VOL. 13 • NO. 4 • APRIL 2018

CHEST® Physician

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ANDREW BOWSER/FRONTLINE MEDICAL NEWS

"Workplace violence is not just active shooter – it's ubiquitous, and we only know a little bit about it," noted Dr. Lewis J. Kaplan.

How to manage workplace violence

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – Active-shooter events and other episodes of workplace violence can be better managed with proper planning and training by hospitals and staff, Lewis J. Kaplan, MD, said in a late-breaking session at the Critical Care Congress.

"Workplace violence is not just active shooter – it's ubiquitous, and we only know a little bit about it," noted Dr. Kaplan, section chief, surgical critical care, Corporal Michael J. Crescenz VA Medical Center, Philadelphia. "The facility and everyone in the health care team have a role in being an active participant, rather than a passive one."

To actively prepare for premeditated events, clinicians should develop partnerships with local law enforcement officials and initiate active training that involves anyone who could come into contact with an active shooter, Dr. Kaplan recommended.

There are many steps that can be taken to protect the facility, including visitor screening and management, security that extends to the perimeter of the facility, building design that limits access to specific places in the facility, and deployment of firearm-detection canines, Dr. Kaplan said, during the session at the congress, sponsored by the Society of Critical Care Medicine.

WORKPLACE VIOLENCE // *continued on page 6*

Prehospital antibiotics improved sepsis care

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – Training EMS personnel in early recognition of sepsis improved some aspects of care within the acute care chain, but did not reduce mortality, according to results of a randomized trial.

Emergency medical service (EMS) personnel were able to recognize sepsis more quickly, obtain blood cultures, and give antibiotics after the training, reported investigator Prabath Nanayakkara, MD, PhD, FRCP, at the Society of Critical Care Medicine's Critical Care Congress.

However, the hypothesis that this training would lead to increased survival was not met, noted Dr. Nanayakkara, of the acute medicine section of the department of internal medicine at VU University Medical Center, Amsterdam.

At 28 days, 120 patients (8%) in the prehospital antibiotics group had died, compared with 93 patients (8%) in the usual care group (relative risk, 0.95; 95% confidence interval, 0.74-1.24), according to the study's results that were simultaneously published online in Lancet Respiratory

PREHOSPITAL ANTIBIOTICS // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Bringing respiratory care for asthma to Guyana

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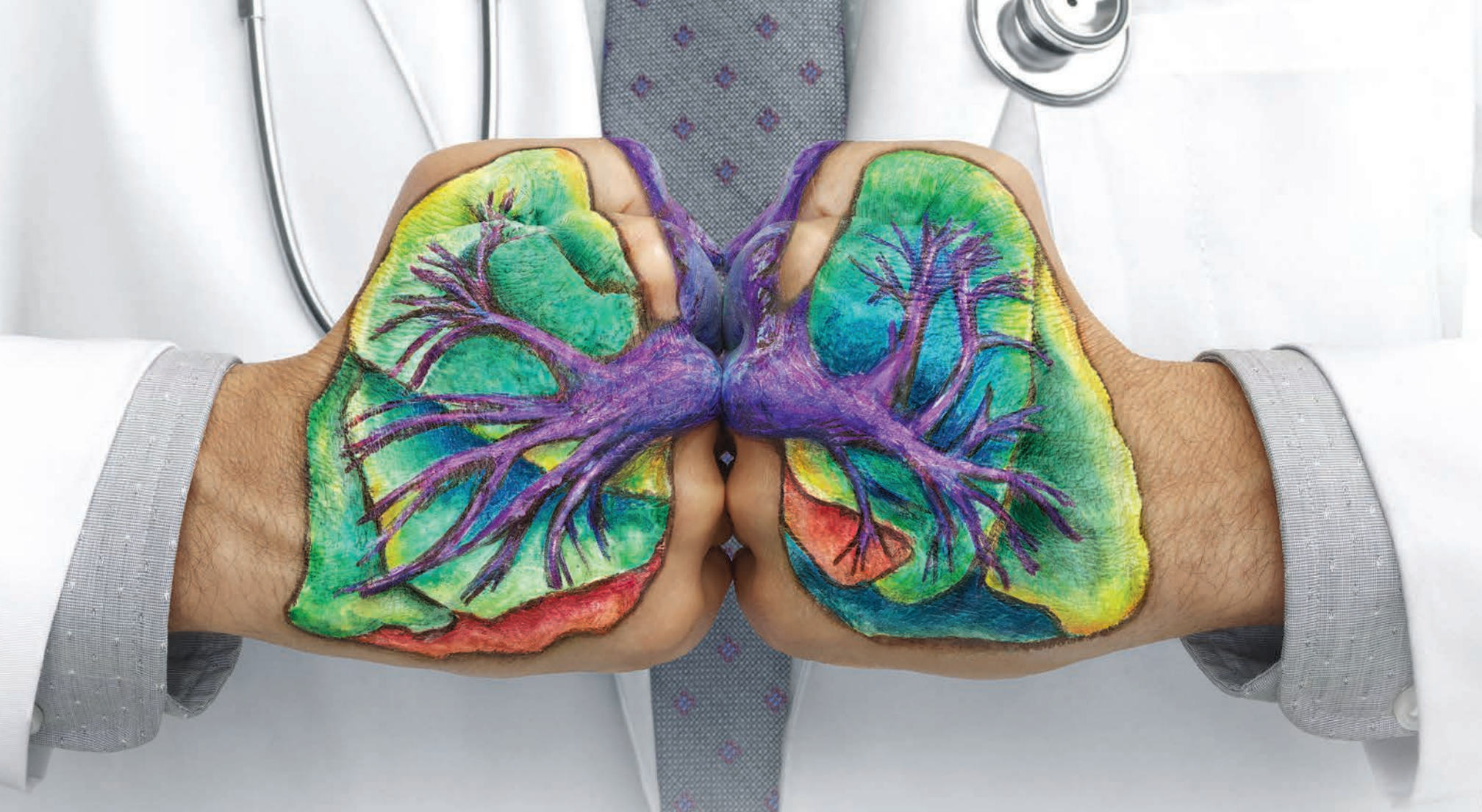

Indication

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

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Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. In some cases these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

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

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and

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pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal diseases requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

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

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

References: 1. Data on file. Genentech, Inc. 2016. **2.** Esbriet Prescribing Information. Genentech, Inc. January 2017. **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.

Learn more about Esbriet and how to access medication at EsbrietHCP.com

IPF=idiopathic pulmonary fibrosis.

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

†In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[2]

‡Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet® Inspiration Program™ motivates patients to stay on treatment.

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[2]

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Climate change is worsening allergies, expert says

BY THOMAS R. COLLINS
Frontline Medical News

ORLANDO – Climate change is not just eroding coastlines and threatening seaside cities and taking lives with increasingly powerful hurricanes, but appears to be contributing to increases in allergy and asthma, an expert told the audience at the joint congress of the American Academy of Allergy, Asthma, and Immunology and the World Asthma Organization.

Longer pollen seasons, allergens unleashed by felled trees and ripped-up plants, mold growth following floods, and irritants launched into the air by wildfires are some of the concerns that should be alarming physicians and policy makers, said Nelson A. Rosario, MD, PhD, professor of pediatrics at Federal University of Paraná (Brazil).

"This is related to disease," he said. "I'm trying to convince you that something is happening. This is not a matter of believe it or not."

And evidence suggests that his fellow allergists and their patients agree.

A 2015 international survey found that 80% of rhinitis patients blamed climate change for contributing to their symptoms.

GILITUKHA/THINKSTOCK

In a survey published in 2016, 63% of AAAAI members said that climate change was relevant to patient care either "a great deal" or in "a moderate amount." Only 11% said that climate change wasn't relevant at all. Asked how patients have been affected by climate change, about two-thirds said "increased care for allergic sensitization and symptoms on exposure to plants or mold."

Science supports these views, Dr. Rosario said.

A 2011 study of North American pollen seasons found that some cities had significant increases of 11-27 days, compared with 15 years before.

DR. ROSARIO

This year, a New England Journal of Medicine (2018 Mar 8;378[10]:881-3) article pointed out the respiratory dangers of increasing wildfires, noting the carbon dioxide, particulate matter, trace minerals, and thousands of other compounds that are unleashed.

"This is related to disease. ... This is not a matter of believe it or not," Dr. Rosario said.

And a 2017 review noted the impacts of the consequences of climate change, from increased allergies due to heavy precipitation events, asthma prompted by intense tropical cyclones, and allergic conditions caused by extremely high sea levels.

Dr. Rosario suggested that, rather than wait for official agencies to take action, physicians need to adapt and help their patients adapt. A team of doctors wrote in 2013 that while "improved governmental controls" could lead to cleaner air, they "meet strong opposition because of their effect on business and productivity." So, they said, the allergy community should adjust, by "anticipating the needs of patients and by adopting practices and research methods to meet changing environmental conditions."

Dr. Rosario urged physicians to think of the climate-change effects on allergy and asthma as a "collective action" problem, not an individual one.

"The consequences will come," he said. "There must be international cooperation."

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Jim Varney/Science Source

Workplace violence // continued from page 1

In all, Dr. Kaplan listed 19 steps that facilities could take to avert a planned attack, drawing in part on recommendations from the FBI publication, Workplace violence: Issues in response.

"This is a lot, and you don't need to do all of it," Dr. Kaplan said. "But you need to have an internally consistent plan for how you will do this at your facility, and it must involve everyone. They all need to be able to be part of your team."

Recent data on workplace violence

The latest data show that the great majority of workplace violence is perpetrated by individuals outside the organization. According to the International Association for Healthcare Security and Safety Foundation 2017 Healthcare Crime Survey, 89% of events involved a customer or patient of the workplace or employees.

In-hospital violence is prevalent, according to 2016 data from Occupational Safety and Health Administration that identified 24,000 workplace assaults in a 3-year span covering 2013-2015, including 33 homicides, 30 assaults, and 74 rapes.

Many in-hospital incidents are marked by failures in communication, patient observation, noncompliance with workplace violence policies or lack of such policies, and perhaps most importantly, an inadequate assessment for the violent potential of the perpetrator, according to Dr. Kaplan.

In a 2017 survey of 150 trauma nurses, 67% said they had been the victim of physical violence at work, though many did not report the incidents, Dr. Kaplan noted. Some reasons nurses gave for not reporting violence included the feeling that it was "just part of the job" in 27% of cases, and concerns about patient satisfaction scores in 10% of the cases.

Active-shooter events in the workplace are of particular concern, though they are relatively rare; one recent report identified 160 events that occurred during 2000-2013 in which 1,043 individuals were injured, according to Dr. Kaplan.

Other presentations in the late-breaking session covered issues related to disaster preparedness and the Charlie Gard case.

"We picked these three topics to be in a late-breaker session not only because of the recent events that had happened, but because they have a common thread – it's not a matter of if it will happen, but when will it happen, and are you ready and how do we prepare," said session chair Gloria M. Rodriguez Vega, MD.

"One of the things I learned as a fellow was that part of the success in critical care was attention to detail and layers of safety," said Dr. Rodriguez Vega, an intensivist in Bayamon, Puerto Rico. "I think you can apply that to all these situations."

Dr. Kaplan had no industry disclosures related to his presentation.

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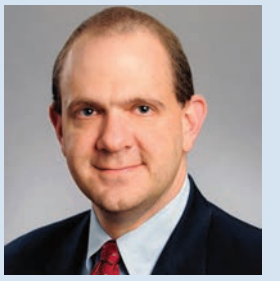

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434,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

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ICU corticosteroid insufficiency guidelines explained

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – When corticosteroids are used for septic shock, the dose should be low to moderate, the timing should be early, and the duration should be at least 3 days, said a speaker at the Critical Care Congress sponsored by the Society for Critical Care.

Dosing, timing, and duration are "three critical questions" critical care specialists face that are answered by the new critical illness–related corticosteroid insufficiency (CIRCI) guidelines, continued Stephen M. Pastores, MD, a cochair of the task force that developed guidelines for the diagnosis and management of CIRCI in critically ill patients.

The recently published guidelines come in two parts. The first takes into account the most current evidence on the use of corticosteroids in disorders that most clinicians associate with CIRCI, including sepsis/septic shock, acute respiratory distress syndrome, and major trauma (Crit Care Med. 2017 Dec;45[12]:2078-88). Part two of the guidelines, published separately, covers other syndromes, such as influenza, meningitis, burns, and other conditions that at least 80% of the task force members agreed were associated with CIRCI (Crit Care Med. 2018 Jan;46[1]:146-8).

During his presentation, Dr. Pastores limited his remarks to discussion of sepsis and septic shock with corticosteroids. He cautioned that, despite careful deliberations by the panel, the level of evidence behind some of the recommendations was "low to moderate and never high" and that not all task force members agreed with all recommendations.

"There were a lot of back and forth disagreements behind these recommendations," said Dr. Pastores, who is the director of the critical care medicine fellowship training and research programs at Memorial Sloan Kettering Cancer Center, New York. "We only required 80% of the panelists to agree that these were the recommendations and statements that we were going to go by."

The guidelines recommend against the use of corticosteroids in adult patients who have sepsis without shock, Dr. Pastores noted.

In contrast, the guidelines do suggest using corticosteroids for hospitalized adults patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy.

In an analysis of available data from randomized clinical trials including patients with septic shock, corticosteroids significantly reduced 28-day mortality when compared with placebo, Dr. Pastores said.

That survival benefit seems to be dependent on several factors: dose of the corticosteroids (hydrocortisone less than 400 mg/day), longer duration (at least 3 or more days), and severity of sepsis. "The more severe the sepsis, the more septic shock the patient was in, the more likely the corticosteroids were likely to help those patients," Dr. Pastores explained.

Accordingly, the guidelines further suggest using long-course, low-dose corticosteroid treatment, namely intravenous hydrocortisone at no more than 400 mg/day for at least 3 days.

The expert panel specifically recommended hydrocortisone as the corticosteroid of choice in this setting, according to Dr. Pastores. That recommendation was based in part on a recent systematic review and meta-analysis showing that hydrocortisone, given as a bolus or an infusion, was more likely than placebo or methylprednisolone to result in shock reversal.

Dr. Pastores reported disclosures related to Theravance Biopharma, Bayer HealthCare Pharmaceuticals, Spectral Diagnostics, and Asahi-Kasei.

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Prehospital antibiotics

// continued from page 1

Medicine.

The intervention group received antibiotics a median of 26 minutes prior to emergency department arrival. In the usual care group, median time to antibiotics after ED arrival was 70 minutes, versus 93 minutes prior to the sepsis recognition training ($P = .142$), the report further says.

"We do not advise prehospital antibiotics at the moment for patients with suspected sepsis," Dr. Nanayakkara said, during his presentation at the conference.

Other countries might see different results, he cautioned.

In the Netherlands, ambulances reach the emergency scene within 15 minutes 93% of the time, and the average time from dispatch call to ED arrival is 40 minutes, Dr. Nanayakkara noted in the report.

"In part, due to the relatively short response times in the Netherlands, we don't know if there are other countries with longer response times that would have other results, and whether they should use antibiotics in their ambulances," Dr. Nanayakkara said in his presentation.

The study was the first-ever prospective randomized, controlled open-label trial to compare early prehospital antibiotics with standard care.

Before the study was started, EMS personnel at 10 large regional ambulance services serving 34 secondary or tertiary hospitals were trained in recognizing sepsis, the report says.

A total of 2,672 patients with suspected sepsis were included in the intention-to-treat analysis, of whom 1,535 were randomized to receive prehospital antibiotics and 1,137 to usual EMS care, which consisted of fluid resuscitation and supplementary oxygen.

ANDREW D. BOWSER/FRONTLINE MEDICAL NEWS

"[We] don't know if there are other countries with longer response times that would have other results, and whether they should use antibiotics in their ambulances," Dr. Prabath Nanayakkara (left) noted.

The primary end point of the study was all-cause mortality at 28 days.

The negative mortality results of this trial are "not surprising," given that the trial's inclusion criteria allowed individuals with suspected infection but without organ dysfunction, said Jean-Louis Vincent, MD, PhD, of Erasmus Hospital, Brussels, in a related editorial appearing in the Lancet Respiratory Medicine (2018 Jan. doi: 10.1016/S2213-2600[17]30446-0).

Recent consensus definitions of sepsis recognize that sepsis is the association of an infection with some degree of organ dysfunction, according to Dr. Vincent.

"After this initial experience, I believe that a randomized, controlled trial could be done to assess the potential benefit of early antibiotic administration in the ambulance for patients with organ dysfunction associated with infection," Dr. Vincent wrote in his editorial.

Dr. Nanayakkara and his coauthors declared no competing interests related to their study.

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SOURCE: Alam N et al. Lancet Respir Med. 2018 Jan;6(1):40-50.

FDA proposes lower nicotine levels in cigarettes

BY GREGORY TWACHTMAN
Frontline Medical News

Nicotine levels in cigarettes could see a significant reduction under regulatory options being considered by the Food and Drug Administration.

Cigarettes "are the only legal consumer product that, when used as intended, will kill half all long-term users," FDA Commissioner Scott Gottlieb, MD, said in a statement announcing the effort.

The agency is seeking comment on a proposed regulation regarding "a potential maximum nicotine level that would be appropriate for the protection of public health, in light of scientific evidence about the addictive properties of nicotine in cigarettes." An advance notice of proposed rule making was posted online March 15 and published in the Federal Register on March 16.

The FDA also is seeking comments on a number of other areas to help inform potential regulatory action down the road, including whether a new standard for lower nicotine levels should be implemented at once or whether a phased-in approach should be taken; whether FDA should specify a method for manufacturers to use in order to detect nicotine levels in their products; and whether the proposed lower level is technically achievable.

The agency also is seeking comment on potential unintended effects of lowering the amount of nicotine in cigarettes, such as turning to other combustible tobacco products including cigars in conjunction with or as a replacement for cigarette use; increasing the number of cigarettes smoked; or seeking comparable nicotine from noncombustible tobacco sources.


RICKY_68FR/FOTOLIA

At this time, FDA is not suggesting what the target might be on a specific nicotine level. While the advanced notice asks specifically about the "merits of nicotine levels like 0.3, 0.4, and 0.5 mg nicotine/g of tobacco filler," it is not suggesting that this is the range being considered.

"Not to prejudge any possible proposed rule that we would do or any possible level, that is the purpose of an advanced proposed rule making, but we share all the science that we are aware of, and we characterize the studies that have been done to date in trying to find out what that right level is," Mitch Zeller, director of the FDA Center for Tobacco Products, said during a March 15 press call.

He said that the FDA aiming to make sure the level is low enough that it cannot be compensated for by smoking more or inhaling deeper and holding the breath in longer, much like how smokers compensated when they smoked "light" cigarettes in the unregulated market.

Mr. Zeller said that seeking comments on those levels is based on the scientific evidence that is laid out in the advanced notice, but it is not necessarily foreshadowing where the standard will be set.

Drastically reducing the amount of nicotine in cigarettes is expected to significantly lower not only the number of people addicted to cigarettes but also the negative health effects of nicotine addiction, FDA experts wrote in a perspective piece published March 15 in the New England Journal of Medicine (doi: 10.1065/NEJMsr1714617).

"Our findings show that reducing the nicotine level in cigarettes has the potential to substantially reduce the enormous burden of smoking-related death and disease," Benjamin J. Apelberg, PhD, director of the Division of Population Health Science, Office of Science, within the FDA Center for Tobacco Products, and his colleagues, wrote in the report.

Modeling for the implementation of a lower nicotine level policy suggests that smoking prevalence will decline from a median of 12.8% in baseline scenario to a median of 10.8% within a year of implementation, with the increase related to smoking cessation.

"We estimate that approximately 5 million additional smokers would quit smoking within a year after implementation of the hypothetical policy," Dr. Apelberg and his colleagues wrote. "By 2060, smoking prevalence drops from 7.9% in the baseline scenario to 1.4% in the policy scenario."

Their analysis is based on a nicotine level that is "so low that there would not be enough nicotine available in cigarette tobacco for smokers to sustain addiction," they noted.

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FDA wants data on flavored tobacco products

BY GREGORY TWACHTMAN
Frontline Medical News

The Food and Drug Administration is seeking data on the role that flavors, including menthol, in tobacco products play in the initiation, use, and cessation of tobacco products, with an emphasis on how flavoring impacts young people.

"In the spirit of our commitment to preventing kids from using tobacco, we are taking a closer look at flavors in tobacco products to better understand their level of impact on youth initiation," FDA Commissioner Scott Gottlieb, MD, said in statement. It is important "that we also explore how flavors, under a properly regulated framework that protects youth, may also be helping some currently addicted adult cigarette smokers switch to certain noncombustible forms of tobacco products."

The agency issued an advance notice of proposed rule making March 20 that seeks information on flavoring in tobacco products to inform future policy making.

"Youth consistently report product flavoring as a leading reason for using tobacco products," Dr. Gottlieb noted. "In fact, there is evidence indicating that youth tobacco users who reported their first tobacco was flavored had a higher prevalence of current tobacco product use, compared to youth whose product was not flavored."

The advance notice calls for information across a number of areas, including the role of flavors other than tobacco in tobacco products; flavors and initiation and patterns of tobacco product use, particularly among youths and young adults; and flavors and cessation, dual-use, and relapse among current and former tobacco product users.

It also is seeking comment on whether standards should be set on tobacco flavoring, including whether there should a prohibition or restriction on flavors and to which types of products these standards should apply. The notice specifically asks about menthol and its role in cigarette initiation and whether limitations on menthol could lead to use of other tobacco products.

"Because almost 90% of adult smokers started smoking by the age of 18, it's imperative we look at new ways we can ensure that kids don't progress from experimentation to regular use," Commissioner Gottlieb said.

The American Heart Association called the action "long overdue."

"We encourage the FDA to quickly move beyond information gathering and develop a strong flavoring product standard," CEO Nancy Brown said in a statement. "There is already clear evidence that flavored tobacco products, including menthol, harm the public health. To make it worse, fruit- and candy-flavored e-cigarettes, cigars, and other tobacco products are highly attractive to kids and make it more likely that they will take up this addiction."

The action comes less than a week after FDA published an advance notice seeking information comments on reducing nicotine levels in cigarettes to help combat nicotine addiction.

The advance notice was published in March in the Federal Register.

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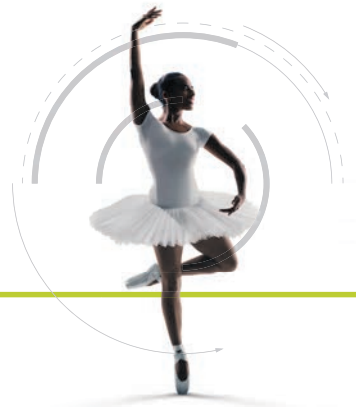
The majority of FEV_1 improvement occurred at:

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



SYMBICORT 160/4.5 for reducing COPD exacerbations

...THE CONTROL THEY NEED

REDUCTION IN COPD EXACERBATIONS

- In a 12-month exacerbation clinical trial (Study 4), SYMBICORT 160/4.5* significantly reduced the annual rate of moderate/severe COPD exacerbations by 35% vs formoterol (Estimate Rate Ratio=0.65; 95% CI: 0.53, 0.80; $p<.0001$)[3,4]
  - Annual rate estimate was 0.68 for SYMBICORT 160/4.5 mcg* (n=404) vs 1.05 for formoterol 4.5 mcg* (n=403)
- In a second exacerbation clinical trial of 6-month duration (Study 3), SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations by 26% vs formoterol (Estimate Rate Ratio=0.74; 95% CI: 0.61, 0.91; $p=.004$)[3,4]
  - Annual rate estimate was 0.94 for SYMBICORT 160/4.5 mcg* (n=606) vs 1.27 for formoterol 4.5 mcg* (n=613)

- The most common adverse reactions ≥3% reported in COPD lung function clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection. The safety findings from the two exacerbation clinical trials were consistent with the lung function studies

Please see additional Important Safety Information throughout and Brief Summary of full Prescribing Information on following pages.

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (CONT'D)

- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the administration of ICS

Study Designs

Study 2 (SUN): A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg, SYMBICORT pMDI 80/4.5 mcg, formoterol 4.5 mcg, and placebo, each administered as 2 inhalations twice daily. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1 (coprimary endpoints). The prespecified primary comparisons for predose FEV_1 were vs placebo and formoterol, and the primary comparison for 1-hour postdose was vs placebo.

Comparator Arms in the SUN Study

Mean improvement in 1-hour postdose FEV_1 (mL/%) over 12 months (serial spirometry subset)

Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%)

6 months: SYMBICORT 160/4.5 mcg (270 mL/28%), formoterol 4.5 mcg (200 mL/23%), placebo (60 mL/7%)

End of month 12 (last observation carried forward [LOCF]): SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (170 mL/19%), placebo (30 mL/5%)

SYMBICORT 160/4.5 mcg* (n=121), formoterol 4.5 mcg* (n=124), placebo* (n=125)

Study 3 (RISE): A 6-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 1219 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg with formoterol 4.5 mcg, each administered as 2 inhalations twice daily. This study was designed to assess the annual rate of moderate and severe COPD exacerbations for SYMBICORT vs formoterol.

Study 4: A 12-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 811 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg with formoterol 4.5 mcg, each administered as 2 inhalations twice daily. This study was designed to assess the annual rate of COPD exacerbations for SYMBICORT vs formoterol.

Exacerbation Definitions

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

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

- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients

Symbicort® 160/4.5

(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

A reassuring sense of control

IMPORTANT SAFETY INFORMATION (CONT'D)

- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to ICS. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available ICS
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of ICS may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of ICS, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts
- In rare cases, patients on ICS may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

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

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

References: 1. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. **2.** Data on File, REF-4960, AZPLP. **3.** SYMBICORT [package insert]. Wilmington, DE: AstraZeneca; December 2017. **4.** Data on File, REF-16658, AZPLP.

AstraZeneca

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

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

INDICATIONS AND USAGE

Treatment of Asthma

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

SYMBICORT should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitations of Use:

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

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

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

Important Limitations of Use:

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

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

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

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

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

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

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist

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

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

Salmeterol Multicenter Asthma Research Trial (SMART)

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

Formoterol Monotherapy Studies

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

Deterioration of Disease and Acute Episodes

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

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of SYMBICORT and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

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

Pneumonia and Other Lower Respiratory Tract Infections

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

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

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

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

Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

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

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

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

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

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

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

Effect on Growth

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

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

Glaucoma and Cataracts

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

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

Eosinophilic Conditions and Churg-Strauss Syndrome

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

LABA use may result in the following:

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

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

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

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

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

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

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

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

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

Pediatric Patients 6 to Less than 12 Years of Age

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

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

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

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

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

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

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

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

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

Postmarketing Experience

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

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

DRUG INTERACTIONS

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

Inhibitors of Cytochrome P4503A4

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

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

Beta-Adrenergic Receptor Blocking Agents

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

Diuretics

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

OVERDOSAGE

SYMBICORT

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

Budesonide

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

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France Rev. 12/2017 US-17406 1/18

Different OSA subtypes respond differently to therapy

BY MADHU RAJARAMAN
Frontline Medical News

Patients with obstructive sleep apnea can be grouped into distinct clinical subtypes that differ in response to positive airway pressure treatment, according to two studies published in the March issue of the journal Sleep.

In the first study, investigators evaluated whether patients in different clinical clusters responded differently to positive airway pressure (PAP) treatment. Authors identified 706 patients with moderate to severe obstructive sleep apnea (OSA) from the Icelandic Sleep Apnea Cohort. All patients completed a sleep study prior to starting PAP treatment, and completed questionnaires to assess symptoms. Patients were grouped into one of three clusters based on symptomatology: disturbed sleep, minimally symptomatic, or sleepy, wrote Grace W. Pien, MD, of the division of pulmonary and critical care medicine at Johns Hopkins University, Baltimore, and her coauthors.

PAP adherence was assessed using questionnaires and PAP device memory card data. At the 2-year follow-up, 457 (64.7%) patients reported PAP adherence. Objective adherence measures were available for 351 (76.8%) patients; for the remainder, PAP adherence was determined using self-reported data. Patients in the sleepy cluster were more likely than the other two subtypes to be PAP users at 70.0% usage, compared with 61.1% of those in the disturbed-sleep group and 60.0% in the minimally symptomatic group (P = .034), the authors said in Sleep.

Patients in the minimally symptomatic cluster reported symptoms at lower rates than patients in the other clusters at baseline, and they remained relatively asymptomatic at follow-up, the authors noted. By comparison, patients in the sleepy group reported the highest Epworth Sleepiness Scale scores at baseline (16.0 plus or minus 3.4), which fell by five points at follow-up (mean change, −5.3; 95% confidence interval, −5.8 to −4.8). Also, patients in the sleepy group reported higher rates of drowsy driving (37.8%) at baseline, which dropped to 8.1% at follow-up (odds ratio, 0.06; 95% CI, 0.03-0.14).

At baseline, the disturbed-sleep group reported mainly insomnia-related symptoms, including difficulty falling asleep (43.2%), waking often at night (90.8%), restless sleep (74.2%), and waking up early (62.3%). At follow-up, improvements in the frequency of insomnia-related symptoms ranged from 0.28 to 1.25 points, and Epworth Sleepiness Scale scores fell significantly (−2.06; 95% CI, −2.64 to −1.48). Reductions in the proportion of patients with insomnia symptoms ranged from 13.1% (OR, 0.35; 95% CI, 0.20-0.59) for difficulty falling asleep to 39.0% (OR, 0.08; 95% CI, 0.04-0.14) for restless sleep, the researchers noted.

The results "demonstrate that although symptoms improved overall among each of the three clinical phenotypes of moderate to severe OSA, patterns of treatment response … varied based on initial clinical presentation," the authors wrote. "Our findings underscore the need to consider initial OSA phenotype when designing future trials."

In the second study, also published in Sleep, investigators confirmed the three clinical OSA subtypes previously identified in the Icelandic Sleep Apnea Cohort. In analysis of an international sample, they also expanded these clusters to include two additional disease subtypes. One of these subtypes consisted of patients with symptoms dominated by indications of upper airway obstruction. The other new subtype, sleepiness dominant OSA, included patients who had excessive sleepiness but no symptoms of upper airway obstruction.

The study authors performed a cluster analysis using data from 972 patients from the Sleep Apnea Global Interdisciplinary Consortium with moderate to severe OSA, with 215 of these patients being from Iceland.

In total, 688 (70.8%) patients were diagnosed using laboratory-based polysomnography and 284 (29.2%) with home-based sleep studies. Patients completed questionnaires related to symptoms including sleepiness, insomnia, sleep disturbance, abnormal behaviors during sleep, upper airway symptoms, and other symptoms such as headaches and excessive sweating, wrote Brendan T. Keenan, of the University of Pennsylvania, Philadelphia, and his coauthors.

In the Icelandic group, results identified 72 (33.5%) patients in the disturbed-sleep cluster, 62 (28.8%) in the minimally symptomatic cluster, and 81 (37.7%) in the excessively sleepy cluster, similar to prior research. The three subtypes were found in the international sample of patients as well, with 150 (19.8%) in the disturbed-sleep cluster, 306 (40.4%) in the minimally symptomatic cluster, and 301 (39.8%) in the excessively sleepy cluster.

Both studies were funded by the National Institutes of Health.

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SOURCES: Pien GW et al. Sleep. 2018 Mar. doi: 10.1093/sleep/zsx201; Keenan BT et al. Sleep. 2018 Mar. doi: 10.1093/sleep/zsx214.

VIEW ON THE NEWS

Results underscore importance of personalized treatment

The results of these studies "advance the personalization of sleep apnea care by validating distinct symptom-based groups that generalize across nations and assessing how members of these clinical phenotypes respond to therapy," wrote Vishesh K. Kapur, MD, of the division of pulmonary, critical care and sleep medicine at the University of Washington, Seattle, in an editorial published in the March issue of Sleep (2018 Mar. doi: 10.1093/sleep/zsy042).

"Patients with OSA differ in their presenting symptoms," he said, and future studies should aim to "elucidate whether the proposed phenotypes will enable a more personalized paradigm of sleep apnea care that results in better tailored and more effective care."

Dr. Kapur did not report any relevant disclosures.

Effectiveness, adherence similar for nasal pillows and standard masks

BY MADHU RAJARAMAN
Frontline Medical News

Nasal pillows showed equal long-term efficacy as standard nasal masks and both tools were used equally in patients treated with continuous positive airway pressure therapy, according to results of a study.

In a retrospective observational study of 144 patients with obstructive sleep apnea, respiratory measures including apnea-hypopnea index (AHI), oxygen desaturation index, mean oxygen saturation, and Epworth Sleepiness scale scores did not differ between the two treatment groups at baseline and during a 12-month follow-up appointment. Treatment adherence was also similar between the two groups, reported Andrea Lanza of the Sleep Medicine Center at Niguarda Hospital in Milan and coauthors in Sleep Medicine.

Patients received continuous positive airway pressure (CPAP) treatment between May 2012 and September 2014, and were assigned to one of two groups based on their choice of treatment. Initially, 102 opted for nasal pillows (Group P), and 42 chose the standard nasal mask (Group N). Patients who either changed masks or add-

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ed a new one during titration or follow-up were assigned to a third group, Group C.

AHI did not differ significantly between groups at baseline or follow-up. In Group P, mean AHI at titration was 1.2 events per hour, compared with 1.8 in Group N and 1.9 in Group C ($P = .109$). At follow-up, AHI was 0.7 in Group P, 1.1 in Group N, and 0.9 in Group C ($P = .172$). Oxygen desaturation index and oxygen saturation also remained similar between the groups at baseline and follow-up, the investigators reported.

Additionally, long-term adherence did not differ significantly between the groups, with mean daily CPAP usage of 5.5 hours per night in Group P, 5.3 in Group N, and 5.6 in Group C. Mean usage was less than 4 hours per night for 11.6% in group P, 18.5% in group N, and 13.9% in group C, the authors added.

The frequency of side effects occurring in patients in two of the groups were similar (49% in Group P, vs. 61% in Group N; $P = .212$), though the nature of the side effects differed. Nostril pain or burning was reported only by patients in the nasal pillows group, and skin breakdown was reported only in the nasal mask group.

Though nasal pillows have typically been reserved for patients who do not tolerate the standard mask, the results of this study suggest that "nasal pillows could be safely prescribed as first-line interfaces," the authors wrote. "They seem to be efficacious for CPAP titration and long-term treatment, ensuring a good rate of adherence."

All of the authors reported having no disclosures.

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SOURCE: Lanza A et al. Sleep Med. 2018 Jan;41:94-9.

VIEW ON THE NEWS

Retitration may be necessary with mask changes

These results add to the body of evidence about the efficacy of nasal pillows and nasal masks. Future research should address the need for retitration when changing mask type, said Matthew R. Ebben, PhD, associate clinical professor at Cornell University, New York, in an editorial published with the study in Sleep Medicine.

"Many working in the field of sleep medicine continue to be unaware that differences in efficacy exist between mask styles, particularly in cases of moderate to severe obstructive sleep apnea," he wrote.

"New clinical practice guidelines are needed to promote the necessity for PAP [positive airway pressure] retitration when changes in mask style are required," he added. "Ensuring that PAP therapy is as effective as possible will reduce the need for patients and clinicians to investigate other treatment options for obstructive sleep apnea, which may be both less effective and have an inferior side effect profile compared to PAP treatment."

Intermittent dosing cuts time to extubation for surgical patients

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – Intermittent administration of sedation and analgesia significantly reduced mechanical ventilation time among surgical patients requiring ventilation, according to a preliminary analysis of a randomized trial.

Additionally, the researchers found that much lower amounts of sedation and analgesia were given to patients who underwent intermittent dosing, compared with patients who received a continuous infusion.

Lead investigator Nicholas Sich, MD, presented these findings of the SATIRE trial (Sedation Administration Timing: Intermittent Dosing Reduces Times to Extubation), at the Critical Care Congress sponsored by the Society for Critical Care Medicine. Dr. Sich's study was a 2-year, single-blinded, randomized, controlled trial of surgical patients requiring ventilation.

Of the 95 patients in the trial, 39 were randomized to intermittent dosing and 56 to the control group of continuous infusion, with the drugs midazolam and fentanyl having been given to both groups.

Mean mechanical ventilation time was 65 hours in the intermittent-dosing arm versus 111 hours in the continuous-infusion arm (*P* less than .03), noted Dr. Sich, a fourth-year general surgery resident at Abington (Pa.) Memorial Hospital, during his presentation.

"This is a new way to use an old drug, and it really might be beneficial, and can even be used as first-line therapy and a way to keep patients awake and off the ventilator," said Dr. Sich.

Patients in the continuous-infusions arm of the trial received a mean of 73.1 mg of midazolam, compared with 18 mg for the intermittent-dosing arm, a difference that approached very closely to statistical significance (*P* = .06) and was thrown off in the latest iteration by an outlier, Dr. Sich explained. The relative difference between the mean fentanyl doses administered was even greater between the two groups, with 5,848 mcg given to patients in the control group, versus the 942 mcg given to participants in the intermittent-dosing group (*P* less than 0.01).

"This is a new way to use an old drug, and it really might be beneficial, and can even be used as first-line therapy and a way to keep patients awake and off the ventilator," said Dr. Sich, referring to the intermittent dosing. Continuous infusions leave patients oversedated and prolong ventilation time.

"What we propose, rather, is using a sliding-scale intermittent pain and sedation regimen," he said. "We believe that it won't compromise patient care and won't compromise patient comfort, and it will lead to shorter mechanical ventilation times for surgical patients than continuous infusions."

Dr. Sich also pointed out that there was no difference in time spent at target levels of sedation and analgesia between the two trial groups. Referring to this finding, he noted that "we wanted to make sure that in the intermittent arm we're giving them less drug, but we don't want them to be [less comfortable]."

One potential drawback to the intermittent-dosing approach is that it is more nursing intensive, according to Dr. Sich, since it is based on a nursing treatment protocol to give medications every hour.

Intermittent dosing is "more hands-on" than a typical continuous-infusion approach and so was more challenging for nurses who, per the treatment protocol, had to give medications every hour, he explained. However, "when they saw the data in the months and year as we've been going on, they're actually quite proud of our work and their work."

Gilman Baker Allen, MD, a pulmonologist and intensivist at the University of Vermont Medical Center, Burlington, said the study was "terrific work" and acknowledged the importance of gauging nurse satisfaction with the protocol.

"I think that when you feed this kind of data back to nursing staff, they may not be satisfied with the intensity of the work, but when they see the rewards at the end, it oftentimes is a very positive experience," said Dr. Allen, who moderated the session.

Dr. Sich and his colleagues had no financial disclosures or conflicts of interest related to the study.

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SOURCE: Sich N et al. CCC47, Abstract 18.

Haloperidol does not prevent delirium in ICU patients

BY M. ALEXANDER OTTO
Frontline Medical News

Prophylactic haloperidol did not prevent delirium or improve survival in a placebo-controlled trial of 1,789 critically ill adults at 21 ICUs in the Netherlands.

Haloperidol is used routinely in ICUs to both treat and prevent delirium, which strikes up to half of ICU patients and is associated with prolonged mechanical ventilation, longer ICU and hospital stays, and increased mortality. Results of past studies have been mixed, with some showing a benefit for haloperidol in the ICU and others not.

"These findings do not support the use of prophylactic haloperidol in critically ill adults," said the authors of a new study, led by Mark van den Boogaard, PhD, of Radboud University Medical Center, Nijmegen, the Netherlands (JAMA. 2018 Feb 20;319[7]:680-90).

The subjects were all expected to be in the ICU for at least 2 days, and were not delirious at baseline. The patients were randomly assigned to receive one of two treatments or a placebo three

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VIEW ON THE NEWS

Nondrug options may be the key

The study has demonstrated that, in critically ill patients currently receiving best-practice nonpharmacological interventions to prevent delirium, the addition of haloperidol does not improve survival nor reduce the incidence of delirium or the harms associated with delirium. The findings challenge the current model that the addition of psychoactive medication to patients who are already receiving multiple interventions may be beneficial. Prophylactic haloperidol is not the solution for the complex problem of delirium in critically ill patients. It may be that no single pharmacological intervention can provide a solution.

Future research is warranted into nonpharmacological interventions. They generally involve either doing less for patients (avoiding excessive sedation, benzodiazepines, nocturnal noise, and stimulation) or ensuring the continued provision of relatively simple therapies (mobilization, maintaining a day-night schedule, and noise reduction). Although some of these interventions may require planning and cooperation of a multidisciplinary team, a strength of ICU care in general, other interventions may be as simple as providing earplugs and eye patches to improve sleep.

Anthony Delaney, MD, PhD, is associate professor of intensive care medicine at the University of Sydney. Naomi Hammond, PhD, is a research fellow and senior lecturer at the University of New South Wales, Sydney. Edward Litton, MD, PhD, is an intensive care specialist in Perth, Australia. They made their comments in a JAMA editorial, and had no disclosures (JAMA. 2018 Feb 20;319[7]:659-60).

On-demand nebulization in ICU equivalent to standard

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – Among ICU patients receiving invasive ventilation, on-demand nebulization of acetylcysteine or salbutamol was noninferior to routine nebulization with both medications, according to the results of a randomized clinical trial presented by Frederique Paulus, RN, PhD.

ANDREW BOWSER/FRONTLINE MEDICAL NEWS

"On-demand nebulization was noninferior to routine nebulization, but routine nebulization is associated with more side effects," said Dr. Frederique Paulus.

In this study, adverse events such as tachyarrhythmia and agitation were less frequent with the on-demand approach, in which patients receive nebulization based on strict clinical indications, Dr. Paulus reported at the Critical Care Congress sponsored by the Society for Critical Care Medicine. The study was published simultaneously in JAMA.

"On-demand nebulization was noninferior to routine nebulization, but routine nebulization is associated with more side effects, so we think on-demand nebulization may be a reasonable alternative to routine nebulization," said Dr. Paulus of the department of intensive care at the Academic Medical Center, University of Amsterdam, during her presentation.

The on-demand approach may also be cost saving, she noted, citing an economic analysis underway that is not yet ready for publication.

"In our ICU, it will save us 350,000 Euros a year," she said. "In the Netherlands, 40,000 patients will be mechanically ventilated in a year, so it will save us millions in the Netherlands alone."

The study included adult ICU patients who were expected not to be extubated for at least 24 hours. Dr. Paulus presented the primary analysis of the study, which included data for 922 patients who were randomized either to the on-demand group (n = 455) or the routine nebulization group (n = 467) and completed follow-up.

Patients assigned to the on-demand group received acetylcysteine-containing solutions if they had thick or tenacious secretions, or salbutamol-containing solutions if wheezing was observed or suspected or when findings were suggestive of lower-airway obstruction, according to the paper, published in JAMA.

The primary outcome, number of ventilator-free days at day 28 of the study, was noninferior in the on-demand group versus the routine group, Dr. Paulus said.

The median number of ventilator-free days was 21 for the on-demand group and 20 for the routine group, said the paper.

The length of stay, mortality, and proportion of patients developing pulmonary complications did not differ between the two study arms, the investigators also reported in JAMA.

However, adverse events occurred in just 13.8% of the on-demand group, compared with 29.3% of the routine group (*P* less than .001), with the difference in adverse events mainly attributable to less tachyarrhythmia and agitation in the experimental group, according to the researchers.

Dr. Paulus and coauthors reported no conflicts of interest related to the study.

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SOURCE: van Meenen DMP et al. JAMA. 2018 Feb. doi: 10.1001/jama.2018.0949.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: I would not say there is necessarily a standard way people do this, and practice patterns likely vary widely. There are some places where respiratory therapy has wide control of vented patients and often implements protocols, while at other places every vented patient has to have specific orders for things by the providers. I would find it very likely that more patients receive standing bronchodilator therapy than should (thus the reason for the study). Our practice pattern locally mirrors the idea of the study (where a patient's therapy is tailored to the reason for their intubation).

I would suspect local practice patterns with nebulized acytylcysteine to vary even more widely than bronchodilator administration strategies.

Continued from previous page

times daily, with 350 receiving 1 mg of haloperidol; 732 receiving 2 mg of haloperidol; and 707 receiving a 0.9% sodium chloride placebo. The 1-mg haloperidol arm was stopped early because of futility.

The ICUs also used nonpharmacologic interventions to prevent delirium, including early mobilization and noise reduction.

There was no statistically significant difference in survival at the primary endpoint of 28 days following entrance into the study. At that point, 83.3% of the patients who received 2-mg doses of haloperidol and 82.7% of the of the subjects who received the placebo were alive (absolute difference, 0.6%; 95% confidence interval, –3.4% to 4.6%).

Prophylactic haloperidol had no effect on reducing the incidence of delirium, which was diagnosed in 33.3% of haloperidol subjects and 33.0% of placebo patients. Likewise, there were no significant differences between the groups in the number of delirium-free and coma-free days, duration of mechanical ventilation, and ICU and hospital length of stay. The number of reported adverse events with treatment also did not differ significantly between the groups: 0.3% in the 2-mg haloperidol group versus 0.1% in the placebo arm.

The duration of prophylactic therapy was a median of 2 days, but a subgroup analysis in patients treated for more than 2 days also did not show any benefits with haloperidol.

DR. OUELLETTE

"The study population included severely ill ICU adults whose brains may have been too seriously affected for haloperidol to exert a prophylactic effect, since in non-ICU adults, prophylactic haloperidol may have beneficial effects. But the subgroup of patients with a low severity of illness score also demonstrated no beneficial effects," the investigators said.

Subjects were a mean of 66.6 years old; 61.4% were men. Most of the ICU admissions were urgent and for medical or surgical reasons.

"Delirium and other problems of cognition are important epi-phenomenon of critical illness. Not only do these conditions obstruct management and impair recovery, but they may have long term sequelae," noted Daniel Ouellette, MD, FCCP, of the Henry Ford Hospital in Detroit and member of *CHEST Physician*'s editorial advisory board, in an interview. "My hospital has developed protocols based on best evidence to provide pain relief and sedation to critically ill patients in order to avoid these problems. The use of haloperidol as a prophylactic agent for delirium is an intriguing idea; unfortunately early research does not show that it benefits patients."

He added, "When I was a resident in medicine in the ICU during the 1980s, I was taught that we should reduce ICU noise to allow for rest, orient our patients to a day/night cycle, and provide for early mobilization. Those teachings are still important!"

This study was supported by ZonMw, the Netherlands Organization for Health Research and Development. Dr. van den Boogaard had no disclosures. One author reported grants and consultant and speaker fees from Pfizer, Merck, Astellas, and Gilead, among others.

aotto@frontlinemedcom.com

SOURCE: van den Boogaard M et al. JAMA. 2018 Feb 20;319(7):680-90.

NOW AVAILABLE

THE ELIQUIS STARTER PACK
Designed to support DVT/PE treatment initiation

Not actual size.

IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.
  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Eliquis®
(apixaban) tablets

THE ELIQUIS STARTER PACK OFFERS YOUR PATIENTS:

- Their first **30-day supply** of ELIQUIS treatment complete with daily dosing instructions
- **2 separate wallets** per box
  - **Wallet 1** contains ELIQUIS treatment for days 1-14 along with directions on how to step down dosing after week 1
  - **Wallet 2** contains ELIQUIS treatment for days 15-30

DVT=deep vein thrombosis; PE=pulmonary embolism.

WARNINGS AND PRECAUTIONS (cont'd)

Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

- **Refill reminder:** prompts DVT/PE patients to refill their ELIQUIS prescription

No cost to eligible patients when using the ELIQUIS **Free Trial Offer***

For more information, speak to your ELIQUIS Sales Representative or visit hcp.eliquis.com

*Eligibility Requirements and Terms of Use apply.

INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

Please see Brief Summary of Full Prescribing Information, including **Boxed WARNINGS**, on the following pages.

432US1800647-02-01 03/18

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery— ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse the bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS (apixaban) have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions]*

Clinical Trials Experience

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

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.

† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).

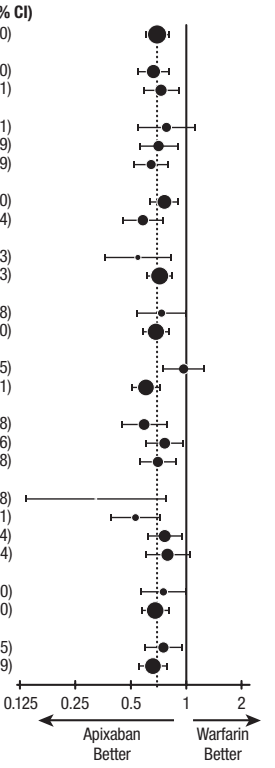
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).

§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma and catheter-site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1) in full Prescribing Information]*:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

Marketed by:
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Princeton, New Jersey 08543 USA
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New York, New York 10017 USA

Rev February 2018

432US1800289-03-01

Increasing sepsis survivorship creates new challenges

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – An upward trend in sepsis survivorship drove increases in sepsis survivors at risk for readmission and returns of these patients to the hospital via the emergency department, results of a retrospective, single-center analysis suggest.

ANDREW BOWSER/FRONTLINE MEDICAL NEWS

Dr. Mark E. Mikkelsen

The number of sepsis survivors at risk for hospital readmission rose substantially in recent years, according to the analysis of 17,256 adult medical and surgical admissions to University of Pennsylvania Health System hospitals between July 1, 2010, and June 30, 2015. The journal Critical Care Medicine published these results online as Mark E. Mikkelsen, MD, was presenting them at the Critical Care Congress sponsored by the Society for Critical Care Medicine.

While 30-day readmission rates declined modestly over the same time period, that decrease was offset by a rise in emergency department treat-and-release visits, explained Dr. Mikkelsen, who coauthored the study.

Over the time period that Dr. Mikkelsen and his colleagues analyzed, the proportion of sepsis hospitalizations more than doubled from 3.9% to 9.4%, while in-hospital mortality rates for sepsis hospitalizations fell from 24.1% to 14.8%. As a result, the proportion of discharged patients at risk for readmission increased from 2.7% to 7.8%, noted Dr. Mikkelsen, associate professor of medicine at the Hospital of the University of Pennsylvania, Philadelphia.

Thirty-day hospital readmission rates modestly declined from 26.4% to 23.1% over that time period, driven by reduced readmissions among survivors of nonsevere and non-pneumonia sepsis, Dr. Mikkelsen said. This decline in overall sepsis patient readmissions was offset by an increase in emergency department treat-and-release visits. Such visits rose from 2.8% in 2010 to a peak of 5.4% in 2014, Dr. Mikkelsen

explained. Generally, readmission rates for severe sepsis patients have not changed over time, he added.

"I anticipate that each and every hospital represented in this room will experience a similar phenomenon," he said. "Therefore, high-quality postdischarge care is in fact urgently needed," he added. "It is warranted that there is an international spotlight on sepsis beginning in the hospital but now continuing thereafter into the phase of life after sepsis."

These findings reflect "great sepsis survivorship" and suggest new challenges to address, said Timothy G. Buchman, MD, PhD, editor-in-chief of the Critical Care Medicine and past president of the Society for Critical Care Medicine.

"It's really extraordinary to see that the efforts that have been made by the Surviving Sepsis campaign have paid off," Dr. Buchman said in an interview. "Now we need to look much more carefully at both the readmission issues, as well as the consequences of long-term sepsis survivorship, not just on patients, but also on their families."

Dr. Mikkelsen and a study co-author received support for article research from the National Institutes of Health.

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SOURCE: Meyer N et al. Crit Care Med. 2018 Mar. doi: 10.1097/CCM.0000000000002872.

Corticosteroid combo cuts deaths in septic shock

BY IAN LACY
Frontline Medical News

Hydrocortisone in combination with fludrocortisone significantly reduced 90-day mortality in septic shock patients in a double-blind, randomized, controlled trial.

Prior to this study, two large trials had displayed that corticosteroids were beneficial in improving hemodynamic status and organ function, but little was known about corticosteroids' ability to increase survival in sepsis patients.

"[Corticosteroids] improve cardiovascular function by restoring effective blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance, an effect that is partly related to endothelial glucocorticoid receptors," wrote Djillali Annane,

MD, of the University of Paris and his colleagues in the New England Journal of Medicine. "This might explain why in our trial there was less need for vasopressors with hydrocortisone plus fludrocortisone than with placebo."

The study, named the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial, was designed to assess the benefit/risk ratio of using activated protein C – drotrecogin alfa (activated) – and corticosteroids together or separately in septic shock patients. The original design of the study included Xigris (drotrecogin alfa) and was composed of four parallel groups, but Xigris was removed from the market in October of 2011, so the study continued with only two parallel groups.

"[Corticosteroids] improve cardiovascular function by restoring effective blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance, an effect that is partly related to endothelial glucocorticoid receptors."

A total of 1,241 patients experiencing chronic septic shock were recruited into the two double-blind, parallel groups, with patients in one group receiving hydrocortisone plus fludrocortisone and the other receiving placebos. The placebos used in this study were similar in appearance to the actual treatment drugs. The placebos for hydrocortisone and fludrocortisone were either parenteral mannitol (133.6 mg), disodium phosphate (8.73 mg), and sodium phosphate (0.92 mg) or tablets of microcrystalline cellulose (59.098 mg), respectively.

Hydrocortisone was given intravenously every 6 hours as a 50-mg intravenous bolus, and fludrocortisone was given once a day as a 50-mcg tablet through a nasogastric tube. Patients in ICUs who had septic shock for less than 24 hours were included in the study. Septic shock was identified by the presence of a clinically or microbiologically documented infection, a Sequential Organ Failure Assessment score of 3 or 4 for at least two organs and for at least 6 hours, and receipt of vasopressor therapy for at least 6 hours.

DigitalVision/Thinkstock

After 90 days, 264 of 614 of the patients (43%) in the hydrocortisone/fludrocortisone group and almost half (49.1%) of 627 patients in the placebo group had died (P = .03). The relative risk of death was 0.88 (95% confidence interval, 0.78-0.99), which favored the hydrocortisone/fludrocortisone group. The researchers also observed that death was significantly lower in the hydrocortisone/fludrocortisone group, compared with the placebo group, at time of ICU discharge (35.4% vs. 41.0%, respectively; P = .04).

While mortality was reduced, patients still experienced adverse

Continued on following page

discontinuation due to an adverse reaction occurred in 3.7% (16/436) of patients receiving AVYCAZ and 3% (13/434) of patients receiving meropenem. There was no specific adverse reaction leading to discontinuation. Adverse reactions occurring at 5% or greater in patients receiving AVYCAZ were diarrhea and vomiting. **Table 11 lists selected adverse reactions occurring in 1% or more of patients receiving AVYCAZ and with incidences greater than the comparator in the Phase 3 HABP/VABP clinical trial. The first value is for AVYCAZ[a] (N=436). The second value is for Meropenem[b] (N=434). Gastrointestinal disorders:** Nausea: 3%, 2%. **Skin and subcutaneous tissue disorders:** Pruritis: 2%, 1%. [a] 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) IV over 120 minutes every 8 hours [b] 0.5 grams IV over 60 minutes every 8 hours. Other Adverse Reactions of AVYCAZ and Ceftazidime - The following selected adverse reactions were reported in AVYCAZ-treated patients at a rate of less than 1%in the Phase 3 trials and are not described elsewhere in the labeling. *Blood and lymphatic disorders* - Thrombocyto-penia, Thrombocytosis, Leukopenia; *General disorders and administration site conditions* - Injection site phlebitis; *Infections and infestations* - Candidiasis; *Investigations* - Increased aspartate aminotransferase, Increased alanine aminotransferase, Increased gamma-glutamyltransferase; *Metabolism and nutrition disorders* - Hypokalemia; *Nervous system disorders* - Dysgeusia; *Renal and urinary disorders* - Acute kidney injury, Renal impairment, Nephrolithiasis; *Skin and subcutaneous tissue disorders* - Rash, Rash maculo-papular, Urticaria; *Psychiatric disorders* - Anxiety. Additionally, adverse reactions reported with ceftazidime alone that were not reported in AVYCAZ-treated patients in the Phase 3 trials are listed below: *Blood and lymphatic disorders* - Agranulocytosis, Hemolytic anemia, Lymphocytosis, Neutropenia, Eosinophilia; *General disorders and administration site conditions* - Infusion site inflammation, Injection site hematoma, Injection site thrombosis; *Hepatobiliary disorders* – Jaundice; *Investigations* - Increased blood lactate dehydrogenase, Prolonged prothrombin time; *Nervous system disorders* - Paresthesia; *Renal and urinary disorders* - Tubulointerstitial nephritis; *Reproductive and breast disorders* - Vaginal inflammation*; Skin and subcutaneous tissue disorders* - Angioedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis. Laboratory Changes - In the Phase 3 trials, seroconversion from a negative to a positive direct Coombs' test result among patients with an initial negative Coombs' test and at least one follow up test occurred in 3.0% (cUTI), 12.9% (cIAI), and 21.4% (HABP/VABP) of patients receiving AVYCAZ and 0.9% (cUTI), 3% (cIAI) and 7% (HABP/VABP) of patients receiving a carbapenem comparator. No adverse reactions representing hemolytic anemia were reported in any treatment group.

DRUG INTERACTIONS: Probenecid - *In vitro*, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake from the blood compartment, and thereby its excretion. As a potent OAT inhibitor, probenecid inhibits OAT uptake of avibactam by 56% to 70% *in vitro* and, therefore, has the potential to decrease the elimination of avibactam when co-administered. Because a clinical interaction study of AVYCAZ or avibactam alone with probenecid has not been conducted, co-administration of AVYCAZ with probenecid is not recommended *[see Clinical Pharmacology in the full Prescribing Information]*. **Drug/Laboratory Test Interactions -** The administration of ceftazidime may result in a false-positive reaction for glucose in the urine with certain methods. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

USE IN SPECIFIC POPULATIONS: Pregnancy - Risk Summary - There are no adequate and well-controlled studies of AVYCAZ, ceftazidime, or avibactam in pregnant women. Neither ceftazidime nor avibactam were teratogenic in rats at doses 40 and 9 times the recommended human clinical dose. In the rabbit, at twice the exposure as seen at the human clinical dose, there were no effects on embryofetal development with avibactam. The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies within the general population. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed. Data - *Animal Data:* Ceftazidime - Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and showed no evidence of harm to the fetus due to ceftazidime. Avibactam - Avibactam was not teratogenic in rats or rabbits. In the rat, intravenous studies with 0, 250, 500 and 1000 mg/kg/day avibactam during gestation days 6-17 showed no embryofetal toxicity at doses up to 1000 mg/kg/day, approximately 9 times the human dose based on exposure (AUC). In a rat pre- and post-natal study at up to 825 mg/kg/day intravenously (11 times the human exposure based on AUC), there were no effects on pup growth and viability. A dose-related increase in the incidence of renal pelvic and ureter dilatation was observed in female weaning pups that was not associated with pathological changes to renal parenchyma or renal function, with renal pelvic dilatation persisting after female weaning pups became adults. Rabbits administered intravenous avibactam on gestation days 6-19 at 0, 100, 300 and 1000 mg/kg/day showed no effects on embryofetal development at a dose of 100 mg/kg, twice the human exposure (AUC). At higher doses, increased post-implantation loss, lower mean fetal weights, delayed ossification of several bones and other anomalies were observed. **Lactation -** Risk Summary - Ceftazidime is excreted in human milk in low concentrations. It is not known whether avibactam is excreted into human milk, although avibactam was shown to be excreted in the milk of rats. No information is available on the effects of ceftazidime and avibactam on the breast-fed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AVYCAZ and any potential adverse effects on the breastfed child from AVYCAZ or from the underlying maternal conditions. Data - In a rat pre- and post-natal study at doses up to 825 mg/kg/day intravenously (11 times the human exposure based on AUC), the exposure to avibactam was minimal in the pups in comparison to the dams. Exposure to avibactam was observed in both pups and milk on PND 7. **Pediatric Use -** Safety and effectiveness in patients less than 18 years of age have not been established. **Geriatric Use -** Of the 1809 patients treated with AVYCAZ in the Phase 2 and Phase 3 clinical trials 621 (34.5%) were 65 years of age and older, including 302 (16.7 %) patients 75 years of age and older. In the pooled Phase 2 and Phase 3 cIAI AVYCAZ clinical trials, 20% (126/630) of patients treated with AVYCAZ were 65 years of age and older, including 49 (7.8%) patients 75 years of age and older. The incidence of adverse reactions in both treatment groups was higher in older patients (≥ 65 years of age) and similar in both treatment groups; clinical cure rates for patients 65 years of age or older were 73.0% (73/100) in the AVYCAZ plus metronidazole arm and 78.6% (77/98) in the meropenem arm. In the Phase 3 cUTI trial, 30.7% (157/511) of patients treated with AVYCAZ were 65 years of age or older, including 78 (15.3%) patients 75 years of age or older. The incidence of adverse reactions in both treatment groups was lower in older patients (≥ 65 years of age) and similar between treatment groups. Among patients 65 years of age or older in the Phase 3 cUTI trial, 66.1% (82/124) of patients treated with AVYCAZ had symptomatic resolution at Day 5 compared with 56.6% (77/136) of patients treated with doripenem. The combined response (microbiological cure and symptomatic response) observed at the test-of-cure (TOC) visit for patients 65 years of age or older were 58.1% (72/124) in the AVYCAZ arm and 58.8% (80/136) in the doripenem arm. In the Phase 3 HABP/VABP trial, 54.1% (236/436) of patients treated with AVYCAZ were 65 years of age or older, including 129 (29.6%) patients 75 years of age or older. The incidence of adverse reactions in patients ≥ 65 years of age was similar to patients < 65 years of age. The 28-day all-cause mortality was similar between treatment groups for patients 65 years of age or older (12.7% [29/229] for patients in the AVYCAZ arm and 11.3% [26/230] for patients in the meropenem arm). Ceftazidime and avibactam are known to be substantially excreted by the kidney; therefore, the risk of adverse reactions to ceftazidime and avibactam may be greater in patients with decreased renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. Healthy elderly subjects had 17% greater exposure relative to healthy young subjects when administered the same single dose of avibactam, which may have been related to decreased renal function in the elderly subjects. Dosage adjustment for elderly patients should be based on renal function *[see Dosage and Administration and Clinical Pharmacology in the full Prescribing Information]*. **Renal Impairment -** Dosage adjustment is required in patients with moderately or severely impaired renal function (CrCl 50 mL/min or less). For patients with changing renal function, CrCl should be monitored at least daily, particularly early in treatment, and dosage of AVYCAZ adjusted accordingly. Both ceftazidime and avibactam are hemodialyzable; thus, AVYCAZ should be administered after hemodialysis on hemodialysis days *[see Dosage and Administration and Clinical Pharmacology in the full Prescribing Information]*.

OVERDOSAGE: In the event of overdose, discontinue AVYCAZ and institute general supportive treatment. Ceftazidime and avibactam can be removed by hemodialysis. In subjects with end-stage renal disease (ESRD) administered 1 gram ceftazidime, the mean total recovery in dialysate following a 4-hour hemodialysis session was 55% of the administered dose. In subjects with ESRD administered 100 mg avibactam, the mean total recovery in dialysate following a 4-hour hemodialysis session started 1 hour after dosing was approximately 55% of the dose. No clinical information is available on the use of hemodialysis to treat AVYCAZ overdosage [*see Clinical Pharmacology in the full Prescribing Information*].

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A 'silver bullet' for ventilator liberation?

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – Among medications to facilitate extubation, dexmedetomidine offers favorable attributes, but whether it's the best choice for patients who have difficulty being liberated from the ventilator remains to be proven, said Gilles L. Fraser, BS Pharm, PharmD.

The current CHEST/ATS guidelines on liberation from mechanical ventilation in critically ill adults strongly suggest extubation to noninvasive mechanical ventilation in high-risk patients (Chest. 2017 Jan;151[1]:160-5. doi: 10.1016/j.chest.2016.10.037). Guideline authors also suggested protocols attempting to minimize sedation for acutely hospitalized patients ventilated for more than 24 hours, based on some evidence showing a trend toward shorter ventilation time and ICU stay, as well as lower short-term mortality.

"Is dexmedetomidine the silver bullet to facilitate extubation? It's absolutely not clear," said Dr. Fraser, one of the coauthors of the guidelines, during his presentation at the Critical Care Congress sponsored by the Society for Critical Care Medicine.

"I'll leave you up to your own devices," he told attendees, at a session on conundrums in critical care that are not addressed in current guidelines. "We use it all the time, frankly, but I don't have any firm data to support that contention."

Despite best practices, extubation attempts are not always successful: "If you follow the rules of the road, success is going to occur about 85% of the time," said Dr. Fraser, who is a clinical pharmacist at Maine Medical Center, Portland, and professor of medicine at Tufts University, Boston. "That means that about 15% of our patients have difficulties in being liberated from the ventilator."

In terms of medications to facilitate ventilator liberation, benzodiazepines, dexmedetomidine, and propofol all have roles to play, according to Dr. Fraser. Clinicians have to consider agent-specific side effects, pharmacokinetics and dynamics, and "econotoxicity," or the cost of care, he added.

Although there are few comparative data available to guide choice of medication, Dr. Fraser and his colleagues have published a systematic review and meta-analysis of randomized trials of benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adult patients (Crit Care Med. 2013 Sep;41[9 Suppl 1]:S30-8. doi: 10.1097/CCM.0b013e3182a16898).

They found that dexmedetomidine- or propofol-based sedation regimens appeared to reduce mechanical ventilation duration and length of ICU stay versus benzodiazepine-based sedation, but they stated that larger controlled studies would be needed to further define outcomes in this setting.

More recently, other investigators reported an evaluation of 9,603 consecutive mechanical ventilation episodes (Chest. 2016 Jun;149[6]:1373-9. doi: 10.1378/chest.15-1389). In this large, real-world experience, propofol and dexmedetomidine were both associated with less time to extubation versus benzodiazepines, and dexmedetomidine was associated with less time to extubation versus propofol.

Relatively few patients (about 12%), however, received dexmedetomidine in that large series, and that was mostly in the setting of cardiac surgery, Dr. Fraser noted. Moreover, the investigators reported finding no differences between any two agents in hospital discharge or mortality hazard ratio.

"We're not suggesting the benzodiazepines as routine sedative agents in our patient populations," Dr. Fraser said in his presentation. "The primary reason is that they result in a longer time on the vent, typically between 1 and 2 days."

But this doesn't mean that the benzodiazepines are the "devil's handiwork," he added, noting that they may be useful in patients with anxiety related to ventilator weaning and those recovering from hemodynamic instability or at risk for GABA-agonist withdrawal.

Dexmedetomidine is opioid sparing and has a minimal effect on respiratory drive, among other advantages; however, some potential drawbacks include its hemodynamic effects and its cost, noted the speaker during his presentation at the conference.

Dr. Fraser said that his institution's daily acquisition cost for dexmedetomidine is $500, compared with $120 for propofol and $40 for benzodiazepines, but some pharmacoeconomic evaluations suggest use of dexmedetomidine may actually save between $3,000 and $9,000 per ICU admission. "At least in our place, one day in the ICU costs about $5,000, so that all makes sense … and I can argue fairly effectively that dexmedetomidine really isn't that expensive compared to midazolam," he said.

Dr. Fraser reported having no disclosures related to his presentation.

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Continued from previous page

events. 326 of 614 (53.1%) patients in the hydrocortisone/fludrocortisone group and 363 of 626 patients (58.0%) in the placebo group experienced at least one serious adverse event by day 180 ($P = 0.08$).

"Seven-day treatment with a 50-mg intravenous bolus of hydrocortisone every 6 hours and a daily dose of 50 mcg of oral fludrocortisone resulted in lower mortality at day 90 and at ICU and hospital discharge than placebo among adults with septic shock," concluded Dr. Annane and his coauthors.

The majority of researchers had no relevant financial disclosures to report, while some doctors received grants and personal fees unrelated to this study. This study was funded in part by public grants from the French Ministry of Health.

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SOURCE: Annana A et al. N Engl J Med. 2018 Feb 28. doi: 10.1056/NEJMoa1705716.

VIEW ON THE NEWS

Corticosteroids: What's their place in treating septic shock?

The results of the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial and the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL), both reported in the latest issue of NEJM, are landmark studies detailing the largest analyses of hydrocortisone use in patients with septic shock.

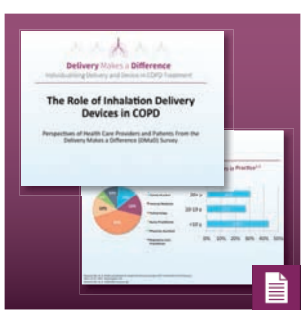
Both of these trials were massive, with over 5,000 patients combined, which is much larger than all previous studies according to Anthony Suffredini, MD, of the National Institutes of Health. An additional useful feature of these trials was that they had clear criteria for entry into the study. These criteria included "vasopressor-dependent shock and respiratory failure leading to the use of mechanical ventilation, details of antimicrobial therapy, assessment of survival at 90 days, and well-defined secondary outcomes and analyses of adverse events."

The ADRENAL and APROCCHSS had vastly different 90-day mortality rates: ADRENAL had mortality rates of 27.9% with hydrocortisone and 28.8% with placebo ($P = .50$), while APROACCHSS had mortality rates of 43.0% with hydrocortisone plus fludrocortisone and 49.1% with placebo ($P = .03$). Despite this, they both display the beneficial effect anti-inflammatory therapies, such as hydrocortisone, have on secondary outcomes of shock reversal and the reduction in duration of mechanical ventilation. "It is unlikely that in the near future sufficiently powered trials will provide us with better data" than the ADRENAL and APROCCHSS trials, Dr. Suffredini wrote.

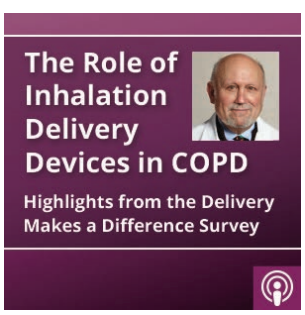
Dr. Suffredini made these comments in an editorial accompanying this study in the New England Journal of Medicine. He is the deputy chief of the critical care medicine department at the National Institutes of Health Clinical Center, and he has served on the executive committee of the Department of Veteran Affairs Cooperative Studies Program. He has no other relevant financial disclosures to report.

How can you help the 64% of patients who are unconcerned about proper device technique?[1]

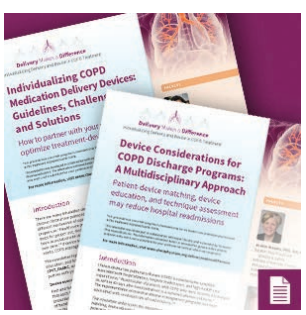
Explore **Delivery** Makes a **Difference**, an online program with a variety of educational resources.



A **slide presentation** with surprising results from the Delivery Makes a Difference (DMaD) surveys



A **podcast** highlighting health care provider *and* patient responses from the DMaD survey



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The **Delivery** Makes a **Difference** initiative examines patient and provider perspectives on inhalation-device use and education in COPD.

Reference: 1. Hanania NA, Braman S, Adams SG, et al. The role of inhalation delivery devices in COPD: perspectives of patients and health care providers. Submitted manuscript.

This promotional, non-CME program is intended only for US health care professionals involved in the treatment of patients with COPD and is provided by Sunovion Pharmaceuticals Inc.

Death rate steady with pediatric early warning system

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – Use of a pediatric early warning system reduced the incidence of late ICU admissions among hospitalized pediatric patients, but did not reduce the rate of all-cause hospital mortality, according to results of a large, multicenter trial.

Taken together, the findings of the trial do not support the use of the Bedside Pediatric Early Warning System (BedsidePEWS) to reduce hospital mortality, noted investigator Christopher S. Parshuram, MBChB, DPhil, during a presentation at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

BedsidePEWS is a documentation-based care system that combines a validated severity of illness score, a specialized documentation record, and specific recommendations for care escalation.

The multicenter randomized cluster study, called the EPOCH trial, included 21 hospitals in seven countries that provided inpatient pediatric care. Ten of the hospitals delivered the BedsidePEWS intervention, while the remaining 11 provided usual care. The study data included 144,539 patient discharges comprising 559,443 patient days. Enrollment began Feb. 28, 2011, and ended on June 21, 2015.

For the BedsidePEWS group, all-cause hospital mortality was 1.93 per 1,000 patient discharges, versus 1.56 per 1,000 patient discharges for usual care (adjusted odds ratio, 1.01; 95% confidence interval, 0.61-1.69; $P = .96$), according to a report on this study that was published in JAMA.

Taken together, the findings of the trial do not support the use of the Bedside Pediatric Early Warning System to reduce hospital mortality, according to the study investigators led by Dr. Parshuram.

However, the BedsidePEWS group had a significant improvement in the secondary outcome of significant clinical deterioration events, a composite outcome reflecting late ICU admissions.

In the BedsidePEWS group, the rate of significant clinical deterioration events was 0.50 per 1,000 patient-days, compared with 0.84 per 1,000 patient-days at hospitals with usual care (adjusted rate ratio, 0.77; 95% CI, 0.61-0.97; $P = .03$), the investigators wrote.

The goal of the EPOCH trial was to determine whether BedsidePEWS could reduce rates of all-cause hospital mortality and significant clinical deterioration among hospitalized children, according to the researchers.

"The BedsidePEWS versus usual care did improve processes of care and early detection of critical illness, aligned with the notion of providing the right care, right now," Dr. Parshuram, associate professor of critical care medicine and pediatrics at the University of Toronto, said during his presentation at the meeting. "Certainly more vital signs were documented, and anecdotally there were reports of culture change.

"However, when we looked further, there was no difference in hospital mortality, nor hospital resource utilization," Dr. Parshuram added.

The Canadian Institutes of Health Research funded the study. Dr. Parshuram is an inventor of BedsidePEWS and owns shares in a company that is commercializing it.

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SOURCE: Parshuram CS et al. JAMA. 2018 Feb 27. doi: 10.1001/jama.2018.0948.

Marik proclaims end to corticosteroid monotherapy for sepsis

BY ANDREW D. BOWSER
Frontline Medical News

SAN ANTONIO – While critical care specialists await more data on a so-called sepsis cocktail with varying degrees of hope and skepticism, Paul E. Marik, MD, FCCP, has proclaimed the dawning of a new era.

Dr. Marik became a celebrity in the critical care medicine community after he and his colleagues reported the results of his retrospective study evaluating the combination of hydrocortisone, vitamin C, and thiamine for treatment of severe sepsis and septic shock (Chest. 2017 Jun. doi: 10.1016/j.chest.2016.11.036).

Since this study, several physicians have already been putting Dr. Marik's method to practice, the investigator and audience members noted during a session at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

"My point is, steroids work, but they don't work well alone, and the era of glucocorticoid monotherapy has come to an end," Dr. Marik said in his presentation at the meeting.

These comments echoed Dr. Marik's May 2017 editorial in Critical Care Medicine, in which he suggested that critically ill and injured patients may benefit from combination therapy with hydrocortisone and vitamin C (Crit Care Med. 2017 May;45[5]910-1).

Andrew D. Bowser/Frontline Medical News

Dr. Paul E. Marik

That editorial was quickly followed by the report on Dr. Marik and colleagues' before-after study, in which hospital mortality was 8.5% versus 0.4% in the treatment and control groups, respectively (P less than .001). This finding led the investigators to suggest that intravenous vitamin C administered along with corticosteroids and thiamine is "effective" in reducing mortality, in their paper published in CHEST®.

During Dr. Marik's presentation at the meeting, he noted that he had been "misquoted" with regard to the finality of his study's results. The final line of the CHEST® paper reads, "Additional studies are required to confirm these preliminary findings," he emphasized.

Nevertheless, Dr. Marik alluded to a "big paradigm shift" in the treatment of sepsis.

"Our experience has been echoed by now hundreds, if not thousands, of clinicians across the world," said Dr. Marik, chief of the division of pulmonary and critical care medicine, Eastern Virginia Medical School, Norfolk.

He recounted an anecdotal case submitted by "Josh from Ohio" describing an elderly man who was "started on cocktail and within a day his pressor requirements melted away and he was extubated." Quoting "Josh from Ohio," Dr. Mark continued, "Tomorrow he will probably leave the ICU with no residual organ dysfunction, no volume overload, [and] no ICU complications."

Eddy Gutierrez, MD, of Jacksonville, Fla., noted in a question-and-answer period that he has had "positive results" with a similar approach.

"When we first learned about the vitamin C and the 'Marik protocol,' so to speak, I was in fellowship and I got laughed at," Dr. Gutierrez said. "Nobody would let me try it."

Others are taking a wait-and-see approach.

Greg S. Martin, MD, secretary of the Society of Critical Care Medicine, said in an interview that there are "at least two schools of thought" among critical care specialists regarding the use of hydrocortisone, vitamin C, and thiamine for treatment of sepsis and septic shock.

"One school of thought is that this is incredibly important if this is even fractionally as effective as what [Dr. Marik] showed, because we have not found an effective therapy for sepsis," said Dr. Martin, associate professor of medicine at Grady Memorial Hospital, Atlanta.

"The contrarian approach is to say, 'yes, but this seems remarkably unlikely to be as effective as what he has shown,'" Dr. Martin added. "Particularly in sepsis, people are very skeptical of whether a drug or a drug combination is going to be as effective when you really get down to a high-quality randomized controlled trial that would be the definitive level of evidence."

The wait may not be long for at least some data. Multiple clinical trials are recruiting or planned, according to Dr. Marik. These included a 140-patient U.S. randomized, double-blind trial of vitamin C, hydrocortisone, and thiamine vs. placebo that started in February 2018, according to the study's ClinicalTrials.gov listing.

As part of his presentation, Dr. Marik reported a disclosure related to Baxter (advisory board).

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MOMENTUM 3 HeartMate 3 LVAD 'practice changing'

BY BRUCE JANCIN
Frontline Medical News

FRONTLINE MEDICAL NEWS

"I think this is going to open the gates for more referrals ... for destination therapy in patients who are deemed ineligible for transplant," noted Dr. Mandeep R. Mehra (right).

ORLANDO – The HeartMate 3 magnetically levitated left ventricular assist device (LVAD) provided far superior outcomes, compared with the widely used HeartMate II axial-flow pump at 2 years of follow-up in patients with advanced heart failure in the large multicenter MOMENTUM 3 trial, Mandeep R. Mehra, MD, reported at the annual meeting of the American College of Cardiology.

HeartMate 3 recipients had a 90% lower risk of undergoing reoperation to replace or remove their device because of malfunction, and a stroke rate half that in the HeartMate II group.

"This was the lowest rate of stroke ever seen in any LVAD trial," according to Dr. Mehra, medical director of the Brigham and Women's Hospital Heart and Vascular Center, Boston, and professor of medicine at Harvard Medical School.

"We believe this is a practice-changing result in the field, and that the real implication of our findings is to reassure those who refer or treat patients with advanced heart failure that it is perhaps going to be ignorant not to refer patients for consideration for destination therapy," he said at a press conference highlighting the MOMENTUM 3 results, also presented in a late-breaking clinical trials session.

The HeartMate 3 is a miniaturized centrifugal-flow device that fits entirely within the chest, whereas the HeartMate II requires creation of a pocket in the abdomen. The HeartMate 3 was designed to prevent pump thrombosis – a common limiting problem with the HeartMate II and other LVADs – by employing three innovations: use of wide blood-flow passages to reduce shear stress and minimize disruption of red blood cells as they pass through the pump; reliance on magnetic levitation technology to create a frictionless pump with no mechanical bearings, which are subject to wear and tear; and incorporation of an artificial fixed pulse that speeds up and slows every 2 seconds in order to minimize blood stasis, which promotes thrombosis, the cardiologist explained in a video interview.

MOMENTUM 3 is the largest-ever randomized trial of LVAD therapy, involving 1,028 advanced heart failure patients at 69 U.S. centers. The study population is a mix of bridge-to-transplant patients and others who weren't eligible for heart transplantation and are using their device as lifelong destination therapy. In an earlier report on the first 294 patients to reach 6 months of follow-up post implantation, Dr. Mehra and his coinvestigators showed that the HeartMate 3 group had a significantly lower incidence of the composite endpoint of disabling stroke or reoperation to replace or remove the device (N Engl J Med. 2017 Feb 2;376[5]:440-50).

BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. James L. Januzzi Jr.

At ACC 2018, he presented the prespecified 2-year analysis of results in the first 366 patients to reach that benchmark. The rate of survival free of disabling stroke or reoperation for device malfunction was 79.5% in the HeartMate 3 group and 60.2% with the HeartMate II, for a highly significant 54% reduction in the risk of bad outcome. Reoperation for device malfunction occurred in 1.6% of HeartMate 3 patients versus 17% of those with a HeartMate II, for a 92% reduction in risk. Two-year survival was 82.8% in the HeartMate 3 group and 76.2% in HeartMate II recipients.

The overall stroke rate was 10% with the HeartMate 3, compared with 19% with the older, axial-flow LVAD. The incidence of disabling stroke was 3% in the HeartMate 3 group and at 2% with the HeartMate II; however, nondisabling stroke occurred in only 3% of HeartMate 3 recipients, compared with 14% of patients with the HeartMate II.

"There has always been this notion that, 'There are so many complications with this device, so let's suffer with the disease rather than suffer with the pump.' Now we're showing that you don't suffer with the pump as with the earlier-generation devices. I think this is going to open the gates for more referrals ... for destination therapy in patients who are deemed ineligible for transplant."

Discussant James L. Janzuzzi Jr., called the MOMENTUM 3 results "a very-much-needed step forward."

"Perhaps the most dramatic observation in this study is the dramatic reduction in thrombosis events requiring reoperation. In essence, this problem was entirely prevented by the use of this magnetically levitated centrifugal-flow device. Reoperation for thrombosis accounted for two-thirds of the reoperations in the HeartMate II group and the rate was zero in the HeartMate 3 population. Essentially, with this technology we've addressed a very important unmet need by reducing the onset of pump thrombosis, which is the precursor to either pump dysfunction or embolic stroke," commented Dr. Januzzi, professor of medicine at Harvard Medical School, Boston.

Given the 83% survival rate at 2 years in the HeartMate 3 group in the MOMENTUM 3 trial, the on-average 50% survival at 10 years for heart transplant recipients, and the perpetual enormous shortage of donor organs, it's time to consider a randomized trial of an advanced LVAD such as the HeartMate 3 versus heart transplantation, with quality-of-life outcomes front and center, he noted.

The MOMENTUM 3 trial is funded by Abbott. Dr. Mehra reported receiving research funds from and serving as a consultant to the company.

The 2-year results of MOMENTUM 3 were published online at NEJM.org (doi: 10.1056/NEJMoa1800866) during the presentation.

bjancin@frontlinemedcom.com

SOURCE: Mehra MR et al. ACC 18.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:
The reported 2- year follow-up results of MOMENTUM 3 trial on the new generation HeatMate-III magnetically levitated LVAD gives more hope to patients with end-stage heart failure for a better quality of life and longer survival and opens new doors for potentially becoming an alternative to cardiac transplantation for patients with a long waiting time on the transplant list.

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FASENRA is proven to reduce annual exacerbation rate and improve lung function in patients with severe eosinophilic asthma. Improvements in lung function were observed as early as Week 4.*[1-4]

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

*Statistical significance for FEV_1 improvement was established at end of treatment. Week 4 results were descriptive only. FASENRA demonstrated greater improvements in change from baseline in pre-bronchodilator FEV_1 compared with placebo at Week 4 (first measured time point after administration of treatment dose) that were maintained through end of treatment.[2-4]

†The pharmacodynamic response (blood eosinophil depletion) following repeat SC dosing was evaluated in asthma patients in a 12-week phase 2 trial. Patients received 1 of 3 doses of benralizumab [25 mg (n=6), 100 mg (n=6) or 200 mg (n=6) SC] or placebo (n=6) every 4 weeks for a total of 3 doses. Twenty-four hours post dosing, all benralizumab dosage groups demonstrated complete or near complete depletion of blood eosinophil levels, which was maintained throughout the dosing period.[1,5]

The relationship between the pharmacologic properties and clinical efficacy has not been established.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

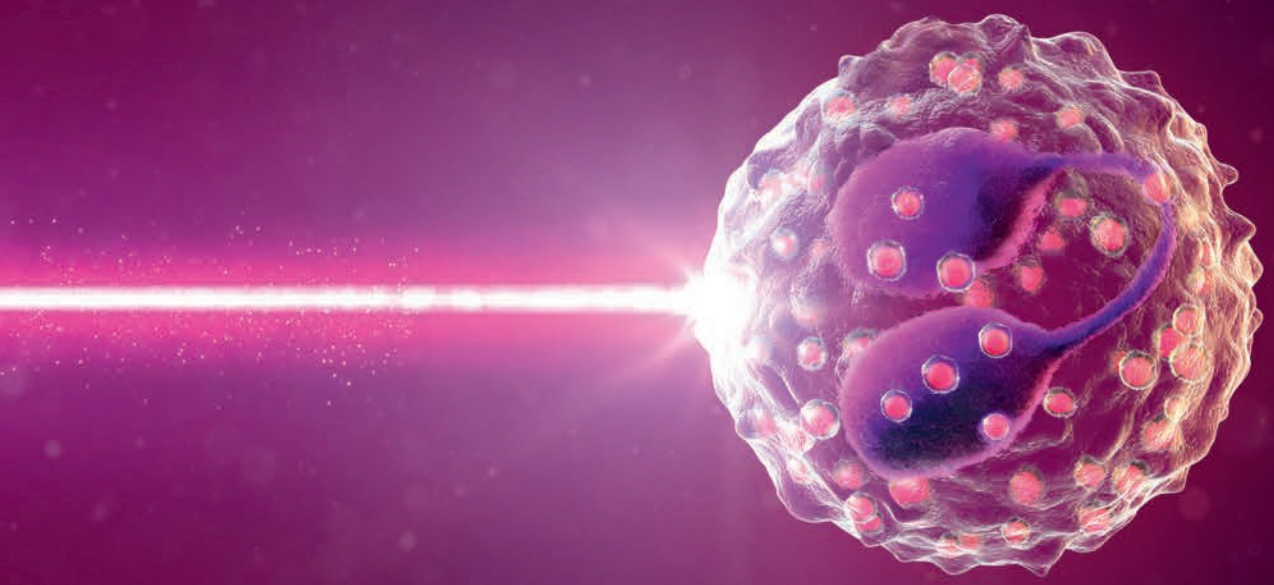
Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

- **FASENRA is the first and only biologic that provides near complete depletion of blood eosinophils in 24 hours[†1,5]**
  - **The mechanism of action of benralizumab in asthma has not been definitively established**
    - The relationship between the pharmacologic properties and clinical efficacy has not been established.
- **FASENRA is the first and only biologic for severe asthma with a prefilled syringe and Q8W maintenance dosing schedule[1]**
- **The most common adverse reactions (incidence greater than or equal to 5%) include headache and pharyngitis[1]**



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IMPORTANT SAFETY INFORMATION (cont'd)

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

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

Please see additional Important Safety Information on next page and accompanying Brief Summary of full Prescribing Information.

Fasenra™
(benralizumab) Subcutaneous injection 30 mg
FROM THE START

STUDY DESIGNS

TRIALS 1 AND 2

Trial 1 (48-week) and Trial 2 (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (Trial 1) and 1306 (Trial 2) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (Trial 1) and medium- to high-dose ICS (Trial 2) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. The primary endpoint was annual exacerbation rate ratio versus placebo in patients with blood eosinophil counts of ≥300 cells/µL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (Trial 1) and Week 56 (Trial 2) in the same population.[2,3]

TRIAL 3

A 28-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter OCS reduction study comparing the efficacy and safety of **FASENRA** (30 mg SC) Q4W for the first 3 doses, then Q8W thereafter; benralizumab (30 mg SC) Q4W, and placebo (SC) Q4W. A total of 220 adult (18-75 years old) patients with severe asthma on high-dose ICS plus LABA and chronic OCS (7.5 to 40 mg/day), blood eosinophil counts of ≥150 cells/µL, and a history of ≥1 exacerbation in the previous year were included. The primary endpoint was the median percent reduction from baseline in the final daily OCS dose while maintaining asthma control.[6]

PHASE 2 STUDY

A 12-week, phase 2, randomized, double-blind, placebo-controlled, dose-increase study of benralizumab in adults with mild to moderate asthma. Patients were randomized to receive SC administration of benralizumab 25 mg (n=6), benralizumab 100 mg (n=6), benralizumab 200 mg (n=6), or placebo (n=6) Q4W for a total of 3 doses. One objective was to assess the effect of benralizumab on blood eosinophil counts and protein biomarkers. Median blood eosinophil levels at baseline were 400, 200, 120, and 200 cells/µL in the 25, 100, and 200 mg benralizumab and placebo groups, respectively.[5]

References: 1. FASENRA [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017. **2.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127. **3.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128-2141. **4.** Data on File, REF-19697, AZPLP. **5.** Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21-29. **6.** Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448-2458.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

INDICATION

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

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

Please see adjacent Brief Summary of full Prescribing Information on reverse side.

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****.*

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

FASENRA™ (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

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

Limitations of use:

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

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

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

Preparation and Administration

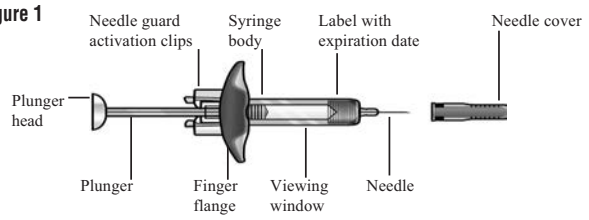
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

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

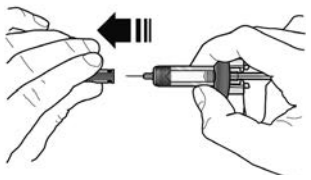
Figure 1



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

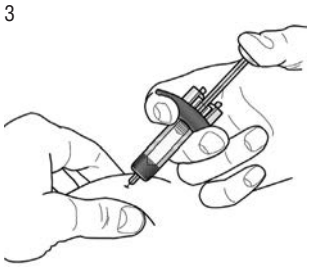
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



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

3



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

4

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

5

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

6 Discard the used syringe into a sharps container.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

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

ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

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

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

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

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

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

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

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

28-Week Trial

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

Injection site reactions

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

Immunogenicity

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

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

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

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Clinical Considerations

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

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

Not for Acute Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Manufactured by
AstraZeneca AB
Södertälje, Sweden SE-15185
US License No. 2059

Distributed by
AstraZeneca Pharmaceuticals LP,
Wilmington, DE 19850

Iss. 11/17 US-12989 12/17

New frontier in TAVR is bicuspid disease

BY BRUCE JANCIN
Frontline Medical News

DENVER – Thirty-day transcatheter aortic valve replacement (TAVR) outcomes in real-world clinical practice using the Evolut R self-expanding valve were as good in patients treated for bicuspid disease as for tricuspid disease, according to a retrospective analysis of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) national registry.

This is encouraging news because at present only tricuspid aortic valve disease is an approved indication for TAVR. Bicuspid disease isn't an approved indication because of a lack of supporting evidence regarding safety and efficacy. The new STS/ACC TVT registry data, which capture all commercial TAVR procedures done in the United States, lay the groundwork for an announced Medtronic-sponsored prospective study of Evolut Pro TAVR in patients with bicuspid disease aimed at winning an expanded indication for the device, which would open the door to on-label TAVR for patients with bicuspid disease, Jeffrey J. Popma, MD, explained at the Transcatheter Cardiovascular Therapeutics annual educational meeting (www.crf.org/tct).

Bruce Jancin/Frontline Medical News

Dr. Jeffrey J. Popma

"I've always been insecure about whether we have the right technology to be able to treat bicuspid disease. This registry data is reassuring to me that we might. I think it may be time to do a prospective registry for low-surgical-risk patients with bicuspid disease and see if we can emulate these kinds of results," said Dr. Popma, the director of interventional cardiology at Beth Israel Deaconess Medical Center and a professor of medicine at Harvard Medical School, both in Boston.

"I think that the one limitation to recruitment in our low-risk TAVR trial is patients with bicuspid disease. Probably 25%-30% of low-risk patients are bicuspid, so we can't include them right now in our low-risk trial," he added at the meeting sponsored by the Cardiovascular Research Foundation.

Even though TAVR for patients with bicuspid disease is off label, operators do perform the procedure. All of these cases are captured in the STS/ACC TVT registry. Dr. Popma reported on 6,717 patients who underwent TAVR with placement of the Evolut R valve at 305 U.S. centers during 2014-2016. The pur-

pose of this retrospective study was to compare 30-day outcomes in the 191 TAVR patients with native valve bicuspid disease with the outcomes in the 6,526 with tricuspid disease.

The two groups were evenly matched in terms of key baseline characteristics, including aortic valve mean gradient, severity of aortic, mitral, and tricuspid regurgitation, and comorbid conditions – with the exception of coronary artery disease, which was present in 48% of the bicuspid group versus 65% of those with tricuspid disease. Also, the bicuspid disease group was younger by an average of nearly 9 years, and their mean baseline left ventricular ejection fraction of 52.5% was lower than the LVEF of 55.5% seen in the tricuspid group.

Procedure time averaged 126 minutes in the bicuspid group and 116 in the tricuspid group. Femoral access was utilized in 87% of the bicuspid patients and in 92% of tricuspid patients. The device was implanted successfully in 97% of the bicuspid group and in 99% of the tricuspid group. More than one valve was required in 3.7% of the bicuspid disease group, a rate similar to that in the tricuspid group. Total hospital length of stay was roughly 6 days in both groups.

Rates of symptomatic improvement at 30 days were closely similar in the two groups. Preprocedurally, two-thirds of patients in both

Continued on following page

Continued from previous page

groups had a New York Heart Association class III; at 30 days, however, that was true for a mere 2.4% of the bicuspid patients and 10.3% of the tricuspid patients. By day 30, 52% of the bicuspid group and 48% of the tricuspid group were NYHA class I.

Also, 30-day rates of all-cause mortality, stroke, MI, major bleeding, and major vascular complications were similar in the two groups. The only striking difference in 30-day clinical outcomes involved the need for aortic valve reintervention, which occurred in 1.8% of the bicuspid versus only 0.2% of tricuspid patients.

No or only trace aortic regurgitation was present at 30 days in 62% of the bicuspid group and in 61% of the tricuspid group, while mild aortic regurgitation was noted in 31% and 33%, respectively.

Thirty-day mean aortic valve gradient improved to a similar extent in the two groups: from a baseline of 47.2 mm Hg to 9.4 mm Hg in the bicuspid group and from 42.9 mm Hg to 7.5 mm Hg in the tricuspid group.

Dr. Popma noted that an earlier analysis he carried out comparing outcomes of TAVR using the earlier-generation CoreValve in bicuspid versus tricuspid disease showed suboptimal rates of paravalvular regurgitation and an increased need for multiple valves in the bicuspid group.

"The lesson is 'Thank God we've got new technology!' because the new technology has made a big difference for us," the cardiologist observed. "We think that the advancement in the technique and the advancement in the valves is going to give us fairly comparable outcomes with Evolut in bicuspid and tricuspid patients."

Discussant Hasan Jilaihawi, MD, a codirector of transcatheter valve therapy at New York University, pronounced the short-term outcomes in patients with bicuspid aortic valve disease "better than I would have expected," adding that he, too, thinks it's time for a prospective registry study of the Evolut valve in such patients.

Dr. Popma's study was supported by Medtronic. He reported having received research grants from Medtronic and other medical device companies.

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SOURCE: Popma JJ. TCT 2017.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: This retrospective study is an encouraging report on 30-day outcomes of a new generation TAVR valve, Evolut R, in patients with bicuspid aortic valve stenosis. The bicuspid valve sample size was small compared to the tricuspid group (191 vs. 6,526) and, not unexpectedly, much younger than the tricuspid valve group. It is worth noting that, despite the younger age, "Femoral access was utilized in 87% of the bicuspid patients and in 92% of tricuspid patients." The bicuspid group also had a significantly higher rate of aortic valve reintervention at 30 days than the tricuspid cohort (1.8% vs. 0.2%). We should await the longer-term follow-up results to see if these reported short-term outcomes would last beyond 1 year.

Dabigatran effective for myocardial injury after noncardiac surgery

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – Treating patients who developed myocardial injury after noncardiac surgery with the anticoagulant dabigatran significantly cut the rate of subsequent major vascular complications in a randomized, multicenter trial with 1,754 patients, a result that gives surgeons and physicians the first evidence-based intervention for treating a common postsurgical condition.

"Because we have not systematically followed noncardiac surgery patients, it's easy to presume that everyone is okay, but all the epidemiology data show that these patients [who develop myocardial injury after noncardiac surgery] don't do okay. We need to be aggressive with secondary prophylaxis," P.J. Devereaux, MD, said at the annual meeting of the American College of Cardiology. "The unfortunate thing is that right now, we don't do much for these patients," said Dr. Devereaux, professor of medicine and director of cardiology at McMaster University in Hamilton, Ont.

Results from prior epidemiology studies have shown that, among the roughly 200 million patients who undergo noncardiac surgery worldwide each year, 8% will develop MINS (myocardial injury after noncardiac surgery) (Anesthesiology. 2014 Mar;120[3]:564-78). The myocardial injury that defines MINS is identified by either an overt MI that meets the universal definition, or an otherwise unexplained rise in serum troponin levels from baseline in the first couple of days after surgery. In the new study, Dr. Devereaux and his associates identified 80% of MINS by a troponin rise and 20% by a diagnosed MI.

The challenge in diagnosing MINS and then administering dabigatran will be implementation of this strategy into routine practice, commented Erin A. Bohula May, MD, a cardiologist at Brigham and Women's Hospital in Boston. "The problem is, troponin is not routinely measured in postoperative patients. It will be hard to change practice," she noted.

Dr. Devereaux agreed that a significant barrier is convincing clinicians, especially surgeons, to routinely measure a patient's troponin levels just before and immediately after surgery. "People are lulled into a false sense of security because patients [who develop MINS] usually don't have chest pain," he said in a video interview. "When we first showed that patients with MINS have bad outcomes, that convinced some [surgeons] to measure troponin after surgery. "Showing we can do something about it" is another important step toward fostering more awareness of and interest in diagnosing and treating MINS.

The Management of Myocardial Injury After Noncardiac Surgery Trial (MANAGE) enrolled 1,754 patients at 82 centers in 19 countries. Researchers randomized patients to treatment with either 110 mg dabigatran b.i.d. or placebo. A majority of patients in both arms also received aspirin and a statin, treatments that Dr. Devereaux should be used along with dabigatran in routine practice, based on observational findings, although the efficacy of these drugs for MINS patients has not been tested in randomized studies. The study's primary endpoint was the incidence of major vascular complications, a composite that included vascular mortality, nonfatal MI, nonfatal and nonhemorrhagic stroke, peripheral arterial thrombosis, amputation, or symptomatic venous thromboembolism.

After an average follow-up of 16 months, the primary endpoint occurred in 11% of the dabigatran-treated patients and in 15% of controls, which represented a 28% risk reduction that was statistically significant. The study's primary safety endpoint was a composite of life-threatening, major, and critical organ bleeds, which occurred in 3% of the dabigatran-treated patients and in 4% of controls, a nonsignificant difference. The dabigatran-treated patients showed a significant excess of both minor bleeds – 15% compared with 10% in controls – and "nonsignificant" lower gastrointestinal bleeds, 4% with dabigatran and 1% in the controls. The dabigatran-treated patients also had a significantly higher incidence of dyspepsia.

MANAGE was funded by the Population Health Research Institute and had no commercial funding. Dr. Devereaux has received research support from Abbott Diagnostics, Boehringer Ingelheim, Philips Healthcare, and Roche Diagnostics. Dr. May has been a consultant to Daiichi Sankyo, Merck, and Servier and has received research funding from Eisai.

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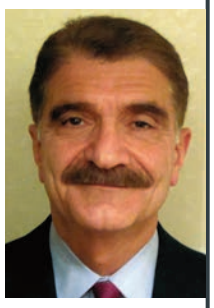
SOURCE: Devereaux P et al. ACC 18.

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

"We need to be aggressive," Dr. P.J. Devereaux noted.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:



Myocardial injury after on-cardiac surgery procedures could be a hallmark of significant yet asymptomatic coronary artery disease. The reported results of a significantly lower rate of vascular complications with dabigatran treatment are encouraging and especially, in the face of the similar safety endpoints to those of the control group. What remains is convincing the surgeons to change their practice.

Shift work's influence on cardiometabolic risk

BY DOUG BRUNK
Frontline Medical News

LOS ANGELES – Current and previous night workers had significantly increased levels of hemoglobin A_{1c}, compared with diurnal workers, preliminary results from an ongoing study showed. The finding sheds further insight into the link between environmental light, circadian rhythms, and metabolic disorders.

"To date, observational studies on bright light have revealed that evening bright light is associated with increased appetite and that bedroom light intensity is correlated with obesity," Massimo Federici, MD, said at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease. "It's also been reported that artificial light is correlated with type 2 diabetes in the home setting and that daytime light exposure is positively correlated with body mass index. However, no studies have directly investigated the effect of acute light on human glucose metabolism."

At the same time, observational studies of shift workers have shown that shift work is associated with metabolic disorders, but evidence for a causal relationship is limited, said Dr. Federici, professor of medicine and nutritional science at the University of Rome Tor Vergata. One study of night shift workers revealed reduced meal frequency but increased consumption of high energy snacks, physical activity, and altered sleep pattern, while a separate analysis found that permanent night shift workers showed only partial adaptation in 24-hour circadian rhythm of glucose and insulin levels (Am J Physiol Endocrinol Metab.

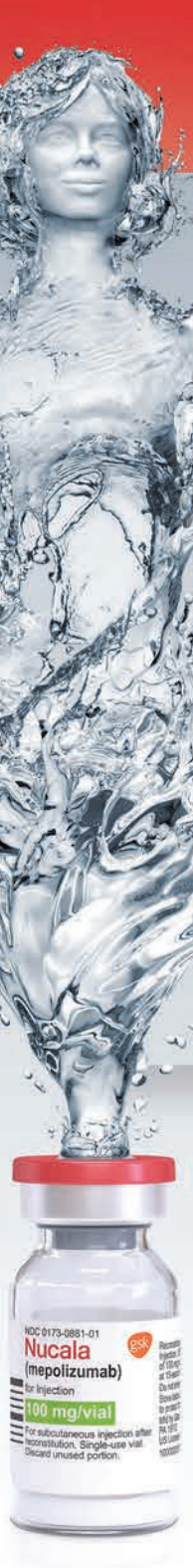
Continued on page 42

NUCALA—Prescribe with confidence

The first anti-interleukin 5 (IL-5) for severe eosinophilic asthma

NUCALA is indicated for the add-on maintenance treatment of patients 12 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DiscoverNucalaHCP.com



IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred with NUCALA compared to none with placebo. Consider vaccination if medically appropriate.

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasms, 3% (<1%).

*As of January 2018, more than 20,000 patients have received NUCALA**

*December 2015 to January 2018 data sourced from IQVIA and GSK. Claims data based on total number of unique patients who had at least 1 claim for NUCALA in the United States. Not all patients remain on therapy. Individual results may vary.[1]

In patients with blood eosinophil levels ≥150 cells/µL,

NUCALA provided a strong and consistent reduction in exacerbations[2,3†]

MENSA

53%

Reduction in exacerbation frequency at Week 32
(*P*<0.001)[2]

MUSCA

58%

Reduction in exacerbation frequency at Week 24
(Rate ratio: 0.42; 95% CI: 0.31, 0.56)[3]

Other endpoint; results are descriptive.
CI=confidence interval.

MENSA (Trial 2) Study Description[2]: 32-week study comparing treatment with NUCALA or placebo added to standard of care (SOC) in 576 patients with severe eosinophilic asthma. **Primary Endpoint:** Frequency of exacerbations.† **Results:** Exacerbations/year 0.83 for NUCALA vs 1.74 for placebo.

MUSCA Study Description[3]: 24-week study comparing treatment with NUCALA or placebo added to SOC in 551 patients with severe eosinophilic asthma. **Primary Endpoint:** Mean change from baseline in St George's Respiratory Questionnaire total score at Week 24. **Results:** –15.6 for NUCALA vs –7.9 for placebo; treatment difference of –7.7 (*P*<0.0001). The improvement in both treatment arms was clinically meaningful (defined as a reduction in score of ≥4 points). **Other endpoint:** Included frequency of exacerbations. **Results:** Exacerbations/year 0.51 for NUCALA vs 1.21 for placebo.

†Exacerbations were defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients on maintenance oral/systemic corticosteroids, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

SOC=regular treatment with high-dose inhaled corticosteroids and at least 1 other controller with or without oral corticosteroids

The approved dose of NUCALA for severe eosinophilic asthma is 100 mg administered every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

USE IN SPECIFIC POPULATIONS

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

The data on pregnancy exposures are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al; for the MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207. **3.** Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390-400.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.

Printed in USA. 828398R0 March 2018

Nucala
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

NUCALA
(mepolizumab) for injection, for subcutaneous use

BRIEF SUMMARY

The following is a brief summary only and is focused on the indication for maintenance treatment of severe asthma with an eosinophilic phenotype. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

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

Limitation of Use

NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions (6.1)]*. Consider vaccination if medically appropriate.

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS

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

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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.

6.1 Clinical Trials Experience in Severe Asthma

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1) of full prescribing information]*. Of the subjects enrolled, 59% were female, 85% were white, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg SC) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects receiving mepolizumab 75 mg IV compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA 100 mg. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA 100 mg. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA 100 mg and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects receiving NUCALA 100 mg compared with 3% in subjects receiving placebo.

Long-term Safety

Nine hundred ninety-eight subjects received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

6.3 Immunogenicity

In subjects with asthma receiving NUCALA 100 mg, 15/260 (6%) developed anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 subject with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.4 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg SC *(see Data)*.

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

Clinical Considerations

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

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

(continued on next page)

8 USE IN SPECIFIC POPULATIONS (cont'd)

8.4 Pediatric Use
The safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the Phase 3 asthma studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.
The safety and efficacy in pediatric patients other than those with asthma have not been established.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 46) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE
Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.
Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.
Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease
Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster
Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.

Reduction of Corticosteroid Dosage
Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

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

Manufactured by
GlaxoSmithKline LLC
Philadelphia, PA 19112
U.S. License Number 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

Printed in USA. 828398R0 March 2018

Phosphodiesterase-5 inhibitors prescribed incorrectly

BY NICOLA GARRETT
Frontline Medical News

While most veterans with pulmonary hypertension are treated in accordance with clinical guidelines, almost two-thirds who are prescribed therapy are being treated with pulmonary vasodilators inappropriately, an analysis of veteran prescription data reveals.

Little was known about how pulmonary vasodilators were used in practice prior to the publication of this study. While pulmonary vasodilators are considered effective for group 1 pulmonary hypertension (PH), clinical guidelines and advice from the Choosing Wisely campaign recommend against their routine use for PH patients classified into the most common types of PH – groups 2 and 3 – because of a lack of benefit, potential for harm, and high cost, the authors wrote. The report was published in Annals of the American Thoracic Society.

The new analysis shows that patients with PH are potentially being exposed to unnecessary harm, according to study author Renda Soylemez Wiener, MD, MPH, of the Center for Healthcare Organization & Implementation Research at Bedford (Mass.) Veterans Affairs Medical Center, and her colleagues. Their findings also reveal that inappropriate prescribing of pulmonary vasodilators, mostly by specialist clinicians, is contributing to the financial burden of an already stretched health system.

The research team looked at prescription data for veterans prescribed a phosphodiesterase-5 inhibitor (PDE5i), which causes pulmonary vasodilation, between 2005 and 2012 at any VA site. The primary outcome of the study was the proportion of patients who received potentially inappropriate PDE5i as classified in guideline recommendations. Patients with group 1 PH were deemed to have been treated appropriately, while those with group 2 and 3 PH were deemed to have been potentially treated inappropriately. Those with groups 4 and 5 PH were thought to have received treatment of "uncertain value."

Among 108,777 veterans with at least one ICD-9CM diagnosis code for PH, 2,790 (2.6%; 95% confidence interval, 2.5-2.7%) received daily treatment with PDE5is. Among these, 541 (19.4%; 95% CI, 18.0%-20.9%) were being treated appropriately, 1,711 (61.3%; 95% CI, 59.5%-63.1%) were receiving potentially inappropriate treatment, and 358 (12.8%; 95% CI, 11.6%-14.1%) were receiving treatment of uncertain value.

In a chart abstraction analysis from a randomly selected subset of PDE5i-treated patients, half (110/230, 47.8%; 95% CI, 41.3%-54.5%) had documented right heart catheterization to confirm the presence of PH. After factoring this into their algorithm, the investigators determined that only 11.7% (95% CI, 8.0%-16.8%) of these patients received clearly appropriate treatment.

Over the 8-year study period, the number of patients with PH group 2 or 3 prescribed PDE5i rose more than 14-fold, the researchers said. They speculated that this figure was likely to continue to rise with the increasing use of echocardiography and detection of PH.

According to the authors, the cost of treating one PH patient for 1 year with PDE5i therapy was between $10,000 and $13,000.

The 1,711 PH patients classified as being treated inappropriately in the study translated into a cost of over $20 million, if each patient were treated for only 1 year, but many of the patients were treated for a longer period of time.

The researchers suggested that there were several reasons why clinicians might choose to deviate from the guidelines, including lacking familiarity with them or disagreeing with them.

"While guidelines do allow trials of PDE5i in treatment for groups 2 or 3 PH on a case-by-case basis after consultation with a PH expert and a confirmatory [right heart catheterization], even PH experts disagree about whether a trial of PDE5i therapy is reasonable and appropriate for patients with group 3 PH," they wrote.

They may also overestimate the potential benefits of treatment and/or underestimate potential harm.

Clinicians may believe that guidelines developed for a general population do not apply to the patients they are treating.

"It is understandable why clinicians may offer unproven therapies like PDE5i in hopes of providing relief to very sick patients with groups 2 or 3 PH, especially if they do not believe the recommendation applies to their individual patient or they are not convinced about the potential harms of pulmonary vasodilators," they said.

The authors expressed concern about VA clinicians' allowing patients to take PDE5i therapy that had been initially prescribed by clinicians outside of VA hospitals. The researchers said such drugs, which potentially had been prescribed inappropriately, "were continued by VA clinicians without much apparent scrutiny."

The chart abstraction analysis also showed that specialists prescribed the majority of potentially inappropriate PDE5i treatment, suggesting "that other interventions to prevent inappropriate use may be required."

The researchers concluded that "[the] time has come to develop interventions to optimize prescribing for PH in order to improve the value, quality, and safety of care."

One potential intervention suggested by the researchers was to require patients with PH to be evaluated at a PH expert center, as recommended by treatment guidelines.

The study was funded by the Department of Veterans Affairs with resources from the Edith Nourse Rogers Memorial VA Hospital. Elizabeth S. Klings, MD, one of the study's authors, declared receiving research support from several pharmaceutical companies.

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SOURCE: Wiener RS et al. Ann Am Thorac Soc. 2018 Feb 27. doi: 10.1513/AnnalsATS.201710-762OC.

Continued from page 37

2000;278[3]:E413-20).

Although few metabolic intervention studies using light have been done, Dr. Federici mentioned three of note. One, in patients with seasonal affective disorder and type 2 diabetes, showed reduced insulin requirements after light therapy (Lancet. 1992;339[8800]:1065-6). Another, a short-term study of 25 obese subjects treated with 5,000 lux bright light therapy in addition to exercise, showed reduced body fat after 6 weeks (Obesity. 2007; 15[7]:1749-57). A third, in 34 obese subjects who were exposed to 1,300 lux bright light every morning for 3 weeks, showed a small but significant reduction in fat mass (Obes Facts. 2013;6:28-38).

As part of an ongoing project known as EuRhythDia, researchers including Dr. Federici set out to identify metabolic and molecular variables associated with shift work, and to test the effect of a lifestyle intervention that comprised light exposure, exercise, and melatonin. He presented unpublished results from one aspect of the trial: a cross-sectional analysis of 273 nurses divided into one of three groups: 64 diurnal workers (DW), 111 active night shift workers (aNW), and 98 prior night shift workers (pNW). Those with diabetes or taking oral antidiabetic drugs were excluded from the study.

The analysis showed that nurses in the pNW group were significantly older, at a mean of 39.7 years, than those in the DW group, whose mean age was 37 years, and the aNW group, who averaged 36.1 years. Those in the pNW group also had a significantly greater body mass index, compared with their counterparts in the aNW and DW groups (a mean of 25.7 kg/m^2, vs. 24.8 and 23.7, respectively) as well has a higher mean waist circumference (a mean of 87.2 cm, vs. 84.6 cm and 82 cm).

The mean HbA_{1c} was higher in the nurses with prior and active night shift work, at 5.3% each, than in the diurnal workers (5.1%, *P* less than .001).

When Pittsburgh Sleep Quality Index scores were used to evaluate sleep quality independent of work status, more than half of the study subjects (163) were classified as being "good sleepers," while 110 were considered to be "bad sleepers." Bad sleepers had a significantly higher mean HbA_{1c} level compared with good sleepers (5.3% vs. 5.2%). Bad sleepers also had higher levels of HDL cholesterol (a mean of 60.8 mg/dL vs. 56.3 mg/dL).

Dr. Federici highlighted preliminary findings from a study of 32 aNW subjects who were assigned to treatment with warm light therapy at 1,000 lux for 30 minutes at 30 cm every morning for 3 months. They observed a mild improvement in the area under the curve of the oral glucose tolerance test at 24 weeks (12 weeks' washout after 12 weeks of light therapy). "However, the effect was obtained not at the end of the intervention but at the end of the washout period," he said.

He called for more studies going forward that take into account the effect of seasons as well as the effects of diet and exercise.

Dr. Federici disclosed that he receives editorial fees from Springer Nature group.

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Swamp coolers not linked to dust-mite sensitization in atopic children

BY THOMAS R. COLLINS
Frontline Medical News

ORLANDO – Swamp coolers – a low-cost alternative to air-conditioning in dry regions – weren't found to increase sensitization to house dust mites or mold in atopic pediatric patients, researchers reported.

Neema Izadi, MD, and his associates say the findings, seen in a pediatric Colorado population in a study evaluating data over 10 years, could mean that not everyone at risk of dust-mite and mold sensitization needs to avoid these cooling systems.

Swamp coolers, or evaporative coolers, draw water from a reservoir with a pump and the water is placed on a cooling pad. Then a fan pulls the air through the pad. This cools the air inside the home, but also increases the moisture in the air.

"Evaporative coolers have been shown to raise relative humidity by about 10%," said Dr. Izadi, a pediatric allergy and immunology fellow at National Jewish Health, Denver, presenting at the joint congress of the American Academy of Asthma, Allergy and Immunology and the World Asthma Organization. "They work best in environments where the air is very warm and dry."

House dust mites and mold thrive in higher humidity. Small studies performed in Colorado, Utah, and other locations have shown that the swamp coolers increase house dust-mite allergen content, but there have been very few studies that have looked at actual sensitization. One smaller study in Nevada did find that the coolers increased sensitization to dust mites and mold.


DR. IZADI

In this study – thought to be the largest ever to look at this question – Dr. Izadi and his colleagues assessed data on patients aged 21 years and younger who were seen at National Jewish Health during 2008-2017 and who had at least one positive environmental skin-prick test. The average age was about 9 years. The cohort included 8,503 patients with sensitization to house dust mites and 9,286 with sensitization to mold. Researchers examined data on swamp coolers in their homes.

The researchers found that 29% of those with swamp coolers were dust-mite positive on skin testing, and 28% of those without one were positive. This was not a significant difference ($P = .85$). They found that 45% of those with the coolers were positive for sensitization to any mold, compared with 44% without one – also not a significant difference ($P = .43$).

They also found no difference according to age group, sex, or individually for atopic dermatitis, asthma, or allergic rhinitis.

He acknowledged that the study had no way to reliably account for patients who were transplants to Colorado, having moved there from somewhere else. The study also didn't examine the age of homes, whether it had carpeting, or other factors.

He noted that the amount of time the coolers were run in the home was not examined and that "it might matter how much it is on." This, he said, might account for differences in these results, compared with the Nevada study that did find a sensitization increase cause by the coolers.

"Evaporative coolers or swamp coolers are a great low-cost alternative in semiarid and arid environments – they can cut costs from 15% from 35%," Dr. Izadi said. "These data may indicate that it may be unnecessary to recommend that patients remove their swamp cooler, at least from a dust-mite and mold sensitization standpoint."

Dr. Izadi had no relevant financial disclosures.

chestphysiciannews@chestnet.org

SOURCE: Izadi N et al. AAAAI/WAO Joint Congress, Abstract 586.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Swamp coolers are used in semi-arid and arid climates like Arizona, where I did my fellowship training but they didn't work well to keep apartments and homes cool enough if over about 100°F outside! The system is cheaper than air conditioning. So it is great to know that this type of cooling system does not cause more mold and dust mite allergies.

Artificial intelligence streamlines asthma care

BY THOMAS R. COLLINS
Frontline Medical News

ORLANDO – Reviewing patient charts for asthma risk factors using natural language processing can be done 8 times faster than reviewing the charts by hand, and with high levels of accuracy, researchers reported here.

Natural language processing (NLP) is a kind of artificial intelligence in which computers are "trained" through a reiterative process to understand human language.

Researchers at Mayo Clinic previously have shown that a program created in-house can successfully and quickly determine patients' asthma status. In this study, they turned to assessment of asthma risk factors, Chung-Il Wi, MD, assistant professor of pediatrics at Mayo said in a presentation at the joint congress of the American Academy of Allergy, Asthma, and Immunology and the World Asthma Organization.

They used a convenience sample of 177 patient charts to train the NLP system. The system extracted – from key terms and sentences in the electronic health record (EHR) – data such as breastfeeding history and history of atopic conditions such as allergic rhinitis, eczema, and food allergy. From parent charts, the system extracted terms related to family history of asthma and other atopic conditions. The performance of the NLP algorithm was assessed by comparison with results of a manual chart review in a test cohort of 220 patient charts.


DR. WI

Researchers found a high level of agreement between the NLP analysis and the manual review. For breastfeeding, the positive predictive value (PPV) of the NLP was 98% and the negative predictive value (NPV) was 86%. For history of atopic conditions the PPV was at or near 100%, with a NPV of 97%-99%, depending on the condition.

For family history of atopic conditions, the PPV was 91%-100%, depending on the condition, and the NPV was 96%-99%.

"Childhood asthma risk factors identified (an) NLP algorithm using EHR has excellent concordance with chart review," researchers wrote.

Using an average time per chart, researchers found that it would take 7 hours to complete a manual review for the information presented in the study, compared to 50 minutes for the NLP.

The findings, thought to be the first demon-

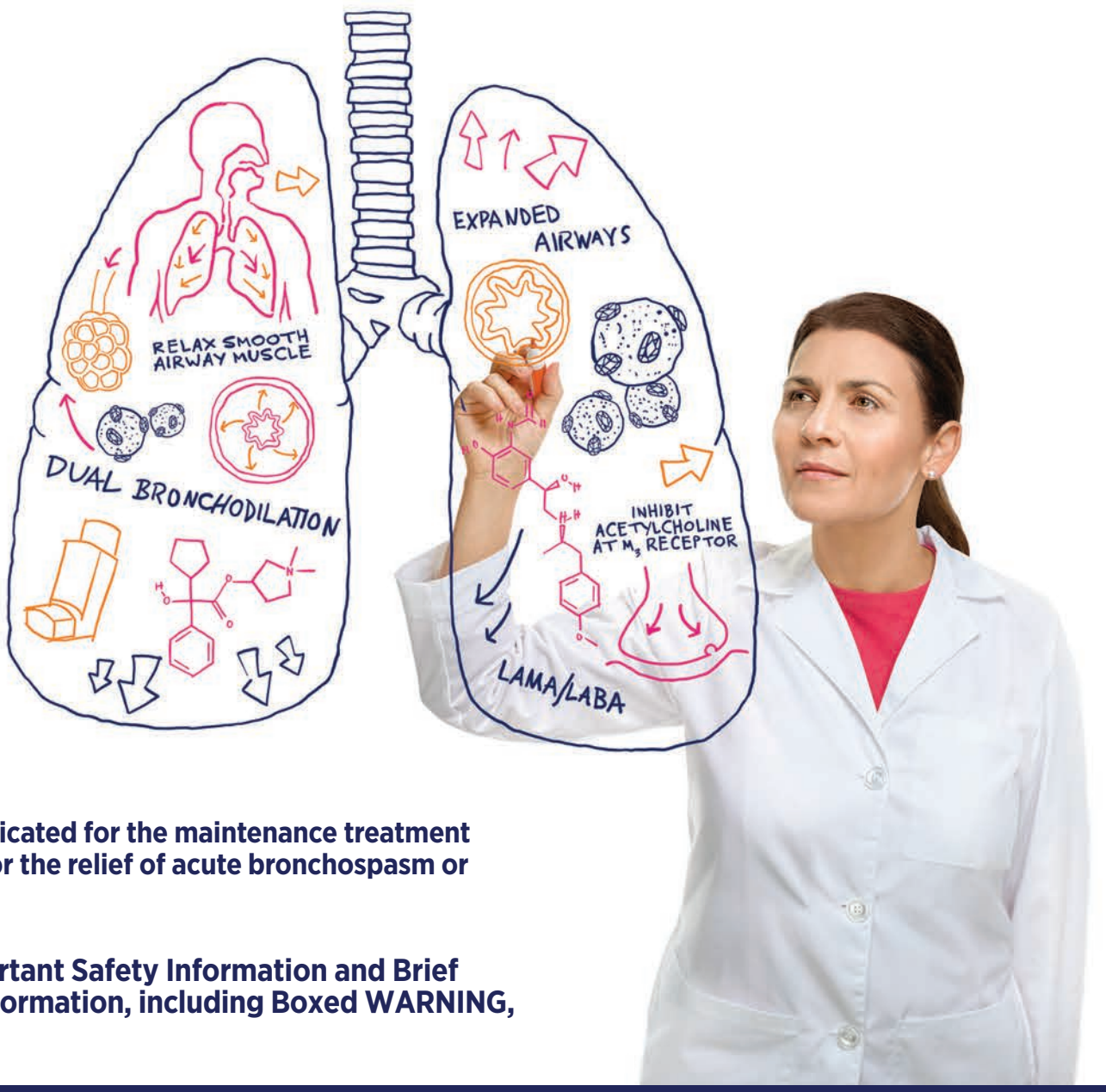
Continued on page 48

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This article brings mixed emotions. On one hand, using artificial intelligence brings a more thorough evaluation regarding asthma risk. On the other hand, our pediatric pulmonary subspecialty has gotten diluted over the last 3 decades. We used to regularly do arterial puncture, thoracentesis, and chest tube placement procedures. Now a computer might replace another aspect of our job, too? The practice of medicine is an art and that art should not be lost.

BEVESPI AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting $beta_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

CONTRAINDICATIONS: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating chronic obstructive pulmonary disease (COPD), which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions occur, in particular, angioedema, urticaria, or skin rash, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction, and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

2017 GOLD Report

LAMA/LABAs RECOMMENDED

1ST-LINE FOR MOST PATIENTS*

MAXIMIZE BRONCHODILATION[1,2†]

Improved lung function including predose FEV_1 and peak FEV_1 at 24 weeks[1,2‡]

In a separate study vs placebo, improvement in peak inspiratory capacity at Day 29[3§‖]

INTELLIGENT FORMULATION[1¶]

Intelligent formulation for a pMDI using patented, phospholipid-based AEROSPHERE™ Delivery Technology[1]

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.

*Initial treatment in Group B patients with severe breathlessness and in Group D patients.

†Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials (n=3699).

‖In a separate Phase IIIb trial (n=35), there was a significant improvement in the primary endpoint, FEV_1 $AUC_{0\text{-}24}$, on Day 29 vs placebo. Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint. Similar results seen in a second Phase IIIb trial (n=75).

¶BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.

by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore, BEVESPI should be used with extreme caution in patients being treated with these agents

- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

‡**PINNACLE 1 & 2 Pivotal Trials:** Two 24-week efficacy and safety studies were conducted in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV_1 of <80% of predicted normal values, and FEV_1/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; *P*<0.0001 for all treatment comparisons.[1,2] Trial 1 also included an open-label active control.[1] Statistically significant results were also seen in Trial 2.[1,2] Secondary endpoints included change from baseline in peak FEV_1 at Week 24 for BEVESPI BID compared with placebo BID (291 mL), glycopyrrolate 18 mcg BID (133 mL), and formoterol fumarate 9.6 mcg BID (93 mL); results are from Trial 1; *P*<0.0001 for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,2]

§**Separate Phase IIIb Trials (Study A & B):** Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID in patients with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Study B also included an open-label active control.[3] Inclusion criteria were consistent with the two 24-week pivotal trials.[1,3] Adverse events were numerically similar across treatment arms.[3] Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: Study A – BEVESPI (n=35) vs placebo (n=31) = 249 mL (baseline FEV_1 1.382 L and 1.345 L, respectively); Study B – BEVESPI (n=65) vs placebo (n=65) = 265 mL (baseline FEV_1 1.328 L and 1.333 L, respectively); both *P*<0.0001.[4] Secondary endpoint, Peak IC (evening): Study A – BEVESPI (n=34) vs placebo (n=30) = 381 mL (baseline IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 1.877 L and 1.913 L, respectively); both *P*<0.0001.[4]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2017. **2.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357. **3.** Reisner C, Gottschlich G, Fakih F, et al. 24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD. *Respir Res*. 2017;18:157. **4.** Data on File, 3270300, AZPLP.

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AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI 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]*.

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions (5.1) in the full Prescribing Information]*. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.

A 28-week, placebo-controlled US trial comparing the safety of another LABA (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 vs. 3/13,179 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

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

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI 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 BEVESPI 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 medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI 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 BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, 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, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI 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, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

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, or symptoms *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. If such effects occur, BEVESPI 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, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

BEVESPI 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.

Worsening of Urinary Retention

BEVESPI AEROSPHERE should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (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.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma *[see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information]*.

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Hypersensitivity reactions *[see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]*
- Cardiovascular effects *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9) in the full Prescribing Information]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10) 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 clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions: Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

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

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 BEVESPI 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 any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI 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-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI 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 BEVESPI 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]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

Pregnancy Category C. There are no adequate and well-controlled trials of BEVESPI AEROSPHERE or its individual components, glycopyrrolate and formoterol fumarate, in pregnant women. Because animal reproduction studies are not always predictive of human response, BEVESPI AEROSPHERE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BEVESPI AEROSPHERE.

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m^2 basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m^2 basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m^2 basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of BEVESPI AEROSPHERE in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m^2) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI 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.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI 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. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

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 abuse of formoterol fumarate.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom
or By: AstraZeneca Dunkerque Production (AZDP), Dunkerque France

06/17 US-15356 10/17

Yellow-zone management - What is the best plan for asthma?

BY BIANCA NOGRADY
Frontline Medical News

Significantly escalating the dose of inhaled glucocorticoids at the first sign of an imminent asthma exacerbation has had mixed results in preventing the exacerbation from occurring, according to the results of two trials in adults and children.

Presented at the joint congress of the American Academy of Allergy, Asthma, and Immunology and the World Asthma Organization and simultaneously published in the March 3 online edition of the New England Journal of Medicine, one study explored the effect of quadrupling the inhaled glucocorticoid dose in adults and adolescents with asthma, while the other looked at quintupling the dose in children.

The first study involved 1,922 participants who were aged 16 years or above, who were receiving inhaled glucocorticoids, and who had experienced at least one asthma exacerbation in the previous year. They were randomized to a self-management plan that instructed them to either take quadruple their usual dose of inhaled glucocorticoids at the first sign of worsening asthma – more use of reliever inhaler, difficult sleeping, or reduced peak flow – or to continue using their usual dose of inhaled glucocorticoids.

At 1 year, there was a significantly lower incidence of severe asthma exacerbations in the group who used the higher dose of inhaled glucocorticoids (45% vs. 52%; hazard ratio, 0.80; P = .001) after adjustment for age, sex, and peak flow measures at randomization, according to Tricia McKeever, PhD, from the department of epidemiology and public health at the University of Nottingham (England), and her coauthors.

Researchers also saw a lower percentage of participants using systemic glucocorticoids in the quadruple-dose group, compared with the normal-dose group (33% vs. 40%), and the quadruple-dose group also showed a 14% lower incidence of unscheduled health care consultations.

At the end of the 12-month follow-up, the estimated mean total dose of inhaled glucocorticoids was 385 mg in the quadruple-dose group and 328 mg in the normal-dose group.

The most common serious adverse event was hospitalization for asthma, which occurred three times in the quadruple-dose group and 18 times in the normal-dose group. However the incidence of oral candidiasis and dysphonia – both potentially treatment related – was significantly higher in the quadruple-dose group (36 events vs. 9 events).

Overall, the number needed to treat with the quadruple dose to prevent one severe asthma exacerbation was 15.

The second study, which was double blinded, investigated whether quintupling the dose of inhaled glucocorticoids might avoid exacerbations in children. They randomized 254 children who had mild-moderate persistent asthma and had had at least one exacerbation treated with systemic glucocorticoids in the previous year to manage "yellow-zone" early-warning signs with either normal dose or five times their usual dose of inhaled glucocorticoids.

The rate of severe asthma exacerbations did not differ significantly between the quintuple-dose and normal-dose groups at the 1-year follow-up (0.48 vs. 0.37; P = .3), nor did the time to the first severe exacerbation or the rate of emergency department or urgent care visits.

The four hospitalizations for asthma all occurred in the high-dose group. However, there was a lower growth rate seen in children in the high-dose group than in the low-dose group (5.43 cm/yr vs. 5.65 cm/yr; P = .06). There were no significant differences between the two groups in other adverse events.

However, Daniel J. Jackson, MD, and his coauthors noted that there were fewer yellow-zone episodes and fewer exacerbations in both groups than they had anticipated.

"It is important to recognize that our findings are specific to school-age children with mild to moderate persistent asthma regularly treated with daily low-dose inhaled glucocorticoids (with good adherence)," wrote Dr. Jackson from the department of pediatrics at the University of Wisconsin–Madison and his coauthors.

Possible subgroup benefit from high-dose inhaled steroids

These two trials address the important question of whether substantial escalation of regularly used inhaled glucocorticoids prevents exacerbations if started at the first sign of deterioration, as this so-called yellow zone has long been thought the perfect time to initiate more aggressive care, noted Philip G. Bardin, PhD, of the Monash Lung and Sleep Unit at the Monash University Medical Centre in Melbourne in an editorial. However glucocorticoids have serious side effects, and there is some preclinical evidence that they may enhance viral replication.

One trial shows that an escalating dose in this yellow zone does not prevent exacerbations in children with the early signs of asthma instability. The second trial is more complex and more controversial, as the open-label design may have biased the outcome, and the degree of benefit is debatable, Dr. Bardin noted in the New England Journal of Medicine (2018 Mar 3. doi: 10.1056/NEJMe1800152).

Together, these studies suggest that high doses of inhaled glucocorticoids either do not prevent exacerbations or only do so in a small subgroup of patients with as-yet-undefined baseline and exacerbation characteristics, he added in the editorial, which was published in the same issue as these two studies.

The first study was supported by the National Institute for Health Research. Six authors declared grants, personal fees, and other funding and support from the pharmaceutical industry outside the submitted work.

The second study was supported by the National Heart, Lung, and Blood Institute. Fifteen authors declared grants, personal fees and other funding from the pharmaceutical industry, as well as other private industry, outside the submitted work. Several also declared grants from organizations including the National Institutes of Health.

Dr. Bardin reported personal fees from GlaxoSmithKline outside the submitted work.

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SOURCES: McKeever T et al. N Engl J Med. 2018 Mar 3. doi: 10.1056/NEJMoa1714257; Jackson DJ et al. N Engl J Med. 2018 Mar 3. doi: 10.1056/NEJMoa1710988.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: The STICS trial reported by Jackson, et al has been heavily discussed since hitting the press at the AAAAI meeting! The STICS trial focused on children whereas the NEJM paper authored by McKeever, et al included patients who were age 16 and above but the mean age was 56 years. The STICS study showed no difference in the primary outcome for patients who had significantly elevated inhaled steroid dosing in the yellow zone compared with controls. The primary outcome was the rate of severe asthma exacerbations treated with systemic glucocorticoids. Also, the P value for difference in linear growth per year was .06, but they did a subset analysis of children younger than 8 years of age. The younger children who received the significantly higher dose of inhaled steroids in their yellow zones had a 0.12 cm per year lower growth per yellow-zone episode than the control patients with a p value of 0.02. This landmark study is making us all re-think how we build an asthma action plan for our pediatric patients.

Continued from page 43

strating NLP's value for this purpose, suggest "the huge potential of leveraging NLP for asthma care and research," researchers said.

Dr. Wi said the system can be applied to any EHR system. He said it only makes sense to put an algorithm to use in this way – it saves both clinical time and time in doing research projects.

"Whenever we do asthma research we need to collect asthma risk factors anyway, but we don't want to do manual chart review anymore in this EMR era," he said. "Now, the computer can do it."

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SOURCE: Wi C-I. AAAAI/WAO Joint Congress 2018, Abstract 637.

TB in 2017: Good news and bad news

BY RICHARD FRANKI
Frontline Medical News

The rate and number of new tuberculosis cases in the United States for 2017 were the lowest since national surveillance started in 1953, but news on the TB elimination front is not so good, according to the Centers for Disease Control and Prevention.

Those new lows – TB incidence of 2.8 per 100,000 persons and 9,093 new cases – continue a downward trend that started in 1993, but the current rate of decline is much lower than the threshold needed to eliminate TB by the year 2100, Rebekah J. Stewart and her associates at the CDC's Division of Tuberculosis Elimination, Atlanta, wrote in the Morbidity and Mortality Weekly Report.

TB incidence for 2017 was, in fact, 28 times higher than the U.S. elimination threshold of less than one case per 1,000,000 persons, and the average annual rate of decline since 2014, 2.0%, is only about half the sustained annual decline of 3.9% needed to eliminate TB by the year 2100. "Ongoing efforts to prevent TB transmission must be sustained, and efforts to detect and treat [latent TB infection], especially among groups at high risk, must be increased," they said.

Geographically, at least, the states with populations at the highest risk are Hawaii, which had a TB incidence of 8.1 per 100,000 persons in 2017, and Alaska, with an incidence of 7.0 per 100,000. California and the District of Columbia were next, each with an incidence of 5.2. The states with the lowest rates were Montana and Wyoming at 0.3 per 100,000, the investigators reported, based on data from the National Tuberculosis Surveillance System as of Feb. 12, 2018.

Groups most affected by TB include persons housed in congregate settings – homeless shelters, long-term care facilities, and correctional facilities – and those from countries that have high TB prevalence. Overall incidence for non–U.S. born residents was 14.6 per 100,000 in 2017, compared with 1.0 for the native born, with large discrepancies seen between U.S. and non–U.S. born blacks (2.8 vs. 22.0), native Hawaiian/Pacific Islanders (6.5 vs. 21.0), and Asians (2.0 vs. 27.0), Ms. Stewart and her associates said.

"Increased support of global TB elimination efforts would help to reduce global … prevalence, thereby indirectly reducing the incidence of reactivation TB in the United States among non–U.S. born persons from higher-prevalence countries," they wrote.

The issue of global action on TB was addressed by the Forum of International Respiratory Societies in a statement recognizing World TB Day (March 24). "TB is the world's most common infectious disease killer, yet is identifiable, treatable and preventable; what is missing is the political will to dedicate the resources necessary to eradicate it, once and for all," said Dean E. Schraufnagel, MD, the organization's executive director.

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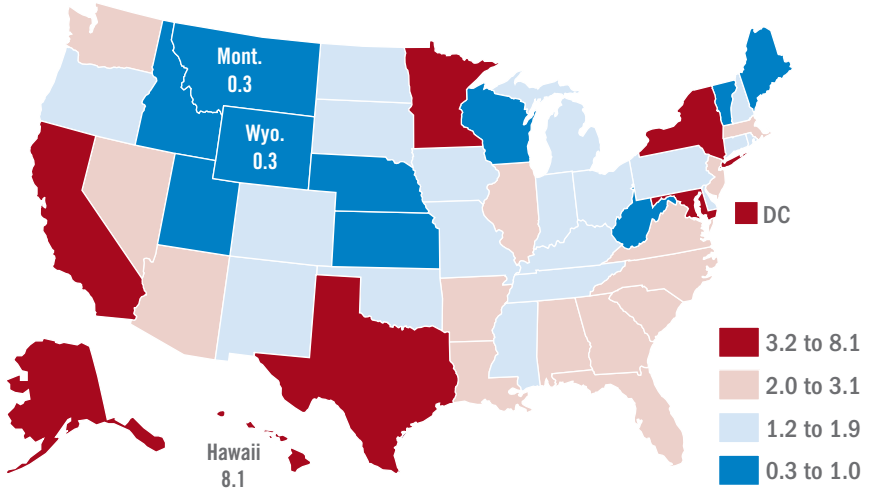
Tuberculosis incidence per 100,000 persons, 2017



Frontline Medical News

Note: Based on cases reported to the National Tuberculosis Surveillance System.
Source: MMWR. 2018 Mar 23;67(11):317-23

SOURCE: Stewart RJ et al. MMWR. 2018 Mar 23;67(11):317-23.

CDC: Flu levels highest since pandemic year 2009

BY RICHARD FRANKI
Frontline Medical News

Influenza activity continued to increase in the week ending Jan. 20, and the 2017-2018 flu season continues to look a lot like the 2009-2010 pandemic, according to data from the Centers for Disease Control and Prevention.

That season was dominated by influenza A (H3N2), and the 2017-2018 season seems to be going down that same path. For the week ending Jan. 20, the proportion of outpatient visits for influenza-like illness increased to 6.6%, which is, for the second consecutive week, the highest level reported since October of – you guessed it – 2009, when it hit 7.7%, the CDC said in its weekly flu surveillance report.

The level reported last week, 6.3%, has been revised downward and now stands at an even 6%.

It turns out that 2018 is something of a milestone for the H3N2 virus. The virus first emerged in 1968, so it has reached its 50th anniversary, Dan Jernigan, MD, director of the influenza division at the CDC's National Center for Immunization and Respiratory Diseases, Atlanta, said on Jan. 26 in a weekly briefing.

H3N2 must not be happy about hitting the big 5-0, however, because the map of influenza-like illness activity looks pretty red and angry. For the week ending Jan. 20, there were 30 states at the highest level of flu activity on the CDC's 1-10 scale, with another nine in the "high" range at levels 8 and 9.

Dr. Jernigan did suggest that activity may have peaked in some areas of the country, with California among them.

There were seven pediatric deaths reported for the week ending Jan. 20, although six occurred in previous weeks. There have been 37 flu-related deaths among children so far during the 2017-2018 season, the CDC said.

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Alternative oxygen therapy reduces treatment failure in bronchiolitis

BY RANDY DOTINGA
Frontline Medical News

High-flow oxygen therapy outside the ICU boosts the likelihood that infants with bronchiolitis will avoid treatment failure and an escalation of treatment, a study finds.

"High flow can be safely used in general emergency wards and general pediatric ward settings in regional and metropolitan hospitals that have no immediate direct access to dedicated pediatric intensive care facilities," study coauthor Andreas Schibler, MD, of University of Queensland in Australia, said in an interview. The findings were published March 22 in the New England Journal of Medicine.

Bronchiolitis is quite common in children, and a 2002 report found that respiratory syncytial virus (RSV) bronchiolitis was the most common reason for infants under the age of 1 year to be hospitalized in the United States during 1997-1999 (Pediatr Infect Dis J. 2002 Jul;21[7]:629-32).

"The typical treatment for bronchiolitis is supportive therapy, providing nutrition, fluids, and if needed, respiratory support including provision of oxygen," Dr. Schibler said.

The prognosis is generally good thanks to improvements in intensive care, he said, which some infants need because the standard oxygen therapy provided in general pediatric wards is insufficient. The new study examines whether high-flow oxygen therapy through a cannula – which he said has become more common – reduces the risk of treatment failure in non-ICU therapy, compared with standard oxygen treatment.

Dr. Schibler and his colleagues tracked 1,472 patients under 12 months with bronchiolitis and a need for oxygen treatment who were randomly assigned to high-flow or standard oxygen therapy to maintain their oxygen saturation at 92%-98% or 94%-98%, depending on policy at the hospital. The subjects were patients at 17 hospitals in Australia and New Zealand.

A total of 739 infants received high-flow treatment that provided heated and humidified oxygen at a rate of 2 L/kg of body weight per minute. The other 733 infants received standard oxygen therapy up to a maximum 2 L/min.

The treatment failed, requiring an escalation of care, in 87 of 739 patients (12%) in the high-flow group and 167 of 733 (23%) in the standard-therapy group. (risk difference = –11% points; 95% confidence interval, –15 to –7; *P* less than .001).

"The ease of use and simplicity of high flow made us recognize and think that this level of respiratory care can be provided outside intensive care," Dr. Schibler said. "This was further supported by the observational fact that most of these infants with bronchiolitis showed a dramatically improved respiratory condition once on high flow."

Dr. Schibler said there haven't been any signs of adverse effects from high-flow oxygen therapy. As for the cost of the treatment, he said it is "likely offset by a reduced need for intensive care therapy or costs associated with transferring to a children's hospital."

What should physicians and hospitals take from the study findings? "If a hospital explores the option to use high flow in bronchiolitis, then start the therapy early in the disease process or once an oxygen requirement is recognized," Dr. Schibler said. "Implementation of a solid and structured training program with a clear hospital guideline based on the evidence will ensure the staff who care for these patients will be empowered and comfortable to adjust the oxygen levels given by the high-flow equipment. The greater the confidence and comfort level for the nursing and respiratory technician staff, the better for these infants, as they will sooner observe those infants who are not responding well and may require a higher level of care such as intensive care or they will recognize the infant who responds well."

The National Health and Medical Research Council (Australia) and the Queensland Emergency Medical Research Fund provided funding, and sites received grant funding from various sources. Fisher & Paykel Healthcare, a respiratory care company based in Auckland, New Zealand, donated high-flow equipment and consumables and travel/accommodation support. Study authors reported various grants and other support.

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SOURCE: Franklin D et al. N Engl J Med. 2018 Mar 22;378(12):1112-31.

Xenon imaging could detect lung involvement after HSCT

BY SHARON WORCESTER
Frontline Medical News

SALT LAKE CITY – Hyperpolarized xenon-129 magnetic resonance imaging, or ^{129}Xe MRI, showed strong promise for revealing early lung ventilation deficits in pediatric hematopoietic stem cell transplant (HSCT) patients in a proof-of-concept study.

The use of hyperpolarized xenon gas in this setting remains investigational, but is emerging as a safe nonionizing approach for mapping and quantifying regional airway obstruction in the pediatric population. It has been shown to be more sensitive to early disease than the current clinical gold standard of measuring forced expiratory volume in 1 second (FEV_1) by spirometry, Laura L. Walkup, PhD, said at the combined annual meetings of the Center for International Blood & Marrow Transplant Research and the American Society for Blood and Marrow Transplantation.

The ^{129}Xe MRI provides regional information that spirometry cannot, allowing for a targeted approach to planned procedures such as bronchoscopy, said Dr. Walkup of Cincinnati Children's Hospital Medical Center.

"We hypothesized that hyperpolarized ^{129}Xe MRI would be sensitive to lung abnormalities in the pediatric HSCT population," she said.

Of 13 patients aged 6-13 years (mean, 10 years) who were enrolled in the study and underwent ^{129}Xe-MRI, 9 also completed spirometry successfully, and the average FEV_1 in those patients was 83% of the predicted value.

Ventilation deficits were apparent on the ^{129}Xe MRI imaging in 8 of the 13 subjects and varied in regional distribution. The whole-lung ^{129}Xe ventilation defect percentage for the HSCT group was 14%, which was significantly greater than the approximately 6% ventilation defect percentage in a cohort of age-matched controls, Dr. Walkup said, noting that ventilation deficits were seen in three of four subjects who were unable to complete reliable spirometry.

"So those are lung abnormalities that may have otherwise gone undetected," she said, adding that hyperpolarized xenon gas also highlighted the wide individual variation in ventilation, even among cases with similar FEV_1 percentages.

The findings are notable, because pulmonary complications such as bronchiolitis obliterans are a major source of morbidity and mortality in the pediatric HSCT population, and an accurate and early diagnostic tool identifying the location and severity of suspected obstructive lung pathology following HSCT is desperately needed, she said.

The HSCT patients in the current study included four boys and nine girls. Isotopically-enriched xenon gas (86% ^{129}Xe) was hyperpolarized using a commercial polarizer and images were acquired during a breath hold of up to 16 seconds and up to 1 L of xenon gas. Conventional anatomic MR images also were acquired.

The ^{129}Xe ventilation was quantified using a less than 60% mean whole-lung ^{129}Xe signal threshold, and was compared to FEV_1 percentage predicted as measured via spirometry.

The procedure was well tolerated by all patients, Dr. Walkup said, noting that no patients withdrew from the study, and all were able to maintain the required breath hold.

Drops in blood oxygen saturation level did occur, but were transient and resolved within 10-30 seconds of normal breathing. Further, there were no changes in heart rate during imaging, and any side effects related to xenon, such as tingling in extremities, dizziness, or euphoria, were also quickly resolved with normal breathing, she said.

"There were no serious adverse events related to the study ... these results are in good agreement with

Continued on following page

Hurricane relief and patient care

BY LTC HERBERT KWON, MC, USA

In October 2017, in support of the Federal Emergency Management Agency's response to assist the Governor and people of Puerto Rico, three Department of Defense (DOD) military hospital platforms were deployed; one each, by the US Army, Navy, and Air Force. They arrived on the island at different times with predominantly wartime surgical capabilities and augmented the Federal Emergency Management Agency (FEMA), US Public Health Service, National Guard, and Puerto Rico Department of Health efforts. My perspective is that of patient care and transport between the Centro Medico hospital complex in San Juan, the larger regional hospitals, the Veterans Administration hospital, the DOD response, FEMA Disaster Medical Assistance Teams (DMAT), and FEMA Federal Medical Shelters about 4 to 6 weeks after Hurricanes Maria and Irma struck. Based upon this experience, I would like to offer the following.

Pre-Disaster: All clinicians have a few patients that teeter "on the edge." When basic services go away, these patients fall over that edge and become inpatients. Establish a list of patients who require oxygen and devices such as vests, cough-assist, or ventilation. If evacuation before the disaster is possible, those patients need to leave. If they refuse, or are unable to leave, they need to be able to supply their own generated power for a prolonged period of time, as batteries will run out prior to power restoration. They must be able to use oxygen concentrators, as tank re-supply may not be readily available. By law, FEMA cannot give generators to individuals, so individuals must prepare for themselves. In a hurricane-prone area where seasonal risk can be established, planning medication refills at the beginning of the season or giving a larger than normal supply may prove useful. In an area prone to sudden disaster, such as earthquake or tornado, then counseling patients to request refills at least 2 weeks early may be adequate.

Post-Disaster: The most reliable form of communication will be text. You likely already have text contacts for your staff and family members; add other providers, responders, planners, pharmacists, and oxygen suppliers to your text contacts. While you may wish to share a text point of contact with patients, understand that your ability to actually help during the initial disaster will likely be limited. Identify possible language translation needs and possible translators among your staff and/or friends as telephone services will be limited or absent following the disaster. Finally, identify your local emergency response planners on Facebook, Twitter, or other social media feeds. This will allow you to direct others to these sites for accurate information after the disaster.

Responder Recommendations: A single social media post can DESTROY your plans and hamper your efforts. Advertise a single contact point and an information resource (eg, bulletin board, webpage) early and often. Publicly and accurately declare the means by which people will access health care and health-care services, such as medications, dialysis, and oxygen. There will be nongovernment organizations (NGOs), friends, and other well-meaning individuals who will try to assist people in need through unconventional channels. Yet, by requesting assistance through nonroutine channels, those efforts tend to delay assistance, cause confusion, and/or squander resources. Continue to direct those requests through the established response channels, ie, the local 911 equivalent.

Plan to use cellular texts to communicate. While satellite telephones are great in concept, in execution, they are difficult to utilize when transmitting complex medical information. If you have an expansive budget, there are now devices available that allow for Iridium satellite-based text communications that require batteries but not intact cellular towers.

Facilities with electricity, water, oxygen, medications, laboratory testing, and CT scanners need to be identified and advertised within the responder community. If FEMA is involved, these resources will be identified and updated on a routine basis. The information will be distributed to their DMAT teams. Those DMAT teams will be distributed throughout the response area. Additionally, if the resources and budgeting are approved, then FEMA will also help re-establish medical transport, as well as Federal Medical Shelters (FMS). The FMS can temporarily house patients who can perform basic activities of daily living but require power, oxygen, or medication administration. For those patients in need of medications without insurance, FEMA may activate medication assistance through the Emergency Prescription Assistance Program. This will allow up to 30 days of medication to be distributed at no cost to the individual through participating pharmacies.

External responders will obviously need to pair with local providers/professionals who can navigate the system and, if necessary, can translate medical terms and care plans. Additionally, external responders will be targets for individuals looking to obtain resources for secondary gain or profit. Establishing a plan or consistently redirecting people to the appropriate resources for those needs may limit the inevitable damage these individuals will cause. Additionally, understand that the efficiencies of the modern society will be gone, and tasks will take much longer than expected. Even if you can communicate by text, the transporting of patients, delivering supplies, meeting with groups, and assessing sites will take far longer than you are used to when none of the stoplights are functional or if gasoline is in limited supply.

Finally, there will be patients for whom no solution, short of an intact, well-resourced medical system, exists—those with severe congenital issues, patients with advanced dementia, patients with advanced cancer, and those with multiple-antibiotic-resistant osteomyelitis are a few of the patients that this response encountered. If transport out of the area is unavailable, NGOs and other charities may be the best, and at times, the only resource for these patients. During this response, I observed NGO and charities helping individual patients and their families with their power, shelter, and medical needs that could not be legally provided by federal government response.

While I hope you may never need to use them, preparations for evacuation, medication, power, and communications before a potential disaster occurs will prove helpful to your patients. After the disaster, consistent and simple communications to the public will be necessary to limit the damage from the social media rumor mill. Working within the organized response framework and leveraging local knowledge and targeted NGO involvement will maximize the effect of your efforts.

Dr. Kwon is Chief, Pulmonary-Critical Care-Sleep Medicine Service, Madigan Army Medical Center, Tacoma, Washington. The views expressed are those of the author and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US Government.

Continued from previous page

previously published safety assessments of xenon in kids and in adults, and at our institution we routinely perform xenon imaging in children as young as age 6," she added.

The findings, which are consistent with those seen in studies of other conditions such as cystic fibrosis, asthma, and chronic obstructive pulmonary disease, suggest that ^{129}Xe MRI is an emerging modality with strong translational potential for detecting early pulmonary involvement following HSCT, she said.

"The real power of the xenon MRI is the spatial information that it provides; we can use that information to plan targeted procedures like bronchoscopy and biopsies ... and since it is nonionizing, it may be used serially to assess disease progression or response to an intervention," Dr. Walkup said.

She noted, however, that, because it is not yet approved by the Food and Drug Administration and because it requires specialized expertise and hardware, it is available at only a handful of centers worldwide.

There is a long way to go before the technology will be widely clinically implemented, but work is ongoing at Cincinnati Children's Hospital to determine how xenon MRI may play a role in pulmonary screening of patients, she said.

Dr. Walkup reported having no financial disclosures.

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SOURCE: Walkup LL et al. 2018 BMT Tandem Meetings, Abstract 56.

Higher rifampin doses for pulmonary TB discussed

BY NEIL OSTERWEIL
Frontline Medical News

BOSTON – Current daily doses of rifampin for treating pulmonary tuberculosis may be too low and could be safely increased, results of a randomized phase 2 study suggest.

"Back in the 1970s, rifampin was an expensive drug, and attempts to shorten TB therapy using higher but intermittent doses of rifampin were unsuccessful at that time because of increased toxicity. That line of inquiry was essentially dormant for 40 years," said Gustavo Velásquez, MD, from Brigham & Women's Hospital in Boston.

Neil Osterweil/Frontline Medical News

Dr. Gustavo Velásquez

More recent controlled trials have evaluated higher daily doses of rifampin, but none thus far have looked at concentration-dependent drug activity in Latin American patients or at efficacy as a function of the parameter that is thought to best predict rifampin activity, which is the ratio of the area under the curve to the maximum inhibitory concentration (AUC/MIC) of rifampin, he said at the Conference on Retroviruses and Opportunistic Infections.

To get a better idea of optimal rifampin dosing for the treatment of pulmonary TB, Dr. Velásquez and his colleagues conducted the HIRIF (High-Dose Rifampin in Patients With TB) trial. The phase 2 study was designed to evaluate the pharmacokinetics, efficacy, and safety of higher daily rifampin doses for pulmonary TB.

They looked at the three parameters across three treatments arms: 10 mg/kg rifampin (the current standard of care), 15 mg/kg, or 20 mg/kg.

Patients in Peru were screened, enrolled, and randomized in cohorts of 60 patients each to one of the three specified dose levels, which they received either as additional rifampin tablets or placebo for the first 8 weeks of treatment, after which all patients were continued on rifampin 10 mg/kg to complete a 6-month regimen. All patients were followed for an additional 6 months for assessment of TB recurrence.

Rifampin total doses ranged from as low as 300 mg for patients in the 30-kg to 37-kg weight range, to as high as 1,500 mg for those weighing more than 70 kg.

The efficacy analysis was by

modified intention to treat, excluding 6 patients who had insufficient $\log_{10}$ colony-forming units (CFUs) of TB, and a per-protocol analysis excluding an additional 42 patients whose doses of rifampin were affected by three study halts for adverse events. After each halt and review by the data safety–monitoring board, the trial was allowed to resume, but because enrollment and experimental dosing also were suspended, patients in the 15- and 20-mg/kg arms received 10 mg/kg during the 2- to 5-week halts. The number of patients in the 10-, 15-, and 20-mg/kg doses included in the per-protocol analysis were 56, 38, and 38, respectively,

Controlled trials have evaluated higher daily doses of rifampin, but none thus far have looked at concentration-dependent drug activity in Latin American patients or at efficacy as a function of the parameter that is thought to best predict rifampin activity.

Pharmacokinetic evidence from this study, previously published, showed that the median maximum drug concentration (C_{max}) in serum

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in the experimental arms reached the lower end of the targeted range of 8 mcg/mL or greater, whereas the median in the standard-of-care arm was 6.2 mcg/mL. Only 33% of patients in the 10-mg/kg arm reached the minimum 8-mcg/mL level, Dr. Velásquez noted, vs. 72% and 81% of patients in the 15- and 20-mg/kg doses, respectively.

In the modified intention-to-treat population, for every 5-mg/kg increase in rifampin dose, there was a nonsignificant trend toward faster decline in TB CFUs in sputum. Similarly, for every 1-log increase in rifampin AUC/MIC, there was a trend, albeit nonsignificant, toward faster decline.

However, in patients in the per-protocol analysis, every 5-mg/kg dose increase and 1-log increase in rifampin AUC was associated with significantly faster declines in CFUs (P = .022 and .011, respectively).

An analysis of treatment outcomes at 12 months, a secondary endpoint, showed that there were five cases of treatment failure, including three in the control arm and one each in 15- and 20-mg/kg arms, and six cases of recurrence after cure, which occurred in three, one, and two patients, respectively,

The safety analysis by intention-to-treat showed that the incidence of grade 2 or greater rifampin-related adverse events

(AEs) were 43.3%, 51.7%, and 38.3% in the 10-, 15-, and 20-mg/kg doses, differences that were not statistically significant.

In addition, there were no significant differences among the treatment arms in either time to first grade 2 or greater rifampin-related AEs, the occurrence of one or more grade 2 or greater hepatic rifampin AEs, or time to first hepatic rifampin-related AEs of grade 2 or above.

"[With] high-dose rifampin, I think we have a really very robust body of literature to which this study can be added, demonstrating the safety of high-dose rifampin in the context of TB treatment," noted Dr. Benson.

Dr. Velásquez noted that the study was limited by the possibility that the study halts could have biased efficacy effect estimates toward null and by differences in weight distribution among the three treatment arms.

"This actually is the first trial that shows not only a dose response of rifampin but also an exposure response of rifampin in combination therapy," he said. "Our study supports that even higher doses of rifampin beyond what we studied of 20 mg/kg should be studied for potential treatment shortening." The evidence also suggests that the current 10-mg/kg dose is low and could be safely increased to a 15- or 20-mg/kg dose, he concluded.

In a media briefing following the presentation, moderator Constance Benson, MD, from the University of California San Diego, who was not involved in the study, commented that, with "high-dose rifampin, I think we have a really very robust body of literature to which this study can be added, demonstrating the safety of high-dose rifampin in the context of TB treatment."

"There are some circumstances where I think using a much higher dose than we've been using would be an appropriate thing to do," she added.

Examples of patients who might benefit include patients with disseminated TB or people with more serious TB than the average case, she said.

The study was supported by the National Institute of Allergy and Infectious Diseases. Dr. Velásquez and Dr. Benson reported no relevant conflicts of interest.

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SOURCE: Velásquez G et al. CROI 2018, Abstract 39LB.

Women working in medicine shout #MeToo

BY CHRISTINA JEWETT
Kaiser Health News

Annette Katz didn't expect to be part of a major social movement. She didn't set out to take on a major health organization. But that all began to change when a coworker saw her fighting back tears and joined Ms. Katz to report to her union what amounted to a criminal sexual offense at a Cleveland Veterans Affairs Medical Center in 2012 and 2013.

Four years later, Ms. Katz, a licensed practical nurse at the hospital, testified in a court deposition that a male nursing assistant had shoved her into a linen closet and groped her and subjected her to an onslaught of lewd comments.

In speaking out and taking legal action, Ms. Katz joined a growing group of women who are combating sexual harassment in the medical field at every level, from patients' bedsides to the executive boardroom.

Much as the #MeToo moment has raised awareness of sexual harassment in business, politics, media, and Hollywood, it is prompting women in medicine to take on a health system where workers have traditionally been discouraged from making waves and where hierarchies are ever present and all commanding. While the health care field overall has far more women than men, in many stations of power the top of the pyramid is overwhelmingly male, with women occupying the vast base.

In a recent survey, 30% of women on medical faculties reported experiencing sexual harassment at work within the past 2 years, said Reshma Jagsi, MD, who conducted the poll. That share is comparable to results in other sectors, and as elsewhere, in medicine it had been mostly taboo to discuss before last year.

"We know harassment is more common in fields where there are strong power differentials," said Dr. Jagsi, director of the Center for Bioethics and Social Sciences in Medicine at the University of Michigan, Ann Arbor. "And we know medicine is very hierarchical."

Workers in the health care and social assistance field reported 4,738 cases of sexual harassment from fiscal 2005 through 2015, eclipsed only by fields such as hospitality and manufacturing, where men make up a greater proportion of the workforce, according to data gathered by the Equal Employment Opportunity Commission.

A Kaiser Health News review of dozens of legal cases across the United States shows similar patterns in the waves of harassment cases that have cropped up in other fields, from entertainment to sports to journalism: The harassers are typically male; the alleged harasser supervises or outranks the alleged victim; there are slaps on the butt, lewd comments, and requests for sex; and when superiors are confronted with reports of bad behavior, the victims, mostly women, are disbelieved, demoted, or fired.

But recently, physicians have taken to Twitter using the #MeTooMedicine tag, sharing anecdotes and linking to blogs that chronicle powerful doctors harassing them or disrobing at professional conferences.

Women who work in cardiology recently told the cardiology trade publication TCTMD that they felt the problem was particularly widespread in their specialty, where females account for 14% of the physicians. A Los Angeles anesthesiologist made waves in a blog post urging "prettier" women to adopt a "professional-looking, even severe, hair style" to be taken seriously and to consider self-defense classes.

Among those speaking out is Jennifer Gunter, MD, a San Francisco obstetrician-gynecologist who recently wrote a blog post about being groped in 2014 by a prominent colleague at a medical conference – even naming him.

In a recent survey, 30% of women on medical faculties reported experiencing sexual harassment at work within the past 2 years, said Dr. Jagsi, who conducted the poll. That share is comparable to results in other sectors.

"I think nothing will change unless people are able to name people and institutions are held accountable," she said in an interview. "I don't think without massive public discourse and exposure that things will change."

Lawsuits, many settled or still making their way through the courts, describe encounters.

A Florida nurse claimed that in 2014, a surgeon made lewd comments about her breasts, asking her in a room full of people whether he should "refer to her as 'JJ' or 'Jugs,'" the nurse's lawsuit says. The nurse said she "responded that she wished to be called by her name."

In other cases: A phlebotomist in New York alleged in a lawsuit that a doctor in her medical practice gave her a box of Valentine's Day candy and moved in for an unwanted kiss on the mouth. A Florida medical resident alleged that a supervising doctor told her she looked like a "slutty whore." A Nebraska nurse claimed that a doctor she traveled with to a professional conference offered to buy her a bikini, if he could see her in it, and an extra night in a hotel, if they could share the room. She declined.

A Pennsylvania nurse described the unsatisfying response she got after reporting that a colleague had pressed his pelvis against her and flipped through her phone for "naked pictures." A supervisor to whom she reported the conduct expressed exasperation, saying "I can't deal with this" and "What do you want?"

Kayla Behbahani, DO, chief psychiatry resident at University of Massachusetts Memorial Medical Center, Worcester, did not file a lawsuit but recently wrote about sexual harassment committed by a subordinate. In an interview, she said her instincts were to pity the man and also to follow a dictate that's drilled into medical students: Don't make waves. So, she disclosed the harassment only after another woman's complaint launched an investigation.

"As a professional, I come from a culture where you go with the flow," Dr. Behbahani said. "You deal with what you're dealt. In that regard, it was a dilemma for me."

Ms. Katz, the Veterans Affairs nurse, initially didn't complain about the harassment. A single mother with two children, she needed her job. Her attacker, M.D. Garrett, was also a nursing assistant but had more seniority, was a veteran, and was friends with her boss.

"I really did feel that I would lose my job," Ms. Katz said in an interview. "I would be that troublemaker."

But as the abuse escalated, she went to the VA inspector general and the Cleveland police.

She estimated that five times Mr. Garrett pushed her into a closet where he would ask for sex. She would "tell him 'no' and fight my way out of [his] grip," her statement said. He shoved her into an unconscious patient's bathroom and would "try to restrain me, but I eventually could break free."

After one such assault, a colleague noticed tears in Ms. Katz's eyes. The coworker shared with Ms. Katz that she, too, had been a target of Mr. Garrett's lewd behavior.

Ms. Katz and the colleague filed complaints in March 2013 with their union, with the police, and with their managers. That July, Mr. Garrett was indicted by a grand jury and later pleaded guilty to three counts of sexual imposition and one count of unlawful restraint. He was also dismissed from his job.

Reached by phone, Mr. Garrett said he agreed to the plea because he was facing multiple felonies and didn't know what a jury would do. He said that, even though he pleaded guilty to four misdemeanors, he did not commit the crimes of which he was accused. "There was no harassment; she and I were friends," he said.

In 2013, Ms. Katz sued the VA, alleging that it failed to protect her from harassment and retaliated against her by refusing to give her a job-site transfer before firing her for not showing up to work.

The VA attorneys argued that the department had no direct knowledge of harassing behavior before Ms. Katz reported it and that, once it was informed, immediate action was taken. Veterans Affairs Deputy Press Secretary Lydia Blaha said in an email that anyone engaged in sexual harassment is swiftly held accountable.

The U.S. Department of Veterans Affairs agreed in February 2018 to pay $161,500 to settle Ms. Katz's lawsuit.

Ms. Katz said it was costly and emotional to press on with her legal case but hopes it helps other women see that seeking justice is worthwhile. "I do think there are a lot of women who just suffer in silence," she said.

Dr. Gunter, the San Francisco physician-blogger, said that needed change will come only when people who are more established across all professions stand up for those who are more junior.

KHN's coverage of these topics is supported by the John A. Hartford Foundation and The David and Lucile Packard Foundation. Kaiser Health News is a nonprofit news service covering health issues. It is an editorially independent program of the Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

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Gender bias in academic medicine is treatable

BY TED BOSWORTH
Frontline Medical News

TAMPA – Gender bias that disadvantages women from rising in academic medicine might require specific habit-changing strategies rather than efforts that draw on goodwill alone, according to new follow-up data from a randomized trial discussed and reevaluated at the annual meeting of the American College of Psychiatrists.

One premise of this trial, supported by other research, is that entrenched gender stereotypes drive both male and female behavior and must be addressed directly for change, said Molly Carnes, MD, professor of psychiatry at the University of Wisconsin, Madison.

The initial results of the trial, which randomized academic departments at the University of Wisconsin to participate in habit-changing workshops or to serve as controls, were published almost 3 years ago (Acad Med. 2015 Feb;90[2]:221-30). It is the most recent follow-up (Devine et al. J Exp Soc Psychol. 2017 Nov;73:211-5) that corroborates that long-term changes are possible with intervention.

The published findings showed that, when 1,137 faculty members from 46 departments in the experimental arm were compared with 1,153 faculty members from 46 departments in the control arm, there were significant improvements in the experimental arm in surveyed attitudes reflecting personal bias awareness ($P = .001$) and willingness to support gender equity ($P = .013$).

These changes in attitude translated into concrete changes in new female faculty hires in the most recent analysis. From 32% in a 2-year period before the workshops, the new female hires climbed to 46% in the 2-year period after the workshops – a relative increase of 44% in the departments participating in the experimental arm. In the control departments, female new faculty hires remained at 32% in both time periods.

"Basically, there are 20 new women faculty members at the University of Wisconsin because of this study," Dr. Carnes said.

The training was not designed to change just male faculty perceptions but perceptions of both males and females. The result was a fundamental change in culture within departments randomized to the experimental arm, according to data generated by a variety of study analyses.

"When we looked at questions about department climate, we found that both male and female faculty members in the experimental groups were significantly more likely to say they fit in their department, they felt respected for their research and scholarship by their colleagues, and they felt comfortable raising personal and family issues even if they conflicted with departmental activities," Dr. Carnes said.

This general attitude change is important because, Dr. Carnes emphasized, women share the cultural biases that can result in reduced female career opportunities in clinical and academic medicine. In addition, women generally are aware that stereotypical positive "agentic" adjectives for men, such as decisive, competitive, and ambitious, often are viewed negatively and generate backlash when applied to women. They therefore act on this awareness.

"Stereotype-based bias is a habit that can be broken, but it requires more than good intentions," said Dr. Carnes, who emphasized that "gender-based assumptions and stereotypes are deeply embedded in the patterns of thinking of both men and women."

As one example, Dr. Carnes cited her work evaluating female resident behavior when leading in-hospital code resuscitations. There are data to show that there is no difference in the effectiveness of male and female resident code leaders, but women typically feel that the assertive, aggressive behavior required for code leadership is "counternormative." After the code, some women feel compelled to apologize to team members for being demanding or assertive, a step that Dr. Carnes attributed at least in part to fear of backlash from stepping out of gender-expected behavior.

The fix is not necessarily suppression of gender-related attributes. Dr. Carnes cited evidence that the stereotypical positive communal adjectives for women, such as nurturing, supportive, and sympathetic, might explain why studies suggest that women are more likely than men to be transformational leaders who inspire team members to contribute beyond their own self-interest in achieving goals.

Ultimately, the fix is replacement of stereotypes that keep men as well as women from defusing biases that "lead to subtle unintentional advantages in academic career advancement for Jack not afforded to Jill," Dr. Carnes said. Based on the low numbers of female leaders in academic medicine decades after medical schools began enrolling women in substantial numbers, she concluded that meaningful change in gender bias is not likely to occur without implementation of specific proactive strategies aimed at challenging current perceptions. Her published study confirms that such strategies can help.

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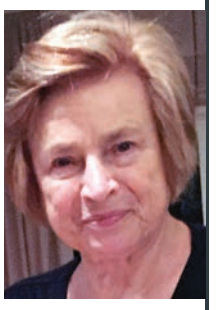
VIEW ON THE NEWS

Giving women a start on university science faculties



Hiring of women increased in the intervention group, compared with the control (odds ratio, 2.23). However, since women faculty left at a higher rate than did men during the same period, the gender distribution within these STEMM departments did not change. It seems that this one-time short workshop altered behavior to allow more highly educated women to get a first faculty position at a prominent university. This is a good start but does not address the problem of women getting to the top on the faculty.

Bevra H. Hahn, MD, is Distinguished Professor of Medicine (emeritus) at the University of California, Los Angeles.

Cyberliability insurance: Should you purchase a policy?

BY ALICIA GALLEGOS
Frontline Medical News

As hackers become more sophisticated, these cybercriminals are finding novel ways to access protected health data, leaving health care providers to pick up the costly pieces of their crimes.

In 2017, there were at least 477 publicly reported health data breaches in the United States, affecting some 5.6 million patients, up from 450 health care breaches in 2016, according to Protenus, a health care cybersecurity vendor that tracks data breaches reported to the U.S. Department of Health & Human Services.

When medical files are stolen, physicians are on the hook for more than just a possible ransom request; they also face thousands of dollars in potential fines, fees, and legal costs, said Joshua R. Cohen, JD, a medical malpractice defense attorney based in New York. To mitigate the consequences, cybersecurity experts say physicians should consider purchasing cyberliability insurance, a relatively new coverage policy that protects against data breaches and subsequent lawsuits.

"A breach is very expensive," said Mr. Cohen, chair for the New York City Bar Association Committee on Medical Malpractice. "You have the fine to the Office for Civil Rights, which can be in the millions of dollars, and you're going to have to ameliorate the breach, which can be hundreds of dollars per person, let alone deal with lawsuits from the patients."

Cyberliability: What's the risk?

Cyberliability refers to legal dangers arising from data breaches, privacy law violations, and ransomware/cyberextortion threats, as well as data loss and business interruption from computer system failures.

Of the 477 breaches in 2017 analyzed by Protenus, 37% were from hacking, 37% resulted from insider incidents, and 16% stemmed from data loss or theft. About 10% of cases resulted from unknown causes, according to the report.

Data breaches caused by hackers and malware attacks are rising in the health care sector, said Katherine Keefe, global head of breach response services for Beazley, a national cyberliability insurer and risk management company. Beazley handled 2,615 data breaches in 2017, more than half of which were health care related, Ms. Keefe said in an interview. The top three causes of health care breaches reported to Beazley in 2017 were accidental disclosure, hack or malware, and insider incidents, according to a recent report from that company

Ms. Keefe noted that Beazley has seen a recent surge of phishing emails – electronic attempts to gain sensitive information for malicious reasons by disguising the sender as a trusted source. The emails often request that employees click on a link and change a password in an effort to steal data or gain access to medical records.

"We see an awful lot of that," Ms. Keefe said. "There's been a real surge in successful phishing emails and social engineering that enables criminals to identify medical practice leaders. It's not hard to dress up an email to look like it's coming from a specific individual. There are all kinds of increasingly sophisticated tactics to trick people into letting criminals into their systems or tricking people into forwarding money or valuable information."

Hackers frequently use phishing emails to get employees to download a payload, the portion of malware that performs malicious actions, Mr. Cohen added. Once downloaded, payloads can do significant damage to a medical practice.

"Once you get hit with these payloads, not only can they start pulling information out of the computer system, they can also start doing things such as turning on laptop cameras, reading emails, listening in on computer microphones," he said. "All they need is one employee to click."

Cybercoverage: Is it needed?

To protect themselves from potential breach expenses, more medical practices are purchasing cyberliability insurance policies. A 2017 survey of 270 insurance brokers and 125 underwriters found that health care has more first-time buyers of standalone cyberliability insurance than does any other industry.

However, Mr. Cohen advises that practices should do their research before buying and be aware of the different types of policies, coverage limits, and insurance options.

"Be careful about what it covers," he said. "Are they going to pay for all the amelioration for all the patients affected? Some policies will cover 'repairing and disinfecting the system,' but they will not likely cover all the [Office for Civil Rights] fines."

The Doctors Company, a national medical liability insurer, provides $50,000 in cybersecurity coverage to all its insured physician members and the option to increase coverage by $1 million in additional protection, according to Crystal Brown, senior vice president of underwriting for the Doctors Company. The coverage protects against regulatory and liability claims arising from theft, loss, or accidental transmission of patient or financial information, as well as the cost of data recovery. Another policy offered protects against claims arising from administrative actions pertaining to utilization, licensing, credentialing, and misconduct.

"In health care, data breaches are not a matter of 'if' but 'when,'" Ms. Brown said in an interview. "With the costs of breach response and potential HIPAA violations now reaching several hundred dollars per stolen medical record, we urge physicians to carefully evaluate their risks and make certain they are adequately protected."

Meanwhile, national medical liability insurer ProAssurance offers health providers a basic cyberliability coverage endorsement in most states on its medical professional liability policy. The insurer also has a branded cyberprogram that allows clients to buy additional and broader coverage at a discounted premium.

"In today's electronic environment, we are hearing about breaches occurring at both small and large health care practices," said Melanie Tullos, vice president for ProAssurance. "Small physician practices are just as vulnerable, if not more so, to a cyberbreach and should take the necessary steps to protect patient data against an attack at all measures, including, but not limited to, purchasing cyberliability coverage.

The price of cyberliability insurance varies by risk and other factors, Ms. Tullos said. Generally, the cost of a $1 million cyberliability policy for a single physician practice is less than $1,000, whereas a group of 10 physicians can pay up to $8,000-$9,000, she said in an interview.

Beazley offers policies that cover the expenses and services associated with investigating whether a data breach has occurred, responding to breaches, and handling liability that may arise from the breach, said Ms. Keefe, of Beazley, which works with companies such as the Doctors Company to provide coverage and also works with state-run malpractice programs to offer a cyberliability component for a small additional premium, she said.

Ms. Keefe stressed that cyberliability coverage can ensure that physician practices don't run up a hefty bill in the event of a data breach by paying for separate specialists and damage control.

"One of the reasons doctors should have cyberliability coverage are the costs associated with figur-

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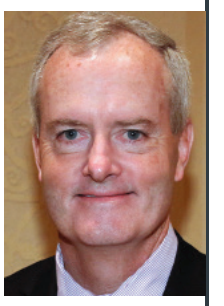
VIEW ON THE NEWS



Michael E. Nelson, MD, FCCP, comments: Being old enough to remember a paper chart and scheduling book, I can't help but marvel at the how the electronic health record (EHR) has fallen short of its expectations and added to the cost of medical care. Well, let's add cybersecurity insurance to the cost of doing business. While I love the ability to look at a chest x-ray or CT without a viewbox, I can't think of many other things that the EHR has done to make me a more efficient physician. It has, however, spawned many cottage industries that provide "must have" services with their attendant fees. The ever-increasing regulatory and administrative burdens and costs placed on physicians' practices is making it impossible for smaller practices to remain financially viable, leaving smaller communities without medical services. I don't think this was the intent when we decided to "modernize" medicine. It makes me want to go back to those Halcyon days of the paper chart – try phishing one of those, you hackers.

Expert argues for improving MACRA, not scrapping it

BY DENISE FULTON
Frontline Medical News

Even given the notable problems and challenges associated with Medicare's Merit-Based Incentive Payment System (MIPS), the program should be improved via pilot programs and demonstration projects, according to Gail R. Wilensky, PhD, economist and senior fellow at Project Hope and a former top health aide to President George H.W. Bush.

The Medicare Payment Advisory Committee (MedPAC) is set to recommend to Congress that the MIPS portion of the value-based reforms enacted under the Medicare Access and CHIP Reauthorization Act (MACRA) be eliminated and replaced with a Voluntary Value Program. MedPAC's report is due to Congress in March.

"Although I agree with MedPAC about the problems it has identified, I am also concerned about the commission's proposal," Dr. Wilensky wrote in an editorial published in the New England Journal of Medicine (doi: 10.1056/NEJMp1801673). She noted that a lack of support from major medical associations, combined with the impending midterm elections, means that it would be challenging to get a legislative fix through Congress.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: Dr. Wilensky made some cogent arguments as to why scrapping MIPS may not be such a good idea. In my mind, however, the final paragraph of the editorial was the most important. "Practicing physicians need make their views about the MIPS and its alternatives known to their representative medical groups and, if necessary, to their representatives in Congress as well. In the past, practicing clinicians have been woefully bad at making their voices heard. Now is a good time for that to change." Your future is being decided without you. The squeaky wheel gets the grease.

Continued from previous page

ing out what to do if patient records are lost or stolen," she said. "The cost of hiring a lawyer, hiring a forensics investigator to assess the situation, the cost of notifying the patients, and taking all the steps required by HIPAA can really add up. Most practices don't have those costs built into their annual budgets. A cyberpolicy acts as a buffer against those expenses."

Risk: Can it be managed?

Of course, there is plenty that practices can do to prevent – and protect themselves from – a health data breach before it happens. Providing employee awareness training is an important step, said Craig Musgrave, chief information officer of the Doctors Company. Institute a training program for staff at all levels and go over the basics, such as refraining from opening emails from senders they don't know, Mr. Musgrave wrote in a recent column. Updating all software regularly and backing up data is also essential. And Mr. Musgrave emphasizes the importance of "whitelisting."

"Health care systems are fragmented in their management of systems and data," Mr. Musgrave wrote in his column. "Their ability to patch legacy systems and employ cybersecurity staff varies enormously. Therefore, application whitelisting is essential. Rather than blacklisting known malicious software, an application whitelist prevents the launching of any executable program (known or unknown) that does not have explicit authorization. This, in combination with strong firewalls and network segmentation tools like micro-segmentation, provides stronger security."

In addition, consider implementing data security policies and incident response protocols, as well as employee training on securing patient data, ProAssurance's Ms. Tullos said.

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MedPAC to Congress: Eliminate MIPS

BY GREGORY TWACHTMAN
Frontline Medical News

The Medicare Payment Advisory Commission has formally recommended to Congress that it repeal the Merit-based Incentive Payment System track of Medicare's Quality Payment Program.

MedPAC "has concluded that ... the Merit-Based Incentive Payment System (MIPS) will not fulfill its goals and therefore should be eliminated," the commission said in its March 15 report to Congress. MedPAC added that the "basic design of MIPS is fundamentally incompatible with the goals of a beneficiary-focused approach to quality measurement."

The commission notes that the design of MIPS measures quality and adjusts payments based on measures chosen by the individual physician. "But a system built on this design will be inequitable, because clinicians will be evaluated and compared on dissimilar measures. In addition, many clinicians will not be evaluated at all because, as individuals, they will not have a sufficient number of cases for statistically reliable scores."

MedPAC adds that, by the Centers for Medicare & Medicaid Services' own estimates, more than half of clinicians will be exempt from reporting on MIPS based on the low-volume threshold that exempts providers who bill for $90,000 or less in Medicare claims or see 200 or fewer Medicare patients.

The advisory panel also highlighted other flaws. Those include MIPS' onerous reporting burden; measures that do not allow for meaningful comparisons among clinicians; differing rules for clinicians depending on location, practice size, and other factors; and payment adjustments that could vary wildly from year to year, creating financial uncertainty for physicians.

The commission, which voted 14-2 in favor of eliminating MIPS, also recommended it be replaced with a "voluntary value program." But it has offered Congress only a conceptual direction for that replacement program.

"This voluntary value program (VVP) is based on the premise that patient outcomes rely on the combined contributions of clinicians and emphasizes that quality improvement is a collective effort," according to the report.

The VVP would measure all clinicians based on the same set of measures: clinical quality, patient experience, and value. And it would do so on a population level, rather than the individual patient level.

MedPAC sees the VVP not as an end goal in the transition to paying for value but rather a stepping stone to get clinicians more comfortable with value-based payments en route to moving into the QPP's advanced alternative payment model (A-APM) track.

MedPAC "has concluded that ... the Merit-based Incentive Payment System (MIPS) will not fulfill its goals and therefore should be eliminated," the commission said.

"A VVP's penalties and rewards might not be significant enough to meaningfully change clinician behavior," the report stated. "However, the intent is to get clinicians comfortable with being measured in a manner similar to the way they would be in A-APMs. With that experience, clinicians would be poised to form or join robust A-APMs, under which the risk and reward are more meaningful, and the potential for true delivery system reform is within reach."

There was a near unanimous consensus among MedPAC commissioners that MIPS is flawed, but not all commissioners were ready to give up on it – especially considering how much clinicians have already invested in the program.

MedPAC also heard from the American Medical Association, which voiced opposition to the idea of ending MIPS. In addition, the commission received written feedback from physicians against its proposal.

Other experts, such as Gail R. Wilensky, PhD, support preserving MIPS. (Some of Dr. Wilensky's comments on this topic are summarized in a separate article on this page.)

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For patients with COPD taking fluticasone furoate/vilanterol who need additional lung function improvement

LESS TO TAKE.
MORE TO TAKE IN.

TRELEGY – The only once-daily triple therapy (ICS/LABA/LAMA) for COPD delivered in a single inhaler

COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroid; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

INDICATION

TRELEGY is for maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema, who are on fluticasone furoate and vilanterol (FF/VI) and need additional treatment of airflow obstruction or who are already taking umeclidinium and FF/VI. TRELEGY is NOT indicated for relief of acute bronchospasm or asthma.

IMPORTANT SAFETY INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA.

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

Please see additional Important Safety Information for TRELEGY on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for TRELEGY following this ad.

gsk | INNOVIVA

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

Patients experienced greater lung function with TRELEGY vs patients taking fluticasone furoate/vilanterol (FF/VI)

Primary endpoint: Change from baseline in trough FEV_1 at Day 85[1,2]
In patients with COPD run-in on FF/VI 100/25, TRELEGY provided

124 mL ADDITIONAL LUNG FUNCTION IMPROVEMENT

vs FF/VI
($P < 0.001$)

Similar results were demonstrated in a replicate study.

STUDY DESCRIPTION[1,2]

Design: 12-week, randomized, double-blind, parallel-group study. Following a 4-week run-in period on FF/VI 100/25, patients were randomized to treatment with umeclidinium (n=206) or placebo (n=206) added to FF/VI 100/25 (each administered once daily in the morning by the ELLIPTA inhaler). Treatment with TRELEGY refers to patients who received UMEC added to FF/VI 100/25.

Patients: COPD patients (mean age: 64 years). At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 46%, a mean postbronchodilator FEV_1/FVC ratio: 0.48, and a mean mMRC score of 2.5.

FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; UMEC=umeclidinium; VI=vilanterol.

IMPORTANT SAFETY INFORMATION (cont'd)

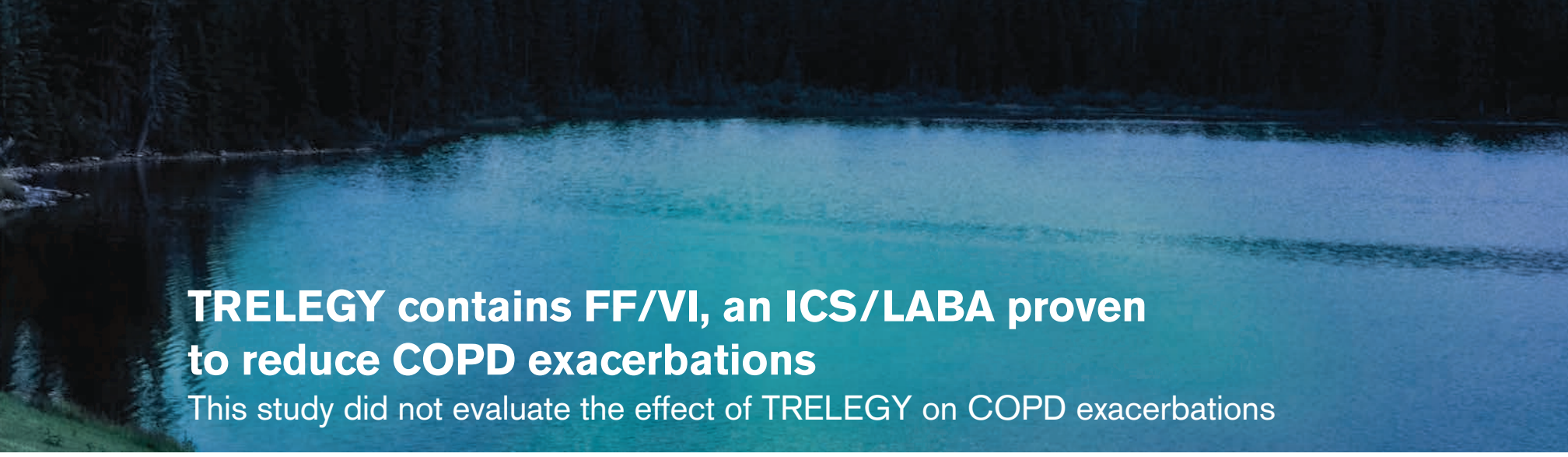
CONTRAINDICATIONS

- TRELEGY is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following use of inhaled corticosteroids, like fluticasone furoate.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.
- Particular care is needed for patients transferred from systemic corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.

Please see additional Important Safety Information for TRELEGY on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for TRELEGY following this ad.



TRELEGY contains FF/VI, an ICS/LABA proven to reduce COPD exacerbations

This study did not evaluate the effect of TRELEGY on COPD exacerbations

Primary endpoint: Annual rate of moderate/severe exacerbations[1,3]

In patients with a history of COPD exacerbations, FF/VI 100/25 provided

21% EXACERBATION REDUCTION

in annual rate vs vilanterol

0.90 vs 1.14 for FF/VI 100/25 and VI, respectively; *P*=0.024

Similar results were demonstrated in a replicate study.

STUDY DESCRIPTION[1,3]

Design: 12-month, randomized, double-blind, parallel-group study that evaluated the effect of FF/VI 100/25 mcg (n=403) and VI 25 mcg* (n=409) (each administered once daily by the ELLIPTA inhaler) on the rate of moderate/severe exacerbations. Patients with a history of ≥1 moderate or severe exacerbation in the previous year were randomized to treatment following a 4-week run-in period on fluticasone propionate/salmeterol 250/50 mcg twice daily.

Patients: COPD patients (mean age: 64 years). At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 46% and a mean postbronchodilator FEV_1/FVC ratio: 0.46.

Exacerbation severity criteria: Moderate if treatment with systemic corticosteroids and/or antibiotics was required and severe if hospitalization was required.

* Vilanterol is not approved as monotherapy.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects 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. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

To learn more, go to TrelegyMD.com

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

100% of eligible commercially insured patients will pay no more than $10 a month* for TRELEGY with savings offer

*Subject to eligibility. Restrictions apply. Offer is good for up to 12 uses. Patients in government programs, including Medicare, are not eligible for savings offers. Please see the savings offer for complete rules and eligibility.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids. 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 (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of inhaled corticosteroids or inhaled anticholinergics; therefore, monitoring is warranted.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develops.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develops.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in two 12-week clinical trials with umeclidinium + FF/VI, the components of TRELEGY, (and placebo + FF/VI) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% (<1%); diarrhea, 2% (<1%); cough, 1% (<1%); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).

DRUG INTERACTIONS

- TRELEGY 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 they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution, as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of TRELEGY with other anticholinergic-containing drugs, as this may lead to an increase in anticholinergic adverse effects.

USE IN SPECIFIC POPULATIONS

- Use TRELEGY with caution in patients with moderate or severe hepatic impairment, as fluticasone furoate systemic exposure may increase by up to 3-fold. Monitor for corticosteroid-related side effects.

Please see additional Important Safety Information for TRELEGY on the previous pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for TRELEGY following this ad.

References: 1. Data on file, GSK. **2.** Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. *Respir Med*. 2015;109(9):1155-1163. **3**. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*. 2013;1(3):210-223.

To learn more, go to TrelegyMD.com

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

Printed in USA. 831276R0 January 2018

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

BRIEF SUMMARY

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA *[see Warnings and Precautions (5.1)]*.

The safety and efficacy of TRELEGY in patients with asthma have not been established. TRELEGY is not indicated for the treatment of asthma *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

TRELEGY is indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.

Important Limitations of Use

TRELEGY is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

The use of TRELEGY is contraindicated in the following conditions: 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 Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death.

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (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 vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25,15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in TRELEGY.

No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with TRELEGY has been conducted. The safety and efficacy of TRELEGY in patients with asthma have not been established. TRELEGY is not indicated for the treatment of asthma.

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. TRELEGY has not been studied in subjects with acutely deteriorating COPD. The initiation of TRELEGY in this setting is not appropriate.

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.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If TRELEGY 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, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of TRELEGY beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of TRELEGY and Use With Other Long-acting Beta$_2$-agonists

TRELEGY should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines 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 TRELEGY should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of Inhaled Corticosteroids

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

5.5 Pneumonia

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

In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was less than 1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.
In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (less than 0.2 per 100 patient-years for each treatment group).

5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox 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 affect 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 a patient is 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 chickenpox 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; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients From Systemic Corticosteroid Therapy

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 with asthma 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 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 TRELEGY may control 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 physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRELEGY. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRELEGY. Lung function (forced expiratory volume in 1 second [FEV$_1$]), 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.

Continued on next page

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

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

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of fluticasone furoate in TRELEGY. 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), Drug Interactions (7.1)]*.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with TRELEGY 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 considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.10 Paradoxical Bronchospasm

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

5.11 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY *[see Contraindications (4)]*.

5.12 Cardiovascular Effects

Vilanterol, 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. If such effects occur, TRELEGY 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 *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

TRELEGY, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of adjudicated cardiovascular events (composite of myocardial infarction, stroke, unstable angina, transient ischemic attack, or on-treatment death due to cardiovascular events) was 2.5 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 2.7 for placebo, 2.4 for fluticasone furoate 100 mcg, and 2.6 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to cardiovascular events occurred in 82 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 86 subjects receiving placebo, 80 subjects receiving fluticasone furoate 100 mcg, and 90 subjects receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).

5.13 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 (eg, 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 TRELEGY and periodically thereafter. If significant reductions in BMD are seen and TRELEGY is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

5.14 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. TRELEGY should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (eg, 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 healthcare provider immediately if any of these signs or symptoms develops. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, and/or cataracts.

5.15 Worsening of Urinary Retention

TRELEGY, like all medicines containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

5.16 Coexisting Conditions

TRELEGY, like all medicines 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.

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines 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-agonist medications may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. TRELEGY is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

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

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10)]*
- Cardiovascular effects *[see Warnings and Precautions (5.12)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.14)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15)]*

6.1 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 TRELEGY is based on the safety data from two 12-week treatment trials with the coadministration of umeclidinium and the fixed-dose combination fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol, and on the long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, the fixed-dose combination of umeclidinium/vilanterol, and umeclidinium monotherapy. *[see Description (11), Clinical Pharmacology (12.3), and Clinical Studies (14.1) of full prescribing information]*.

Confirmatory Trials

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + 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 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/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 mcg/25 mcg presented in Table 1 is based upon the two 12-week trials.

Continued on next page

Table 1. Adverse Reactions With Umeclidinium + Fluticasone Furoate/Vilanterol With ≥1% Incidence and More Common Than Placebo + Fluticasone Furoate/Vilanterol (Trials 1 and 2)

Adverse Reaction	Umeclidinium + Fluticasone Furoate/ Vilanterol (n=412) %	Placebo + Fluticasone Furoate/ Vilanterol (n=412) %
Nervous system disorders		
Headache	4	3
Dysgeusia	2	<1
Musculoskeletal and connective tissue disorders		
Back pain	4	2
Respiratory, thoracic, and mediastinal disorders		
Cough	1	<1
Oropharyngeal pain	1	0
Gastrointestinal disorders		
Diarrhea	2	<1
Infections and infestations		
Gastroenteritis	1	0

Supporting Long-Term Safety Data

The long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, the fixed-dose combination of umeclidinium/vilanterol, and umeclidinium monotherapy are similar to that reported in the 12-week clinical trials described in Table 1. *[See full prescribing information for BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder), ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder), and INCRUSE ELLIPTA (umeclidinium inhalation powder).]*

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 long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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. Therefore, patients with COPD 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 when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRELEGY with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.14, 5.15)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY or its individual components, fluticasone furoate, umeclidinium, and vilanterol, in pregnant women to inform a drug-associated risk.

Clinical Considerations

Labor and Delivery: TRELEGY should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol, or from the underlying maternal condition.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of TRELEGY in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

TRELEGY has not been studied in subjects with hepatic impairment. Information on the individual components is provided below.

Fluticasone Furoate/Vilanterol

Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

Umeclidinium

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

TRELEGY contains fluticasone furoate, umeclidinium, and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to TRELEGY. Treatment of overdosage consists of discontinuation of TRELEGY 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 medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Fluticasone Furoate

Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.3 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use *of full prescribing information*).

Asthma-Related Death

Inform patients that LABA, such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. TRELEGY is not indicated for the treatment of asthma.

Not for Acute Symptoms

Inform patients that TRELEGY is not meant to relieve acute symptoms of COPD, and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Continued on next page

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with TRELEGY without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other LABA.

Local Effects

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing therapy with TRELEGY, but at times therapy with TRELEGY may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression

Advise patients that TRELEGY may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to TRELEGY.

Paradoxical Bronchospasm

As with other inhaled medicines, TRELEGY can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue TRELEGY and contact their healthcare provider right away.

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Ocular Effects

Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (eg, 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 if any of these signs or symptoms develops.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

Risks Associated With Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 09/2017 TRL:1BRS

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Printed in USA. 831276R0 January 2018

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

CHEST NETWORKS

Palliative care screening, sleep devices, novel biologics

Palliative and end-of-life care

Nurse-driven palliative care screening

Palliative care (PC) aims to improve quality of life for patients with a life-threatening illness, providing holistic patient-centered support along the continuum of the disease process. Although frequently implemented in critical care settings, integrating PC in the neuro ICU has been difficult to adopt in practice due to the uncertainty in prognostication of definitive outcomes and practice culture beliefs such as the self-fulfilling prophecy (Frontera, et al. *Crit Care Med.* 2015;43[9]:1964; Rubin, et al. *Curr Opin Crit Care.* 2017;23[2]:134; Knies, et al. *Semin Neurol.* 2016;36[6]:631).

DR. McCAMEY

At our institution, a nursing education project was conducted to pilot nurse-driven PC screenings on admission to the neuro ICU. The project evaluated nurse comfort and knowledge with identifying and recommending PC consults. Pre- and post-intervention surveys revealed that education and introduction of a PC screening tool significantly increased nurse comfort and knowledge of PC eligibility.

The screening also revealed that 62% of patients demonstrated a PC need. This pilot highlighted the neuro ICU patient population's need for routine PC screenings and that nurse-driven screenings can provide early identification of potential PC consultations.

PC in the neuro ICU can exist to contribute to successful outcomes in patient and family care. Within neurocritical care, incorporating PC is essential to provide extra support to patients and families (Frontera, et al. 2015).

For these reasons and data from the project, nurse-driven screening may encourage appropriate early PC consults. Patient-centered care is the ultimate goal in the management of our patients. Nurse-driven PC screening can help bring various unmet PC needs to the health-care team for opportunities that might not have been met or otherwise assessed. Consider implementing nurse-driven PC screening protocols at your institution to aid in collaborative and proactive interdisciplinary care.

Danielle McCamey, ACNP
Steering Committee Member

Sleep medicine

Diagnostics, devices, and sleep

The past several months have been busy for the Sleep Medicine NetWork. We have been working to represent the interests of our membership and our patients in many arenas.

Devices coded as **E0464**, defined as life support mechanical ventilators used with mask-based ventilation in the home are being more frequently used. According to the Office of the Inspector General (OIG), there has been an 89-fold increase in billing for **E0464** ventilators for Medicare and its beneficiaries between 2009 and 2015, increasing from $3.8M to $340M. In response, the Agency for Healthcare Research and Quality (AHRQ) requested a response to specific questions related to these devices.

DR. DAS

The CHEST Sleep Medicine NetWork, in conjunction with NAMDRC, submitted a document emphasizing the unique needs of patients of differing disease states (ie, how someone with neuromuscular disease differs from one with COPD) and why some patients may require an **E0464** device. The ability of CHEST staff and leadership to streamline evaluation and response allowed our voice to be heard in real-time.

In 2018, the CHEST Sleep Medicine NetWork will be participating in a Federal Drug Association-sponsored workshop entitled "Study Design Considerations for Devices including Digital Health Technologies for Sleep-Disordered Breathing (SDB) in Adults," along with other national organizations and leaders in our field. This workshop will address available technologies for the diagnosis, monitoring, and treatment of SDB, as well as trends for digital health technologies and clinical trial design considerations.

Finally, the Sleep Medicine NetWork has wasted no time after a successful CHEST 2017 in Toronto in planning for the next annual meeting in San Antonio. We are excited to present an exciting curriculum in Sleep Medicine at CHEST 2018, so stay tuned.

Aneesa M. Das, MD, FCCP
NetWork Chair

Occupational and environmental health

Post-deployment lung disease

Since the early 1990s, ongoing military deployments to Southwest Asia remain a unique challenge from a pulmonary symptomology and diagnostic perspective.

Various airborne hazards in the deployment environment include geologic dusts, burn pit smoke, vehicle emissions, and industrial air pollution. Exposures can give rise to both acute respiratory symptoms and, in some instances, chronic lung disease. Currently, data are limited on whether inhalation of airborne particulate matter by military personnel is linked to increases in pulmonary diseases (Morris MJ, et al. *US Army Med Dep J.* 2016:173).

Over the last 17 years, we learned that acute eosinophilic pneumonia and exacerbation of preexisting asthma is well documented, and the development of uncommon pulmonary disorders, such as constrictive bronchiolitis, remains controversial (Morris MJ, et al. *Ther Adv Respir Dis.* 2013;7[4]:235).

Ongoing research by the Veterans Affairs continues to enroll post-deployed personnel in an Airborne Hazard and Burn Pit Registry. Past approaches in evaluation of deployed individuals ranged from common tests such as spirometry, HRCT scanning, full PFTs, bronchoprovocation challenges, and, in some instances, lung biopsies (Krefft SD, et al. *Fed Pract.* 2015;32[6]:32). More novel evaluations of postdeployment dyspnea include impulse oscillometry, exhaled nitric oxide, bronchoscopy, and cardiopulmonary exercise testing (Huprikar, et al. *Chest.* 2016;150[4]:S934A).

Members of the CHEST Occupational and Environmental Health NetWork are currently updating comprehensive approaches to evaluate military personnel with chronic respiratory symptoms from deployments. Continued emphasis, however, should be placed on diagnosing and treating common diseases such as asthma, exercise-induced bronchospasm, GERD, and upper airway disorders.

Pedro F. Lucero, MD, FCCP
Steering Committee Member

Clinical pulmonary medicine

Biologics – Birth of a new era of precision management in asthma

An estimated 10% to 20% of patients with severe uncontrolled asthma do not respond to maximal best standard treatments, leading to substantial health-care costs. A paradigm shift is now underway in our approach to the care of these patients with the emergence of novel biologics targeting the complex and interconnected inflammatory pathways in asthma that result in a diverse profile of asthma endotypes and phenotypes (Fig 1).

Current FDA-approved biologics primarily target patients with a T2 high phenotype (Table1).

Table 1: Biologics currently approved in asthma

Biologic agent	Target	Route	Dosage	Anaphylaxis warning	CPT code J code
Omalizumab	IgE	SC	Based on weight & IgE 150-375 mg every 2-4 weeks	Yes	**96372 J2182**
Mepolizumab	IL-5	SC	100 mg every 4 weeks	No	**96372 J2357**
Reslizumab	IL-5	IV	3 mg/kg every 4 weeks	Yes	**96365 J2786**
Bernalizumab	IL-5 Receptor-a	SC	30 mg every 4 weeks for 1st 3 doses then every 8 weeks	Yes	**96372 J3490** (temp)

Table 2: Biologics in development

	Target
Quilizumab	IgE M1 epitope
Legelizumab	IgE Ce3 domain
Pitrakinra	IL-4/ IL-13
Altrakincept	IL-4 / IL-13
Pascolizumab	IL-4
Lebrikizumab	IL-13
Trakolinumab	IL-13
Anrukinzumab	IL-13

Dupilumab binds to the alpha unit of the IL-4 receptor and blocks both IL-4 and IL-13. It shows potential efficacy in patients with T2 high asthma

Continued on following page

AMA Insights

As many who read *CHEST® Physician* may know, we have a nucleus of dedicated volunteers who give unselfishly of their time and talent to represent our members in the area of "regulatory advocacy" and "policy advocacy" in the areas of pulmonary, critical care, and sleep medicine. It is our goal to recognize and support this valuable group of individuals who represent us in the space of coding and reimbursement, RUC activities, relationships with organizations like the ACP and the AMA, as well as our sister societies, such as ATS, SCCM, NAMDRC, CCNA, APSR, ALAT, and ERS, among others.

One of our goals, in addition to recognizing this group, is to identify and mentor the next generation of representatives. A great example of this mentorship is reflected in our involvement with the AMA. Dr. Bob McCaffree has represented CHEST for 22 years and is now mentoring Dr. Raj Desai who will be assuming this role of AMA Delegate this year. Special thanks to Dr. McCaffree for his unselfish service in this capacity and for his mentorship of Dr. Desai. I hope that you enjoy this and future *CHEST® Physician* articles summarizing and reflecting on the activities pertinent to CHEST at the AMA.

John Studdard, MD, FCCP
CHEST President

Collaborating with societies: CHEST and AMA

BY NEERAJ R. DESAI, MD, MBA, FCCP; AND D. ROBERT MCCAFFREE, MD, MSHA, MASTER FCCP

While the American Medical Association (AMA) is the oldest and largest national medical association, many physicians, both members and nonmembers, have limited understanding of the policies, processes, and strategic foci of the AMA. It is our goal to inform our membership about the workings of the AMA and how those interact with the goals of CHEST and our members. We hope to do this by publishing periodic articles in *CHEST® Physician*. One of the authors (DRM) has been the CHEST delegate to the AMA for more than 20 years, and the other (NRD) is CHEST's new delegate.

The AMA was founded in 1847 at a convocation of physicians following a call by Dr. Nathan Davis at the New York Medical Society for such a convocation to establish a national organization of physicians "to promote the science and art of medicine and the betterment of public health." One early focus was the development of a Code of Ethics, which remains a major focus of the AMA. The current strategic plan has three major goals:

- Create thriving physician practices.
- Create the medical school of the future.
- Improve health outcomes.

We will expand on these in future articles.

The AMA is both an individual member organization and a federation of geographic, ie, county and state, societies and specialty societies, as well as the uniformed services and the VA. It is this federation that comprises the House of Delegates (HOD or House), which is the principle policy-making body of the AMA. The number of delegates from each member organization (now numbering more than 170 organizations) depends on the number of individual AMA members among that organization's members. Due to recent bylaws changes, CHEST now has two delegates. The HOD meets twice per year to establish policy on health, medical, professional, and governance matters, as well as the principles within which the AMA's business activities are conducted.


DR. DESAI


DR. McCAFFREE

Most policies originate via resolutions submitted by individuals or societies. These resolutions then go to one of several Reference Committees for open discussion. These committees then report their recommendations back to the House, which then discusses and votes on the recommendations. In some instances, the question is referred for further studies by one of several councils, whose reports go to the Board of Trustees or back to the House.

Most member societies meet in caucuses or Section Councils prior to the voting in the House to discuss the pending business. The Specialty and Service Society (SSS) is the largest caucus in the AMA's House of Delegates. The SSS meets twice annually in conjunction with the Interim and Annual Meetings of the HOD. There are two categories of groups in the SSS: those societies that have seats in the HOD and those seeking admission to the house.

SSS groups in the HOD include:

- 119 national medical specialties
- 2 professional interest medical associations
- 5 military service groups

An association must first be represented in the SSS for 3 years and meet the required number of AMA members before it is eligible to seek admission to the HOD.

The American College of Chest Physicians (CHEST) is an active member of the SSS but also joins with other societies of similar interests in the Section Council on Chest and Allergic Diseases. This caucus includes the ATS, SCCM, ASSM, and several allergy societies. Through the HOD, the SSS, and the Section Council, CHEST can partner with the AMA and other societies, such as ATS, to support each other's resolutions or important regulatory issues.

In summary, the AMA plays an important role in many areas of interest to our members. And, it can be a useful forum for connecting with societies with similar interests in directing advocacy and setting policy. We plan to continue this update in future issues of *CHEST® Physician*.

References

1. https://www.ama-assn.org/content/ama-house-delegates Accessed: January 28, 2018
2. https://www.ama-assn.org/practice-management/ama-steps-forward-practice-improvement-strategies Accessed: January 28, 2018

Continued from previous page

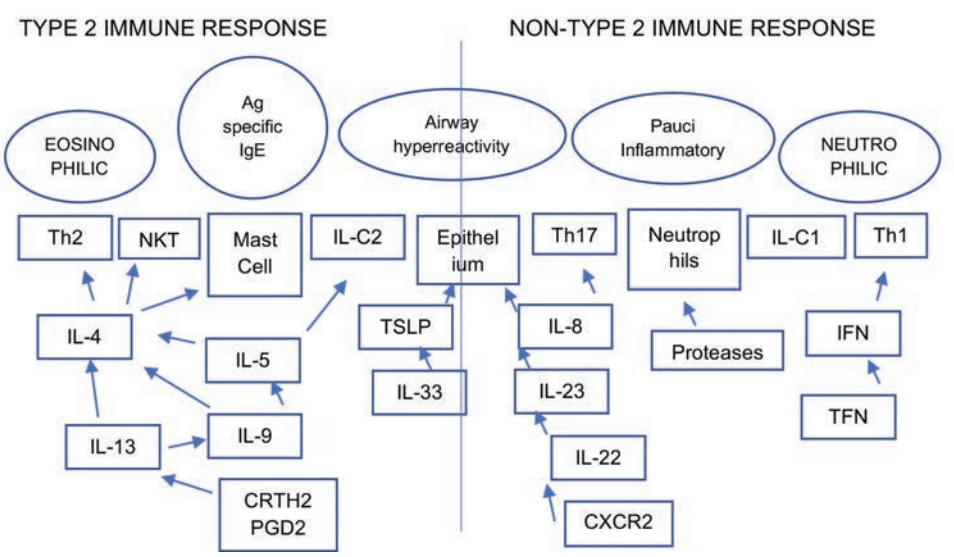
with or without eosinophilia but has not yet received FDA approval.

Multiple newer biologics are currently in development (Table 2).

Pulmonologists need to get familiar with the logistics of administration of these novel agents. The two common methods of administering biologics are (1) buy and bill – where the provider buys the drug directly from the distributor; and (2) assignment of benefits (typically administered by a Pharmacy Benefit Manager) - specific dose of the medication is shipped to the physician's office and physician only bills for the administration. CPT and J codes are shown in Table 1.

Shyamsunder Subramanian, MD, FCCP
Steering Committee Member

Figure 1: Inflammatory pathways in asthma and endotype.



SAVE LIVES: Clean your hands

WHO's global annual call to action for health-care workers

The World Health Organization (WHO) has announced its annual SAVE LIVES: Clean Your Hands 2018 campaign (Saito, et al. *J Hosp Infect.* 2018;98[4]:321), designating May 5, 2018, as world hand hygiene day.

Health-care-associated infections are a major patient safety problem. Unfortunately, their spread is common in hospitals and ICUs around the globe. The vehicle for these infections, including multidrug-resistant organisms, is frequently the contaminated hands of health-care workers. Health-care-acquired infections, as any other infection, can lead to sepsis and death. Infections acquired in the ICU are especially deadly, with mortalities that can be as high as 80%. Proper hand hygiene, despite being simple and inexpensive, is the single most important means of reducing the prevalence of hospital-acquired infections and the spread of antimicrobial resistance.

We have known about the significance of hand washing since the early 19th century. More recent data show that hand washing can reduce the overall prevalence of hospital-acquired infections and the cross-transmission of multidrug-resistant organisms. It is estimated that we can prevent 15% to 30% of these infections with adequate hand washing alone.

Despite the clear benefit and the understanding of the importance of hand washing, compliance with this simple intervention is only about 50%. Health-care workers tend to overestimate these rates, self-reporting a compliance of 75%. Even the latter number represents a lot of missed opportunities, and we must do something about it.

A multifaceted approach that combines education with written material, reminders, and continued feedback on performance can have an important effect on hand washing compliance and rates of hospital-acquired infections.

Sepsis is the single most important cause of death in hospitals in the United States. The campaign (http://www.who.int/infection-prevention/campaigns/clean-hands/en/), sponsored by the World Health Organization, should serve as a reminder to all health-care workers about the importance of adequate hand washing and as an opportunity to improve our compliance moving forward.

Despite the progress made, there is still a lot of room for improvement. We can have an impact on the number of deaths from sepsis by preventing them to occur in the first place. Wash your hands and do it well, it does not cost us anything.

Remember: It is in our hands – prevent sepsis and save lives!

Shruti Gadre, MD
Steering Committee Member, Critical Care NetWork
Angel Coz, MD, FCCP
Chair, Critical Care NetWork

In memoriam

W. Gerald Rainer, MD, FCCP, died November 14, 2017, one day after his 90th birthday Dr. Rainer was President of the American College of Chest Physicians in 1982-1983. He practiced thoracic and cardiovascular surgery for 50 years with St. Joseph Hospital in Denver as his professional home.

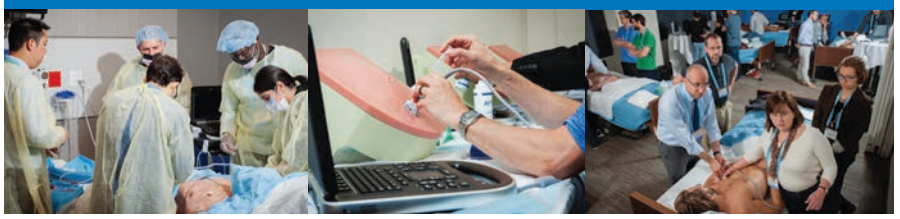
He was a respected leader, researcher, and educator, helping and mentoring countless residents, fellows, and many other health-care professionals. Dr. Rainer was also a distinguished clinical professor of surgery at the University of Colorado School of Medicine and served on many University boards and committees.

He published prolifically in many respected surgical journals and was able to masterfully blend his private practice with strong academic involvement.

As President of the American College of Chest Physicians and many other respected medical and surgical organizations, he was also actively involved in international professional societies. CHEST extends its condolences to Dr. Rainer's wife of 67 years, Lois, and to his family and friends.

CHEST®

2018 Education Calendar



Live Learning Courses

Courses held at the CHEST Innovation, Simulation, and Training Center in Glenview, Illinois.

Bronchoscopy Procedures for the ICU
May 5-6

Advanced Critical Care Echocardiography
June 1-3

Difficult Airway Management
June 8-10 | September 7-9

Lung Cancer: A Multidisciplinary Course for Pulmonologists Covering Current Paradigms for Diagnosis and Management
July 13-15

Bronchoscopy and Pleural Procedures for Pulmonary and Critical Care Medicine Fellows
July 20

Mechanical Ventilation: Advanced Critical Care Management
July 26-28

Advanced Diagnostic and Therapeutic Bronchoscopy
August 4-5

Cardiopulmonary Exercise Testing (CPET)
August 10-12

Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers
August 24-26

Ultrasonography: Essentials in Critical Care
September 13-15
November 29-December 1

Comprehensive Bronchoscopy With Endobronchial Ultrasound
September 20-22

Comprehensive Pleural Procedures
November 3-4

Critical Care Ultrasound: Integration Into Clinical Practice
November 9-11

Extracorporeal Support for Respiratory and Cardiac Failure in Adults
December 7-9

Advanced Critical Care Board Review Exam Course
December 7-9

Learn More **livelearning.chestnet.org**

Calendar subject to change. For most current course list and more information, visit livelearning.chestnet.org.

This month in the journal *CHEST*®

Editor's Picks

RICHARD S. IRWIN, MD, MASTER FCCP
Editor in Chief, the journal CHEST®

GIANTS IN CHEST MEDICINE
Professor Emeritus Elizabeth F. Juniper, MCSP, MSc
By Dr. P. M. O'Byrne

ORIGINAL RESEARCH
A Population-Based Cohort Study on the Drug-Specific Effect of Statins on Sepsis Outcome.
By Dr. C-C Lee, et al.

A Multicenter Randomized Trial of a Checklist for Endotracheal Intubation of Critically Ill Adults.
By Dr. D. R. Janz, et al.

Determinants of Unintentional Leaks During CPAP Treatment in OSA.
By Dr. M. Lebret, et al.

EVIDENCE-BASED MEDICINE
Screening for Lung Cancer: CHEST Guideline and Expert Panel Report.
By Dr. P. J. Mazzone, et al.

Treating Cough Due to Non-CF and CF Bronchiectasis With Non-pharmacological Airway Clearance: CHEST Expert Panel Report.
By Dr. A. T. Hill, et al.

New strategic plan for CHEST

We are pleased to announce the completion of a new, multiyear strategic plan for CHEST. Over the past few years, key stakeholders have provided essential input, resulting in a plan that identifies a very focused set of priorities we'll pursue to help achieve our overarching strategy. Having selected these priorities, which leverage our strengths and strategic advantages, we are committed to dedicating sufficient resources toward their accomplishment over the next several years.

Each year, the plan will be reviewed and modified to reflect changes to CHEST priorities.

A strategic plan is an important tool for our organization because it truly does focus and direct our efforts and resources. Guided by our 2013-2017 strategic plan, we were able to accomplish the following:

- Developed events, products, and services that produced meaningful education for the CHEST community and generated positive financial margins;
- Optimized our membership model to increase engagement of all clinicians on the health-care team;
- Enhanced our global presence through guideline development and increased educational offerings;
- Launched a new Association Management System (AMS) and made strides to becoming a data-driven organization;
- Built and moved into a new building that enhanced our ability to develop and host courses in the CHEST Innovation, Simulation, and Training Center;
- Increased our visibility through our rebrand as "CHEST";
- Fostered relationships and collaborated with other organizations to promote lung health through the CHEST Foundation; and
- Met our budget goals and financial covenants with our bank, and increased the CHEST Foundation's corpus for grants and awards.

This new strategic plan can be found on chestnet.org under the "About" section. As members of CHEST, we invite you to review what's outlined and become familiar with what the plan encompasses. This plan provides details to help you understand the future direction of CHEST, and we know you'll support us in these important endeavors.

CRITICAL CARE COMMENTARY

Life after angiotensin II

BY JONATHAN CHOW, MD; AND ASHISH K. KHANNA, MD, FCCP

Hypotension is an often-underestimated adversary. Even brief periods of intraoperative mean arterial pressure (MAP) <65 mm Hg increase the odds of both myocardial ischemia and acute kidney injury in the postoperative period. The threshold may be even higher in the postoperative critically ill population (Khanna, et al. *Crit Care Med.* 2018;46(1):71). Hypotension that is refractory to high-dose vasopressors is associated with an all-cause mortality of 50% to 80%.

The vasopressor toolbox centers around escalating doses of catecholamines with or without the addition of vasopressin. High-dose catecholamines, albeit a frequent choice, is associated with adverse cardiac events (Schmittinger, et al. *Intensive Care Med.* 2012;38[6]:950) and is an independent predictor of ICU mortality (Sviri, et al. *J Crit Care.* 2014;29[1]:157).

The evidence behind angiotensin II

Angiotensin II (AT II) is a naturally occurring hormone in the renin-angiotensin-aldosterone (RAA) system that modulates blood pressure through direct arterial vasoconstriction and direct stimulation of the kidneys and adrenal cortex to release vasopressin and aldosterone, respectively.

Positive results from the recent phase 3 trial for AT II have offered hope that this agent would add the needed balance to the current scarcity of vasopressor options (Khanna, et al. *N Engl J Med.* 2017;377[5]:419). AT II would provide the missing piece in the jigsaw that would allow the intensivist to manage refractory hypotension, while keeping a multimodal vasopressor dosing regimen within therapeutic limits.

Irvine Page and coworkers are credited with most of the initial work on AT II, which they did nearly 70 years ago. Anecdotal use in humans has been reported since the early 1960s (Del Greco, et al. *JAMA* 1961;178:994). After a prolonged period of quiescence, the Angiotensin II in High-Output Shock (ATHOS) pilot study, which was done in 2014 as a single-center "proof of concept" study of 20 patients, reinvigorated clinical enthusiasm for this agent (Chawla, et al. *Crit Care.* 2014;18[5]:534). ATHOS demonstrated the effectiveness of AT II at decreasing norepinephrine (NE) requirements of patients in vasodilatory shock (mean NE dose in AT II group 7.4 ug/min vs 27.6 ug/min in placebo, *P*=.06). These promising results were followed by ATHOS-3, a phase 3, double-blind, multicenter randomized controlled trial of stable human synthetic AT II. This trial was conducted under a special protocol assessment agreement with the US Food and Drug Administration (FDA). A total of 344 patients with predefined criteria for vasodilatory shock were randomized to AT II or placebo as the intention-to-treat population. The primary end-point was a response in MAP by hour 3 of AT II initiation; response was defined as either a MAP rise to 75 mm Hg or an increase in MAP ≥ 10 mm Hg. The primary end-point was reached more frequently in the AT II group than in the placebo group (69.9% AT II vs 23.4% placebo, OR 7.95, 95% CI 4.76-13.3, *P*<.001). The AT II group had significantly lower cardiovascular sequential organ failure assessment (SOFA) scores at 48 hours and achieved a consistent decrease in background vasopressor doses. Post-hoc data analysis found that the highest benefit was in patients who were AT II deficient (high ratio of AT I:AT II) (Wunderink, et al. *Intensive Care Med Exp.* 2017;5(Suppl 2):44). The patients who were AT II depleted and received placebo had a higher hazard ratio of death (HR 1.77, 95% CI 1.10-2.85, *P*=.019), while those who were AT II depleted and received AT II had a decreased risk of mortality (HR 0.64, 95% CI 0.41-1.00, *P*=.047). The data suggest not only that AT II levels may be predictive of mortality in vasodilatory shock but also that exogenous AT II administration may favorably modulate mortality in this population. Further, a subset data analysis of severely ill patients (APACHE II scores > 30) showed that those who received AT II and standard vasopressors had a significantly lower 28-day mortality compared with patients who only received standard vasopressors (Szerlip, et al. *Crit Care Med.* 2018;46[1]:3). Considering that the endothelial cells in the lungs and kidneys are locations where AT I is hydrolyzed by angiotensin-converting enzyme (ACE) into AT II, patients receiving ACE-inhibitors and individuals with pulmonary or renal disease are at greatest risk for AT II deficiency. As such, the use of AT II in the extra-corporeal membrane oxygenation (ECMO), post cardiopulmonary bypass, acute respiratory distress syndrome (ARDS), and renal failure populations are of future interest.

DR. CHOW

DR. KHANNA

Is there a downside?

Appropriate caution is necessary when interpreting these outcomes. One criticism that ATHOS-3 received was the use of a MAP goal of 75 mm Hg, a higher value than currently recommended by clinical guidelines, in the first 3 hours of AT II administration. Because this was a phase 3 trial, both the safety and efficacy of the drug were examined. These goals are difficult to accomplish if simultaneously manipulating other variables. Therefore, to isolate the effects of drug efficacy and safety, a higher MAP goal (75 mm Hg) was established to minimize any effect from varying background vasopressor doses during the first 3 hours of the study.

Furthermore, ATHOS-3 did find an increase in venous and arterial thromboembolic events in patients who received AT II (13% AT II vs 5% placebo). Previously, a systematic review of over 30,000 patients did not report this increased thromboembolic risk (Busse, et al. *Crit Care.* 2017;21[1]:324). According to the package insert, all patients receiving AT II should receive appropriate thromboembolic prophylaxis if medically indicated.

Where does AT II fit in our algorithm for resuscitation and the vasopressor toolbox?

Data from Wunderink et al indicate a potential mortality benefit in populations who are AT II depleted. However, we can only infer who these patients may be, as no commonly available assay can measure AT I and AT II levels. ATHOS and ATHOS-3 used AT II late during resuscitation, as did the Expanded Access Program (EAP) of the FDA, which gave physicians preliminary access to AT II while it was undergoing FDA review. Using similar inclusion criteria as ATHOS-3, the EAP did not permit patients to receive AT II until doses greater than or equal to 0.2 ug/kg/min of NE-equivalents were reached.

In a recently published case report, AT II was successfully used in a patient with septic shock secondary to a colonic perforation (Chow, et al. Accepted for e-publication: *A&A Practice.* April 2018.). This individual was in vasodilatory shock despite standard resuscitation, 0.48 ug/kg/min of NE, and 0.04 units/min of vasopressin. Methylene blue and hydroxocobalamin had failed to relieve the vasoplegia, and only after the initiation of AT II at 40 ng/kg/min, the patient could be relieved of vasopressors and survived to be discharged from the hospital. In our opinion, best clinical practices would allow for an early multimodal vasopressor regimen that should include AT II at the earliest sign of rapid clinical decline (Jentzer, et al. *Chest.* 2018. Jan 9. pii: S0012-3692(18)30072-2. doi: 10.1016/j.chest.2017.12.021. [Epub ahead of print]).

Angiotensin II was recently approved by the FDA in December 2017 and is now available on the market for management of vasodilatory shock. This will undoubtedly have a profound impact on the way clinicians treat vasodilatory shock. Previously, we were confined to agents such methylene blue and hydroxocobalamin to rescue patients from profound vasoplegia. However, none of these agents are supported by robust evidence from randomized control trials.

Now, we can openly welcome a new challenger to the campaign, a new hue to the palette of vasopressor colors. This new class of vasopressor makes complete physiological sense and will provide an invaluable tool in our daily battle against sepsis and vasodilatory shock.

Continued on following page

"No consequence" Knowledge Check-In expands

In 2018, ABIM is introducing the new Knowledge Check-In assessment option, an every-2-year assessment option serving as an alternative to the 10-year assessment model. Initially, for 2018, this option will be piloted for both Internal Medicine and Nephrology. In 2019, the Knowledge Check-In will expand to several additional specialties, including Pulmonary Disease. The remaining specialties, including Critical Care Medicine, will become available in 2020.

Previously, ABIM announced that physicians taking the Knowledge Check-In in 2018—the initial year it is offered in Internal Medicine or Nephrology—would have another chance to take it again 2 years later if they were unsuccessful, even if they were due to pass the exam that year. Based on feedback ABIM received from the physician community, this feature is now being extended to include all other Internal Medicine subspecialties in the future. Therefore, if a physician opts to take the Knowledge Check-In the first year it is offered in their subspecialty and is unsuccessful, they will get at least one additional opportunity to take it 2 years later.

For more information visit www.abim.org/checkin.

Continued from previous page

Dr. Chow is Assistant Professor, Division of Critical Care Medicine, Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD; Dr. Khana is Assistant Professor of Anesthesiology, Staff Intensivist, Vice-Chief for Research, Center for Critical Care, Department of Outcomes Research & General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH.

Editor's note

For decades, our options to treat patients with profound vasoplegia have been limited to high-dose catecholamines and vasopressin. Clinicians are often faced with the need to initiate multiple catecholamine agents knowing that these drugs stimulate similar receptors. The recent ATHOS-3 trial introduces AT II as a new option for the management of patients with refractory vasodilatory shock. This drug has a distinct mechanism of action that complements the effect of other vasopressors. Moreover, recent data suggest that this new agent is most beneficial in patients who are AT II deficient. Just like cancer therapies have evolved to precision medicine, will we perhaps face the need to better understand and promptly identify patients with AT II deficiency? For now, we have a new player on our vasopressor team.

Angel Coz, MD, FCCP
Section Editor

FDA to host meeting about sleep apnea devices

You are invited to attend this open meeting on April 16, held at the FDA White Oak Campus in Silver Spring, Md. (https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm596147.htm). The FDA is soliciting ideas or opinions about criteria or processes for FDA review of medical devices to diagnose or treat sleep apnea. CHEST is represented by Dr. Neil Freedman (neilfreedman@comcast.net) and Dr. Barbara Phillips (bphil020@gmail.com) who also welcome your input by email prior to the meeting. Home testing, "apps," and the criteria to diagnose sleep apnea and/or its resolution are among the topics to be discussed.

Bringing respiratory care to asthma clinics in Guyana

BY SHARON ARMSTEAD, EMBA, RRT

How it all started

The study abroad project was truly a goal and vision that came about after returning to Guyana after approximately 46 years. I was born in Guyana but left as a child and returned later and joined a mission group. In 2015, I began a personal journey of missionary service with the team of Bridge Global Medical Missions (BGMM) in Georgetown, Guyana. I was the first respiratory therapist to join the team.

I remember during the first few days in the hospitals I was told that there was "a lot of wheezing" in the EDs. Treating patients consisted of just administrating short-acting nebulizer treatments, but I remember being very impressed with the ICU at the main public hospital, Georgetown Public Hospital Corporation (GPHC), because they had the ventilators I could use. However, physicians only managed the patients while the nurses were left to monitor the ventilators and equipment, which they did not understand.

At the Linden Hospital in Guyana, the ED was constantly full of the "wheezers," and the ICU only had ventilators that were basically nonfunctioning due to language barriers or a lack of biomed professionals. One of my fondest memories was fixing two ventilators from China. I could get the ventilators to work and explain the basic modes because in my mind, it was just a ventilator, and they could see the modes. The problem was the language was all in Chinese! So, we all got together: a Cuban doctor, a Cuban biomed, and a nurse with a translation program and, finally, changed the language to English. It was an interesting day!

When we were on our study abroad trip this past January, I was able to place an intubated patient on that same ventilator. After my first visit to Linden Hospital, I addressed a few of my observations with the medical director, and I will never forget his comment. He said, "I thought respiratory would just come do some nebulizer treatments and show us oxygen."

Study abroad and respiratory care

Then the vision of my project began, because I needed to show him the scope of the practice of a respiratory therapist. I asked Dr. Heyliger-Thomas of BGMM if she could assist me in promoting a study abroad program in Guyana with the Ministry of Health. It was very important for me to bring my students to Guyana for many reasons, the most important being the profession was needed there, and our students would be excellent representatives.

In 2015, the study "Introduction of spirometry into clinical practice in Georgetown, Guyana: quality and diagnostic outcomes" highlighted increased physician referral to the country's only COPD/asthma clinic. I wanted to promote the importance of study abroad and international mission work, especially when promoting the care of asthma and the pulmonary patient, which I believe we did. The main project during study abroad was to test the school-aged children in Linden, thereby showing that there was undiagnosed asthma.

The 2 days that we were in Linden brought the largest sign-up for their clinic. When we did our screening at Mackenzie High School, we were able to utilize the portable spirometers and printer purchased by the CHEST Foundation community service grant. We are still collecting data, but the one thing that was revealed was the difficulty in obtaining medication for the treatment of asthma and COPD in some areas.

This project was also a learning experience for our students in many ways: in how they performed their interviews, how the culture affected the way their patients answered their questionnaires, and even how they performed on the tests. The value to the student and the individual of working within a different culture, far away from the norms of North America, allows them to appreciate their patients, the work they do, and their interprofessional team in a whole new light.

I want this experience to have an impact on each student's life. You are a teacher, an instructor, a mentor, professor, and much more when traveling with 10 students. The most satisfying moment is the transformation you see in them. They are no longer timid and unsure of themselves; they have greater confidence in their abilities and a deeper understanding of the needs of a patient. They finally understand the importance of culture as it pertains to health care.

Students at Mackenzie High School thanking CHEST Foundation donors for their support of a lung screening event at their institution.

Clinicians at Linden Hospital in Guyana in training with Ms. Armstead's team.

Sharon Armstead, EMBA, RRT, is a winner of the 2017 CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP. Sharon acts as a Clinical Assistant Professor and is the Director of Clinical Education at Texas State University's Department of Respiratory Care.

The effect of the CHEST Foundation grant

Applying for the CHEST Foundation community service grant was the largest grant I had ever attempted. Having a support system behind you is the most important piece of advice I can give to future grant applicants. I could not have completed my grant without our grant team at Texas State University. They truly had my back; and close to the deadline when it seemed insurmountable, they helped push me through it. The other piece of advice is to have a true vision and stick to that vision. The most difficult part of my project was the budget, prioritizing the things or people that I needed. Honestly, I needed help here, because for me, I needed everything. I had to make choices and leave some things out. I focused on what the actual need was for the many.

My ultimate goal for Guyana is to promote and show the need for respiratory care professionals to have that education offered at the University of Guyana as part of its allied health program and assist those in the application to the International Fellowship Program of the American Association of Respiratory Care—there has never been a fellow from Guyana. I believe that Guyana will have the resources, and with assistance, could achieve the goal. My vision and goal started in 2016, and I want to achieve it in the next 10 years.

I would like to thank all the CHEST Foundation donors from the bottom of my heart. This project was real and, as a CHEST member myself, it encourages me to be a better donor. Thank you—for it was and is much appreciated. Finally, I would like to express my thanks to my Co-Assistant Program Director, Holly Wise (Mass Communications) and Amber Hazelett, RRT (RC assistant), and the BGMM team for their entire support throughout the study abroad journey.

(This article was previous published in CHEST Thought Leaders.)

This grant is supported in full by the CHEST Foundation. Donors like you make grants like this possible. Thank you for your generosity and passion for community service and moving the needle forward on improving patient outcomes. To support community service initiatives, and the next generation of lung health champions, please go to foundation.chestnet.org/donate

New lung cancer screening guideline from CHEST

BY PETER MAZZONE, MD, FCCP

An update to CHEST's lung cancer screening guideline, *Screening for Lung Cancer: CHEST Guideline and Expert Panel Report*, has just been published online in the journal *CHEST*®. This update was made possible by the hard work of my co-authors and the amazing support of the CHEST staff.

Our goal was to update the evidence base for the benefit, harms, and implementation of low-radiation dose chest CT screening, then use this evidence base to produce meaningful and usable recommendations. The process for developing the guideline followed the rigorous methodological standards of CHEST in which the evidence was gathered from a systematic literature review, and the overall quality of the body of evidence was assessed using the GRADE approach. Recommendations were developed and graded based on this assessment.

There are a few aspects of the new guidelines to highlight. First, we have updated some of the core recommendations; second, we have developed new recommendations related to the implementation of high-quality screening; and third, the CHEST approach to guideline development has evolved to allow us to provide recommendations in which the evidence allows and statements based on experience and expert consensus in which it does not. Through this process, we developed six graded recommendations and nine ungraded consensus-based statements.

In this update, a few changes to the core recommendations about who should be screened are worthy to note:

- We have recommended an increase to the upper age of the screen-eligible cohort from 74 to 77, in line with CMS coverage and reflecting the oldest age of participants in the National Lung Screening Trial at the end of the screening period.
- We have directly addressed the cohort of individuals who are at high risk for having/developing lung cancer based on clinical risk prediction calculators but do not meet the current eligibility criteria. We recommended that this cohort should not be routinely screened given the greater potential for this cohort to have comorbid conditions that would influence morbidity from the evaluation and treatment of screen-detected findings and death from any cause. We did, however, state that there will be individuals within the cohort deemed to be at high risk for lung cancer from a clinical risk prediction calculator who are healthy enough to benefit from lung cancer screening and that low-radiation dose CT screening could be considered in these individuals.
- We recommended against low-radiation dose CT screening in cohorts at low risk of developing lung cancer and in individuals with comorbidities that adversely influence their ability to tolerate the evaluation of screen-detected findings, tolerate treatment of an early stage screen-detected lung cancer, or that substantially limit their life expectancy.
- We also highlighted that screening is reserved for patients without symptoms that could be caused by the presence of lung cancer, stressing that all symptomatic patients should receive an appropriate diagnostic evaluation.

Our remaining recommendation and statements are focused on aspects of screening implementation that influence the balance of benefit and harms of screening and lend to an approach to screening that respects patient values. An extensive literature review, followed by a recommendation or statement, is provided to guide programs in the following areas:

- the choice of nodule size to define what constitutes a positive test;
- maximizing compliance with annual screening exams;
- developing a comprehensive approach to lung nodule management;
- minimizing overtreatment of potentially indolent lung cancers;
- the provision of evidence-based tobacco cessation treatment;
- providing effective counseling and shared decision-making visits prior to the low-radiation dose CT scan;
- how to perform the low-radiation dose CT scan;
- structured reporting of the exam results, management of non-nodule findings on the low radiation dose CT; and
- the development of data collection and reporting tools that are capable of assisting with quality improvement initiatives.

Throughout the recommendations and statements, we have tried to be sensitive to the variety of acceptable approaches to screening program organization, ranging from program structures that are entirely decentralized (test ordering, counseling, and management of the findings by the referring provider) to those that are entirely centralized (test ordering, counseling, and management of the findings by the screening program).

Though we have attempted to comprehensively evaluate the literature and balance available evidence with pragmatism and the needs of our patients, we recognize that well-intentioned and informed experts can have different opinions about aspects of our guidelines. This highlights the need for further research to guide the screening community. Most will agree that it is time to increase access to high- quality lung cancer screening programs across the country. We hope that the updated CHEST lung cancer screening guidelines can help catalyze this.

Coinciding with the publication of the guideline, CHEST has developed new e-learning modules on the benefits and harms of CT screening for lung cancer. The modules are based on the CHEST 2018 educational session on the Screening for Lung Cancer Guidelines. The modules are available at chestnet.org/lungcancerscreening.

INDEX OF ADVERTISERS

Five things to do around the convention center at CHEST 2018

Planning to attend CHEST 2018? We know you're always on the go, so we've come up with a few quick things to do in San Antonio without having to go more than a few blocks outside of the convention center.

KYLE MONAHAN

FLICKR

Whataburger

While some may be hardcore In-N-Out fans, there's another well known burger joint in Texas with a location that happens to be next to the convention center on E Commerce St. Head on over to Whataburger and experience what the company calls a "bigger, better burger."

San Antonio Riverwalk

Want to experience the San Antonio, Texas atmosphere but don't have time for a long excursion? The Henry B. Gonzalez Convention Center is a few steps away from the Riverwalk, which winds throughout the city. Off of the northwest corner of the convention center, take a stroll and experience the picturesque beauty of the San Antonio river, the restaurants, and the bright colorful surroundings.

La Villita Historic Arts Village

Interested in art? Interested in architecture? La Villita, located on the west side of the convention center on S Alamo St, is on the US government's National Register of Historic Places as a Historic District. Take a look at different architectural styles, like adobe, early Victorian, and Texas vernacular limestone buildings. You'll find markers throughout La Villita with information about each building's history. You'll also find local artists, custom art, and unique dining options.

Tower of the Americas

Exit the south end of the convention center to go to the Tower of the Americas for a spectacular view of the city. This 750-foot tall tower has an observation deck, revolving restaurant with panoramic views, a stationary bar, and a 4D theater adventure ride great for the whole family. This is a great stop for lunch, dinner, or a nice afternoon activity.

The Alamo

Lastly, if you have an hour to spare, take a tour of the Alamo that commemorates the 1836 siege and battle. There are free and ticketed activities, including audio or guided tours (ticketed) or history talks, visiting the Alamo Church, exhibitions, and more! Don't forget to stop at the gift shop for a souvenir or two to take home.

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EKOS® — Setting the standard in PE treatment.

1 Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL Feb 2018

2 Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

3 Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

The EkoSonic™ Endovascular System is not available for sale in Canada.

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