have also changed drastically over time as oncologists have grown more comfortable managing immune-related adverse events."

Another factor is potential confounding. For example, patients with melanoma are more likely to receive combination immunotherapy given its longstanding approval for this cancer, whereas it is comparatively new for other cancers. Also, age may differ across cancers.

"The data the authors have provided are a great starting point, but I think further analysis is needed before these observations can be validated and integrated into practice," Dr. Betof Warner concluded.

This study did not receive any specific funding. Mr. Murphy and Dr. Betof Warner disclosed no relevant conflicts of interest.

chestphysiciannews@chestnet.org

SOURCE: Murphy W et al. SITC 2020, Abstract 854.

Frivolous lawsuits: Still a big a threat to doctors?

BY ALICIA GALLEGOS

Dr. G, a New York surgeon, was only a couple years into practice when he faced his first lawsuit.

After undergoing liposuction surgery on the area of her calf and ankle, a patient claimed she had developed a severe allergic reaction, characterized by small areas of necrosis on the lower extremities, said Dr. G, who asked to remain anonymous. However, the alleged injury seemed suspicious, said Dr. G, considering that 3 weeks after the surgery, the area had shown a successful result with minimal swelling.

Six months into the suit, Dr. G received a shocking phone call. It was the patient's estranged husband, who revealed that his wife was having an affair with another man, a physician. In recorded phone calls, the patient and her paramour had discussed causing an injury near the patient's calf in an attempt to sue and get rich, the husband relayed. Dr. G immediately contacted his insurance carrier with the news, but his attorney said the information would not be admissible in court. Instead, the insurer settled with the patient, who received about $125,000.

At the time, Dr. G did not have a consent-to-settle clause in his contract, so the insurer was able to settle without his approval.

In legal practice, a frivolous claim is defined as one that lacks a supporting legal argument or any factual basis. A claim issued with the intent of disturbing, annoying, or harassing the opposing party can also be described as legally frivolous, said Michael Stinson, vice president of government relations and public policy for the Medical Professional Liability Association (MPL Association), a trade association for medical liability insurers.

However, when most physicians refer to "frivolous claims," they often mean a claim in which there is no attributable negligence. Such suits represent a second category of claims – nonmeritorious lawsuits.

"I think people intermix nonmeritorious and frivolous all the time," Mr. Stinson said. "In the vast majority of nonmeritorious claims, the patient has suffered an adverse outcome, it's just that it wasn't the result of negligence, whereas with a frivolous lawsuit, they really haven't suffered any damage, so they've got no business filing a lawsuit on any level."

A third type of so-called frivolous suit is that of a fraudulent or fake claim, in which, as Dr. G experienced, a patient causes a self-injury or lies about a condition to craft a false claim against a physician.

If a patient files a claim that the patient knows is false, the patient commits fraud and may be subject to counterclaims for malicious prosecution or abuse of process, said Jeffrey Segal, MD, JD, a neurosurgeon and health law attorney. Further, the patient would be testifying under oath, and such testimony can be considered perjury, a criminal offense with criminal penalties.

KUZMA/ISTOCKPHOTO

In legal practice, a frivolous claim is defined as one that lacks a supporting legal argument or any factual basis. A claim issued with the intent of disturbing, annoying, or harassing the opposing party can also be described as legally frivolous.

Sadly, Dr. G was the target of another frivolous lawsuit years later. In that suit, a patient claimed the surgeon had left a piece of sponge in her breast cavity during surgery. The case was dismissed when medical records proved the patient knew that the foreign body resulted from an unrelated procedure she had undergone years earlier.

Frivolous claims have long been a subject of debate. Tort reform advocates often contend that such claims are pervasive. They cite them as key reasons for high health care costs and say that they have led to the rise of defensive medicine. Plaintiffs' attorneys counter that the rate of frivolous claims is widely exaggerated and argue that the pursuit of frivolous claims would be "bad business" for legal firms. The debate begs the question: Do frivolous cases still exist, and if so, how common are they?

"I have never seen a frivolous malpractice claim," says Malcolm P. McConnell III, JD, a Richmond, Va., medical malpractice attorney and chair of the Medical Malpractice Legislative Subcommittee for the Virginia Trial Lawyers Association. "I cannot say that such things never happen, but any lawyer bringing such a thing is foolish, because there is no reward for it."

Are shotgun lawsuits frivolous?

To many physicians, being dragged into a lawsuit over a complaint or medical outcome in which they were not involved is frivolous, said Stanislaw Stawicki, MD, a trauma surgeon and researcher based in Bethlehem, Pa. Dr. Stawicki was named in a lawsuit along with a long list of medical staff who interacted in some way with the plaintiff. Dr. Stawicki himself saw the patient once and made a note in the chart but had nothing to do with the patient's surgery or with any critical decisions regarding his care, he said.

"Nothing really prepares you for seeing your name on a legal complaint," Dr. Stawicki said. "It's traumatic. I had to block out entire days to give depositions, which were really kind of pointless. Questions like, 'Is this really your name? Where did you train? Were you there that morning?' Stuff that was really not consequential to the fact that someone had surgery a month earlier and had some sort of complication."

Dr. Stawicki was eventually dropped from the claim, but not before a nearly year-long ordeal of legal proceedings, meetings, and paperwork.

It is common practice for plaintiffs' attorneys to add codefendants in the early stages of a claim, said David M. Studdert, ScD, a leading health law researcher and a professor of law at Stanford (Calif.) Law School. Defendants are gradually dismissed as the case moves forward and details of the incident become clearer, he said.

"Plaintiffs' attorneys have strong incentives to try and choose claims that will be successful," Dr. Studdert said. "However, in the early point in the process, neither the patient nor the attorney may have a good idea what has actually happened with care. So sometimes, filing a lawsuit may be the only way to begin the process of opening up that information."

A study by Dr. Studdert in which medical malpractice claims, errors, and compensation payments were analyzed found that, out of 1,452 claims, about one-third (37%) did not involve errors.

"Many physicians might call those frivolous lawsuits, but in fact, most of those don't go on to receive compensation," he said. "We suspect that in many instances, those claims are simply dropped once it becomes apparent that there wasn't error involved."

"They can still be burdensome, anxiety provoking, and time consuming for physicians who are named in those suits, so I don't want to suggest that claims that don't involve errors are not a problem," said Dr. Studdert. "However, I think it's wrong to assume, as many people do when they use the term 'frivolous lawsuit,' that this is really an

extortionary effort by a plaintiffs' attorney to try to get money out of a hospital or a physician for care that was really unproblematic."

Common frivolous claims

Nonmeritorious claims still occur relatively frequently today, according to data from the Medical Professional Liability Association's Data Sharing Project. Of about 18,000 liability claims reported from 2016 to 2018, 65% were dropped, withdrawn, or dismissed. Of the 6% of claims that went before a jury, more than 85% resulted in a verdict for the defendant, the researchers found.

"Basically, any claim that does not result in a payment because the underlying claim of negligence on the part of a health professional had been demonstrated, proven, or adjudicated false is one we would describe as nonmeritorious," Mr. Stinson said.

Malpractice claims are risky, expensive, and aggressively defended, says Mr. McConnell, the plaintiffs' attorney. Mr. McConnell, who has been practicing for 30 years, said his own claim selection process is very rigorous and that he cannot afford to pursue claims that aren't well supported by science and medicine.

"Pursuing frivolous cases would bankrupt me and ruin my reputation," he said. "A lawyer I know once said he would write a check for $10,000 to anyone who could show him a lawyer who makes a living pursuing frivolous medical malpractice cases. It's a fair challenge. The economics and the practices of liability carriers and defense lawyers make frivolous cases a dead end for plaintiff lawyers."

Most medical malpractice cases are taken on a contingency fee basis, Mr. McConnell noted, meaning that the plaintiff's lawyer is not paid unless the claim is successful.

"This means that the plaintiff's lawyer is risking 2 years of intensive labor on a case which may yield no fee at all," he said. "Obviously, any reasonable lawyer is going to want to minimize that risk. The only way to minimize that risk is for the case to be solid, not weak, and certainly not frivolous."

But Dr. Segal, the health law attorney, says that plenty of frivolous liability claims are levied each year, with attorneys willing to pursue them.

It's true that seasoned plaintiffs' attorneys generally screen for merit and damages, Dr. Segal said, but in some instances, attorneys who are not trained in malpractice law accept frivolous claims and take them forward. In some cases, they are slip-and-fall accident attorneys accustomed to receiving modest amounts from insurance companies quickly, said Dr. Segal, founder of Medical Justice, a company that helps deter frivolous lawsuits against physicians.

"If we lived in a perfectly rational universe where plaintiffs' attorneys screened cases well and only took the meritorious cases forward, we would see less frivolous cases filed, but that's not the universe I live in," Dr. Segal said. "There are well over a million attorneys in this country, and some are hungrier than others. The attorneys may frequently get burned in the end, and maybe that attorney won't move another malpractice case forward, but there's always someone else willing to take their place."

Of about 18,000 liability claims reported from 2016 to 2018, 65% were dropped, withdrawn, or dismissed. Of the 6% of claims that went before a jury, more than 85% resulted in a verdict for the defendant, the researchers found.

Medical Justice has twice run a Most Frivolous Lawsuit Contest on its website, one in 2008 and one in late 2018. The first contest drew 30 entries, and the second garnered nearly 40 submissions, primarily from physicians who were defendants in the cases, according to Dr. Segal.

In one case, an emergency physician was drawn into litigation by the family of a deceased patient. The patient experienced sudden cardiac arrythmia at home, and paramedics were unable to intubate her or establish IV access. She was transferred to the hospital, where resuscitation efforts continued, but she remained in asystole and was pronounced dead after 15 minutes.

At the hospital, blood tests were conducted. They showed that her serum potassium concentration was elevated to about 12 mEq/L, Dr. Segal said. The family initiated a claim in which they accused the emergency physician of failure to diagnose hyperkalemia. They alleged that had the hyperkalemia been discovered sooner, the patient's death could have been prevented.

"If you had no other facts about this, you would wonder how a person with potassium that high would even be alive," Dr. Segal said. "But what they were looking at was the body decomposing and all the potassium in the cells being released into the bloodstream. It wasn't the cause of the problem, it was an effect of the problem. She really was dead on arrival, and she was probably dead at home."

The case was eventually dropped.

Fraudulent claims uncommon

As for fraudulent medical liability claims, legal experts say they're rare. J. Richard Moore, JD, an Indianapolis-based medical liability defense attorney, said he's never personally encountered a medical malpractice claim in which he believed a plaintiff caused an injury or an illness and attempted to blame it on a physician.

However, Mr. Moore has defended many claims in which the illness or condition the plaintiff claimed was caused or was made worse through medical negligence was actually a preexisting condition or a preexisting condition that worsened and was not related to any medical negligence, Mr. Moore said.

"Although I have often felt in such cases that the plaintiff really knew that the condition was not affected by any alleged medical negligence, I would not put that in the 'fraudulent claim' category because it can be very difficult to establish a person's subjective state of mind," he said. "Usually in those cases, the plaintiff just denies memory of previous medical records or claims that the previous doctor who treated him or her for the same condition 'got it wrong.' In those cases, it is generally left to the jury whether to believe the plaintiff or not."

Mr. Stinson also says he has not come across a truly fraudulent medical liability case. He noted that such a claim might be similar to a person falsely claiming a soft-tissue injury following an alleged slip-and-fall accident.

"Clearly, a fraudulent claim could be viewed as riskier from the plaintiff's perspective because they could face criminal prosecution for insurance fraud, whereas if a claim is merely frivolous, they probably only run the risk of court-issued fine, if even that. That may be why we don't often see fraudulent MPL claims."

Ways to prevent or fight frivolous lawsuits

Since Dr. Stawicki's legal nightmare as a resident, rules have tightened in Pennsylvania, and it is now more difficult to file frivolous claims, he said.

Pennsylvania is one of at least 28

Continued on following page

Health sector lobbying: $464 million spent so far in 2020

BY RICHARD FRANKI
MDedge News

The Pharmaceutical Research and Manufacturers of America led the health sector in spending on lobbying through the first three-quarters of 2020, and health care as a whole spent more than any of the other 12 sectors of the U.S. economy, according to the Center for Responsive Politics.

PhRMA spent $20.7 million on lobbying through the end of September, good enough for third on the overall list of U.S. companies and organizations. Three other members of the health sector made the top 10: the American Hospital Association ($18.3 million), BlueCross/BlueShield ($16.3 million), and the American Medical Association ($15.2 million), the center reported.

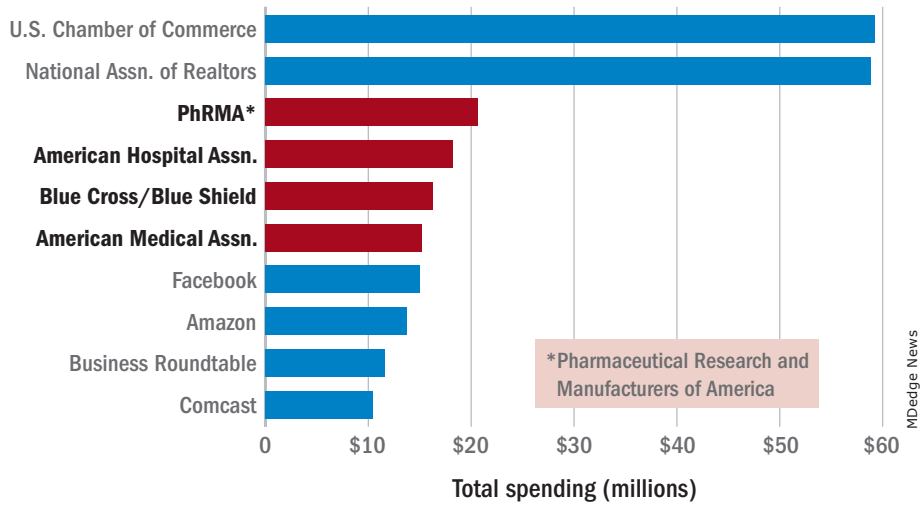
Total spending by the health sector was $464 million from Jan. 1 to Sept. 30, topping the finance/insurance/real estate sector at $403 million, and miscellaneous business at $371 million. Miscellaneous business is the home of the U.S. Chamber of Commerce, the annual leader in such spending for the last 20 years, based on data from the Senate Office of Public Records.

The largest share of health sector spending came from pharmaceuticals/health products, with a total of almost $233 million, just slightly more than the sector's four other constituents combined: hospitals/nursing homes ($80 million), health services/HMOs ($75 million), health professionals ($67 million), and miscellaneous health ($9.5 million), the center said on OpenSecrets.org.

Taking one step down from the sector level, that $233 million made pharmaceuticals/health products the highest spending of about 100 industries in 2020, nearly doubling the efforts of electronics manufacturing and equipment ($118 million), which came a distant second. Hospitals/nursing homes was eighth on the industry list, the center noted.

rfranki@mdedge.com

Highest-spending lobbyers through third quarter, 2020



Note: Data downloaded Oct. 23, 2020, from the Senate Office of Public Records includes spending from Jan. 1 to Sept. 30.
Source: Center for Responsive Politics

Continued from previous page

states that require a certificate of merit in order for a medical liability claim to move forward. The provisions generally state that an appropriately licensed professional must supply a written statement attesting that the care the patient received failed to meet acceptable professional standards and that such conduct was a cause in the alleged harm.

"There is now a much greater burden of proof regarding what can proceed," Dr. Stawicki said. "I've been involved in a couple cases that did not proceed because there was no certificate of merit."

Although these reforms may help, not all merit rules are created equal. Some states require that the expert who signs the affidavit be knowledgeable in the relevant issues involved in the action. Other states have looser requirements. In one of the cases featured in Medical Justice's Most Frivolous Lawsuit Contest, a podiatrist signed a supporting declaration for a claim related to obstetric care.

For physicians facing a frivolous claim, fighting it out in court depends on a number of factors. Without a consent-to-settle clause in the contract, an insurer can make the final decision on whether to defend or settle a case.

Resolving a malpractice claim is generally a business decision for the insurer, Dr. Studdert said.

"When the claim is for a relatively low amount of money, the costs of moving forward to defend that claim may be much more than the costs of simply settling it would be," he said. "On the other hand, liability insurers and their lawyers are repeat players here, as are the plaintiffs' attorneys. They don't want to incentivize plaintiffs' attorneys to bring questionable claims, and if they settle quickly, that may do so."

Mr. Stinson, of the MPL Association, said a truly frivolous claim – one with no legal basis – is highly unlikely to be settled, "especially by MPL Association members who go beyond having a purely financial interest in their insureds to also focus on their professional reputation/integrity." MPL Association members insure nearly 2 million health care professionals globally, including 2,500 hospitals and more than two-thirds of America's physicians who are in private practice.

> *"Liability insurers and their lawyers are repeat players here, as are the plaintiffs' attorneys. They don't want to incentivize plaintiffs' attorneys to bring questionable claim."*

Should I countersue?

For truly frivolous claims, physicians have the legal right to sue for damages caused by the unfounded complaint.

Perhaps the most well-known case of a successful malpractice countersuit is that of Louisville neurosurgeon John Guarnaschelli, MD, who in 2000 won $72,000 in damages against a plaintiffs' attorney for malicious prosecution.

The physician's countersuit followed the dismissal of a negligence claim against Dr. Guarnaschelli by a patient who contracted meningitis. The plaintiffs' attorney had made little effort to gather evidence to connect Dr. Guarnaschelli to the patient's injuries and had consulted only one other physician, a client of his, before filing the lawsuit, according to a summary of the case in the American Bar Association Journal.

Malicious prosecution is the most common legal theory of recovery for physicians in countersuits, according to a review of successful countersuits by doctors. Dr. Stawicki is a coauthor of that review. Other legal theories that physicians can raise include abuse of process, negligence, defamation, invasion of privacy, and infliction of emotional distress. Of the 13 cases evaluated in the article by Dr. Stawicki and colleagues, damages awarded to physicians ranged from about $13,000 to $125,000.

Although some doctors have success, pursuing a counterclaim can be a difficult feat, said Benjamin Braslow, MD, a trauma surgeon and professor of clinical surgery at the University of Pennsylvania in Philadelphia.

"The main takeaways were it's an uphill battle often met with not only resistance but diminishing returns to countersue," said Dr. Braslow, a coauthor of the countersuits analysis. "You have to meet very specific criteria regarding leveling the suit, and it may end up being a costly, time-consuming battle."

As for Dr. G, the surgeon, he now has a contract with a consent-to-settle clause and has taken other legal precautions since his lawsuits. He requires that his patients sign an agreement that any negligence claims they levy go to arbitration. If an arbitrator finds in the patient's favor, the case may proceed to court, he said. However, he requires another agreement such that, if patients lose in court, they are responsible for his legal fees.

"I'm just more careful," he said. "I ask all my staff in the office to use their judgment, however superficial: if they feel something is wrong with an individual to tell me so. I'd rather send them away than operate on them and have it result in a lawsuit."

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

TRELEGY ELLIPTA
(fluticasone furoate, umeclidinium, and vilanterol inhalation powder)

TRELEGY is now approved for a

NEW INDICATION

Find out more at
TRELEGYINFO.COM

PAY AS LITTLE AS $0*
Maximum savings $2400/year

Eligible commercially insured patients may pay as little as $0 for each covered 30-, 60-, or 90-day supply of TRELEGY for up to 12 months.

*Restrictions apply. This coupon may not be used by government beneficiaries, including those eligible for or enrolled in Medicare.
See full requirements and restrictions at TRELEGY.com/save

Maximum savings $2400/year

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

AMA tackles vaccine misinformation, systemic racism

BY KEN TERRY

The American Medical Association House of Delegates has adopted a policy to educate physicians on how to speak with patients about COVID-19 vaccination to counteract widespread misinformation about the vaccine development process.

Other highlights of the AMA's recent special meeting include a new policy on the ethics of physicians getting immunized against COVID-19 and a far-reaching statement about racism.

Under the organization's new vaccination education policy, the AMA will provide physicians with "culturally appropriate patient education materials," according to a news release.

This campaign will be conducted "bearing in mind the historical context of 'experimentation' with vaccines and other medication in communities of color," the AMA said, apparently alluding to the infamous Tuskegee study of syphilis in Black men.

Educating the public about the safety and efficacy of the COVID-19 vaccine programs is an "urgent priority," the AMA said. This is especially true among populations that have been disproportionately affected by the disease. Black and Latino people are being hospitalized for COVID-19 at far higher rates than White Americans.

"Under the new policy, the AMA will help address patient concerns, dispel misinformation, and build confidence in COVID-19 vaccination," the release states. The AMA also plans to build a coalition of health care and public health organizations to develop and implement a joint public education program.

Dr. Bailey

Polls have indicated that many people will not get vaccinated when supplies of the new COVID-19 vaccines are available, although public support is rising. A recent Gallup poll found that 58% of surveyed adults were willing to be inoculated, up from 50% in September.

A Kaiser Family Foundation survey in September found that a majority of Americans were skeptical of a rushed vaccine because they were concerned that the Trump administration was pressuring the Food and Drug Administration to approve a vaccine before the election.

"Given the unprecedented situation with COVID-19 and with vaccine development moving at a rapid pace, many of our patients and the public have questions and concerns," said AMA President Susan R. Bailey, MD, in the release. "It is essential that we speak together as a strong, unified voice across health care and public health, inclusive of organizations respected in communities of color; to use scientific, fact-based evidence to help allay public concerns; and build confidence in COVID-19 vaccine candidates that are determined to be safe and effective."

Physician, immunize thyself

The AMA also adopted a new ethics policy about physician immunization. On Monday, the AMA House of Delegates stated that physicians who are not immunized from a vaccine-preventable disease have an ethical responsibility to take appropriate actions to protect patients and colleagues.

The AMA code of ethics has long maintained that physicians have a strong ethical duty to accept immunizations when a safe, effective vaccine is available. However, the organization said in a news release, "it is not ethically problematic to exempt individuals when a specific vaccine poses a risk due to underlying medical conditions."

Ethical concerns arise when doctors are allowed to decline vaccinations for nonmedical reasons, according to a report presented to the House of Delegates by the AMA Council on Ethical and Judicial Affairs.

According to the newly amended AMA ethical guidance, "physicians who are not or cannot be immunized have a responsibility to voluntarily take appropriate actions to protect patients, fellow health care workers and others." This includes refraining from direct patient contact.

The delegates also approved a guidance asserting that physician practices and health care institutions are responsible for developing policies and procedures for responding to pandemics and epidemics. These policies and procedures should outline appropriate protective equipment allocation, staff immunization programs, and infection control practices.

Systemic racism

In an effort to reduce racial disparities in health care, the AMA House of Delegates adopted new policies recognizing race as a social construct, rather than a biological construct.

"The policies aim to advance data-driven, antiracist concepts challenging the current clinical application of race and its effects on vulnerable patient populations," an AMA statement said.

The new AMA policies "reflect an understanding of race as a socially constructed category different from ethnicity, genetic ancestry, or biology, and aim to end the misinterpretation of race as a biological category defined by genetic traits or biological differences," the AMA said.

According to the AMA, the practice of accepting race as a biological construct "exacerbates health disparities and results in detrimental health outcomes for marginalized and minoritized communities."

Specifically, the AMA said it supports ending the practice of using race as a proxy for biology in medical education, research, and clinical practice. It also encourages medical education programs to recognize the harmful effects of this approach. It recommends that clinicians and researchers focus on genetics and biology, the experience of racism, and social determinants of health when describing risk factors for disease.

"The AMA is dedicated to dismantling racist and discriminatory policies and practices across all of health care, and that includes the way we define race in medicine," said AMA board member Michael Suk, MD, in its statement. "We believe it is not sufficient for medicine to be nonracist, which is why the AMA is committed to pushing for a shift in thinking from race as a biological risk factor to a deeper understanding of racism as a determinant of health."

The AMA also plans to partner with physician organizations and other stakeholders "to identify any problematic aspects of medical education that may perpetuate institutional and structural racism." For example, the AMA will work with other organizations to improve clinical algorithms that incorrectly adjust for race and lead to less-than-optimal care for minority patients.

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

HCPs risk of COVID exposure outside of work rising

BY JENNIFER GARCIA

One-third of COVID-19 exposures among health care providers (HCPs) in Minnesota are caused by family or community exposure, not patient care, according to a study conducted by the Minnesota Department of Health and published online Oct. 30 in Morbidity and Mortality Weekly Report. And nonwork exposures were more likely to lead to COVID-19 infections.

Between March 6 and July 11, 2020, researchers with the Minnesota Department of Health evaluated 21,406 incidences of HCP exposure to confirmed COVID-19 cases. Of those, 5,374 (25%) were classified as higher-risk exposures, meaning the provider had close contact for 15 minutes or more, or during an aerosol-generating procedure.

Two-thirds (66%) of the higher-risk exposures occurred during direct patient care and 34% were related to nonpatient care interactions (e.g., coworkers and social and household contacts). Overall, 6.9% (373) of the HCPs with a higher-risk exposure received a positive SARS-CoV-2 test result within 14 days of the exposure. Notably, HCPs with household or social exposure had the highest positivity rate across all exposure types at 13%.

"Since the time period covered in this report, we've seen a significant increase in the proportion of HCPs who have had higher-risk exposures outside of work due to household or social contacts," said lead author Ashley Fell, MPH, from the Minnesota Department of Health.

"HCPs with household or social exposures are also more likely to test positive than HCPs with higher-risk exposures within the health care setting, which is an important message for both HCPs and the community at large that more COVID-19 spreading in our communities poses a greater risk to our HCPs and health care system," Ms. Fell said in an interview.

When evaluating personal protective equipment use among exposed HCPs, researchers found that 90% of providers in acute or ambulatory care were wearing a respirator or medical-grade face mask at time of exposure, compared with just 68% of HCPs working in congregate living or long-term care facilities.

Further, investigators found that an HCP with a positive SARS-CoV-2 test working in a congregate living or long-term care facility resulted in exposure of a median of three additional HCPs (interquartile range, 1-6), compared with a median of one additional HCP exposure in acute or ambulatory care (IQR, 1-3).

The researchers also found that, compared with HCPs in acute or ambulatory settings, HCPs working in long-term care or congregate living settings were more likely to return to work following a high-risk exposure (57% vs. 37%) and work while symptomatic (4.8% vs. 1.3%).

When asked whether these findings apply to HCPs in other states, Andrew T. Chan, MD, from Massachusetts General Hospital, Boston, noted: "These data are not surprising and confirm what many of us have been seeing in our own areas.

"Clearly, the risk of contracting COVID-19 is particularly high for frontline health care workers in long-term care facilities and nursing homes," Dr. Chan said.

"Furthermore, the infection control practices in these care settings are often not as rigorous, and together these factors are probably contributing to higher risks of infection," he said.

The authors acknowledged potential study limitations including misclassification of HCP risk for exposure or misclassification of community exposure as workplace exposure.

"We also recognize that HCPs, like the rest of the community, are experiencing COVID fatigue and that facilities have to constantly be innovative and vigilant to help HCPs maintain rigorous safety precautions with their patients and around their colleagues," Ms. Fell concluded.

The authors and Dr. Chan disclosed no relevant financial relationships.

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

Tax alert: Twelve tips to help reduce COVID-19 bite

BY CAROLYN YUN, CPA, CFP

COVID-19 has had a huge impact on every aspect of physicians' medical practice, incomes, and business. Although this will probably not end soon, there are some key tax strategies that can help your financial position if you take some important actions by the end of the year.

Some of the ways in which physicians were hard hit include:

- Physicians who are self-employed are facing increased costs for personal protective equipment, cleaning protocols, and new telehealth infrastructure. Many are also facing staffing shortages as employees fall to part-time work or take time off work to care for family members.
- Even physicians working for large hospitals are not isolated from the financial impact of the virus. A recent survey conducted by Medscape concluded that over 60% of physicians in the United States have experienced a decrease in income since the start of the pandemic.
- Saving and investing have been affected: Physicians may expect to see that companies in which they are invested are cutting dividends. Interest rates (CDs, bonds) are lower, and capital gains distributions are reduced this year. Overall, that makes for a fairly grim financial picture.

While taxable income this year has mostly declined, the applicable tax rates overall are low. However, federal, state, and local budget deficits have been skyrocketing owing to the demands of the pandemic. That means, in all likelihood, there will

THINKSTOCK

be tax increases in the coming years to cover spending. However, this year's financial challenges could lend themselves to a unique tax-planning scenario that could potentially benefit physicians as they make long-term plans for their investments.

Given these circumstances, these 12 tips can help you to lessen your tax bite this tax season. Many of these tips entail actions that you need to take before Dec. 31, 2020.

1. File for coronavirus stimulus rebates

If you have significantly depressed income this year or have lost your job, you may find that you qualify for an Economic Impact Payment, a refundable tax credit on the 2020 tax return. The credit is $1,200 for individuals or $2,400 for joint filers, plus an additional $500 for each qualifying child aged 16 years or younger. You begin to phase out of the credit at an adjusted gross income (AGI) of $75,000 for individuals and $150,000 for joint filers. People who had AGI below these thresholds in 2019 already would have received the credit in advance, but those who now find themselves qualifying will receive the credit when they file their 2020 tax return. No action is needed on your part; your tax preparer will calculate whether you are eligible for the credit when filing your return.

2. Look to accelerate income at lower brackets

With reduced earned income, many physicians will find themselves in significantly lower tax brackets this year. Once you fall below $200,000 for individuals or $250,000 for joint filers, you no longer trigger two additional surcharge taxes. The first is the additional Medicare tax, which is a further 0.9% applied to earned income above those thresholds, on top of ordinary income tax brackets. The second is the Net Investment Income Tax (NIIT), which is an additional 3.8% applied to your investment income on top of capital gains tax brackets.

If you are someone to whom the additional Medicare tax or NIIT no longer applies for 2020, you might consider generating income this year in order to realize the lower tax rates. You could consider selling highly appreciated investments in your taxable portfolio and reinvest the proceeds by repurchasing the same securities, thereby receiving a step-up in cost basis. Remember, when you go to sell securities in retirement, you are only taxed on the gain on the security over your

Continued on following page

Continued from previous page

cost basis. By bringing the cost basis up to today's fair market value, you could be greatly reducing the future tax applied on a sale.

For those with IRA or inherited IRA accounts who also have required minimum distributions (RMDs), you might consider making voluntary withdrawals this year and then reinvesting the proceeds into a savings or taxable account for when you need it. Keep in mind that, under the CARES Act, you are no longer required to take RMDs for 2020. However, this action would help avoid being forced to withdraw the amount when you may be at a higher tax bracket. You would need to do this before Dec. 31.

3. Build Roth assets strategies

With reduced incomes and lower marginal tax rates applying to the last dollar of income this year, physicians should carefully consider how to take advantage of current tax rates by building Roth assets. There are a few strategies, including switching 401(k) or 457 contributions from pretax to Roth or performing a backdoor Roth IRA contribution. However, neither is as powerful as converting IRA assets to Roth assets because there is no restriction on conversion amount or income cutoffs.

The goal is to convert enough assets to fill up lower applicable marginal tax brackets while avoiding tax surcharges, where possible. Roth IRA conversions can get you in trouble if you don't know what to expect, so it's best to work with a financial advisor or tax professional to give you guidance. For example, Roth conversions can trigger some tax surprises, such as the phaseout for the 199A qualified business income deduction, increased taxation on your Social Security benefits, or higher Income-Related Monthly Adjustment Amount surcharges on Medicare Part B and Part D premiums.

Bear in mind that Roth conversions generate taxable income and cannot be undone once completed. However, paying the lower marginal tax rate today may be a big win when RMDs could push physicians into tax brackets as high as or higher than during their working years.

4. Use coronavirus-related distributions

New this year is a penalty-free way to withdraw qualified retirement plan funds for those who are not yet eligible to make penalty-free withdrawals.

Congress introduced the Coronavirus-Related Distribution under the CARES Act. It allows individuals who have been affected by the pandemic to withdraw up to $100,000 before Dec. 31, 2020, without paying the 10% early withdrawal penalty. If you are considering an early retirement because of the pandemic, it may make sense to take this withdrawal while the option lasts and keep the cash available to help fund the gap before the remainder of your retirement plan assets are available penalty free. Keep in mind that this withdrawal generates taxable ordinary income, even though the early withdrawal penalty does not apply. Taking this withdrawal can boost your taxable income bracket, so calculate carefully before you do this.

5. Explore charitable donations for 2020

There is no shortage of people in need owing to the pandemic. For those who continue to be charitable minded, a decrease in income may mean you have more opportunity for your regularly recurring charitable donations to decrease your taxes this year. Normally, charitable donations for itemizers are limited to 60% of AGI. However, the CARES Act increased the charitable deduction limit to 100% of AGI for 2020. Even those who claim the standard deduction can take advantage of a new "above-the-line" deduction worth $300 for individuals and $600 for joint filers by making qualified cash donations in 2020. Take special note that the contributions do not apply to donor-advised funds or nonoperating private foundations.

6. Make noncash charitable donations

Many physicians are working longer and harder than ever, and for many, that means vacation plans have been placed on hold for the remainder of the year. Don't let your paid-time-off days go to waste! The IRS now permits leave-based donation programs, which allow employers to make deductible charitable donations for the relief of victims of the COVID-19 pandemic on the basis of the value of the sick, vacation, or personal leave that employees voluntarily forgo. The value of the donation will not be treated as compensation for the employee and will be free of any otherwise applicable Federal Insurance Contributions Act (FICA) taxes, and the employer can deduct the donation as ordinary and necessary business expenses if they meet certain requirements.

7. Claim 2020 losses on prior tax returns

For self-employed physicians, a wealth of tax planning strategies are available. One of the most significant may be the new provisions under the CARES Act that allow 100% of net operating losses (NOLs) for 3 calendar years of losses – namely 2018, 2019, and 2020 – to be carried back to the prior 5 tax years. Using these NOLs, you may be able to claim a refund for tax returns from prior tax years when there was otherwise a limit on NOLs at 80% of taxable income. If you think this applies to you, it's wise to meet with your accountant or financial professional to discuss this.

8. Delay payroll taxes where possible

For physicians with employees looking for some cash flow relief, a new payroll tax deferral is available to you this year. Under the CARES Act, employers can delay payment of their 2020 employer payroll tax, namely the 6.2% Social Security tax, with 50% not due until Dec. 31, 2021, and the remainder due Dec. 31, 2022. The deferral will not incur any interest or penalties and is also available to those who are self-employed.

On top of that, a new payroll tax credit was created under the Families First Coronavirus Response Act. Eligible employers can receive this tax credit for the amount of wages they pay to eligible employees who are taking pandemic-related paid family leave or paid sick leave this year. The credit is also available to those who are self-employed. If you think this credit may be applicable to you, it's worth speaking with your tax preparer about it.

9. Increased business property deductions

The nature of many physician business operations has drastically changed this year. For physicians who already have invested in and implemented new telehealth infrastructure, this can create valuable tax deductions to offset their ordinary income. Businesses may take 100% bonus depreciation on the cost of qualified property both acquired and placed in service after Sept. 27, 2017, and before Jan. 1, 2023. In general, during the last quarter of the year, you should look to decelerate business purchases until after Jan. 1, 2021, to get a deduction in 2021 at a higher marginal tax bracket.

10. Switch to cash accounting instead of accrual accounting

With higher expenses and lower profits, some large practice groups may take a second look to see whether they qualify to switch to cash accounting from accrual accounting to defer taxes. This rule change was adopted back in 2017 to allow small-business taxpayers with average annual gross receipts of $25 million or less in the prior 3 years to use the cash method of accounting. Ultimately, this switch should allow practices to owe the IRS money only after invoices were paid.

11. For physicians looking to sell their unprofitable practices

For those looking to make a quick exit from their practice in response to the pandemic, there is some tax relief in the event of a sale at a loss. Certain business owners who sell failed businesses will be able to use up to $50,000 of net losses as individuals or $100,000 as joint filers from the sale to offset ordinary income, current or future, under Internal Revenue Code (IRC) Section 1244. Remember that ordinary income tax rates are much higher than capital gains rates, so you could see some tax relief through a sale. The provision covers shareholders of domestic small-business corporations, both C or S corporations, but not partnerships. You would have to sell the business before Dec. 31 to get this deduction in 2020.

12. For physicians looking to sell their profitable practices

Even self-employed physicians who have managed to maintain profitable practices may be looking for early retirement after the exhaustion of the pandemic. If you own stock in a C corporation engaged in an active trade or business that has not had assets of more than $50 million at any time, you can take advantage of the IRC Section 1202 exemption. Section 1202 provides an exclusion from gain from the sale of stock of either $10 million or 10 times the adjusted basis of the stock, owned at least 5 years, in corporations regarded as "qualified small businesses." This means you may be able to sell your practice at a gain with a handsome tax shield. Again, to get this tax benefit for April's tax return, you'd have to engage in this activity before year end.

Regardless of whether the pandemic has placed financial constraints on you this year, tax-savvy opportunities are available to capitalize on your reduced income and lower tax rates. It's always important to keep in mind not just your taxes in any one given year, but your lifetime tax obligations. Financial advisors and tax planners can perform multiyear tax calculations and recommend ways to manage your tax bracket and help lower your overall lifetime tax obligations.

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

HHS delays deadline for patient access to notes

BY NICK MULCAHY

The Department of Health & Human Services on Oct. 29 extended the deadline for health care groups to provide patients with immediate electronic access to their doctors' clinical notes as well as test results and reports from pathology and imaging.

The mandate, called "open notes" by many, is part of the 21st Century Cures Act, and will now go into effect April 5.

The announcement comes just 4 days before the previously established Nov. 2 deadline and gives the pandemic as the reason for the delay.

FG Trade/Getty Images

Dr. Millen feared open notes initially but, within the first 3 months of usage, about 15 patients gave her direct feedback on how much they appreciated her notes.

"We are hearing that, while there is strong support for advancing patient access … stakeholders also must manage the needs being experienced during the current pandemic," Don Rucker, MD, national coordinator for health information technology at HHS, said in a press statement.

"To be clear, the Office of the National Coordinator is not removing the requirements advancing patient access to their health information," he added.

'What you make of it'

Scott MacDonald, MD, electronic health record medical director at the University of California, Davis, said his organization is proceeding anyway. "UC Davis is going to start releasing notes and test results on Nov. 12," he said in an interview.

Other organizations and practices now have more time, he said, but the law stays the same. "There's no change to the what or why – only to the when," Dr. MacDonald pointed out.

Vanderbilt University Medical Center in Nashville, Tenn., will take advantage of the extra time, Trent Rosenbloom, MD, MPH, director of patient portals, said in an interview.

"Given the super-short time frame we had to work under as this emerged out from dealing with COVID, we feel that we have not addressed all the potential legal-edge cases such as dealing with adolescent medicine and child abuse," he said.

On Oct. 21, this news organization reported on the then-imminent start of the new law, which irked many readers. They cited, among other things, the likelihood of patient confusion with fast patient access to all clinical notes.

"To me, the biggest issue is that we speak a foreign language that most outside of medicine don't speak. Our job is to explain it to the patient at a level they can understand. What will 100% happen now is that a patient will not be able to reconcile what is in the note to what they've been told," Andrew White, MD, wrote in a reader comment.

But benefits of open notes outweigh the risks, say proponents, who claim that doctor-patient communication and trust actually improve with information access and that research indicates other benefits such as improved medication adherence.

Open notes are "what you make of it," said Marlene Millen, MD, an internist at UC San Diego Health, which has had a pilot open-notes program for 3 years.

"I actually end all of my appointments with: 'Don't forget to read your note later,'" she said in an interview.

Dr. Millen feared open notes initially but, within the first 3 months of usage, about 15 patients gave her direct feedback on how much they appreciated her notes. "It seemed to really reassure them that they were getting good care."

Dr. MacDonald and Dr. Millen disclosed no relevant financial relationships.

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

COVID-19 forced residents to adapt quickly, learn new communication skills

BY ANDREW D. BOWSER
MDedge News

THOMAS NORTHCUT/THINKSTOCK

A respondent described the experience as "humbling" but said there were rewarding aspects in patient care during the peak of the pandemic.

FROM THE JOURNAL CHEST® ▪ While the spring peak of COVID-19 was tough and traumatic for many residents and interns in the Icahn School of Medicine at Mount Sinai health system, the experience may have accelerated their patient communication skills regarding difficult goals-of-care discussions, results of a recent survey suggest.

Breaking bad news was an everyday or every-other-day occurrence at that peak of the pandemic for nearly all of 50 of the trainees surveyed. But trainees became significantly more comfortable and fluent in goals-of-care discussions during the pandemic, according to Patrick Tobin-Schnittger, MBBS, a third-year internal medicine resident in the Mount Sinai program.

"COVID-19 has obviously made a huge impact on the world, but I think it's also made a huge impact on a whole generation of junior doctors," said Dr. Tobin-Schnittger, who presented the findings in a late-breaking abstract session at the virtual CHEST annual meeting.

Nevertheless, coping with death may still be a challenge for many residents, according to Dr. Tobin-Schnittger. In the survey, internal medicine residents who had rarely encountered patient deaths suddenly found themselves experiencing deaths weekly, with more than one in five saying they were encountering it every day.

Dr. Narasimhan

When asked to self-rate themselves according to Bugen's Coping With Death scale, most participants had scores that suggested their ability to cope was suboptimal.

To help trainees cope with local COVID-19 surges, internal medicine residency programs should be implementing "breaking bad news" workshops and educating house staff on resilience in times of crisis, especially if it can be done virtually, according to Dr. Tobin-Schnittger.

"We've had several sessions in our health system of letting people vent, talk about what happened, and tell stories about patients that they are still thinking about and haunted by – there was so much death," said Mangala Narasimhan, DO, FCCP, director of critical care services at Northwell Health in New York City.

"People will be suffering for a long time thinking about what happened in March and April and May, so I think our focus now needs to be how to fix that in any way we can and to support people, as we're dealing with these increases in numbers," she said in an interview. "I think everyone's panicking over the increase in numbers, but they're panicking because of the fear of going through what they went through before."

The investigators sent their survey to 94 residents and interns in the Mount Sinai program who had worked through the peak of the pandemic. They received 50 responses. For those individuals, the mean age was 29.5 years, and about 46% had worked for more than 3 years.

Before the pandemic, only 3 of the 50 respondents reported having goals-of-care conversations every day or every other day, while during the pandemic, those conversations were happening at least every other day for 38 of the respondents.

Self-reported fluency and comfort with those discussions increased significantly, from a mean of about 50 on a scale of 100 before the pandemic to more than 75 during the pandemic, according to Dr. Tobin-Schnittger.

A respondent described the experience as "humbling" but said there were rewarding aspects in patient care during the peak of the pandemic, which helped in being able to focus during difficult days.

Negative consequences of the peak pandemic experience included anger, anxiety, professional strain, trauma, and emotional distancing.

"While we did encounter a lot of traumatic experiences, overall, there's a huge sense that there is a lot more camaraderie within our department, but also within other departments," said Dr. Tobin-Schnittger..

chestphysiciannews@chestnet.org

SOURCE: Tobin-Schnittger P. CHEST 2020, Late-breaking abstract. doi: 10.1016/j.chest.2020.09.040.

This month in the journal *CHEST*®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Power Outage: An Ignored Risk Factor for Chronic Obstructive Pulmonary Disease Exacerbations
By Dr. Wangjian Zhang, et al.

PROPHETIC: Prospective Identification of Pneumonia in Hospitalized Patients in the ICU
By Dr. Stephen P. Bergin, et al.

Chronic Beryllium Disease: Update on a Moving Target
By Dr. Maeve MacMurdo, et al.

Development of Learning Curves for Bronchoscopy: Results of a Multicenter Study of Pulmonary Trainees
By Dr. Nha Voduc, et al.

Bias and Racism Teaching Rounds at an Academic Medical Center
By Dr. Quinn Capers, IV, et al.

INDEX OF ADVERTISERS

CRITICAL CARE COMMENTARY

COVID-19: Choosing the proper treatment at the proper time

BY MOHAMMED AMER MEGRI, MD, AND ANGEL O. COZ, MD, FCCP

Coronavirus disease 2019 (COVID-19), the disease caused by the highly contagious virus SARS-CoV-2, has affected over 45 million people worldwide and caused over 1.2 million deaths. Preventative strategies, including social distancing and facial coverings, have proven to be effective to decrease the risk of transmission. Unfortunately, despite these measures, a large number of individuals continue to get infected throughout the world. While most patients typically stay asymptomatic or develop mild forms of the disease, a fraction of them will progress to more severe forms that would necessitate hospital care. Since this is a novel virus, we do not have an effective antimicrobial agent and the care we provide is mostly supportive, aiming to prevent and treat the systemic complications produced by the virus and the inflammatory response that ensues.

The phases of COVID 19

COVID-19 can be clinically divided into three phases (Mason RJ, et al. *Eur Respir J.* 2020 Apr;55[4]).

The asymptomatic phase: Also known as incubation period. During this stage, the SARS-CoV-2 virus binds to the epithelial cells of the upper respiratory tract and starts replicating.

The viral phase: Associated with the classic constitutional symptoms such as fever, chills, headache, cough, fatigue, and diarrhea. This phase typically begins 4-6 days after exposure to SARS-CoV-2 and is characterized by high levels of viral replication and migration to the conducting airways, triggering the innate immune response.

The pulmonary phase: Characterized by hypoxia and ground glass infiltrates on computed tomography of the chest. By now, the virus has reached the respiratory bronchioles and the alveoli. During this phase (about 8-10 days after exposure) the virus begins to die, and the host immune response ensues. By now the number of viral units is very small, but the host immune reaction against the virus has begun to mount.

The virus is actively replicating during the asymptomatic and at the beginning of the viral phase. The severity of symptoms varies according to the viral load and patient comorbidities [mild-moderate (81%), severe (14%), and critical (5%)]. The disease course is characterized by dysregulated immunity, profound inflammatory response, and dysregulated coagulation. By distinguishing these phases, clinicians can start interventions that would aim at the main cause of the derangement at each specific phase.

Dr. Mohammed Amer Megri

For example, antiviral agents seem more appropriate in the early phases of the disease, while anti-inflammatory medications could target the inflammatory response that occurs in the pulmonary phase (Figure 1).

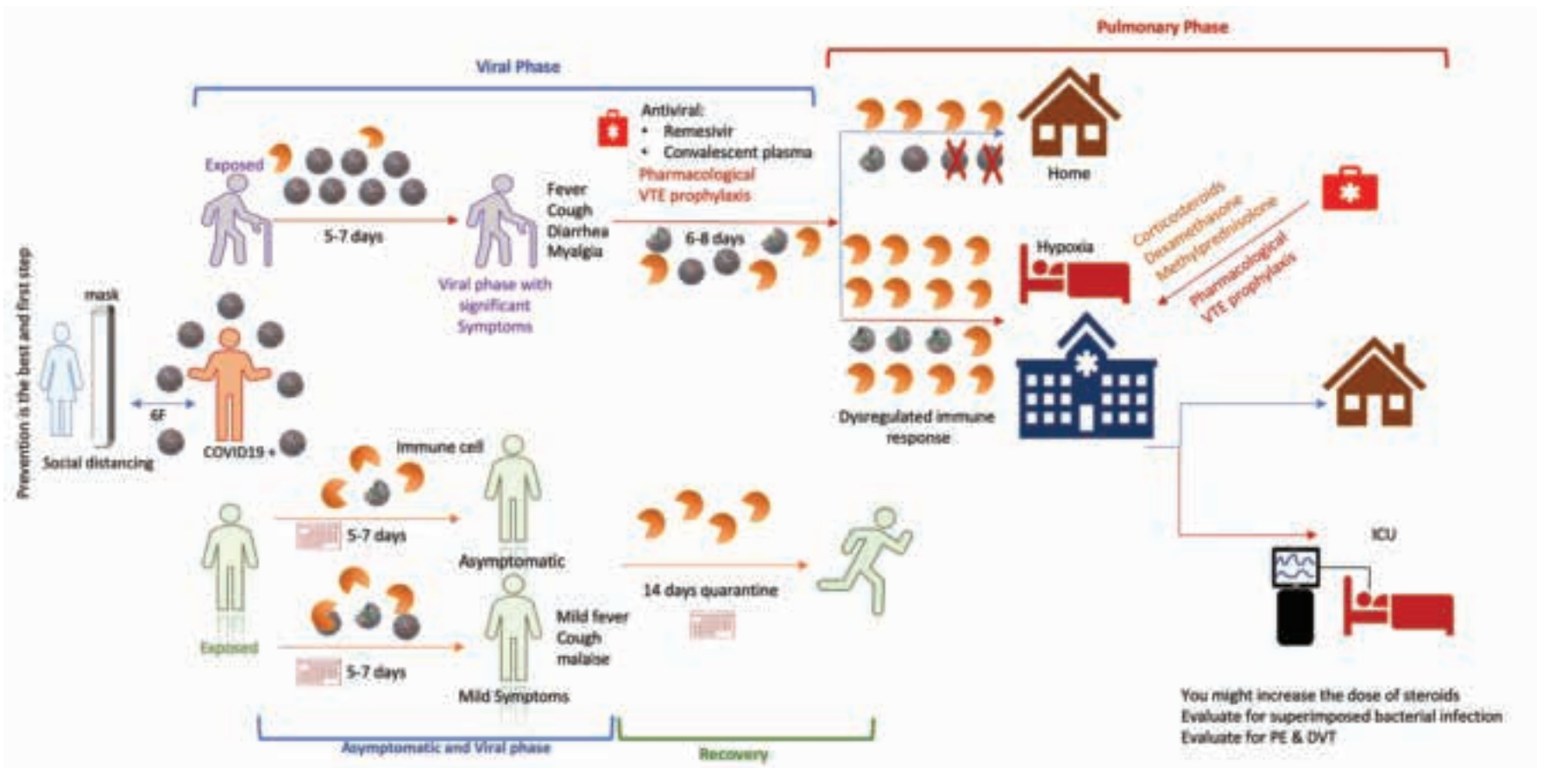
The tools in our toolbox: Timing is paramount

Remdesivir

The preliminary results from a recent trial that compared remdesivir with placebo, given 6-12 days from the onset of symptoms, revealed a shorter time to recovery with Remdesivir (Beigel JH, et al. *N Engl J Med.* 2020 Oct;8. NEJMoa2007764). The patients who received remdesivir within 10 days of the onset of symptoms had a shorter recovery time compared with those who received it after 10 days from the onset of symptoms. Moreover, remdesivir did not alter the disease course in patients who received the drug after the onset of hypoxia. These results are consistent with those of Wang and colleagues who reported no effect in time to clinical improvement in most patients who

Continued on following page

Despite the use of pharmacological prophylaxis, VTE was seen in 13.6% of critically ill patients and 3.6% of medical ward patients and associated with a higher mortality.



Continued from previous page

received the drug 10 days after the onset of symptoms (Wang Y, et al. *Lancet.* 2020 May;395[10236]:1569-78). In most antiviral trials, the agent was potentially given when the immune response had already begun, stage in which the number of viral units is not as large as in the earlier phases, possibly explaining the lack effect in time of clinical improvement or mortality.

Convalescent plasma

Piechotta and colleagues recently showed that convalescent plasma, when given to patients more than 14 days from the onset of symptoms, provided no benefit in time to clinical improvement or 28-day mortality. At 14 days or later, the pulmonary phase (characterized by systemic inflammation) had started in nearly all patients. As it seems apparent, any intervention not targeted to modulate the inflammatory response is unlikely to make a difference in this stage. (Piechotta V, et al. *Cochrane Database Syst Rev.* 2020 Jul;7[7]:CD013600).

The negative results of these studies (antivirals and convalescent plasma) highlight the importance of timing. In most of these trials, the intervention was started at the end of the viral phase or in the pulmonary phase, when the virus was nearly or completely dead, but the host immune response has begun to mount.

Corticosteroids

Corticosteroids (methylprednisolone and dexamethasone) have shown positive effects when given at the proper time (beginning of the pulmonary phase). A recent study revealed a lower 28-day mortality when compared with placebo in hospitalized patients with COVID-19. However, a prespecified subgroup analysis showed no benefit and a signal of possible harm among those who received dexamethasone in the absence of hypoxia (viral phase) (Lim WS, et al. *N Engl J Med.* 2020 Jul;[NEJMoa2021436]). A meta-analysis of seven randomized trials that used different doses and types of corticosteroids (dexamethasone, methylprednisolone, and hydrocortisone) reported a lower 28-day mortality in the corticosteroids group. The benefit was more pronounced when the corticosteroids was used in critically ill patients who were not receiving invasive mechanical ventilation.

Self-proning

Self-proning is also thought to be beneficial during the pulmonary phase. Prone positioning for at least 3 hours improved oxygenation but the result was not sustained (Coppo A, et al. *Lancet Respir Med.* 2020 Aug;8[8]:765-74). A retrospective analysis of 199 patients with COVID-19 in the pulmonary phase who were being supported by high-flow nasal cannula showed that awake proning for more than 16 hours had no effect in the risk of intubation or mortality (Ferrando C, et al. *Crit Care.* 2020 [Oct];24[1]:597) reduce the use of critical care resources, and improve survival. We aimed to examine whether the combination of high-flow nasal oxygen therapy (*HFNOCrit Care.* 2020 [Oct];24[1]:597). There is concern that this intervention might produce a delay in intubation in patients who have worsening oxygenation; this is especially important as delayed intubation can be associated with worse outcomes. Despite the conflicting data, awake self-proning is a reasonable intervention that should be considered provided that it does not interfere with treatments that have been proven beneficial. As prospective evidence becomes available, recommendations may possibly change.

What about thromboembolic events?

Data on arterial and venous thromboembolic events (VTE) in the disease course of COVID-19 are largely variable. The prevalence of VTE in COVID-19 seems to be higher than other in causes of sepsis especially in critically ill patients. (Bilaloglu S, et al. *JAMA.* 2020 Aug;324(8):799-801). Despite the use of pharmacological prophylaxis, VTE was seen in 13.6% of critically ill patients and 3.6% of medical ward patients and associated with a higher mortality. Therefore, more trials are needed to understand the most effective way to prevent VTE. At the current time, clinicians need to be vigilant to detect VTE as early as possible. Some options to consider include performing a daily evaluation of the possible risks (emphasizing prevention), routine bedside point of care ultrasound, early diagnostic imaging studies for clinically suspected VTE, early mobilization and delirium prevention. Prophylactic doses of LMWH or UH for all hospitalized patients with no or low risk of bleeding or non-hospitalized patient with high risk for VTE can be entertained (Bikdeli B, et al. *J Am Coll Cardiol* 2020 Apr;75[23]:2950-73). Therapeutic dose anticoagulation should be only used in confirmed VTE or in highly suspected VTE with difficulties to obtain standard confirmatory imaging. A therapeutic approach based solely on D-dimer should be avoided, because the evidence is insufficient and the risk of bleeding in critically ill patients is not insignificant.

Dr. Angel O. Coz

During the pulmonary phase (about 8-10 days after exposure) the virus begins to die, and the host immune response ensues. By now the number of viral units is very small, but the host immune reaction against the virus has begun to mount.

The available evidence is helpful but not definitive making it difficult to have a clear pathway to effectively treat the systemic effects of COVID-19. One should consider remdesivir and convalescent plasma during the viral phase before hypoxia ensue. Anti-inflammatory interventions (dexamethasone or methylprednisolone) should be given as soon as the pulmonary manifestations start (hypoxia). The type, optimal dose, and duration of corticosteroids vary from trial to trial and no evidence suggests that higher doses are associated with more benefit. It is not only important to choose the right treatment but also the phase when such treatment is most likely to be effective!

Dr. Megri is a Pulmonary and Critical Care Fellow at the University of Kentucky. Dr. Coz is Associate Professor of Medicine, University of Kentucky.

PULMONARY PERSPECTIVES®

Options grow for interstitial lung disease other than idiopathic pulmonary fibrosis

BY COREY D. KERSHAW, MD, FCCP

Care of the patient with a fibrosing interstitial lung disease (ILD) presents constant challenges not just in the diagnosis of ILD but in the choice of treatment. Since the FDA approval of both nintedanib and pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) in 2014, interest has grown for their employ in treating other non-IPF ILDs. This is especially true in cases with the pattern of radiographic or histopathological disease is similar to IPF – a usual interstitial pneumonia (UIP) pattern – despite not meeting criteria for an IPF diagnosis due to the identification of a predisposing etiology. As research evolves, clinicians may have more options to fight the vast variety of fibrosing ILDs encountered in practice.

In 2014, the publication of separate clinical trials of nintedanib and pirfenidone in patients with IPF marked a new beginning in the treatment of this disease. Nintedanib, a tyrosine kinase inhibitor with multiple targets, was shown to decrease progression of disease as measured by the annual rate of decline in forced vital capacity (FVC) (Richeldi L, et al. *N Engl J Med.* 2014 May;370[22]:2071-82). Pirfenidone, whose antifibrotic mechanisms are not completely understood, similarly slowed disease progression via a decrease in the percent change of predicted FVC (Lederer DJ, et al. *N Engl J Med.* 2014 May;370[19]:2083-92). Clinicians were now armed with two therapeutic options following the subsequent FDA approval of both drugs for the treatment of IPF. This represented a giant leap forward in the management of the disease, as prior to 2014 the only available options were supportive care and lung transplant for appropriate candidates.

As IPF represents but 20% of ILDs in the United States, a significant proportion of diseases were left without an antifibrotic option after the arrival of nintedanib and pirfenidone. (Lederer DJ. *N Engl J Med.* 2018 May;378:1811-23). For the others, such as chronic hypersensitivity pneumonitis and the many connective tissue disease-associated ILDs, treatment revolved around a variety of anti-inflammatory pharmaceuticals. Common treatment choices include corticosteroids, mycophenolate, and azathioprine. The data in support of these treatments for non-IPF ILD is comparatively lean in contrast to the more robust pirfenidone and nintedanib IPF trials.

One notable exception includes the Scleroderma Lung Studies. In Scleroderma Lung Study II (SLS II), 142 patients with scleroderma-related interstitial lung disease were randomized to oral mycophenolate for 24 months vs oral cyclophosphamide for 12 months plus placebo for 12 months (Tashkin DP, et al. *Lancet Respir Med.* 2016 Sep;4(9):708-19). The 2006 Scleroderma Lung Study established oral cyclophosphamide in scleroderma lung disease as a reasonable standard of care after demonstrating a slowing of disease progression after 12 months of therapy (Tashkin DP, et al. *N Engl J Med*. 2006 Jun;354[25]:2655-66). In SLS II, both cyclophosphamide and mycophenolate improved lung function at 24 months, but mycophenolate was better tolerated with less toxicity.

Dr. Corey D. Kershaw

Other supportive data for immunosuppressive treatments for non-IPF ILD rely heavily on smaller studies, case reports, and retrospective reviews. Choices of who and when to treat are often unclear and typically come from physician preferences and patient values discussions. In the cases of connective tissue disease-associated ILD, patients may already require treatment for the underlying condition. And, while some therapies could be beneficial in a concurrent manner for a patient's lung disease, many others are not (TNF-alpha antibody therapy, for example).

A major step forward for patients with scleroderma lung disease came with the publication of the SENSCIS trial (Oliver D, et al. *N Engl J Med.* 2019 Jun;380:2518-28). A total of 576 patients with scleroderma of recent onset (< 7 years) and at least 10% fibrosis on chest CT were randomized to receive either nintedanib or placebo. Patients were allowed to be supported by other therapies at stable doses prior to enrollment, and as such almost half of the patients were receiving mycophenolate. A significant improvement in annual FVC decline was reported in the treatment group, although the effect was tempered in the subgroup analysis when considering patients already on mycophenolate. Thus, the role of nintedanib in patients taking mycophenolate is less clear.

An ongoing study may clarify the role of mycophenolate and antifibrotic therapy in these patients. The phase 2 Scleroderma Lung Study III has a planned enrollment of 150 patients who are either treatment-naïve or only recently started on therapy (www.clinicaltrials.gov; NCT03221257). Patients are randomized to mycophenolate plus pirfenidone vs mycophenolate plus placebo, and the treatment phase will last 18 months. The primary outcome is change in baseline FVC. This trial design will hopefully answer whether the combination of an antifibrotic with an anti-inflammatory medication is superior to the anti-inflammatory therapy alone, in patients with at least some evidence of inflammation (ground-glass opacifications) on high-resolution CT scan (HRCT).

In ILD other than that associated with scleroderma, nintedanib was again explored in a large randomized controlled clinical trial. In INBUILD, 663 patients with progressive ILD not caused by IPF or scleroderma were randomized to nintedanib vs placebo for one year (Flaherty KR. *N Engl J Med.* 2019 Sep;381:1718-27). A majority of the patients (62%) had a UIP pattern on CT scan. There was overall improvement in the annual rate of decline in FVC in the treatment group, especially in the pr-determined subgroup of patients with a UIP pattern. The most common ILDs in the study were chronic hypersensitivity pneumonitis and that associated with connective tissue disease.

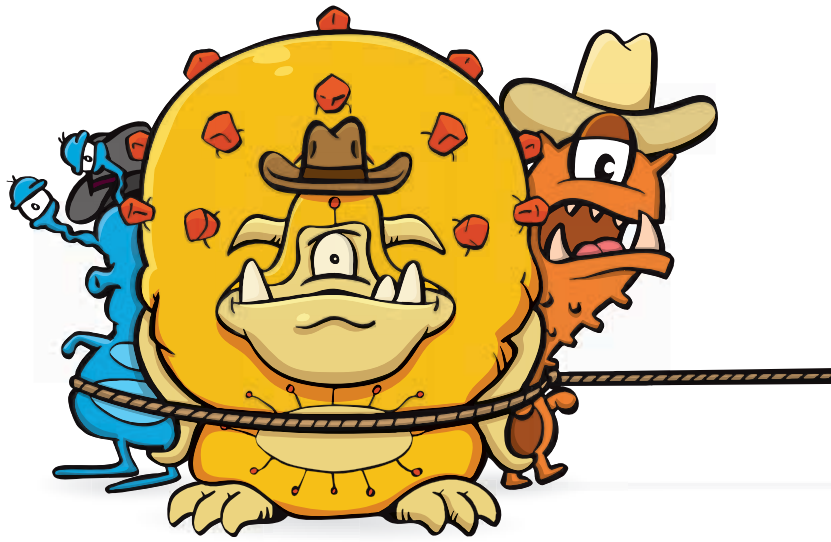
Pirfenidone is also being studied in multiple trials for various types of non-IPF ILD. Studies are either completed and nearing publication, or are ongoing. Some examples include the TRAIL1 study examining pirfenidone vs placebo in patients with rheumatoid arthritis (www.clinicaltrials.gov; NCT02808871), and the phase 2 RELIEF study that explores pirfenidone vs placebo in patients with progressive ILD from a variety of etiologies.

As more clinical trials are published, clinicians are now facing a different dilemma. Whereas the options for treatment were limited to only various anti-inflammatory medications in past years for patients with non-IPF ILDs, the growing body of literature supporting antifibrotics present a new therapeutic avenue to explore. Which patients should be started on anti-inflammatory medications, and which should start antifibrotics? Those questions may never be answered satisfactorily in clinical trials. Mycophenolate has become so entrenched in many treatment plans, enrollment into such a study comparing the two therapeutic classes head-to-head would be challenging.

However, a consideration of the specific phenotype of the patient's ILD is a suggested approach that comes from clinical experience. Patients with more inflammatory changes on CT scan, such as more ground glass opacifications or a non-UIP pattern, might benefit from initiation of anti-inflammatory therapies such as a combination of corticosteroids and mycophenolate. Conversely, initiating antifibrotic therapy upfront, with or without concomitant mycophenolate, is a consideration if the pattern of disease is consistent with UIP on CT scan.

Ultimately, referral to a dedicated interstitial lung disease center for expert evaluation and multidisciplinary discussion may be warranted to sift through these difficult situations, especially as the field of research grows more robust. In any event, the future for patients with these diseases, though still challenged, is brighter than before.

Dr. Kershaw is Associate Professor of Medicine, Division of Pulmonary & Critical Care Medicine, University of Texas Southwestern Medical Center. He is the current section editor for Pulmonary Perpsectives®and Vice Chair of the Interstitial and Diffuse Lung Disease NetWork at CHEST.



How the test was one.

One syndromic panel that tests everything but your patience.

Several years ago, we coined the phrase “Syndromic Testing.” It’s about testing for multiple pathogens simultaneously to determine which pathogen or pathogens are causing the patient’s symptoms. No more guessing. No more testing for one pathogen at a time. No more waiting for days or hours on end for an answer.

BioFire’s syndromic-based testing system does exactly that. Each of our five panels (Respiratory, Blood Culture, Gastrointestinal, Pneumonia, Meningitis/Encephalitis) uses one patient sample to test for the most common culprits. Two minutes of hands-on time. No precise measuring or pipetting. And all five panels can be run on the same machine.

It’s a brand new world out there. You need a frontline testing solution to stay ahead of it. You need the syndromic-based testing solution from BioFire.

biofiredx.com

BioFire® FilmArray® Panels

Respiratory
1 Test. 22 Targets. ~45 Minutes.
Includes SARS-CoV-2. EUA.[1]

Blood Culture Identification
1 Test. 43 Targets. ~1 Hour.

Gastrointestinal
1 Test. 22 Targets. ~1 Hour.

Meningitis/Encephalitis
1 Test. 14 Targets. ~1 Hour.

Pneumonia
1 Test. 33 Targets. ~1 Hour.

BIOFIRE®
BY BIOMÉRIEUX

Syndromic Testing: The Right Test, The First Time.

1. This test has not been FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories. This test has been authorized only for the detection and differentiation of nucleic acid of SARS-CoV-2 from multiple respiratory viral and bacterial organisms. This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

BFR0001-0832-01