



# CHEST<sup>®</sup> Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



“Menthol-flavored products represent one of the most common and pernicious routes by which kids initiate on combustible cigarettes,” said FDA Commissioner Scott Gottlieb, MD.

## FDA takes steps to end marketing of flavored e-cigarettes

BY GREGORY TWACHTMAN

MDedge News

The Food and Drug Administration once again has upped the ante in its war on youth smoking and vaping.

“Today, I’m pursuing actions aimed at addressing the disturbing trend of youth nicotine use and continuing to advance the historic declines we’ve achieved in recent years in the rates of combustible cigarette use among kids,” FDA Commissioner Scott Gottlieb, MD, said in a statement.

First and foremost, the FDA wants to reduce the lure of e-cigarettes by limiting the variety of flavored products for sale in retail outlets.

Under the proposal unveiled Nov. 15, only electronic nicotine delivery systems (ENDS) that are unflavored or have tobacco, mint, or menthol flavors would be widely available. Flavored products – think cherry, cotton candy, and mango – would be sold in age-restricted environments, such as stand-alone tobacco retailers like vape shops. The FDA also seeks more stringent enforcement of age verification on ENDS products sold online.

The proposal also would reexamine regulations governing flavored cigars, with the possible aim of banning them.

“These efforts to address flavors and protect youth would dramatically impact the ability of

E-CIGARETTES // continued on page 6

## Class-action suit filed against ABIM over MOC

BY ALICIA GALLEGOS

MDedge News

A group of internists is suing the American Board of Internal Medicine over its maintenance of certification (MOC) process, alleging that the board is monopolizing the MOC market.

The lawsuit, filed Dec. 6, 2018, in Pennsylvania district court, claims that ABIM is charging inflated monopoly prices for maintaining certification, that the organization is forcing physicians to purchase MOC, and that ABIM is inducing employers and others to require ABIM certification. The four plaintiff-physicians are asking a judge to find ABIM in violation of federal antitrust law and to bar the board from continuing its MOC process. The suit is filed as a class action on behalf of all internists and subspecialists required by ABIM to purchase MOC to maintain their ABIM certifications. The plaintiffs seek damages and injunctive relief, plus lawsuit and attorney costs arising from ABIM’s alleged antitrust violations.

In a statement, ABIM expressed disappointment at the lawsuit and said the organization will vigorously defend itself, adding that doing so will “consume resources far better dedicated

ABIM // continued on page 7

### INSIDE HIGHLIGHT



#### SLEEP STRATEGIES

The emerging role of sleep in the development of Alzheimer disease

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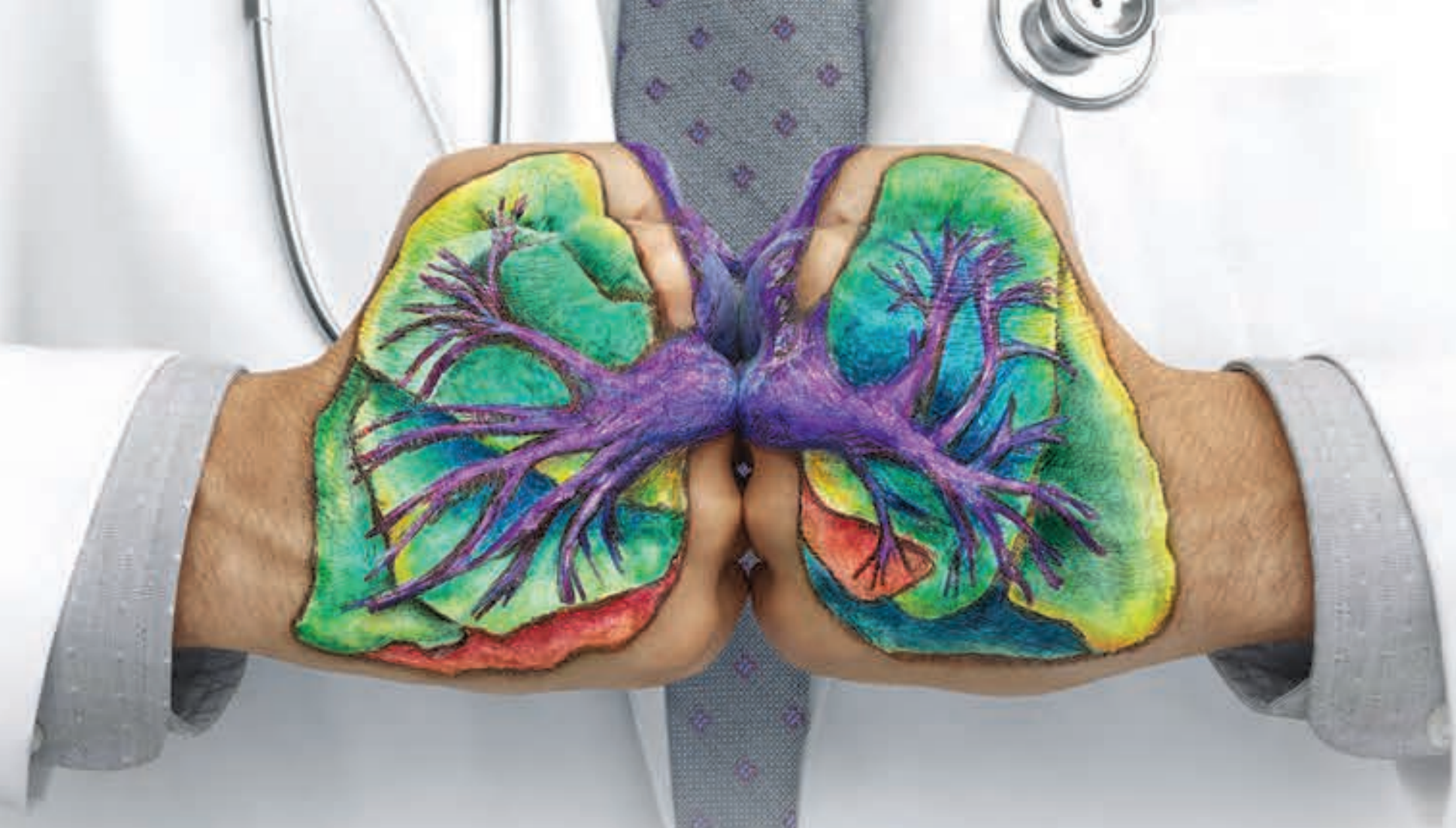


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## Indication

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

## Select Important Safety Information

**Elevated liver enzymes:** Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of  $\geq 3 \times$  ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels 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 placebo patients (1%). Patients should avoid or minimize exposure to sunlight and sunlamps, regularly use sunscreen (SPF 50 or higher), wear clothing that protects against sun exposure, and avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

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

to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary.

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

### Drug Interactions:

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

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

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

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

### Specific Populations:

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

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

**Genentech**

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# WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.<sup>1-3</sup>

## STUDIED IN A RANGE OF PATIENTS



Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications<sup>4</sup>

## DEMONSTRATED EFFICACY



In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF<sup>1-4\*</sup>

## ESTABLISHED SAFETY AND TOLERABILITY



The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials<sup>1†</sup>

## COMMITTED TO PATIENTS



Genentech offers a breadth of patient support and assistance services to help your patients with IPF<sup>‡</sup>

## WORLDWIDE PATIENT EXPERIENCE



More than 37,000 patients have taken pirfenidone worldwide<sup>4§</sup>

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

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

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

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

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

**References:** 1. Esbriet Prescribing Information. Genentech, Inc. October 2017. 2. 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. 3. 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. 4. Data on file. Genentech, Inc. 2016.

Learn more about Esbriet and how to access medication at [EsbrietHCP.com](http://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).<sup>1</sup> 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<sub>co</sub>) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.<sup>2</sup> In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL<sub>co</sub> ≥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<sub>co</sub> ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.<sup>3</sup> Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.<sup>1,2</sup> 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).<sup>1,3,4</sup> **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.<sup>1,3</sup>**

†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).<sup>1</sup>

‡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.<sup>1</sup>

**Esbriet**<sup>®</sup>  
(pirfenidone) tablets 267 mg  
801 mg

# Vaping soars among American teens in 2018 survey

BY HEIDI SPLETE

MDedge News

Teenage use of vaping devices jumped significantly in the past year, with 37% of 12th-grade

students reporting any vaping in 2018, compared with 28% in 2017, data announced Dec. 17 from the 2018 Monitoring the Future survey show.

In particular, nicotine-vaping use in

the 30 days prior to the survey nearly doubled among high school seniors, from approximately 11% in 2017 to 21% in 2018. Nicotine vaping also increased by 7.9% (from 8.2% to 16.1%) among 10th graders and by 2.6%

(from 3.5% to 6.1%) among 8th graders, according to the survey results.

Vaping involves using a device such as an e-cigarette to inhale a heated aerosol product that usually contains nicotine but can be used to



## BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

## 1 INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Elevated Liver Enzymes

Increases in ALT and AST  $>3 \times$  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 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST  $\geq 3 \times$  ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations  $\geq 10 \times$  ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST  $\geq 3 \times$  ULN were reversible with dose modification or treatment discontinuation. 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 the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations [see *Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information*].

### 5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash [see *Dosage and Administration section 2.3 in full Prescribing Information*].

### 5.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. 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. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions [see *Dosage and Administration section 2.3 in full Prescribing Information*].

## 6 ADVERSE REACTIONS

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

- Liver Enzyme Elevations [see *Warnings and Precautions (5.1)*]
- Photosensitivity Reaction or Rash [see *Warnings and Precautions (5.2)*]
- Gastrointestinal Disorders [see *Warnings and Precautions (5.3)*]

### 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials

## ESBRIET® (pirfenidone)

(Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common ( $>1\%$ ) adverse reactions leading to discontinuation were rash and nausea. The most common ( $>3\%$ ) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of  $\geq 10\%$  and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

**Table 2. Adverse Reactions Occurring in  $\geq 10\%$  of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3**

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain <sup>1</sup>	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

<sup>1</sup> Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in  $\geq 5$  to  $<10\%$  of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

## 6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

### Blood and Lymphatic System Disorders

Agranulocytosis

### Immune System Disorders

Angioedema

### Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

## 7 DRUG INTERACTIONS

### 7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

#### Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during

administer other types of drugs, said Nora D. Volkow, MD, director of the National Institute on Drug Abuse at the National Institutes of Health, in a press conference announcing the findings.

The increased prevalence of nicotine vaping in 10th and 12th graders is the largest annual increase in use of any substance recorded by Mon-

itoring the Future, said Richard A. Miech, PhD, MPH, of the Institute for Social Research at the University of Michigan, Ann Arbor, and the principal survey investigator. “Something about this delivery device of vaping seems to really appeal to kids,” he said. The flavors, concealability of the devices (which can be about the size of a

flash drive), and ease of use seem to be contributing to the popularity of vaping, Dr. Miech added.

In addition, marijuana vaping increased significantly across all three grade levels in 2018 from 2017. Within 30 days of the survey, marijuana vaping increased from 4.9% to 7.5% in 12th graders, from 4.3% to 7.0% in 10th graders, and from 1.6%

to 2.6% in 8th graders.

A take-home message for clinicians is the need to emphasize to teens that “vaping is not innocuous and not harmless,” said Dr. Miech in a question-and-answer session. Of note, data from multiple studies show that children who vape are about five times more likely to smoke cigarettes, he said.

The vaping devices are manufactured to deliver drugs into the lungs and ultimately high concentrations into the brain – which suggests the use of vaping devices to deliver other types of drugs might increase in the future, Dr. Volkow added.



LUJBYLAJUPYNSKA/THINKSTOCK

Use of most other substances, including inhalants, heroin, cocaine, and ecstasy; overall marijuana use, alcohol use, and extreme binge drinking remained stable, the researchers said. Cigarette smoking declined slightly among 12th graders but did not change significantly among 8th or 10th graders. Use of prescription opioids and tranquilizers declined in 2018 across all age groups.

“Vaping is reversing hard-fought declines in the number of adolescents who use nicotine,” Dr. Miech said in the news release announcing the results. “These results suggest that vaping is leading youth into nicotine use and nicotine addiction, not away from it.”

The data on vaping and nicotine use among American teens were published in a letter (*N Engl J Med.* 2018 Dec 17. doi: 10.1056/NEJMc1814130) – with a warning. “These results indicate that the policies in place as of the 2017-2018 school year were not sufficient to stop the spread of nicotine vaping among adolescents,” wrote the authors, led by Dr. Miech. “The rapid entry of new vaping devices on the market ... will require continual updates and modification strategies to keep adolescents from vaping and its associated negative health effects.”

The survey is funded by a government grant to the University of Michigan, Ann Arbor, from the NIH’s NIDA.

chestphysiciannews@chestnet.org

## ESBRIET® (pirfenidone)

ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.4 in full Prescribing Information*].

### Moderate CYP1A2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended [see *Dosage and Administration section 2.4 in full Prescribing Information*]. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

### Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

### 7.2 CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults [see *Data*].

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

#### Data

##### Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m<sup>2</sup> basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m<sup>2</sup> basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m<sup>2</sup> basis at a maternal oral dose of 1000 mg/kg/day).

### 8.2 Lactation

#### Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.

#### Data

##### Animal Data

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production.

## ESBRIET® (pirfenidone)

### 8.4 Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

### 8.5 Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

### 8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.3 in full Prescribing Information*].

The safety, efficacy, and 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 [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

### 8.7 Renal Impairment

ESBRIET should be used with caution in patients with mild (CL<sub>cr</sub> 50–80 mL/min), moderate (CL<sub>cr</sub> 30–50 mL/min), or severe (CL<sub>cr</sub> less than 30 mL/min) renal impairment [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.3 in full Prescribing Information*]. 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.

### 8.8 Smokers

Smoking causes decreased exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*], 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.

### 10 OVERDOSAGE

There is limited clinical experience with overdose. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdose, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

## 17 PATIENT COUNSELING INFORMATION

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

### Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see *Warnings and Precautions (5.1)*].

### Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required [see *Warnings and Precautions (5.2)*].

### Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required [see *Warnings and Precautions (5.3)*].

### Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*].

### Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

### Distributed by:

Genentech USA, Inc.  
A Member of the Roche Group  
1 DNA Way, South San Francisco, CA 94080-4990

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American kids to access tobacco products that we know are both appealing and addicting,” Dr. Gottlieb said in a statement.

He concluded, “This policy framework reflects a redoubling of the FDA’s efforts to protect kids from all nicotine-containing products.”

In a move that seems to be aimed at youth-oriented products like Juul, the FDA will be seeking to remove from the market any ENDS product that is marketed specifically to young people.

Finally, the FDA intends to pursue regulation that would ban menthol from combustible tobacco products.

“I believe these menthol-flavored products represent one of the most common and pernicious routes by which kids initiate on combustible cigarettes,” Dr. Gottlieb said. “The menthol serves to mask some of the unattractive features of smoking that might otherwise discourage a child from smoking. Moreover, I believe that menthol products disproportionately and adversely affect underserved communities. And as a matter of public health, they exacerbate troubling disparities in health related to race and socioeconomic status.”

The policy shift comes as the Centers for Disease Control and Prevention released data from the 2018 National Youth Tobacco Sur-

vey showing that use of e-cigarettes among high schoolers is on the rise, growing from 1.5% in 2011 to 20.8% in 2018. Middle schoolers saw use over the same time period increase from 0.6% to 4.9%.

The rise of current use of e-cigarettes was enough to reverse a declining trend in overall tobacco use in recent years between 2015 and 2017.

“FDA’s enforcement efforts and policy framework would restrict access to most flavored e-cigarettes and limit the chances of youth beginning to use these products, while ensuring the products are available to adult smokers as an alternative to combustible cigarettes,” Alex M. Azar II, secretary of the Department of Health & Human Services, said in a statement supporting the FDA’s efforts.

He added, “Our obligation at HHS is always to the public health, and we believe FDA’s goals strike the right public health balance in addressing the multifaceted challenge we have before us today.”

The FDA proposals were published as part of an advance notice of proposed rulemaking in the Federal Register.

Comments can be made at [www.regulations.gov](http://www.regulations.gov) through June 19.

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## FDA warns public about undeclared drugs in e-liquids

BY LUCAS FRANKI

MDedge News

The Food and Drug Administration has issued an alert regarding two e-liquids sold by HelloCig Electronic Technology that contain undeclared prescription drugs. E-liquid is the flavored mixture used in electronic cigarettes.

In a laboratory analysis, the FDA found that “E-Cialis HelloCig E-Liquid” contained both sildenafil and tadalafil, and that “E-Rimonabant HelloCig E-Liquid” contained sildenafil. Sildenafil and tadalafil are approved for the treatment of erectile dysfunction. Unapproved usage of these drugs in over-the-counter e-liquids is therefore illegal.

Both sildenafil and

tadalafil can interact with nitrates found in some prescription drugs and can cause a dangerous lowering of blood pressure. Conditions commonly treated with nitrates include diabetes, high blood pressure, high cholesterol, or heart disease.

“FDA urges consumers to stop using these products and to contact their health care professional with any concerns associated with their use,” the agency stated in a press release.

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to continuous improvement of its programs.”

ABIM declined to answer questions addressing specific accusations from the lawsuit. However, in an interview, ABIM President Richard Baron, MD, said that “ABIM board-certified physicians have taken the initiative to distinguish themselves. This is a credential that physicians earn. We offer certified physicians the opportunity to demonstrate to the medical community, their peers, and the public that they are current and have special expertise.”

At press time, ABIM has not yet filed a formal response to the lawsuit, which was due by Jan. 6. From there, discovery and evidence gathering in the case will begin.

Katherine Murray Leisure, MD, an infectious disease specialist based in Plymouth, Mass., is one of the plaintiffs. While she said that she could not comment specifically on the lawsuit, she has written publicly about her ABIM concerns in the past.

In a 2015 letter to Dr. Baron and posted on an anti-MOC website, Dr. Murray Leisure outlined a litany of complaints against ABIM’s MOC process and called on the U.S. Congress to investigate ABIM’s financial, legal, and ethical conduct.

*The suit is filed as a class action on behalf of all internists and subspecialists required by ABIM to purchase MOC to maintain their ABIM certifications. The plaintiffs seek damages and injunctive relief, plus lawsuit and attorney costs.*

“[The American Board of Medical Specialties] and ABIM collected more than \$10,000 in fees and lost practice hours every decade from each [diplomate] doing MOC,” Dr. Murray Leisure wrote. “MOC took weeks away from our offices, clinics, patients, families, specialty societies, and individual research. ABMS MOC removed hundreds, perhaps thousands ... of America’s best, once board-certified physicians from full hospital careers and earnings whenever [diplomates] did not complete these high-stakes MOC programs. ... The righteous and fast solution to such moral, ethical, scientific, and constitutional problems is to end MOC now.”

Plaintiffs Glen Dela Cruz Manalo, MD; Alexa Joshua, MD; and Gerard Kenney, MD, did not return messages seeking comment. When contacted, attorneys for the plaintiffs declined to comment.

The doctors’ 32-page lawsuit characterizes ABIM as an organization motivated by money that has made its MOC process increasingly more burdensome for physicians over the years without evidence that MOC has any beneficial impact on doctors, patients, or the public. Complying with ABIM’s MOC costs internists an average of \$23,607 in financial cost and time lost over 10 years, and costs up to \$40,495 for some specialists, according to the suit.

The physicians allege that ABIM controls in excess of 95% of the market for MOC of internists, in violation of federal antitrust laws, and that the organization has unlawfully obtained and main-



**Dr. Richard J. Baron**

tained monopoly power for MOC services.

The board’s illegal tying of its initial certification to its MOC results in burdensome conditions, including “raising the cost of the practice of medicine, constraining the supply of internists thereby harming competition, decreasing the supply of certified internists, and increasing the cost of medical services to patients and consumers,” the suit claims.

The legal challenge details how MOC has personally and professionally impacted each of the four plaintiffs. Dr. Manalo, a gastroenterologist, lost his privileges at St. Vincent Healthcare in Billings, Mont., and was subsequently terminated after he declined to maintain his ABIM certification as a gastroenterologist. In a letter to ABIM, Dr. Manalo wrote that it was “unfair and outright discriminatory that practitioners certified on or after 1990 are the only ones required to certify,” according to the lawsuit. Dr. Manalo later took a position as staff gastroenterologist at Jonathan M. Wainwright Memorial Veterans Affairs Medical Center in Walla Walla, Wash., at a substantially reduced salary. He became unemployed in 2017.

Dr. Murray Leisure obtained an initial and lifelong board certification in internal medicine from ABIM in 1984 and an infectious disease certification in 1990. ABIM terminated Dr. Murray Leisure’s infectious diseases certification after she failed her MOC examination in 2009, which led to lost privileges at Jordan Hospital in Plymouth, Mass. The loss caused significant damage to Dr. Murray Leisure, including lost income, a tarnished reputation, and the lost opportunity to help patients, according to the lawsuit. Jordan Hospital restored her privileges after Dr. Murray Leisure passed her MOC examination in 2012.

Dr. Kenney lost a job opportunity with Mount Nittany Physicians Group in State College, Pa., after he declined to renew his ABIM certification in gastroenterology. He is currently a physician with the University of Pittsburgh Medical Center in Seneca, Pa.

That the ABIM website lists him as “not certified,” is misleading, and makes it appear that his initial certifications were revoked due to failure to pass a MOC examination or misconduct, rather than because the certifications lapsed, according to the suit. The description makes Dr.

Kenney appear less qualified to patients, hospitals, insurance companies, medical corporations, other employers, and others, he claims.

Dr. Joshua could not renew her consulting and admitting privileges at Detroit Medical Center after she failed an MOC examination in 2014 and became uncertified in internal medicine, according to the suit. In addition, Blue Cross Blue Shield informed Dr. Joshua it would no longer cover her because it required ABIM certification for coverage. She unsuccessfully appealed based on her certification with the National Board of Physicians and Surgeons. As a result of her certification termination, Dr. Joshua can only practice outpatient medicine at Detroit Medical Center.

In an interview, Dr. Baron emphasized the number of modifications made to its MOC process in recent years after responding to physician concerns. This includes an overhaul of the organization’s governance structure to include more than 200 practicing physicians and opening new avenues for physicians to engage in the creation of assessment content that more closely reflects what they see in practice, he said. In addition, ABIM now surveys all specialists to contribute to the exam blueprint review and the creation of the new Item Writing Task Force.

“We take all suggestions from physicians seriously, and have used it to launch many new initiatives including the Knowledge Check-In, a new Physician Portal, partnerships to give physicians dual credit for CME and MOC, and exploration of alternative assessment models with medical societies,” he said.

Dr. Baron acknowledged past criticism of the MOC process, but said he is proud of the work ABIM has done to address physician concerns about the choice, relevance, and convenience of its MOC program.

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# Non-TB mycobacteria infections rising in COPD patients

BY JENNIE SMITH

MDedge News

Veterans with chronic obstructive pulmonary disease (COPD) have seen a sharp increase since 2012 in rates of non-TB mycobacteria infections, which carry a significantly higher risk of death in COPD patients, according to findings from a nationwide study.

For their research, published in *Frontiers of Medicine*, Fahim Pyarali, MD, and colleagues at the University of Miami, reviewed data from Veterans Affairs hospitals to identify non-TB mycobacteria (NTM) infections among more than 2 million COPD patients seen between 2000 and 2015. Incidence of NTM infections was 34.2 per 100,000 COPD patients in 2001, a rate that remained steady until 2012, when it began climbing sharply through 2015 to reach 70.3 per 100,000 ( $P = .035$ ). Dr. Pyarali and colleagues also found that, during the study period, prevalence of NTM climbed from 93.1 infections per 100,000 population



DR. GEORGE KUBACKA/CDC

in 2001 to 277.6 per 100,000 in 2015.

Hotspots for NTM infections included Puerto Rico, which had the highest prevalence seen in the study at 370 infections per 100,000 COPD population; Florida, with 351 per 100,000; and Washington, D.C., with 309 per 100,000. Additional hotspots were identified around Lake Michigan, in coastal Louisiana, and in parts of the Southwest.

Dr. Pyarali and colleagues noted that the geographical concentration of cases near oceans and lakes was “supported by previous findings that warmer temperatures, lower dissolved oxygen, and lower pH in the soils and waters provide a major environmental source for NTM organisms”; however, the study is the first to identify Puerto Rico as having exceptionally high prevalence. The reasons for this should be extensively investigated,

the investigators argued.

The mortality risk was 43% higher among NTM-infected patients than in COPD patients without an NTM diagnosis (95% confidence interval, 1.31-1.58;  $P$  less than .001), independent of other comorbidities.

Though rates of NTM infection were seen rising steeply in men and women alike, Dr. Pyarali and colleagues noted as a limitation of their study its use of an overwhelmingly male population, writing that this may obscure “the true reach of NTM disease and mortality” in the general population. The average age of NTM diagnosis remained steady throughout the study period, suggesting that rising incidence is not attributable to earlier diagnosis.

Dr. Pyarali and colleagues reported no outside sources of funding or financial conflicts of interest.

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**SOURCE:** Pyarali F et al. *Front Med*. 2018 Nov 6. doi: 10.3389/fmed2018.00311.

## Biomarkers predict asthma/COPD risk in 9/11 first responders

BY HEIDI SPLETE

MDedge News

**FROM THE JOURNAL CHEST®** ■ Elevated eosinophil levels and interleukin-4 (IL-4) levels were significantly associated with an increased risk of overlapping asthma and chronic obstructive pulmonary disease (COPD) in firefighters exposed to toxins at the World Trade Center on Sept. 11, 2001.

Patients with asthma/COPD overlap experience decreased quality of life and increased mortality, compared with patients who have either isolated COPD or isolated asthma, and longitudinal data on risk factors for the overlapping condition are lacking, wrote Ankura Singh, MPH, of Albert Einstein College of Medicine, New York, and colleagues.

In a study published in *CHEST*, the researchers reviewed data from 2,137 firefighters exposed to toxins at the World Trade Center on 9/11. The study participants underwent a bronchodilator pulmonary function test between Sept. 9, 2001, and Sept. 10, 2017, and at least three routine monitoring pulmonary function tests between these two dates.

In a multivariate analysis, eosinophil concentration of at least 300 cells/mcL was a significant predictor of asthma/COPD

overlap. Serum IL-4 levels also were significant predictors of asthma/COPD overlap (hazard ratio, 1.51).

In addition, a greater concentration of IL-21 was associated with both isolated asthma and isolated COPD, but not with the overlap.

The study results were strengthened by the availability of pre-exposure medical data for the firefighters and the close follow-up, although limitations included the mostly white male population and a limited definition of asthma, the researchers noted.

However, the findings suggest that “high eosinophil concentrations, uniquely associated with asthma/COPD overlap in this population, may reflect biological pathways that predispose one to exaggerated inflammation and/or poor counterregulatory responses to inflammation, leading to reversible and fixed airflow obstruction,” they wrote. Consequently, early interventions targeting specific inflammatory pathways may improve lung function outcomes.

The study was supported in part by the National Institute of Occupational Safety and Health and the National Institutes of Health.

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**SOURCE:** Singh A et al. *CHEST*. 2018 Dec;154;1301-10.



NAVY/NTL

A “bucket brigade” works to clear rubble and debris on Sept. 14, 2001, at the World Trade Center.



# New HHS fitness guidelines break new ground

BY BRUCE JANCIN

MDedge News

CHICAGO – The newly released comprehensive second edition of the federal physical activity guidelines have a lofty goal.

“Our overarching vision is to transform the current sick care system into a health promoting system,” Adm. Brett P. Giroir, MD, declared in introducing the recommendations at the American Heart Association scientific sessions.

“Physical activity is one of the most effective preventive health interventions available, and we need more emphasis on prevention as we transition to a value-based reimbursement structure that rewards better health maintenance and avoids chronic conditions,” added Adm. Giroir, assistant secretary for health at the U.S. Department of Health & Human Services.

Although the agency opted to unveil the new guidelines before an audience of cardiologists at the AHA scientific sessions, the report includes sections relevant for a wide range of medical specialists, including primary care physicians, pediatricians, psychiatrists, neurologists, endocrinologists, and geriatricians.

Before launching into a description of what’s new in the second edition, Adm. Giroir set the stage with blunt talk about the nation’s poor state of physical fitness.

“Inactivity causes 10% of premature mortality in the United States. That means if we can just get 25% of inactive people to be active and meet the recommendations, almost 75,000 deaths per year would be prevented in the United States. And on an even larger scale worldwide, if 25% of those same people who are inactive started moving and met the guidelines, more than 1.3 million deaths would be prevented,” according to Adm. Giroir.

At present, only 26% of men, 19% of women, and 20% of teenagers meet the physical activity recommendations.

Failure to meet the federal aerobic physical activity recommendations accounts for an estimated nearly \$117 billion in annual health care costs. And it poses a national security threat, too: Nearly one-third of all 17- to 24-year-olds are disqualified from military service because of obesity. Even more eye-opening, he continued, is that fully 71% of all 17- to 24-year-olds are ineligible for military service because of obesity,

lack of physical fitness, lack of education, or substance use.

The actual recommendations contained in the second edition of the Physical Activity Guidelines for Americans remain unchanged from those in the first, issued a decade earlier. That is, in order to gain substantial health benefits, adults and adolescents should engage in at least 150-300 min/week of moderate intensity aerobic physical activity or 75-150 min/week of vigorous



ADM. GIROIR

DR. KRAUS

intensity aerobic activity. Plus they should do muscle-strengthening exercises such as weight lifting or push-ups at moderate or greater intensity at least 2 days/week.

Asked why the guidelines are sticking with time-based physical activity recommendations in an era when popular smartwatches and other mobile devices can readily spit out number of steps walked, calories burned, and heart-rate data, cardiologist William E. Kraus, MD, 1 of the 17 members of the scientific advisory committee who reviewed and graded the scientific evidence on physical activity, sedentary behavior, and health, answered. He said the group’s careful review concluded that “there’s just not enough evidence at this time to make a recommendation” with regard to mobile device-based measurements of physical activity and their relationship with health benefits.

“We’re hoping to spur more research in this area, so that the next time we make recommendations, that can be incorporated,” added Dr. Kraus, a professor of medicine and cardiologist at Duke University, Durham, N.C., as well as president-elect of the American College of Sports Medicine.

## What’s new in the guidelines

“This edition tells us that it’s easier to meet the recommendations in the physical activity guidelines,” according to Adm. Giroir. “The new guidelines demonstrate, based on the best science, everyone can dramatically improve their health just

by moving: anytime, anywhere, and by any means that gets you active.” He broke the guidelines down as follows:

- “We have new evidence about the risks of sedentary behavior, and new evidence that any amount – *any amount* – of moderate to vigorous physical activity, like walking, dancing, line dancing if you’re from Texas, and household chores is beneficial,” Adm. Giroir observed.
  - While the first edition of the federal guidelines cited strong evidence that physical activity reduces the risk of two types of cancer, breast and colon, the intervening decade has brought forth strong evidence of a protective effect against an additional six types of cancer: bladder, endometrial, kidney, stomach, esophageal, and lung cancer.
  - The guidelines formulate for the first time physical activity standards for children aged 3-5 years. The recommended target is at least 3 hr/day of varied physical activity, consistent with existing guidelines in Australia, Canada, and the United Kingdom.
  - Updated recommendations for children aged 6-17 years call for an hour or more/day of moderate- or vigorous-intensity physical activity on a daily basis, with that activity level falling within the vigorous category on at least 3 days/week. Plus, it recommends bone- and muscle-strengthening activity on at least 3 days.
  - The pediatric guidelines are linked to a planned HHS national strategy to expand children’s participation in youth sports as part of an effort to curb childhood obesity. “We’ll soon announce funding opportunities for communities to increase participation in sports among children and teens through participation in affordable programs with trained coaches,” said Dr. Giroir, a pediatrician.
- “I strongly believe our schools should take action to implement this approach. There is a lot of interest right now to effect change in the schools across our country. Part of the answer, I think, is to provide kids with high-quality physical education, but I think we recognize that alone will not be enough.” The comprehensive school activity model calls for not only enriching school PE programs but also incorporating active transport to school, classroom activity, active

learning, and after school programs – activity in all settings during the school day. “I’m very hopeful that this model, which is endorsed in the guidelines document, will be widely adopted by schools in this country over the next decade,” Dr. Giroir said.

The first edition declared that only bouts of physical activity of at least 10 minutes duration should count toward meeting the guidelines. That requirement is gone in the second edition. It was an impediment to being active, and upon close examination it wasn’t based on scientific evidence. That means taking the stairs instead of the escalator or parking farther away from the store count toward the weekly physical activity goal, Dr. Kraus said.

“It makes it easier to achieve the guidelines and to encourage Americans to move more and sit less just by making a better choice at many times during the day,” observed Dr. Giroir, a four-star admiral in the U.S. Public Health Service Commissioned Corps.

The latest guidelines contain up-to-date information on the benefits of regular physical activity in terms of brain health, including reduced risk of developing Alzheimer disease, and improved cognition, including performance on academic achievement tests and measures of executive function, memory, and processing speed, in preadolescent children as well as older adults. Solid evidence also is cited for improved cognition in patients with MS, dementia, ADHD, and Parkinson’s disease.

The guidelines provide new recommendations for physical activity for women during pregnancy and post partum.

A section of the guidelines is devoted to proven evidence-based strategies to promote physical activity at the individual, small-group, and community level.

Physicians now have a resource to aid them in prescribing an individualized physical activity prescription for their patients with existing health conditions, including osteoarthritis, type 2 diabetes, cancer survivors, and physical disabilities.

The new physical activity guidelines and related resources for health care professionals are available at the Health.gov website.

[bjancin@mdedge.com](mailto:bjancin@mdedge.com)

**SOURCE:** Giroir BP. AHA scientific sessions, Session ME.05.

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# Palliative care update highlights role of nonspecialists

BY ANDREW D. BOWSER

MDedge News

The new edition of national palliative care guidelines provides updated clinical strategies and guidance relevant to all clinicians providing care for critically ill patients, not just those clinicians actively specialized in palliative care.

The Clinical Practice Guidelines for Quality Palliative Care, 4th Edition, emphasizes the importance of palliative care provided by “clinicians in primary care and specialty care practices, such as oncologists,” the authors stated.



DR. LEBLANC

The latest revision of the guideline aims to establish a foundation for “gold-standard” palliative care for people living with serious illness, regardless of diagnosis, prognosis, setting, or age, according to the National Coalition for Hospice and Palliative Care, which published the clinical practice guidelines.

The update was developed by the National Consensus Project for Quality Palliative Care (NCP), which includes 16 national organizations with palliative care and hospice expertise, and is endorsed by more than 80 national organizations, including the American Society of Hematology and the On-

colony Nurses Society.

One key reason for the update, according to the NCP, was to acknowledge that today’s health care system may not be meeting patients’ palliative care needs.

The guidelines call on all clinicians who are not palliative specialists to integrate palliative care principles into their routine assessment of seriously ill patients with conditions such as heart failure, lung disease, and cancer.

This approach differs from the way palliative care is traditionally practiced, often by fellowship-trained physicians, trained nurses, and other specialists who provide that support. The guidelines are organized into sections covering palliative care structure and processes, care for the patient nearing the end of life, and specific aspects of palliative care, including physical, psychological, and psychiatric; social; cultural, ethical, and legal; and spiritual, religious, and existential aspects.

“The expectation is that all clinicians caring for seriously ill patients will integrate palliative care competencies, such as safe and effective pain and symptom management and expert communication skills in their practice, and palliative care specialists will provide expertise for those with the most complex needs,” the authors wrote.

These new guidelines represent a “blueprint for what it looks like to provide high-quality, comprehensive palliative care to people with serious

## VIEW ON THE NEWS

**Eric Gartman, MD, FCCP comments:** The importance of this concept cannot be overstated and is vital not only for hospitalized patients, but for all patients living with chronic illnesses that result in daily reductions in quality of life and shortened life expectancy. A similar effort has been undertaken nationally within the VA as the Life-Sustaining Treatment Decisions Initiative – with the hope that the regular outpatient providers for patients (who are closest to their patients) discuss their individual goals, expectations, and preferences for their care – and then these are reflected as actionable documents and non-expiring orders in the electronic medical record. As with many other initiatives in health care, all of this work requires provider time and administrative resource commitment – which, unfortunately, can be in frustratingly short supply.



illness,” said Thomas W. LeBlanc, MD, who is a medical oncologist, palliative care physician, and patient experience researcher at Duke University, Durham, N.C.

“Part of this report is about trying to raise the game of everybody in medicine and provide a higher basic level of primary palliative care to all people with serious illness, but then also to figure out who has higher levels of needs where the specialists should be applied, since they are a scarce resource,” said Dr. LeBlanc.

An issue with that traditional model is a shortage of specialized clinicians to meet palliative care needs, said Dr. LeBlanc, whose clinical practice and research focuses on palliative care needs of patients with hematologic malignancies.

“Palliative care has matured as a field such that we are now actually facing workforce shortage issues and really fundamental questions about who needs us the most, and how we increase our reach to improve the lives of more patients and families facing serious illness,” he said in an interview.

That’s a major driver behind the emphasis in these latest guidelines on providing palliative care in the community, coordinating care, and dealing with care transitions, he added.

“I hope that this document will help to demonstrate the value and the need for palliative care specialists, and for improvements in primary care. ... To me, this adds increasing legitimacy to this whole field,” he said

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# ICU-acquired pneumonia death risk may be underestimated

BY TED BOSWORTH

MDedge News

In a large prospectively collected database, the risk of death at 30 days in ICU patients was far greater in those with hospital-acquired pneumonia (HAP) than in those with ventilator-associated pneumonia (VAP) even after adjustment for prognostic factors, according to a large study that compared mortality risk for these complications.

The data for this newly published study were drawn from an evaluation of 14,212 patients treated at 23 ICUs participating in a collaborative French network OUTCOMEREA and published Critical Care Medicine.

HAP in ICU patients “was associated with an 82% increase in the risk of death at day 30,” reported a team of investigators led by Wafa Ibn Saied, MD, of the Université Paris Diderot. Although VAP and HAP were independent risk factors (*P* both less than .0001) for death at 30 days, VAP increased risk by 38%, less than half of HAP,

which increased risk by 82%.

From an observational but prospective database initiated in 1997, this study evaluated 7,735 ICU patients at risk for VAP and 9,747 at risk for HAP. Of those at risk, defined by several factors including an ICU stay of more than 48 hours, HAP developed in 8% and VAP developed in 1%.

The 30-day mortality rates at 30 days after pneumonia were 23.9% for HAP and 28.4% for VAP. The greater risk of death by HR was identified after an analysis that adjusted for mortality risk factors, the adequacy of initial treatment, and other factors, such as prior history of pneumonia.

In HAP patients, the rate of mortality at 30 days was 32% in the 75 who were reintubated but only 16% in the 101 who were not. Adequate empirical therapy within the first 24 hours for HAP was not associated with a reduction in the risk of death.

As in the HAP patients, mortality was not significantly higher in VAP patients who received inadequate empirical therapy.

Previous studies have suggested that both HAP and VAP increase risk of death in ICU patients, but the authors of this study believe that the relative risk of HAP “is underappreciated.” The researchers had no disclosures.

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**SOURCE:** Saied WI et al. Crit Care Med. 2018 Nov 7. doi: 10.1097/CCM.0000000000003553.



ANDREI MALOV/THINKSTOCK

# Is metabolic syndrome really circadian syndrome?

BY DOUG BRUNK

MDedge News

LOS ANGELES – In the opinion of Paul Zimmet, MD, PhD, the Western 24/7 lifestyle is plagued by chronic sleep insufficiency, continual caloric excess, modernization, and globalization, which all can cause disruption of circadian rhythm.

This scenario created the “perfect storm” for rising rates of metabolic syndrome, which is related to low HDL cholesterol levels, central obesity, hypertension, hyperglycemia, and high triglyceride levels, Dr. Zimmet said at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease. These cardiometabolic risk factors “all seem to cluster together in relation to the changes in our society,” he said. “It’s on that basis and research findings that I think we should understand that most of them, if not all, have been demonstrated to relate to circadian rhythm disturbance.”

In fact, the associated comorbidities sleep apnea, depression, and fatty liver disease should be included in the metabolic syndrome cluster and should be renamed the



Dr. Paul Zimmet

“circadian syndrome,” according to Dr. Zimmet, professor of diabetes at Monash University, Melbourne.

The term metabolic syndrome is anathema, he said. “There have been numerous different definitions, which finally led to an effort to come up with a harmonized definition” by the International Diabetes Federation Task Force on Epidemiology and Prevention, with involvement from the American Heart Association (*Circulation*. 2009;120[16]:1640-5).

In the early 1970s, Dr. Zimmet and his colleagues at Guys Hospital

in London reported on diurnal variation in glucose tolerance. “If you did a glucose tolerance test in the afternoon it could be diabetic, whereas in the morning it was normal,” he noted. “Other researchers reported similar findings. That created in my own mind interest in this area of circadian rhythm. However, I had neglected this until recently, when I was doing background research while trying to find an answer to the elusive question of a central unifying explanation for the cardiometabolic cluster constituting the metabolic syndrome.” So decades later, Dr. Zimmet extended his research to include epigenetics in the quest. Described as the study of heritable changes in gene function that occur without a change in the sequence of the DNA, epigenetic changes “are closely linked to the circadian rhythm, otherwise known as ‘the body clock,’” said Dr. Zimmet, who also is codirector with Naftali Stern, MD, of the Sagol Center for Epigenetics of Metabolism and Aging at Tel Aviv Medical Center. “

He said, “Many aspects of human behavior and metabolism are closely linked to the circadian clock and affected by its rhythm disturbance. We decided that we wanted to further investigate this area: To what extent is circadian rhythm the central feature to explain the clustering of all of these cardiovascular and metabolic risk factors of the metabolic syndrome.”

In recent years, he has been collaborating with Noga Kronfeld-Schor, PhD, of the department of zoology at Tel Aviv University. The research focuses on a gerbil from the Negev: *Psammomys obesus* (otherwise known as the Israeli fat sand rat), which develops elevated blood sugar, obesity, depression, sleep disturbance, fatty liver, and circadian dysrhythmia when removed from the desert environment to the laboratory. “These are all key features of type 2 diabetes in humans,” he said. “This is probably the best animal model of type 2 diabetes, and we felt that it was worth looking more closely to see if there was a similar relationship in humans as to whether circadian dysrhythmia would be causing all or most of these features in humans including obesity.” An epigenetic study of the gerbil in the laboratory of Prof. Sam El-Osta, also of Monash, has shown that parental diet during early life regulated expression of genes associated with DNA methylation in the key FTO

gene associated with obesity (*Int J Obesity*. 2016;40:1079-88). It suggests that diet-induced metabolic changes can be transmitted from parent to offspring by mechanisms under epigenetic control.

Published studies from other research groups support the link between other of the cardiometabolic metabolic syndrome characteristics, epigenetic modifications, and circadian dysrhythmia including cardiovascular regulation and disease (*Eur Heart J*. 2018;39[14]:2326-9), sleep loss and alterations in DNA methylation (*Science Advances*

*“To what extent is circadian rhythm the central feature to explain the clustering of all of these cardiovascular and metabolic risk factors of the metabolic syndrome?”*

2018;4[8]:eaar8590), and circadian dysrhythmia and fatty liver (*Cell Metab*. 2012;15[6]:848-60). “In 2009, the FDA approved bromocriptine mesylate, a drug which has effects on circadian rhythm, for treatment of type 2 diabetes, suggesting its use in diabetes may have some role through the alteration of circadian rhythm,” continued Dr. Zimmet, who also is honorary president of the International Diabetes Federation. “Depression is also clearly linked to circadian rhythm and there is evidence from research and human studies that light therapy may be an effective treatment for type 2 diabetes and depression.”

Dr. Zimmet ended his presentation with a strong call for adding sleep apnea, fatty liver, and depression to the existing features of the metabolic syndrome “to encourage clinicians and researchers to look at the picture of cardiometabolic risk much more broadly than as just a group of metabolic abnormalities,” he said. “We propose that these comorbidities be embraced within the definition of the cardiometabolic cluster and be renamed the ‘circadian syndrome.’ This cluster is now the main driver of the global chronic disease epidemic and its health burden. This is a disease of civilization – the result of the way we live.”

Dr. Zimmet reported having no disclosures.

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# Comorbid TBI & PTSD up risk for sleep disturbances

BY JILL D. PIVOVAROV

MDedge News

Veterans living with comorbid traumatic brain injury (TBI) and posttraumatic stress disorder were at increased risk for worse pain and sleep disturbances, reported Nadir M. Balba and colleagues at the VA Portland (Ore.) Health Care System.

The authors conducted a retrospective review of medical records at the VA Portland Health Care System (VAPORHCS) that evaluated 639 veterans who were referred to the VAPORHCS Sleep Disorders Clinic between May 2015 and November 2016. They wrote, “The purpose of this study was to determine whether Veterans with comorbid TBI and PTSD exhibit a higher prevalence of sleep disturbances (determined via self-report and objective polysomnography) and pain compared to Veterans with only TBI or PTSD.”

Patients were recruited to participate in the cross-sectional study, which included participation in an overnight sleep clinic as well as patient self-reported sleep quality, pain, and TBI and PTSD symptom severity. Sleep disturbances included insomnia, nightmares, sleep fragmentation, obstructive sleep apnea, and parasomnias. The survey tools used in the study included the Rivermead Post Concussion Questionnaire (RPCQ), the PTSD Checklist DSM-5 (PSTD-5), the Insomnia Severity Index (ISI), and the Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10). Sleep studies were recorded using Polysmith version 9.0 and sleep staging was performed by a certified sleep technician and

verified by a board-certified sleep medicine physician.

Patients were grouped into one of four trauma exposure classifications based on their prior history of trauma, including neither (n = 383), TBI (n = 67), PTSD (n = 126), and TBI+PTSD (n = 63).

Self-reported sleep disturbance, which was the worst among those with PTSD and those with comorbid TBI and PTSD, indicated that PTSD plays a more significant role in the occurrence of disturbed sleep than TBI, the researchers noted. “Participants in the TBI+PTSD and PTSD groups had significantly worse ISI scores (i.e., higher scores) compared to both the TBI and neither groups (*P* less than .001). Furthermore, participants in the TBI+PTSD and PTSD groups had significantly worse FOSQ-10 scores (i.e., lower scores) compared to both the TBI and neither groups (*P* less than .001),” they wrote.

In terms of pain, patients with comorbid TBI and PTSD reported the greatest severity of pain, including more frequent headaches and worse photo and phono sensitivities. The TBI and PTSD groups, however, both scored significantly higher in their pain reports than those in the neither group, which suggests “that each of these conditions independently contributes to increased pain,” the authors observed. Ultimately, they cited multiple linear regression models, which attributed sleep disturbances and TBI symptom severity as the primary contributors to pain presentation.

“It is well established that sleep disturbances and pain are inextricably linked,” they said. The results of this study serve to validate that connection “but also suggest this link may be even stronger in those with comorbid TBI and PTSD,” they added.

## VIEW ON THE NEWS

**Krishna Sundar, MD, FCCP, comments:** Given the high prevalence of sleep disturbances in patients with TBI, the occurrence of PTSD, which peaks 6 months to a year after the TBI, adds to the increased risk of sleep disturbances. Screening and addressing individual aspects of the “polytrauma clinical triad” may be key to addressing sleep problems given the independent contribution of both TBI and PTSD to sleep disturbances and pain intensity.



The researchers cited self-report data as a possible study limitation. They also conceded that comorbid depression and substance use disorder could both play a role in further exacerbating sleep disturbance and pain.

Future research should evaluate how TBI and PTSD, along with other unidentified comorbid conditions, may work together in exacerbating symptoms so that more effective treatment interventions can be developed to address sleep and pain disturbance following multiple traumas.

The authors had no relevant financial disclosures to report.

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**SOURCE:** Balba NM et al. *J Clin Sleep Med*. 2018;14(11):1865-78.

# Nocturnal hypoxemia predicts incident atrial fibrillation in sleep apnea patients

BY JEFF CRAVEN

MDedge News

## FROM THE JOURNAL CHEST®

Researchers have found a significant independent association between nocturnal hypoxemia and risk of incident atrial fibrillation (AF) in patients with obstructive sleep apnea (OSA), which they believe may help prevent the development of AF in this population, according to recent research published in the journal *CHEST*.

“These findings are consistent with those of previous studies suggesting that these groups, who are typically at somewhat lower risk of [atrial fibrillation], might be especially vulnerable to the effects of [obstructive sleep apnea] and hypoxemia,” Tetyana Kendzerska, MD, PhD, of the University of Ottawa, and her colleagues wrote in their study.

They performed an analysis of

8,256 patients with data linked to a provincial health administrative database who had suspected OSA who underwent a sleep study at a large academic hospital between 1994 and 2010. The patients were median 47 years old; 62% of the cohort were men, 28% had an apnea-hypopnea index (AHI) of greater than 30 events per hour, and 6% spent more than 30% of the time during sleep with less than 90% oxygen saturation.

Overall, 173 of 8,256 patients (2.1%) developed AF during the study period. In patients with suspected OSA and who were arrhythmia free, nocturnal hypoxemia significantly increased the risk of incident hospitalized AF (hazard ratio, 2.47; 95% confidence interval, 1.64-3.71) over median 10 years of follow-up (interquartile range, 7-13 years) after the researchers controlled for age, sex, chronic obstructive pulmonary disease, history

## VIEW ON THE NEWS

**Krishna Sundar, MD, FCCP, comments:**

While both AHI and percentage of sleep time spent with oxygen desaturation were associated with incident atrial fibrillation, only nocturnal hypoxemia (SaO<sub>2</sub> < 90% for more than 30% of sleep time) was significant when accounting for confounders. The mechanistic bases of chronic hypoxia in driving atrial remodeling and predisposing to atrial fibrillation needs to be understood to reduce the incidence of atrial fibrillation.

of heart failure, smoking status, nocturnal hypoxemia, and pulmonary embolism, and this association remained significant after adjustment

for body mass index and hypertension (HR, 1.77; 95% CI, 1.15-2.74).

“These findings support a relationship between OSA, chronic nocturnal hypoxemia, and the development of [atrial fibrillation], and may be used to identify those patients with OSA who are at greatest risk of developing AF.”

Researchers cited the observational design, retrospective data collection, and examining hospitalized AF only as limitations in the study. However, they noted that clinical data was collected prospectively and the inability to adjust to positive airway pressure would push results to the null with regard to unstudied confounders.

The authors reported no relevant conflicts of interest.

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**SOURCE:** Kendzerska T et al. *CHEST*. 2018.doi: 10.1016/j.chest.2018.08.1075.

# Single-item scale effective for assessing sleep quality

BY MADHU RAJARAMAN

MDedge News

The single-item sleep quality scale (SQS) produced favorable results comparable to other complex, time-intensive assessment tools, according to findings published in the *Journal of Clinical Sleep Medicine*.

Sleep evaluation is of primary importance in many clinical research contexts, yet “despite their utility in the measurement of sleep quality [sleep assessment tools] are prone to several limitations when used in the context of clinical trials and may not always fulfill industry standards. For example, the Pittsburgh Sleep Quality Index (PSQI) ... was developed as a screening tool and may not be sensitive enough for detecting treatment differences in clinical trials.”

In a study of 70 insomnia patients and 651 depression patients, concurrent criterion validity analysis yielded strong correlations between the SQS and the morning-questionnaire insomnia (MQI) and PSQI in patients with insomnia and

depression, respectively. The investigators wrote, “The single-item format enables a patient-reported rating of sleep quality over a 7-day recall period without greatly increasing the patient’s burden. The use of a discretizing visual analog scale (VAS) increases the potential for a more sensitive measurement.” The SQS is a quick but accurate self-reported assessment of sleep quality.

The SQS was validated based on two studies. Eligible patients in the 4-week, randomized, multicenter insomnia study were aged 30-75 years and were receiving a Food and Drug Administration-approved hypnotic agent as usual treatment for insomnia based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The MQI was used daily for the duration of the study, wrote Ellen Snyder, PhD, of Merck, in Kenilworth, N.J., and her coauthors.

The depression study was a randomized, double-blind, parallel-group, 12-month international trial evaluating the safety of the substance P antagonist aprepitant, compared with paroxetine hydrochloride. Patients were aged 18 years or

older, with a DSM-IV diagnosis of major depressive disorder. Patients completed the SQS and PSQI at baseline, week 1, and week 8.

In insomnia patients, a Pearson correlation of  $-0.76$  was found at week 1 for the SQS in relation to the MQI. In patients with depression, Goodman-Kruskal correlation coefficients for the SQS in relation to the Pittsburgh Sleep Quality Index (PSQI) were  $-0.87$ ,  $-0.88$ , and  $-0.92$  at baseline, week 1, and week 8, respectively. Correlations were negative because “better sleep quality is associated with a lower score on the MQI and PSQI, but a higher score on the SQS,” the authors noted.

The results support the use of the SQS as a “practical sleep measure that can effectively gauge sleep quality without significantly increasing the burden of clinical trial participants,” they added.

Funding for the study was provided by Merck Sharp & Dohme.

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**SOURCE:** Snyder E et al. *J Clin Sleep Med*. 2018;14(11):1849-57.

## OSA linked to resistant hypertension in black patients

BY MADHU RAJARAMAN

MDedge News

Untreated moderate or severe obstructive sleep apnea (OSA) was associated with greater odds of resistant hypertension in black patients, according to findings published in *Circulation*.

In an analysis of 664 patients with hypertension, those with moderate to severe OSA had twofold higher odds of resistant hypertension, compared with those with no or mild OSA (odds ratio, 2.04; 95% confidence interval, 1.14-3.67), reported Dayna A. Johnson, PhD, of the Division of Sleep and Circadian Disorders at Brigham and Women’s Hospital, Boston, and coauthors.

Participants were enrolled in the JHSS, an ancillary trial conducted during December 2012 – May 2016

as part of the Jackson (Miss.) Heart Study, a longitudinal study of 5,306 black adults aged 21-95 years. Patients included in the analysis had hypertension (defined as high blood pressure, use of antihypertensive medication, or self-reported diagnosis). Those without a valid in-home sleep apnea test and with missing data on hypertension, measured blood pressure, or use of antihypertensive medications and diuretics were excluded from analysis.

Sleep apnea was assessed using measures of nasal pressure, thoracic and abdominal inductance plethysmography, finger pulse oximetry, body position, and electrocardiography with a validated Type 3 home sleep apnea device. Obstructive apneas were identified as a flat or nearly flat amplitude of the nasal pressure signal for greater than 10

seconds, accompanied by respiratory effort on the abdominal or thoracic inductance plethysmography bands. Severity was defined by the standard Respiratory Event Index (REI) categories: fewer than 5 events (unaffected), greater than or equal to 5 events to fewer than 15 events (mild), greater than or equal to 15 events to fewer than 30 events (moderate), and greater than or equal to 30 events (severe), the authors reported.

High blood pressure (BP) was defined as systolic BP greater than or equal to 130 mm Hg or diastolic BP greater than or equal to 80 mm Hg. Controlled hypertension was defined as systolic BP less than 130 mm Hg and diastolic BP less than 80 mm Hg.

Uncontrolled BP was defined as high BP with use of one or two classes of antihypertensive medications; resistant hypertension was defined as having high BP while on greater than or equal to three classes of antihypertensive medications with one being a diuretic or as using of greater than four classes of antihypertensive medications regardless of BP control, Dr. Johnson and colleagues reported.

A total of 25.7% of hypertension patients had moderate or severe OSA, though only 6% of these patients had an OSA diagnosis from a physician. In addition, 48.2% of patients had uncontrolled hypertension, and 14.5% had resistant hypertension.

Moderate or severe OSA was associated with nearly twofold higher

unadjusted odds of resistant hypertension (OR, 1.92; 95% CI, 1.15-3.20). In adjusted models, moderate or severe OSA and nocturnal hypoxemia were not associated with uncontrolled hypertension but were associated with resistant hypertension (OR, 2.04; 95% CI, 1.14-3.67; OR, 1.25; 95% CI, 1.01-1.55, respectively).

Compared with no OSA, severe OSA was associated with more than three times higher odds of resistant hypertension (OR, 3.50; 95% CI, 1.54-7.91). This association was even higher after adjustment for covariates (OR, 3.58; 95% CI, 1.39-9.19).

“These data suggest that untreated OSA may contribute to the high burden of resistant hypertension in blacks,” Dr. Johnson and coauthors wrote. “Future studies should test whether diagnosis and treatment of OSA may be interventions for improving BP control” and reducing this burden, they added.

“These findings are particularly important given that most adults with OSA are undiagnosed and untreated.”

The study was funded by grants from the National Heart, Lung, and Blood Institute. One of the authors reported receiving funding from Amgen. No other disclosures were reported.

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**SOURCE:** Johnson DA et al. *Circulation*. 2018. doi: 10.1161/CIRCULATIONAHA.118.036675.



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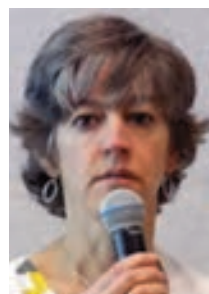
# Discussing immunization with vaccine-hesitant parents requires caring, individualized approach

BY JEFF CRAVEN

MDedge News

ORLANDO – Putting parents at ease, making vaccination the default option during discussions, appealing to their identity as a good parent, and focusing on positive word choice during discussions are the techniques two pediatricians have recommended using to get vaccine-hesitant parents to immunize their children.

“Your goal is to get parents to immunize their kids,” Katrina Saba, MD, of the Permanente Medical Group in Oakland, Calif., said during an interactive group panel at the annual meeting of the American Academy of Pediatrics.



DR. SABA

“Our goal is not to win a debate. You don’t have to correct every mistaken idea.”

“And really importantly, as we know, belief trumps science,” she added.

“Their belief is so much stronger than our proof, and their belief will not be changed by evidence.”

Many parents who are vaccine hesitant also belong to a social network that forms or reinforces their beliefs, and attacking those beliefs is the same as attacking their identity, Dr. Saba noted. “When you attack someone’s identity, you are immediately seen as not like them, and if you’re not like them, you’ve lost your strength in persuading them.”

Dr. Saba; Kenneth Hempstead, MD; and other pediatricians and educators in the Permanente Medical Group developed a framework for pediatricians and educators to talk with their patients about immunization at their center after California passed a law in 2013 that required health care professionals to discuss vaccines with patients and sign off that they had that discussion.

“We felt that, if we were going to be by law required to have that discussion, maybe we needed some new tools to have [the discussion] more effectively,” Dr. Saba said. “Because clearly, [what we were doing] wasn’t working or there wouldn’t have been a need for that law.”

Dr. Hempstead explained the

concerns of three major categories of vaccine-hesitant parents: those patients who are unsure of whether they should vaccinate, parents who wish to delay vaccination, and parents who refuse vaccination of their children.

Each parent requires a different approach for discussing the importance of vaccination based on their level of vaccine hesitancy, he said. For parents who are unsure, they may require general information about the safety and importance of vaccines.

Parents who delay immunization may have less trust in vaccines, may have done research in their own social networks, and may present



DR. HEMPSTEAD

alternatives to a standard immunization schedule or want to omit certain vaccines from their child’s immunization schedule, he noted. Using the analogy of a car seat is one ap-

proach to identify the importance of vaccination to these parents: “Waiting to give the shots is like putting your baby in the car seat after you’ve already arrived at the store – the protection isn’t there for the most important part of the journey!”

In cases where parents refuse vaccination, you should not expect to change a parent’s mind in a single visit, but instead focus on building the patient-provider bond. However, presenting information the parent may have already seen, such as vaccination data from the Food and Drug Administration or Centers for Disease Control and Prevention, may alienate parents who identify with groups that share vaccine-hesitant viewpoints and erode your ability to persuade a parent’s intent to vaccinate.

A study by Nyhan et al. randomized parents to receive one of four pieces of interventions about the MMR vaccine: information from the CDC explaining the lack of evidence linking autism and the vaccine, information about the dangers of the diseases prevented by the vaccine, images of children who have had diseases prevented by the vaccine, and a “dramatic narrative” from a CDC fact sheet about a child

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** I attended the American Academy of Pediatrics (AAP) National Conference and Exhibition (NCE) in Orlando, FL in November 2018 and wished I had signed up for this instructive interactive panel discussion. I bring up the topic of the importance of vaccinations, especially against influenza during this present season, nearly every day in pulmonary clinic. Anti-vaccination parents often treat me like I am selling snake oil! This educational format should be considered for every AAP NCE meeting and would be a great consideration for CHEST annual meeting.



who nearly died of measles. The researchers found no informational intervention helped in persuading to vaccinate in parents who had the “least favorable” attitudes toward the vaccine. And in the case of the dramatic narrative, there was an increased misperception about the MMR vaccine (Pediatrics. 2014;133[4]:e835-42).

Dr. Hempstead and Dr. Saba outlined four rhetorical devices to include in conversations with patients about vaccination: cognitive ease, natural assumption, an appeal to identity, and use of advantageous terms.

### Cognitive ease

Cognitive ease means creating an environment in which the patient is relaxed, comfortable, and more likely to be agreeable. Recognize when the tone shifts, and strive to maintain this calm and comfortable environment throughout the discussion. “If your blood pressure is coming up, that means theirs is, too,” Dr. Hempstead said.

### Natural assumption

How you are offering the vaccination also matters, he added. Rather than asking whether a patient wants to vaccinate (“Have you thought about your flu vaccine this year?”), instead frame the discussion with vaccination as the default option (“Is your child due for a flu vaccination this year? Yes, he is. Let’s get that taken care of today”). Equating inaction with vaccination prevents the risk fallacy phenomenon from occurring in which, when given multiple options, people give equal weight to each option and may choose not to vaccinate, Dr. Hempstead noted.

Dr. Saba cited research that

backed this approach. In a study by Opel et al., using a “presumptive” approach instead of a “participatory” approach when discussing a provider’s recommendation to vaccinate helped: The presumptive conversations had an odds ratio of 17.5, compared with the participatory approach. In cases in which parents resisted the provider’s recommendations, 50% of providers persisted with their original recommendations, and 47% of parents who initially resisted the recommendations agreed to vaccinate (Pediatrics. 2013;132[6]:1037-46).

### Appeal to identity

Another strategy to use is appealing to the patient’s identity as a good parent and link the concept of vaccination with the good parent identity. Forging a new common identity with the parents through common beliefs – such as recognizing that networks to which parents belong are an important part of his or her identity – and reemphasizing the mutual desire to protect the child is another strategy.

### Using advantageous terms

Positive terms, such as “protection,” “health,” “safety,” and “what’s best,” are much better words to use in conversation with parents and have more staying power than negative terms, like “autism” and “side effects,” Dr. Hempstead said.

“Stay with positive messaging,” he said. “Immediately coming back to the positive impact of this vaccine, why we care so much, why we’re doing this vaccine, is absolutely critical.”

Dr. Hempstead and Dr. Saba reported no relevant conflicts of interest.

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# Growing options for treating pediatric asthma with biologics

BY TARA HAELE

MDedge News

ORLANDO – The goal of treatment is the same for all asthma cases, regardless of severity: “to enable a patient to achieve and maintain control over their asthma,” according to Stanley J. Szeffler, MD, a professor of pediatrics at the University of Colorado at Denver.

That goal includes “reducing the risk of exacerbations, emergency department visits, hospitalizations, and progression as well as reducing impairments, including symptoms, functional limitations, poor quality of life, and other manifestations of asthma,” Dr. Szeffler, also director of the Children’s Hospital of Colorado pediatric asthma research program, told colleagues at the annual meeting of the American Academy of Pediatrics.

## Severe asthma challenges

These aims are more difficult with severe asthma, defined by the World Health Organization as “the current level of clinical control and risks

which can result in frequent severe exacerbations and/or adverse reactions to medications and/or chronic morbidity,” Dr. Szeffler explained. Severe asthma includes untreated severe asthma, difficult-to-treat asthma, and treatment-resistant severe asthma, whether controlled on high-dose medication or not.

Allergen sensitization, viral respiratory infections, and respiratory irritants (such as air pollution and smoking) are common features of severe asthma in children. Also common are challenges specific to management: poor medication adherence, poor technique for inhaled medications, and undertreatment. Poor management can lead to repeated exacerbations, adverse effects from drugs, disease progression, possible development of chronic obstructive pulmonary disease (COPD), and early mortality.

The National Heart, Lung, and Blood Institute EPR-3 guidelines for treatment of pediatric asthma recommend a stepwise approach to

therapy, starting with short-acting beta<sub>2</sub>-agonists as needed (SABA p.r.n.). The clinician then assesses the patient’s symptoms, exacerbations, side effects, quality of life, and lung function to determine whether the asthma is well managed or requires inhaled corticosteroids, or another therapy in moving through the steps. Each step also involves patient education, environmental control, and management of the child’s comorbidities.

It is not until steps 5 and 6 that the guidelines advise considering the biologic omalizumab for patients who have allergies. But other biologic options exist as well. Four biologics currently approved for treating asthma include omalizumab, mepolizumab, benralizumab, and reslizumab, but reslizumab is approved only for patients at least 18 years old.

## Biologics for pediatric asthma

Omalizumab, which targets IgE, is appropriate for patients at least 6 years old in whom inhaled cortico-

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** Dr. Szeffler’s talk at the American Academy of Pediatrics National Conference and Exhibition in November 2018 was an excellent review of the exciting new therapies coming to the rescue for severe persistent asthma that is poorly controlled. The next hurdle, though, will be how to get these biologics approved by insurance companies for use in our patients.

steroids could not adequately control the symptoms of moderate to severe persistent asthma. Dosing of omalizumab is a subcutaneous injection every 2-4 weeks based on pretreatment serum IgE and body weight using a dosing table that starts at 0.016 mg/kg per IgE (IU/mL). Maximum dose is 375 mg every 2 weeks in the United States and 600 mg every 2 weeks in the European Union.

The advantages of an anti-IgE drug are its use only once a month and its substantial effect on reducing exacerbations in a clearly identified population. However, these drugs are costly and require supervised

*Continued on following page*

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# New pediatric therapies show promise for influenza

BY JEFF CRAVEN

MDedge News

ORLANDO – More therapies are becoming available for children for the treatment of influenza and multidrug-resistant infections such as *Enterobacteriaceae* and *Acinetobacter*, John S. Bradley, MD, said at the annual meeting of the American Academy of Pediatrics.

Dr. Bradley, director of the division of infectious diseases at Rady Children's Hospital–San Diego, discussed a therapy for influenza, baloxavir, which was recently approved as a fast-acting single-dose medication and currently is under study in children. Also, a recent double-blind, phase 3 trial in the *New England Journal of Medicine* recruited patients as young as 12 years old. In the study, patients in the intervention group resolved their fever in median 25 hours, compared with 42 hours in the placebo group. Baloxavir better reduced viral load at day 2, compared with oseltamivir and placebo, but there was a similar alleviation of symptoms between both groups. There was a greater incidence of nausea and vomiting among the oseltamivir group, while the baloxavir group had a higher rate of diarrhea (*N Engl J Med.* 2018;379:913-23).

However, Dr. Bradley noted baloxavir is much more expensive than oseltamivir, which may not justify the better tolerance of the drug for influenza treatment.

You don't get better with it faster, so I'm not going to be recommending you all run to baloxavir this flu season for kids 12 years of age and older," Dr. Bradley said. "I think oseltamivir is still fine, unless we end up with oseltamivir resistance."

Solothromycin, an intravenous and oral fluoroquinolone, has shown promising results against gram-positive and gram-negative pathogens for community-acquired pneumonia and other infections. During the drug's study period, Cempra sold solothromycin to Melinta. However, one trial showed elevated liver functions in a higher number of patients than expected, and the Food and Drug Administration asked Melinta to conduct



Dr. John S. Bradley

additional studies. Investigations on solithromycin have currently stopped until Melinta secures funding. "Until they get better resources, this particular drug is on hold, but you'll see it again, I'm sure," said Dr. Bradley, who also is professor and chief of the division of infectious diseases at the University of California, San Diego.

Dr. Bradley also discussed the efficacy of tedizolid, a protein synthesis inhibitor similar to linezolid approved in adults for the treatment of skin infections. He noted tedizolid is more active than linezolid, but the treatment course is a shorter dose for a shorter amount of time. Compared with linezolid, which can cause thrombocytopenia or neutropenia if taken for more than 10 days to 14 days, there also are fewer side effects.

"The tedizolid is much, much safer," Dr. Bradley said, who added that trials for efficacy of tedizolid are currently underway in pediatric patients. "We're hoping that will end up being the pediatric oxazolidinone."

Other investigative therapies approved for adults and under study for use in children include ceftazidime/avibactam for treatment of urinary tract and complicated intra-abdominal infections, which is effective against meropenem-resistant *Enterobacteriaceae* and resistant *Escherichia coli*

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** We certainly need new interventions especially for influenza, and especially in seriously ill patients. New antibiotics are also needed for multidrug-resistant bacterial pathogens and will be welcomed as soon as developed with pediatric safety in mind.

with extended-spectrum beta-lactamases (ESBL); ceftolozane/tazobactam has also been approved for adults, is pending approval in pediatric patients, and is active against ESBLs such as *Pseudomonas*; and meropenem/vaborbactam, which is active against *Klebsiella pneumoniae* carbapenemase (KPC)-producing isolates. Plazomicin, an aminoglycoside similar to gentamicin used to treat KPC-producing isolates, is stable against enzymes that degrade gentamicin and tobramycin.

Therapies currently under study for adults and being considered for children include imipenem/relebactam for treatment against *E. coli*, *Enterobacter species*, and KPC-producing isolates, and cefiderocol, a siderophore cephalosporin antibiotic – commonly described as a "Trojan horse" antibiotic because it binds to iron and is actively transported into the organism – is effective against *Pseudomonas* and has finished phase 2 trials in adults, with researchers looking to do single-dose trials in children, Dr. Bradley noted.

More experimentally, phage therapy for multidrug-resistant *Acinetobacter baumannii* proved effective in a 68-year-old patient with necrotizing pancreatitis who continued to deteriorate over a 4-month period despite multiple courses of antibiotics and attempted drainage of a pancreatic pseudocyst. Researchers selected a phage-specific bacterium with specificity for *A. baumannii* and cured him. "This is like science fiction," Dr. Bradley said.

Dr. Bradley reported no relevant conflicts of interest.

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administration, Dr. Szeffler noted. They also carry a risk of anaphylaxis in less than 0.2% of patients, requiring the patient to be monitored after first administration and to carry an injectable epinephrine after omalizumab administration as a precaution for late-occurring anaphylaxis.

Mepolizumab is an anti-interleukin (IL)-5 drug used in patients at least 12 years old with severe persistent asthma that's inadequately controlled with inhaled corticosteroids. Peripheral blood counts of eosinophilia determine if a patient has an eosinophilic phenotype, which has the best response to mepolizumab. People with at least 150 cells per microliter at baseline or at least 300 cells per microliter within the past

year have shown a good response to mepolizumab. Dosing is 100 mg subcutaneously every 4 weeks.

For patients with atopic asthma, mepolizumab is effective in reducing the daily oral corticosteroid dose and the number of both annual exacerbations and exacerbations requiring hospitalization or an emergency visit. Other benefits of mepolizumab include increasing the time to a first exacerbation, the pre- and postbronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) and overall quality of life.

Patient reductions in exacerbations while taking mepolizumab were associated with eosinophil count but not IgE, atopic status, FEV<sub>1</sub>, or bronchodilator response in the DREAM study (*Lancet.* 2012

Aug 18;380[9842]:651-9).

Two safety considerations with mepolizumab include an increased risk of shingles and the risk of a preexisting helminth infection getting worse. Providers should screen for helminth infection and might consider a herpes zoster vaccination prior to starting therapy, Dr. Szeffler said.

Benralizumab is an anti-IL5Ra for use in people at least 12 years old with severe persistent asthma and an eosinophilic phenotype (at least 300 cells per microliter). Dosing begins with three subcutaneous injections of 30 mg every 4 weeks, followed by administration every 8 weeks thereafter.

Benralizumab's clinical effects include reduced exacerbations and oral corticosteroid use, and improved

asthma symptom scores and pre-bronchodilator FEV<sub>1</sub>. Higher serum eosinophils and a history of more frequent exacerbations are both biomarkers for reduced exacerbations with benralizumab treatment.

## Dupilumab: New kid on the block

The newest biologic for asthma is dupilumab, approved Oct. 19, 2018, by the Food and Drug Administration as the only asthma biologic that patients can administer at home. Dupilumab is an anti-IL-4 and anti-IL-13 biologic whose most recent study results showed a severe exacerbations rate 50% lower than placebo (*N Engl J Med.* 2018 Jun 28;378[26]:2486-96.). Patients with

Continued on following page

# Flu vaccine effectiveness drops in children by half after 6 months

BY HEIDI SPLETE

MDedge News

The effectiveness of the influenza vaccine declined significantly after 9 months, according to 5 years of data from approximately 15,000 children in Hong Kong.

The vaccine is known to last less than a year, but the findings support the need for more vaccine availability in areas where influenza activity occurs year-round, wrote Shuo Feng, PhD, and Susan S. Chiu, MD, of the University of Hong Kong, and their colleagues.

In a study published in the *Lancet Respiratory Medicine*, the researchers reviewed how vaccine effectiveness changed over time by analyzing data from children aged 6 months to 17 years admitted to a Hong Kong hospital between 2012 and 2017. The study population involved 15,695 children hospitalized for respiratory infections, including 2,500 who were positive for influenza A or B and 13,195 who were negative. Of these, 6.4% of the positive patients and 11% of the negative patients had been vaccinated; 70% - 80% of the vaccinations occurred before the end of December of a given year.

Overall, the vaccination-effectiveness rate was 79% for 0.5 to 2 months after vaccination, then dropped to 60% at 2-4 months,

57% at 4-6 months, and 45% at 6-9 months.

The researchers estimated vaccine effectiveness by three time periods: September to December, January to April, and May to August. Across seasons, vaccine effectiveness for all age groups was 79% for September to December, 67% for January to April, and 43% for May to August.

The study results were strengthened by the inclusion of year-round activity, but limited by several factors including lack of data on patients' vaccination history and the specifics of each year's flu virus, and lack of generalizability to an adult population, the researchers said.

However, the findings support data from previous studies on the effectiveness of annual vaccination, with the optimal timing from October to December in Hong Kong, they said. "Improved influenza vaccines are needed to provide year-round protection for children, particularly in subtropical and tropical locations," they added.

The study was supported by the Health and Medical Research Fund and the Research Grants Council, Hong Kong. The lead authors had no financial conflicts to disclose.

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**SOURCE:** Feng S et al. *Lancet Respir Med.* 2018;6:925-34.

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higher baseline levels of eosinophils had the best response, although some patients showed hypereosinophilia following dupilumab therapy.

The study had a low number of adolescents enrolled, however, and more data on predictive biomarkers are needed. Dupilumab also requires a twice-monthly administration.

"It could be potentially better than those currently available due to additional effect on FEV<sub>1</sub>," Dr. Szeffler said, but cost and safety may determine how dupilumab is recommended and used, including possible use for early intervention.

As development in biologics for pediatric asthma continues to grow, questions about best practices for management remain, such as what

age is best for starting biologics, what strategies are most safe and effective, and what risks and benefits exist for each strategy. Questions also remain regarding the risk factors for asthma and what early intervention strategies might change the disease's natural history.

"Look at asthma in children as a chronic disease that can result in potentially preventable adverse respiratory outcomes in adulthood," Dr. Szeffler said.

Dr. Szeffler has served on the advisory board for Regeneron and Sanofi, and he has consulted for AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Novartis, and Propeller Health.

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## 2019 Education Calendar



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January 31 - February 2	<b>Comprehensive Bronchoscopy With Endobronchial Ultrasound</b>
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March 7 - 9	<b>Ultrasonography: Essentials in Critical Care</b>
March 21-23	<b>Lung Cancer: A Multidisciplinary Course for Pulmonologists Covering Current Paradigms for Diagnosis and Management</b>
April 4 - 6	<b>Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers</b>
May 3 - 4	<b>Bronchoscopy Procedures for the ICU</b>
May 30 - June 1	<b>Advanced Critical Care Echocardiography</b>
June 6 - 8	<b>Difficult Airway Management</b>
June 28 - 29	<b>Advanced Diagnostic and Therapeutic Bronchoscopy</b>
July 25 - 27	<b>Mechanical Ventilation: Advanced Critical Care Management</b>
August 8 - 10	<b>Cardiopulmonary Exercise Testing (CPET)</b>
September 5 - 7	<b>Difficult Airway Management</b>
September 12 - 14	<b>Ultrasonography: Essentials in Critical Care</b>
September 19 - 21	<b>Comprehensive Bronchoscopy With Endobronchial Ultrasound</b>
November 14 - 16	<b>Critical Care Ultrasound: Integration into Clinical Practice</b>
November 22 - 23	<b>Comprehensive Pleural Procedures</b>
December 5 - 7	<b>Ultrasonography: Essentials in Critical Care</b>
December 12 - 14	<b>Extracorporeal Support for Respiratory and Cardiac Failure in Adults</b>
December 13 - 14	<b>Advanced Critical Care Echocardiography Board Review Exam Course</b>



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# Digital alerts reduced AF-related stroke, MI rates

BY RICHARD MARK KIRKNER

MDedge News

CHICAGO – High-risk hospitalized patients with atrial fibrillation (AF) whose doctors monitored them with a computerized alert system were more than twice as likely to be on anticoagulation and had significantly lower rates of death and other cardiovascular events, compared with patients on a standard admissions protocol, according to results of a randomized, controlled trial presented at the American Heart Association scientific sessions.

“Alert-based computerized decision support [CDS] increased the prescription of anticoagulation for stroke prevention in atrial fibrillation during hospitalization, at



DR. PIAZZA

discharge, and at 90 days after randomization in high-risk patients,” said Gregory Piazza, MD, of Brigham and Women’s Hospital, Boston, in presenting results of the AF-ALERT

trial. “The reduction in major cardiovascular events was attributable to reductions in MI and stroke/transient ischemic attack at 90 days in patients whose physicians received the alert.”

The trial evaluated 458 patients hospitalized for AF or flutter and with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 1-8 randomly assigned to the alert (n = 258) or no-alert (n = 210) groups.

Dr. Piazza explained that, for those in the alert group, the CDS system notified physicians when the patient’s CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased. From there, the physician could choose to open an order template to prescribe evidence-based medications to prevent stroke, to elect to review evidence-based clinical practice guidelines, or to continue with the admissions order with an acknowledged reason for omitting anticoagulation (such as high bleeding risk, low stroke risk, high risk for falls, or patient refusal of anticoagulation).

“In patients for whom their providers were alerted, 35% elected to open the stroke-prevention order set, a very tiny percentage elected to read the AF guidelines, and about 64% exited but provided a rationale for omitting anticoagula-

tion,” Dr. Piazza noted.

The alert group was far more likely to be prescribed anticoagulation during the hospitalization (25.8% vs. 9.5%; *P* less than .0001), at discharge (23.8% vs. 12.9%; *P* = .003),

and at 90 days (27.7% vs. 17.1%; *P* = .007) than the control group. The alert resulted in a 55% relative risk reduction in a composite outcome of death, MI, cerebrovascular event, and systemic embolic event at 90

days (11.3% vs. 21.9%; *P* = .002).

The alert group had an 87% lower incidence of MI at 90 days (1.2% vs. 8.6%, *P* = .0002) and 88% lower incidence of cerebrovascular events or systemic embolism at 90 days (0%

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vs. 2.4%;  $P = .02$ ). Death at 90 days occurred in 10.1% in the alert group and 14.8% in the control group ( $P = .13$ ).

One of the limitations of the study, Dr. Piazza noted, was that the most dramatic finding – reduction of major cardiovascular events – was a secondary, not a primary, endpoint. “CDS has the potential to be

a powerful tool in prevention of cardiovascular events in patients with atrial fibrillation.”

Moderator Mintu Turakhia, MD,

*The alert prompted 35% of physicians to open the stroke-prevention order set. A small percentage elected to read the AF guidelines, and about 64% exited but provided a rationale for omitting anticoagulation.*

of Stanford (Calif.) University, questioned the low rate of anticoagulation in the study’s control arm – 9.5% – much lower than medians

reported in many registries. He also asked Dr. Piazza to describe the mechanism of action for prescribing anticoagulation in these patients.

Dr. Piazza noted the study population was hospitalized patients whose providers had decided prior to their admissions not to prescribe

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anticoagulation; hence, the rate of anticoagulation in these patients was actually higher than expected.

Regarding the mechanism of action, “the electronic alert seems to preferentially increase the prescription of [direct oral anticoagulants] over warfarin, and that may have been one of the mechanisms,” Dr.

Piazza said. Another explanation he offered was “off-target” effects whereby, if providers have a better idea of a patient’s risk for a stroke or MI, they’ll be more aggressive about managing other risk factors.

“There are a number of interventions that could be triggered if the alert prompted the provider to have a conversation with patients about

their risk of stroke from AF,” he said. “This may have impact beyond what we can tell from this simple [Best Practice Advisory in the Epic EHR system]. I think we don’t have a great understanding of the full mechanisms of CDS.”

Dr. Piazza reported financial relationships with BTG, Janssen, Bristol-Myers Squibb, Daiichi Sankyo,

Portola, and Bayer. Daiichi Sankyo funded the trial. Dr. Turakhia reported relationships with Apple, Janssen, AstraZeneca, VA, Boehringer Ingelheim, Cardiva Medical, Medtronic, Abbott, Precision Health Economics, iBeat, iRhythm, MyoKardia, and Biotronik, and an ownership interest in AliveCor.

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# Barbershop BP intervention going strong at 12 months

BY KARI OAKES  
*MDedge News*

**A** novel intervention that brought training to barbers, and pharmacists to barber-

shops, resulted in marked and sustained reduction in blood pressure for a black male cohort of participants, according to 12-month data from the project.

Of the 319 black, non-Hispan-

ic male participants, 180 were randomized to participate in an intensive 6-month hypertension intervention. The study protocol allowed pharmacists, who visited participants at their barbershops, to

prescribe hypertension medication under collaborative practice agreements with participants' primary care providers (PCPs).

Compared with an active control

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group who received instruction about blood pressure and lifestyle modification, participants receiving the intervention saw significant reductions in systolic BP at 6 months (N Engl J Med. 2018 Apr 5;378:1291-391). From 6 months onward, participants in the intervention arm received fewer visits

from pharmacists, though they still regularly visited the barbershop, where blood pressure was recorded. At the end of 12 months, systolic BP – at least 140 mm Hg at enrollment – dropped by 28.6 mm Hg from baseline in the intervention group to a mean 123.8 mm Hg. For those in the control group, the reduction in systolic BP was 7.2 mm Hg, to a

mean 147.4 mm Hg. This 20.8-point difference between the two groups was highly statistically significant ( $P$  less than .0001).

“These new 12-month efficacy data are statistically indistinguishable from our previously reported 6-month data,” wrote Ciantal Blyler, PharmD, a clinical pharmacist at Cedars-Sinai Medical Center, Los

Angeles, and her coauthors.

Diastolic BP, a secondary outcome measure, fell in the intervention group by 14.5 mm Hg more than in the active controls. In the intervention arm, 68% of participants reached the prespecified goal blood pressure of less than 130/80 mm Hg, while just 11% of the control group hit this target, a significant difference. No trial participants experienced treatment-related adverse events or deaths during the 6-month extension phase.

Compared with men in the active control arm, those receiving the intervention were on a greater number of antihypertensive classes per regimen. Also, patients receiving the intervention were more likely to receive first-line drugs as add-on therapy. At the end of the 12-month period, all participants in the intensive arm were on antihypertensives, up from 57% at baseline. For the control group, antihypertensive medication use went from 53% at baseline to 65% at 6 months ( $P$  less than .001).

The intervention group saw their PCP more frequently than did the control group during the study; there was no difference in PCP visit frequency at baseline. “This suggests that the pharmacist intervention did not interfere with the patient-PCP relationship, and perhaps influenced the increase in PCP visits,” noted Dr. Blyler and her colleagues. The investigators noted that the pharmacists’ ability to begin, titrate, and change hypertension medication under a collaborative agreement with physicians was an essential part of the program’s initial and continued success. “Perhaps the most critical first step toward widespread dissemination of our model is the expansion of collaborative practice between pharmacists and physicians, or the elimination of the requirement altogether (as in Canada and the UK),” wrote Dr. Blyler and her coauthors.

The study was funded by the National Institutes of Health, the California Endowment, the Lincy Foundation, the Harriet and Steven Nichols Foundation, the Smidt Heart Institute, and the Division of Community Relations and Development at Cedars-Sinai Medical Center, Los Angeles. One coauthor reported being a consultant for Recor Medical; other authors reported that they had no disclosures.

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**SOURCE:** Blyler C et al. *Circulation*. 2018 Dec 17.

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# Phone app diagnoses STEMI nearly as well as ECG

BY BRUCE JANCIN

MDedge News

CHICAGO – A novel smartphone app performed nearly as well as a standard 12-lead ECG for diagnosis of ST-segment elevation MI (STEMI) in patients presenting with chest pain in ST LEUIS, an international, multicenter study.

“This study demonstrates that a 12-lead-equivalent ECG obtained using a smartphone coupled



Dr. J. Brent Muhlestein

with a software application and inexpensive two-wire attachment can identify STEMI versus non-STEMI with an excellent correlation to a traditional 12-lead ECG. This technology holds substantial promise to improve outcomes in STEMI by enabling more rapid diagnosis and treatment anywhere in the world for inexpensive cost,” J. Brent Muhlestein, MD, said while presenting the ST LEUIS results at the American Heart Association scientific sessions.

This technology could provide a long-sought breakthrough in overcoming patient denial

and motivating hard-headed individuals with a life-threatening MI to get to the hospital more quickly after symptom onset, instead of initially shrugging off the matter as indigestion. If individuals can use their handy cell phone or smartwatch to quickly obtain an ECG that shows they’re having a STEMI, they’re going to seek medical attention much sooner, with resultant greater salvage of heart muscle, noted Dr. Muhlestein of Intermountain Healthcare in Salt Lake City.

ST LEUIS tested whether a smartphone ECG app developed by AliveCor can accurately diagnose STEMI in patients with chest pain. The study, which took place at Intermountain Medical Center and a handful of other sites associated with the Duke University Cooperative Cardiovascular Society, included 204 patients who presented to EDs with chest pain. They simultaneously received both a standard 12-lead ECG and an ECG obtained using the AliveCor smartphone app. The matched ECG pairs were evaluated separately, both quantitatively and qualitatively, by a blinded panel of experienced cardiologists and classified as STEMI, left bundle branch block, non-STEMI, or uninterpretable. The study population included 92 patients with chest pain and activation of a STEMI protocol and 112 who came through the ED chest pain protocol.

Side-by-side ECG comparisons weren’t attempted in 14 pairs deemed not interpretable. In 13 cases this was because of technical problems with the smartphone ECG, and in the 14th because of ventricular pacing in the standard 12-lead ECG.

STEMI was diagnosed in 22.5% of the study population by 12-lead ECG and in 29.4% by smartphone app. The discrepancy was explained by small voltage differences in the ST-segment

## VIEW ON THE NEWS

**G. Hossein Almassi, MD, FCCP, comments:** This is yet another study supporting the promise and the applicability of smart phone technology in early diagnosis and management of STEMI.



elevation which met criteria for STEMI by smartphone but not standard 12-lead ECG in 15 cases.

“It appears that the ST elevation was a little bit more obvious in the smartphone ECG,” Dr. Muhlestein observed.

Left bundle branch block was identified in 5.4% of patients by both methods.

The key performance numbers: The smartphone ECG had a sensitivity of 89%, specificity of 84%, positive predictive value of 70%, and negative predictive value of 95% for diagnosis of STEMI or left bundle branch block. The positive predictive value was diminished by the increased likelihood that the smartphone would call STEMI in discordant cases.

Dr. Muhlestein said that, despite the AliveCor device’s very good correlation with the standard 12-lead ECG, the system needs further tweaking.

“I’m sure smart engineers can make a much more simple, really user-friendly device now that we know it’s actually feasible,” he said.

Dr. Muhlestein had no disclosures regarding the study, which was sponsored by the participating medical institutions.

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# Invasive strategy raised bleeding risk in frail AMI patients

BY ANDREW D. BOWSER

MDedge News

Frail older patients with acute myocardial infarction (AMI) may be at increased bleeding risk if managed with an invasive strategy, results of a large U.S. registry study suggest.

The increased bleeding risk was seen among frail older AMI patients who underwent cardiac catheterization, but it was not seen in those treated with more conservative medical management, according to study results.

That finding highlights the conundrum with invasive management strategies for frail patients with AMI, wrote John A. Dodson, MD, of New York University.

“Awareness of vulnerability and greater utilization of evidence-based strategies to reduce bleeding, including radial access and properly dose-adjusted anticoagulant ther-

apies, may mitigate some bleeding events,” they wrote in JACC: Cardiovascular Interventions.

Results of this study, the first large U.S. registry analysis evaluating in-hospital bleeding risk in frail older adults with AMI, confirm findings from several previous small cohort studies linking frailty in AMI patients to in-hospital bleeding, investigators reported.

The analysis included a total of

129,330 AMI patients in the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry who were aged at least 65 years in 2015 or 2016.

About one in six of these older patients were frail, as defined by a composite score based on impaired walking, cognition, and activities of daily living, investigators reported.

The bleeding rate was significantly higher among frail patients undergoing cardiac catheterization, at 9.4% for patients rated as having vulnerable/mild frailty and 9.9% for patients with moderate to severe frailty (*P* less than .001), compared with fit/well patients, whose rate was 6.5%, investigators wrote. By contrast, there was no significant difference in bleeding rates for frail versus nonfrail patients managed conservatively, they said.

After adjusting for bleeding risk factors, frailty was independently associated with increased risk of

bleeding, compared with fit/well status, with odds ratios of 1.33 for vulnerable/mild frailty and 1.40 for moderate to severe frailty. Again, no association was found between frailty and bleeding risk in patients managed conservatively, according to investigators.

Frail patients in the ACTION registry were more often older and female and less likely to undergo cardiac catheterization when compared with fit or well patients, they added in the report.

Dr. Dodson reported support from the National Institutes of Health/ National Institute on Aging and from the American Heart Association. Study coauthors provided disclosures related to Bayer, Janssen, Abbott Vascular, Jarvik Heart, LifeCuff Technologies, and Ancora Heart.

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**SOURCE:** Dodson JA et al. JACC Cardiovasc Interv. 2018;11:2287-96.

## VIEW ON THE NEWS

**G. Hossain Almassi, MD, FCCP, comments:** Frailty, or in the surgeons’ old jargon, the eyeball test, is an important prognostic variable for patient outcomes. The findings in this study and the suggestions for a more conservative approach to frail patients are well founded.

# Combined risk factors raise coronary event rates

BY RICHARD MARK KIRKNER  
MDedge News

CHICAGO – Individuals with both elevated lipoprotein(a) levels and a family history of coronary heart disease are at a considerably higher long-term risk of atherosclerotic cardiovascular disease and coronary heart disease events than those with one risk factor alone, according to results from a large clinical study presented at the American Heart Association scientific sessions.

“Elevated lipoprotein(a) levels or a positive family history of coronary heart disease each is independently associated with cardiovascular disease risk,” said Anurag Mehta, MD, of Emory University School of Medicine, Atlanta. “This study showed that the presence of both an elevated Lp(a) level and a positive family history has an additive joint association with long-term cardiovascular risk.”

Dr. Mehta reported on an analysis of 12,149 individuals participating in the Atherosclerosis Risk in Communities (ARIC) study. All study participants were free of cardiovascular disease at the time of enrollment. The researchers measured

Lp(a) levels and ascertained family history by self-report. Forty-four percent of the study participants had a family history of coronary heart disease (CHD), and 23% were black.

Black participants had a significantly higher average plasma Lp(a) concentration than white persons, at 16.7 mg/dL vs. 5.7 mg/dL. However, plasma Lp(a) levels between participants with either a positive or a negative family history of CHD were similar on average, 7.6 mg/dL and 7.8 mg/dL, respectively.

The study pooled black and white ARIC participants by race-specific Lp(a) levels (quintiles) and stratified them into four different groups: 1. positive family history and an elevated race-specific Lp(a) level (quintile 5); 2. positive family history and nonelevated race-specific Lp(a) level (quintiles 1-4); 3. negative family history and elevated race-specific Lp(a) level; and 4. negative family history and nonelevated race-specific Lp(a) level. “There was an increase in the proportion of participants with a family history of CHD across race-specific Lp(a) quintiles, highlighting the fact that family history is associated with race-specific

## VIEW ON THE NEWS

**G. Hossain Almassi, MD, FCCP, comments:** This is the latest report from the ARIC study showing that a combination of an elevated level of lipoprotein(a) and a positive family history of coronary heart disease leads to a significantly higher cumulative risk of long-term atherosclerotic cardiovascular and coronary heart disease events.

Lp(a) levels,” Dr. Mehta said.

“The highest ASCVD incidence was noted among participants with an elevated Lp(a) level as well as a positive family history.” Among those patients, the cumulative incidence of ASCVD events was nearly 25%, compared with 22% for those with a positive family history and nonelevated Lp(a) levels (group 2) or those with a negative family history but elevated Lp(a) levels (group 3), and 18% for those with negative family history and nonelevated Lp(a) levels.

Results for the cumulative incidence of coronary events trended similarly,

Dr. Mehta noted: around 22% for group 1, 19% for group 2, 17% for group 3, and 14% for group 4.

“Our findings indicate that these easily measurable nontraditional risk markers can help identify those at an elevated long-term CVD risk and may be useful for informing CVD prevention strategies among asymptomatic individuals,” Dr. Mehta said.

Dr. Mehta had no financial relationships to disclose.

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**SOURCE:** Mehta A et al. AHA scientific sessions, Abstract AT.AOS.03 119.

## Composite screening tools increase PAH detection

BY TED BOSWORTH

MDedge News

**I**n patients at risk for pulmonary arterial hypertension (PAH) due to a connective tissue disease, composite novel screening methods are improving early detection when employed in the context of traditional tools, such as transthoracic echocardiography (TTE), according to a systematic review of studies published over the last 5 years.

The review was conducted to prepare for a guideline update, according to the authors of this recently published summary in *Seminars in Arthritis and Rheumatism*.

In a literature review for 2012-2015, the authors evaluated whether new tools or strategies have improved PAH screening in patients with connective tissue disease since the last review was undertaken (*Semin Arthritis Rheum* 2014;43:536-41).

The latest review found that, although TTE and pulmonary function tests (PFT) remain a mainstay of screening, there is growing evidence that composite measures, such as the DETECT and ASIG algorithms, add sensitivity and specificity, compared with guidelines that rely on TTE and PFT alone.

After a literature search, the sys-

tematic review included 16 cohort studies and 6 case-control studies. Most of these evaluated PAH screening strategies for patients with systemic sclerosis specifically despite the potential for other connective tissue disease etiologies to lead to PAH.

“We need more longitudinal observational studies to develop and validate screening algorithms for non-systemic sclerosis connective tissue diseases,” stated the authors, led by senior investigator Dinesh Khanna, MD, medical director of ambulatory and chronic disease in the University of Michigan’s Office of Research, Ann Arbor.

Relative to screening primarily based on TTE and PFT as advocated in 2009 joint guidelines from the European Society of Cardiology and the European Respiratory Society (ESC/ERS), the preponderance of data supported the addition of DIRECT and ASIG algorithms to improve the sensitivity and specificity of traditional screening and diagnostic tools, according to the data reviewed.

Several of the studies evaluating DETECT and ASIG compared their sensitivities and specificities to the screening strategy recommended in the 2009 ESC/ERS guidelines be-

*Continued on following page*

### 2019 GRANTS CYCLE

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# TRED-HF: Despite recovery, dilated cardiomyopathy returns after halting HF drugs

BY BRUCE JANCIN

MDedge News

CHICAGO – Phased withdrawal of guideline-directed medical therapy in patients who seemed to have recovered from dilated cardiomyopathy resulted in relapses in 40% of patients within 6 months in the TRED-HF trial.

The clinical implications of this small pilot randomized trial are clear: “Withdrawal of therapy should not usually be attempted, at least until we can predict who’s going to relapse and who’s not,” Brian P. Halliday, MD, PhD, said at the American Heart Association scientific sessions.

“Improvement in function represents remission rather than permanent recovery for many patients,” added Dr. Halliday of Imperial College London.

The study was performed to address a question that arises with increasing frequency in clinical practice as a result of the impressive advances in heart failure therapy in recent years, he said. “Patients frequently come to us in clinic and ask us, ‘Do I need to continue to take these medications forever?’ They’re frequently young, and they want to know if they really need to be subject to 40 or 50 years of medication. Some are concerned about side effects, others are interested in pregnancy, and then there is the financial cost.”

Simultaneously published in *The Lancet*, TRED-HF was a single-center, open-label study of 51 patients who had prior dilated cardiomyopathy (DCM) and a median left ventricular ejection fraction (LVEF) of 25% at the time of diagnosis 4.9 years earlier and who subsequently recovered in response to therapy. That is, they became symptom free with an LVEF greater than 50%, a normal left ventricular end-diastolic volume index, and a reassuringly low median N-terminal pro b-type natriuretic peptide (NP-pro-BNP) level of 72 ng/L.

For the study, 25 patients were randomized to phased withdrawal of their heart failure drugs over a 16-week period: First they reduced or stopped loop diuretics, then mineralocorticoid antagonists, then beta-blockers, and finally their ACE inhibitor or angiotensin receptor blocker. The other 26 participants continued therapy during the first 6 months of the study, then 25 of the 26 crossed over to phased withdrawal.

The primary endpoint was relapse of DCM within 6 months of the start of the study. Relapse was defined as either a drop in LVEF of more than 10% to a level below 50%, at least a doubling of NT-pro-



Dr. Brian P. Halliday

BNP to greater than 400 ng/L, clinical evidence of heart failure, or a greater than 10% increase in LV end-diastolic volume as assessed by cardiac MRI.

## Results presented

During the first half of the study, 11 of 25 patients (44%) relapsed during or after medication withdrawal. None of the controls relapsed. In the crossover phase, 9 of 25 patients (35%) relapsed in response to treatment withdrawal. Of the 20 patients who relapsed, 13 did so within 16 weeks of beginning medication withdrawal. Indeed, most patients relapsed within 8 weeks of their last medication. Ten of the twenty fulfilled multiple criteria for relapse.

Medication withdrawal was accompanied not only by a mean 9.5% reduction in LVEF, compared with baseline, but by a 15.4-bpm rise in heart rate, a 7.0-mm Hg increase in diastolic blood pressure, and 5.1-point deterioration in Kansas City Cardiomyopathy Questionnaire scores, demonstrating that what happened off treatment was true DCM recurrence and not simply an imaging artifact.

Everyone who relapsed immediately restarted treatment. At their next follow-up visit, all were once again asymptomatic, and 17 of the 20 (85%) had an LVEF greater than 50%. Two of the other three had an LVEF of 45%-50%, and the other had an LVEF of 43%.

“So they did seem to recover when they went back on medication,” Dr. Halliday observed.

## Experts react

Designated discussant Jane E. Wilcox, MD, commented, “Currently, in 2018, we have no true signature of recovery. These patients are indeed in cardiac remission and have an indefinite indica-



Dr. Jane E. Wilcox

tion for continuing their evidence-based medical therapy without interruption.”

“The clinical implication here is, I think, we should TRED-lightly,” quipped Dr. Wilcox of Northwestern University in Chicago.

Her own research indicates that even patients who have recovered their LVEF and no longer seem to have a heart failure phenotype still have an abnormal myocardial substrate as evidenced by persistent dysfunctional cardiac mechanics on echocardiography. But she remains optimistic.

“I don’t think [TRED-HF] squelches the future of myocardial recovery. I think it actually invigorates the field for an assessment of genomics, proteomics, and metabolomics looking for that true signature of cardiac recovery,” she said.

Donald Lloyd-Jones, MD, who chaired a press conference where Dr. Halliday presented the TRED-HF results, said “I really want to commend the investigators for taking on what, on its face, might be an ethically challenging question by taking treatment away when we don’t know what the answer is likely to be. But they really checked all the boxes to make sure this was done in a very safe and monitored way, so that even though the outcome was what it turned out to be, the harm to patients was minimized. Dr. Lloyd-Jones is professor and chair of the department of preventive medicine and director of the Northwestern University Clinical and Translational Sciences Institute, Chicago.

Dr. Halliday reported no disclosures regarding the study, funded by the British Heart Foundation.

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**SOURCE:** Halliday BP. *Lancet*. 2018 Nov 11. doi: 10.1016/S0140-6736(18)32484-X.

*Continued from previous page*

cause the 2015 ESC/ERS guidelines were not yet available at the time these studies were taking place.

In fact, the advantage of these algorithms has been acknowledged in a set of subsequent ESC/ERS guidelines issued in 2015. These specifically recommend DETECT in selected populations, such as adults

with more than a 3-year history of systemic sclerosis and less than 60% diffusing capacity of the lung for carbon monoxide.

Based on the systematic review, the authors did not conclude that there is a single set of optimal tests for PAH screening whether in patients with systemic sclerosis or other connective tissue disease, but

the authors did conclude that there has been progress in strategies for early PAH detection.

They also speculated that more progress might be coming. They noted that several newer tests, such as stress TTE to assess cardiopulmonary function during exercise, might further improve PAH detection at early stages.

According to the authors, this work is important, because better screening that results in earlier PAH detection means earlier treatment, which, in turn, “may improve survival.”

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**SOURCE:** Young A et al. *Semin Arthritis Rheum*. 2018 Oct 14. doi: 10.1016/j.semarthrit.2018.10.010.

# Smoke-free policies improve public health, lower BP

BY STEVE CIMINO

MDedge News

Areas that have adopted smoke-free policies in their restaurants, bars, and workplaces have seen a corresponding drop in systolic blood pressure, according to data from the Coronary Artery Risk Development in Young Adults (CARDIA) study.

“Among a geographically diverse cohort of black and white nonsmoking adults followed for 15 years, we found that participants living in areas with smoke-free policies in restaurants, bars, and workplaces had lower systolic blood pressure at the end of follow-up, compared with participants living in areas without smoke-free policies,” wrote Stephanie L. Mayne, PhD, of the department of preventative medicine at Northwestern University, Chicago, and her coauthors in the *Journal of the American Heart Association*.

The study analyzed data from 2,606 CARDIA participants, all of whom enrolled in 1985-1986 and underwent follow-up exams after 2, 5, 7, 10, 15, 20, 25, and 30 years. Smoke-free policies were obtained from the American Non-Smokers' Rights Foundation's Local Ordinance Database and linked to participants based on their census tract

and examination date. Systolic and diastolic blood pressure (SBP, DBP), along with physical activity and dietary quality, were measured at each examination.

By year 25, participants in areas with smoke-free restaurants had SBP values that were 1.14 mm Hg lower than participants who lived in areas with smoke-friendly restaurants (95% confidence interval, 2.15-0.12). Participants in areas with smoke-free bars returned similar results, with a SBP difference of 1.52 mm Hg (95% CI, 2.48-0.57). The data were less conclusive for DBP, though CARDIA indicated that SBP was more associated with cardiovascular disease risk than DBP and

“even small reductions in SBP may result in meaningful reductions in CVD risk.”

The coauthors shared the study's potential limitations, including an



Dr. Stephanie L. Mayne



inability to control for antismoking campaigns and the possibility that participants did not report any infrequent smoking habits. They also noted, “Strengths of this study include use of data from a large, geographically diverse cohort with 15 years of follow-up, and use of fixed-effects models to tightly control for both measured and unmeasured time-invariant characteristics of participants.” In addition, previous associations between smoke-free policies and reduced risk of hospitalization for CVD, noting the relation and suggesting “BP reduction as a potential mechanism through which smoke-free policies may reduce rates of CVD at the population level.”

This study was supported by the National Heart, Lung, and Blood Institute, in collaboration with the University of Alabama at Birmingham, Northwestern University, the University of Minnesota, Kaiser Foundation Research Institute, and Johns Hopkins University School of Medicine. It was partially supported by the Intramural Research Program of the National Institute on Aging. No conflicts of interest were reported.

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**SOURCE:** Mayne SL et al. *J Am Heart Assoc*. 2018 Nov 21. doi: 10.1161/JAHA.118.009829.

## Rates, costs, mortality of RA-related interstitial lung disease analyzed in new study

BY STEVE CIMINO

MDedge News

Interstitial lung disease (ILD) is becoming more prevalent in patients with rheumatoid arthritis (RA) while shortening survival and leading to substantial health care costs, according to a retrospective study of RA-ILD prevalence, incidence, costs, and mortality.

“To our knowledge, this is the first study to describe the incidence and prevalence of RA-ILD among the general population and to estimate costs among U.S. patients with RA-ILD,” wrote lead author Karina Raimundo, principal health economist at Genentech, and her coauthors in the *Journal of Rheumatology*.

The study reviewed data from the Truven Health MarketScan Commercial and Medicare Supplemental health insurance databases, along with linking a subset of patients to the Social Security Administration Death Index to determine mortality.

From 2004 to 2013, with the number of patients ranging from 892 to 3,232 per year, yearly prevalence estimates ranged from 3.2

(95% confidence interval, 3.0-3.4) to 6.0 (95% CI, 5.7-6.2) RA-ILD cases per 100,000 people. Yearly incidence ranged from 2.7 (95% CI, 2.5-2.9) to 3.8 (95% CI, 3.5-4.0) cases per 100,000 people.

While incidence was relatively stable, prevalence increased over the 10-year period. The

*By the 5-year mark of first diagnosis, 35.9% of RA-ILD patients who could be linked to the SSDI had died; those patients – with a mean age of 65 years – also had a median survival of 7.8 years.*

authors noted that increased prevalence suggests improved survival of RA-ILD patients but were unable to definitively state why, with explanations ranging from more effective therapies to earlier diagnosis of the disease. “Our data do not allow more in-depth evaluation of this issue, and it merits further analysis.”

In addition, they found that average yearly costs across all study years ranged from

\$40,941 (standard deviation, \$55,682) to \$51,849 (SD, \$77,125), with the main cost drivers being inpatient admissions, outpatient services, and outpatient pharmacy.

By the 5-year mark of first diagnosis, 35.9% of RA-ILD patients who could be linked to the SSDI had died; those patients – with a mean age of 65 years – also had a median survival of 7.8 years (95% CI, 7.1-8.3). Generally, a 65-year-old person in the United States would be expected to live for 19 more years.

The authors acknowledged the study's limitations, including reliance on administrative claims data, subsequent misclassification of RA-ILD status, a lack of information on cause of death, and an underestimation of mortality caused by the inability to link all patients to the Social Security Administration Death Index.

The study was funded by Genentech and F. Hoffmann-La Roche. No other conflicts of interest were reported.

chestphysiciannews@chestnet.org

**SOURCE:** Raimundo K et al. *J Rheumatol*. 2018 Nov 15. doi: 10.3899/jrheum.171315.

## PRESIDENT'S REPORT

# Seeking the wisdom of the CHEST crowd

BY CLAYTON T. COWL, MD, MS, FCCP

The wisdom of the crowd is the collective opinion of a group of individuals rather than that of a single expert. At CHEST, the makeup of our membership is diverse and energetic, and it comprises individuals with unique expertise who not only serve as faculty but who are also eager for opportunities themselves to learn.



DR. COWL

That collective wisdom, leveraged over the entire membership, is what the leadership of CHEST will be listening to this year as we create new educational products and continuously improve the annual meeting and other courses held throughout the year. From broad-based general overviews such as CHEST's board reviews, to more specific courses such as training in bedside ultrasound or ventilator management, each is geared to make all of us better clinicians who will recognize and provide the latest and most effective treatments for our patients.

If you had the opportunity to attend my opening address at the CHEST annual meeting in San Antonio in October, you heard me talk about the innate wisdom of "the crowd." We all have various "crowds" in our lives – our work colleagues, families, and relationships in professional societies.

I reminded the audience that if we take the time to listen to each of these "crowds," they usually know the answers. In the coming year, we, as a leadership team for CHEST, will be focusing on being better listeners and utilizing "our crowd" of members to better connect in order to develop educational products that will train clinicians, educators, and researchers in the very latest and most effective care in pulmonary, critical care, and sleep medicine.

Here are just a few initiatives planned this year that have come in response to member comments and suggestions:

- Digital Strategy Task Force – This multidisciplinary group, composed of both volunteer members and association staff, has been assigned to evaluate the user experience associated with existing CHEST content

delivery platforms and highlight opportunities for improvements. In this effort, they will identify trends that will enable the organization to better execute on the digital-dependent strategies in the organization's strategic plan in a successful way. The group will be making recommendations to the Board of Regents that will include timelines, goals, and specific objectives, define organizational voice and brand messaging present on web and other platforms, and create specific metrics to measure the user experience on an ongoing basis.

- Optimizing Board Review Courses – CHEST will be looking at ways to present some content on digital platforms that are difficult to teach in a classic didactic format. Topics such as acid-base disturbances and biostatistics are more effectively presented using a digital, problem-based format. Efforts will be made to shorten board review courses slightly without compromising quality or jeopardizing coverage of content and to incorporate succinct bulleted summaries of each topic covered. In addition, plans are in place to create new courses that will train learners the techniques for passing the new "low stakes" board examination offered by the ABIM.
- Making membership more affordable for international colleagues – New discounted membership rates have been launched to allow international members to obtain the "Enhanced" level of membership to be eligible for fellowship in the association (ie, the FCCP designation). Volume discounts have been introduced for regional chapters and organizations to allow health-care team members from around the world to join CHEST in conjunction with their local society at a fraction of the cost of a single member rate.
- Patient education modules from the CHEST Foundation – A variety of patient education modules are now available to providers, as well as to the general public for information on a wide array of topics – from correct use of inhalers to state-of-the-art therapies for COPD or lung cancer.
- Improved opportunities for member participation – From improved instructions for joining a CHEST NetWork to specific orientation instructions for new members of the Board of Regents, improved com-

munications have become available to help members become better acquainted with the framework of the organization and allow them to become more effective once they begin new leadership roles.

- Embracing innovation – This year, the organization will launch CHEST Inspiration, a program that involves development of an environmental scan to be shared with our members regarding how CHEST can be a differentiator in an environment where quality education is becoming more accessible and, as a result, more competitive. As part of this initiative, CHEST will plan to host a series of focus group sessions to act on the environmental scan and will also roll out an innovation competition at the 2019 annual meeting in New Orleans in October.
- Expanded international strategy – CHEST is responding to the requests from member groups in countries within Asia, Europe, Latin America, and the Middle East to hold a CHEST Congress each spring to bring the best of the CHEST an-

nual meeting to our colleagues from around the world who may not be able to travel to the meeting held in the United States, as well as a more intimate board review-like meeting each summer in various regions of the world. For example, this year, the College will host a CHEST Congress in Bangkok, Thailand, April 10-12, and a regional meeting in Athens, Greece, June 27-29.

We are committed to improving communication with our members and encouraging innovation regardless of their prior participation levels. CHEST will continue to bring its brand of education focused on more hands-on learning and team-based knowledge using simulation, serious gaming, and artificial intelligence in the years ahead. CHEST leaders have begun to be active on social media, and we will be introducing new platforms for all members to better understand what is happening from a leadership perspective. Together, we will be able to harness the collective wisdom of our talented and innovative members in order to make a lasting difference for our patients.

## Explore the Moderate to Severe Asthma Center of Excellence

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Engage with CHEST and Medscape as they partner on the Moderate to Severe Asthma Center of Excellence, designed to support physicians in addressing the challenges of diagnosing and treating moderate to severe asthma.

Rotating content will include articles, videos, commentary, and news on diagnostic, therapeutic, and prevention strategies, including the latest research and breakthroughs.

**New content will be added often, so check back for updates.**

- JUST ADDED
- Asthma Emergencies: A Guide to Treating Potentially Life-Threatening Exacerbations [video]
  - Biology of Asthma and Biologics: A Primer
  - Transitioning Adolescents With Asthma to the Adult Model of Care [video]

- Other current topics include:
- Asthma Redefined-Managing Multiple Diseases: Unmasking the Culprit
  - Diagnosing Severe Asthma: Not as Easy as it Sounds
  - Bronchial Thermoplasty: A Viable Option for Severe Asthma

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## SLEEP STRATEGIES

# The emerging role of sleep in the development of Alzheimer disease

BY RAMAN K. MALHOTRA, MD; AND  
BRENDAN P. LUCEY, MD, MSCI

**M**ore than 5 million Americans are living with Alzheimer disease (AD), making this the leading cause of dementia in the United States. This number is projected to nearly triple to 14 million people by 2060 (Matthews KA, et al. *Alzheimers Dement*. 2018 Sep 17. doi: 10.1016/j.jalz.2018.06.3063. [Epub ahead of print]).

Experts predict estimated costs related to AD to be more than \$500 billion annually starting in 2040 (Hurd MD, et al. *N Engl J Med*. 2013;368[14]:1326). AD is a neurodegenerative disorder characterized by gradual, progressive decline in memory along with other cognitive functions, eventually leading to impairment in activities of daily living. Most current treatments for AD are symptomatic and only minimally slow progression of disease. The increasing prevalence, overwhelming costs to society, and the absence of a cure for AD have created an impending national health crisis.

As the dementia progresses, sleep also tends to worsen. Currently, clinicians improve sleep



DR. MALHOTRA



DR. LUCEY

in patients already diagnosed with AD through diagnosis and treatment of sleep disorders, such as insomnia and sleep apnea, to improve overall functioning and quality of life. Treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) in patients diagnosed with AD has shown to improve cognition and other neurocognitive measures (Ancoli-Israel S, et al. *J Am Geriatr Soc*. 2008;56[11]:2076).

However, there is mounting interest in evaluating how poor sleep could lead to future development of AD or serve as a marker for

AD disease in preclinical or asymptomatic populations. Sleep symptoms can be a precursor of other neurological diseases; for example, dream enactment (REM sleep behavior disorder) can precede onset of neurodegenerative disease (Parkinson disease) by decades. Increasing evidence suggests that sleep disruption seen in early or even preclinical AD contributes to its onset and progression. In response to this growing body of research, in June 2018, the American Academy of Sleep Medicine (AASM) issued a health advisory to patients and providers to consider early intervention to ensure sufficient sleep and to treat sleep disorders to assist prevention or delaying onset of AD.

## Poor sleep as a risk factor for Alzheimer disease

Epidemiologic studies (both cross-sectional and prospective studies) have demonstrated that fragmented sleep in cognitively normal individuals is a risk factor for the future development of symptomatic AD (Bubu OM, et al. *Sleep*. 2017[Jan]:1;40). The pathogenesis of AD includes abnormal accumulation of the protein, amyloid- $\beta$  ( $A\beta$ ), in the brain as insoluble

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**Case Reports** Submit a case for presentation during a case report slide or poster session at CHEST 2019. Respected experts will moderate the session and lead discussion.

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extracellular plaques followed by intracellular aggregation of tau, neuronal loss, and cognitive dysfunction. A $\beta$  deposition in the brain begins approximately 15 to 20 years before the onset of cognitive impairment and serves as an early biomarker of AD. Accumulation of A $\beta$  results from imbalance between production and clearance of the protein from the central nervous system.

Numerous studies have demonstrated that people with disrupted sleep may show early evidence of AD, such as A $\beta$  deposition compared with healthy sleepers. In one study, cognitively normal people with A $\beta$  plaque disease had worse sleep efficiency and increased nap frequency measured by actigraphy as compared with cognitively normal individuals without A $\beta$  plaques (Ju YE, et al. *JAMA Neurol.* 2013 [May];70[5]:587). Further, a recent study found that self-reported daytime sleepiness was associated with longitudinal increases in A $\beta$  deposition (Carvalho DZ, et al. *JAMA Neurol.* 2018[Jun];75[6]:672).

### Possible mechanisms

Possible mechanisms have been suggested to explain how poor sleep may lead to AD. Over the past 10 years, sleep deprivation was found to increase A $\beta$  concentrations in both a mouse model (Kang JE, et al. *Science.* 2009; 326:1005) and humans, most likely through increased production and/or release of A $\beta$  (Lucey BP, et al. *Ann Neurol.* 2018; 83[1]:197). Sleep also appears to increase clearance of proteins and other mole-

cules via bulk fluid flow (“glymphatic” clearance). Glymphatic clearance may enable the removal of interstitial toxic proteins, such as A $\beta$ , through a dynamic interaction between the cerebrospinal fluid and the interstitial fluid, where astrocytes facilitate extracellular fluid transit through the brain during sleep (Xie L, et al. *Science.* 2013;342:373). Since A $\beta$  deposition in the brain is concentration-dependent, higher A $\beta$  levels from sleep disturbance could lead to greater deposition in the brain.

### Circadian rhythm and Alzheimer disease

Another mechanism linking sleep to the pathogenesis of AD includes disruption of the circadian rhythm, which is commonly seen in patients with AD. Studies have linked populations who suffer from circadian rhythm disorders to higher rates of dementia (Tranah GJ, et al. *Ann Neurol.* 2011;70[5]:722). Circadian disruption may predispose the brain to neurodegenerative conditions by altering immune function, disrupting endocrine function, increasing inflammation and oxidative stress, or affecting neurogenesis (in specific areas such as the hippocampus). Thus, inadequate sleep could prime the brain for neurodegeneration by multiple pathways.

### Obstructive sleep apnea and Alzheimer disease

Sleep disruption and chronic intermittent hypoxia secondary to untreated OSA has also been as-

sociated with AD. Numerous studies have shown that sleep-disordered breathing is associated with AD risk and that AD patients have higher rates of OSA. For instance, a study in older women found that moderate and severe sleep-disordered breathing was associated with an increased risk of future cognitive impairment and dementia (Yaffe K, et al. *JAMA.* 2011[Aug];10;306[6]:613). In addition to sleep disruption from sleep apnea affecting A $\beta$  as detailed above, hypoxia from sleep apnea may also alter risk of future AD.

### Future directions

Studies support a clear bidirectional relationship between AD and sleep. As researchers continue to investigate sleep as a marker for AD, others are exploring the implications of using sleep interventions to prevent and/or delay the onset of AD. Patients with poor and disrupted sleep may be the ideal candidates for sleep interventions to lower the risk of AD, such as treating OSA with CPAP therapy or insomnia with hypnotic medication or cognitive behavioral therapy. These therapies are already well-studied and approved for human use, allowing for rapid translation to future intervention trials.

*Dr. Malhotra is Associate Professor, Sleep Medicine Section; and Dr. Lucey is Assistant Professor, Director-Sleep Medicine Section; Department of Neurology, Washington University School of Medicine, St Louis, Missouri.*

## NIH funds project of CHEST Foundation grant winner Drew Harris, MD

While in San Antonio for CHEST 2018, CHEST Foundation caught up with the recipient of our 2017 CHEST Foundation Research Grant in Asthma, Drew Harris, MD, to learn about the impact of winning a CHEST Foundation Research grant had on his community and career. Dr. Harris’ project created a medical-legal partnership to target many of the social determinants of asthma and help address them beyond the typical scope a provider can offer in a traditional visit.

“Currently, we have a full-time lawyer, two social workers, and people in Public Health Sciences program, as well as law students at The University of Virginia (UVA) all working together to address the needs of the community,” Harris stated. “Public health students conduct asthma screenings in any of the four clinics we partner with within the UVA system and bring their findings to the larger group. From there, we figure out how to best intervene for these people and connect them with our lawyer if there are housing or workplace discrimination concerns.”

Dr. Harris recently received NIH funding for his approach and has since expanded this medical-legal

“A middle-aged textile worker who entered Charlottesville as a Syrian refugee several years ago had been unable to work much in Charlottesville due to work-related asthma. She was denied disability due to insufficient work time. Without a network of friends or family to turn to, this family was struggling in poverty with housing and food insecurity. By connecting with this CHEST Foundation-supported program, this patient received needed advocacy and support of doctors, social workers, and legal aid attorneys. She is now supported in an application for a monthly subsidy to help her immediate social needs while we work towards a more permanent solution. Our program has also helped patients with health-harming social needs, including lack of access to care (by helping patients apply for and enroll in Medicaid, for example), housing issues (such as mold and

unresponsive landlords), and intimate partner violence. Working together as a team, we are able to provide advocacy to improve the health and well-being of our vulnerable community members. This program addresses issues that are important to my community. Without the hard work and dedication of my colleagues, the community at large, and all those committed to confronting these problems, many families would not get what they need to thrive. I am proud and feel lucky to dedicate my time to support my patients and my community. Thank you to the CHEST Foundation and all those who support it to ensure that ALL patients receive the care they deserve.”

—Drew Harris, MD



partnership at the University of Virginia. “The grant I received last year from the CHEST Foundation funded a pilot version of my project that I then was able to share with a larger audience and ultimately secure federal funding for,” Dr. Harris shared.

“The NIH grant was awarded through the lens of implementation science. We know what works in asthma medication and environmental

and social factors that help improve patients’ lives. But we do a poor job on actually DOING it. Our project addresses barriers to fixing these social needs and brings a team together to help fix these other problems that are hard for just a medical provider to address.” Dr. Harris continued, “Social needs and determinants of health are starting to receive more attention in pulmonary medicine, so we are really

hitting the ground at the right time. Everyone understands that these are important determinants of health, but they lack the tools to help improve patients’ lives. We are creating those.”

Your donations support clinical research projects like this grant for Dr. Harris. Please consider making a donation to support next year’s grants. <https://foundation.chestnet.org/donate/>.

## CHEST NETWORK

## Pneumonia, PIONEER-HF, malignant pleural effusion

## Chest Infections

**Pneumonia: It is NOW time to act!**

The upper part of the globe is going through another winter season and this brings large numbers of patients visiting emergency departments and requiring ad-



DR. RESTREPO

mission to the hospital due to pneumonia and influenza. It is concerning to see that despite our knowledge that these events will occur during this season every year, there are no significant improvements in place compared to the prior year. But the most concerning aspect of all, is lack of perception that pneumonia and influenza remain among the most important diseases resulting in morbidity and mortality to both children and adults (GBD 2016 Lower Respiratory Infections Collaborators. *Lancet Infect Dis* 2018; S1473-3099[18]30310).

Every year we read, listen, or watch the alarming news regarding the increasing number of cases of influenza and pneumonia, the number of deaths, the lack of vaccine protection, the concerns about human-to-human transmission, the development of resistance, and the lack of resources to deal with this problem. We wonder why we tolerate this difficult situation over and over again? What can we do as a society to help fight this problem? What else needs to happen, so we take this issue seriously? Why can we not improve the care of patients who suffer from pneumonia? We as part of the Chest Infections NetWork would like to raise the awareness of the pneumonia and influenza problem and unite with our communities to address this calamity once and for all! A recent editorial proposes a series of strategic solutions to address this situation that include increasing the overall resources, more funding for research, and the development of advocacy groups and education programs (Aliberti S, et al. *Lancet Respir Med*. 2018;S2213-2600(18):30470).

Marcos I. Restrepo, MD, MSc, PhD  
Steering Committee Vice-Chair

## Cardiovascular Medicine and Surgery

**PIONEER-HF trial: Changing practice in patients hospitalized for heart failure**

Renin-angiotensin system (RAS) inhibition forms a pivotal part of guideline-recommended therapy for patients with heart failure with reduced ejection fraction (HFrEF).<sup>1</sup> Inhibition of the neutral endopeptidase neprilysin increases levels of several vasoactive peptides that inhibit progression of HF.<sup>2</sup> The randomized PARADIGM HF trial compared sacubitril/valsartan (angiotensin receptor neprilysin inhibition, ARNI) to enalapril in

*The recent PIONEER-HF trial now provides important evidence to support safety of careful initiation of sacubitril-valsartan for hospitalized patients with and without prior exposure to RAS.*

8,434 patients with HFrEF and demonstrated a 20% reduction in the primary outcome of cardiovascular death or HF hospitalization (HR 0.80; CI 0.73–0.87;  $P < .001$ ) in patients treated with ARNI; mortality and rehospitalization were decreased significantly, as well.<sup>3</sup> Importantly, patients had to be clinically stable and complete a sequential run-in period to be eligible for randomization. On this basis, the 2017 HF guideline update recommended transition from RAS inhibition to ARNI in trial-eligible patients.<sup>4</sup>

The recent PIONEER-HF trial now provides important evidence to support safety of careful initiation of sacubitril-valsartan for hospitalized patients with and without prior exposure to RAS.<sup>5</sup> Hemodynamically stable patients were started on a regimen of sacubitril-valsartan, usually at doses half of those used in PARADIGM-HF. The primary endpoint of a decrease in BNP levels was improved significantly with sacubitril-valsartan (ratio 0.71, CI 0.63–0.81;  $P < .001$ ), and this translated into a significant decrease in the important patient-centered secondary endpoint of rehospitalization.<sup>5</sup> ARNI are

underutilized in eligible patients; complexity of outpatient drug initiation may contribute.<sup>6</sup>

Data from this important trial suggest that clinicians should consider initiation of ARNI during hospitalization for acute heart failure. This could increase the number of patients receiving a guideline-recommended therapy that improves outcomes.

Steven M. Hollenberg, MD, FCCP  
Steering Committee Chair

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**Clinical Research Guidelines for the management of malignant pleural effusion**

A multisociety multidisciplinary panel developed recommendations for management of malignant pleural effusions (MPE) by using the PICO (Population, Intervention, Comparator, and Outcomes) format. As per these guidelines, definitive therapy is aimed at minimizing symptoms, re-accumulation and repeated pleural interventions, and risk of interventions in asymptomatic MPE outweighing benefits. Pleural interventions were suggested for indications such as clinical staging, obtaining molecular markers, etc. (Tremblay A. *J Bronchology Interv Pulmonol*. 2007;14:98). Large-vol-

ume thoracentesis is suggested for symptomatic patients and for those where lung entrapment is a concern (Lan RS. *Ann Intern Med*. 1997;126:768). In light of available evidence, the panel noted that the

*As per these guidelines, definitive therapy is aimed at minimizing symptoms, re-accumulation and repeated pleural interventions, and risk of interventions in asymptomatic MPE outweighing benefits.*

outcomes of definitive therapy for symptomatic MPE are equivocal between indwelling pleural catheter (IPC) and pleurodesis. IPC, which was restricted to un-expandable lungs in the previous guidelines, are now suggested for both expandable and un-expandable lungs (Feller-Kopman, et al. *Am J Respir Crit Care Med*. 2018;198[7]:839). Talc, being the most effective and widely use pleurodesis agent, is suggested to be delivered by poudrage or slurry. Higher treatment failure rates with chemical pleurodesis, as well as low incidence rates of IPC-related cellulitis and pleural space infections, led the panel to suggest IPC for un-expanded lungs, treatment failures, and residual symptomatic loculated effusions. In patients with IPC-related infections, treatment of the infection rather than removal of the catheter was suggested unless in events where the infection failed to respond (Feller-Kopman, et al. *Am J Respir Crit Care Med*. 2018;198[7]:839). In view of evidence suggesting improved safety outcomes with ultrasound-guided pleural interventions (Abusedera M, et al. *J Bronchology Interv Pulmonol*. 2016;23:138), ultrasound guidance was recommended.

Bharat Bajantri, MD  
Steering Committee Fellow-in-Training

**Interprofessional Team**

Difficult-to-control asthma, defined as: uncontrolled asthma despite use of maximum dose inhaled corticosteroids or chronic oral corticosteroids with daily asthma symptoms, frequent exacerbations, and/or hospitalization results in a substantial medical and financial

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burden with a resultant decrease in quality-of-life. Extrapulmonary co-morbidities, such as obesity, nicotine use, GERD, allergic rhinitis, chronic rhinosinusitis, sleep apnea, anxiety/depression, females

of older age, vocal cord dysfunction (VCD), and type 2 diabetes mellitus (T2DM) have been shown to increase exacerbation frequency, missed days of school/work, and lessened quality-of life. Of these co-morbidities, that latter has garnered

recent attention as a focal point for asthma management.

As many as one in six asthmatics has T2DM, and the obvious impact of oral/systemic corticosteroids runs counter to the treatment armamentarium for difficult-to-control asthma. Furthermore, patients with concomitant T2DM and asthma have poor glycemic control, higher risk of pneumococcal pneumonia, and poor quality-adjusted life expectancy (Black MH et al. *Pediatrics*. 2014;128:e839-47) Of growing interest is the use of metformin in the treatment of Type 2 diabetes mellitus in patients with asthma. Metformin attenuates eosinophilic airway inflammation and theoretically inhibits airway remodeling through AMP-activated protein kinase (Li, et al. *Respirology*. 2016;21:1210).

The management of this heterogeneous group of patients with difficult-to-control asthma and the aforementioned comorbidities underscores the need for interdisciplinary collaboration as well as orchestration with specialty providers (family/internal



DR. UNKLE

medicine, GI, ENT, endocrine, psych/mental health, et al). Further studies are needed to evaluate the anti-inflammatory properties of metformin and its role in asthma management and improvement in outcome.

David W. Unkle, MSN, APRN, FCCP  
Steering Committee Chair

## New section editor for Pulmonary Perspectives®

We are pleased to announce Corey Kershaw, MD, as the new Section Editor for Pulmonary Perspectives. Dr. Kershaw is the Medical Director of the Medical Intensive Care Unit at Clements University Hospital and an Associate Professor, Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern Medical Center, in Dallas, Texas. He currently serves on the American College of Chest Physicians Interstitial and Diffuse Lung Disease NetWork. Dr. Kershaw's research interests revolve around clinical trials for the treatment of idiopathic pulmonary fibrosis and other fibrosing interstitial lung diseases.

We thank Nitin Puri, MD, FCCP,



Dr. Corey Kershaw

for his outstanding service as the Pulmonary Perspectives Section Editor for the previous 3 years.

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three things to know about chestnet.org

# CHEST website

# 1

**The website averages:**

**93k** Users in a month

**20k** Users in a week

**4.1k** Users in a day

# 2

**The most visitors through Nov 2018 have come from:**

- United States
- India
- United Kingdom
- Canada
- Australia

# 3

**The top 5 search terms in the past 12 months are:**

- VTE
- Anticoagulation
- Pulmonary embolism
- Asthma
- DVT

# CPT® and ICD-10 coding for endobronchial valves

The FDA recently approved endobronchial valves for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation. There are CPT® and ICD 10 codes that are appropriate to report these new services. CPT® codes typically are not product or device specific and the codes below apply to current and future FDA approved endobronchial valves with similar clinical indications and intent for the treatment of emphysema.

To be a candidate for the currently approved service, patients must have little to no collateral ventilation between the target and adjacent lobes. In some patients, this can be determined by a quantitative CT analysis service to assess emphysematous destruction and fissure completeness. If there is radiographic evidence of a complete fissure and anatomic isolation of the treatment target, a bronchoscopy assessment will be made on the patient. A bronchial blocking balloon and flow detection system is used to confirm that the patient has little to no collateral ventilation.

CPT Code	Description
31634	Bronchoscopy, rigid with balloon occlusion, with assessment of air leak or flexible, including fluoroscopic guidance, when performed, with administration of occlusive substance (eg, fibrin glue), if performed (Do not report 31634 in conjunction with 31647, 31651 at the same session)

If the bronchial blocking technique shows evidence of collateral ventilation, the patient would be discharged without valve placement. In that scenario the appropriate CPT® code would be 31634:

If the patient is determined not to have collateral ventilation, the valve procedure would proceed, followed by a minimum three-day inpatient stay to monitor for possible side effects. The appropriate CPT codes for placing, and removing FDA approved valves are:

CPT Code	Description
31647	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe
+31651	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe (Use 31651 in conjunction with 31647)
31648	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe
+31649	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure) (Use 31649 in conjunction with 31648)

The table below identifies potential ICD-10-CM diagnosis codes for emphysema. Applicability and usage of these codes may vary per case. Hospitals and physicians also should check and verify current policies and requirements with the payer for any patient who will be treated with endobronchial valves.

## Emphysema ICD-10-CM Diagnosis Codes

ICD-10 Code	Description
J43.0	Unilateral pulmonary emphysema
J43.1	Panlobular emphysema
J43.2	Centrilobular emphysema
J43.8	Other emphysema
J43.9	Emphysema, unspecified

The CHEST/ATS Clinical Practice Committee provided information for this article.



## This month in the journal CHEST®

### Editor's Picks

BY RICHARD S. IRWIN, MD,  
MASTER FCCP

### Giants in Chest Medicine

Emeritus Professor Peter D. Wagner, MD

By Dr. Tatum S. Simonson

Patients With Stage I Lung Cancer in the National Lung Screening Trial.

By Dr. A. A. Balekian, et al.

### State of the Journal Editorial

Spread the Word About CHEST in 2019: Innovations, Introductions, and Farewells.

By Dr. R. S. Irwin, et al.

### Evidence-Based Medicine

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By Dr. A. Moore, et al.

### Original Research

Meta-analysis of Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis.

By Dr. D. Bedard, et al.

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## The BioFire Pneumonia Panel

### Bacteria (semi-quantitative)

*Acinetobacter calcoaceticus baumannii* complex  
*Enterobacter cloacae*  
*Escherichia coli*  
*Haemophilus influenzae*  
*Klebsiella aerogenes*  
*Klebsiella oxytoca*  
*Klebsiella pneumoniae* group  
*Moraxella catarrhalis*  
*Proteus spp.*  
*Pseudomonas aeruginosa*  
*Serratia marcescens*  
*Staphylococcus aureus*  
*Streptococcus agalactiae*  
*Streptococcus pneumoniae*  
*Streptococcus pyogenes*

### Atypical Bacteria (qualitative)

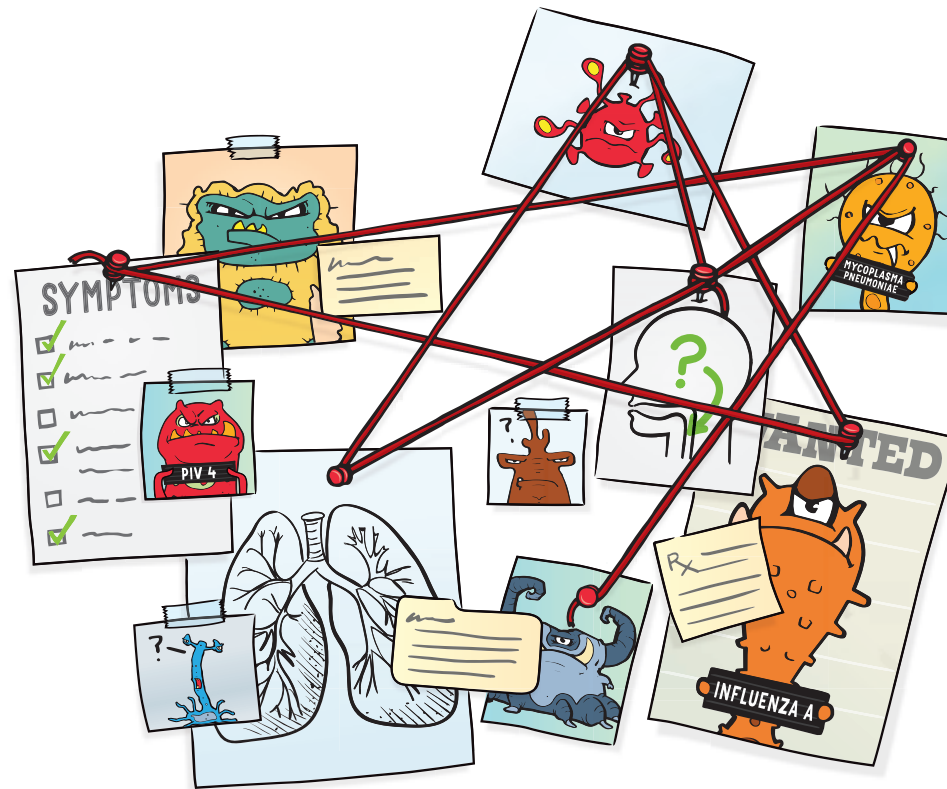
*Chlamydia pneumoniae*  
*Legionella pneumophila*  
*Mycoplasma pneumoniae*

### Viruses (qualitative)

Adenovirus  
Coronavirus  
Human Metapneumovirus  
Human Rhinovirus/Enterovirus  
Influenza A  
Influenza B  
Parainfluenza virus  
Respiratory Syncytial virus

### Resistance Markers

Carbapenemase  
IMP  
KPC  
NDM  
Oxa48-like  
VIM  
ESBL  
CTX-M  
MRSA  
*mecA/C* and MREJ



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