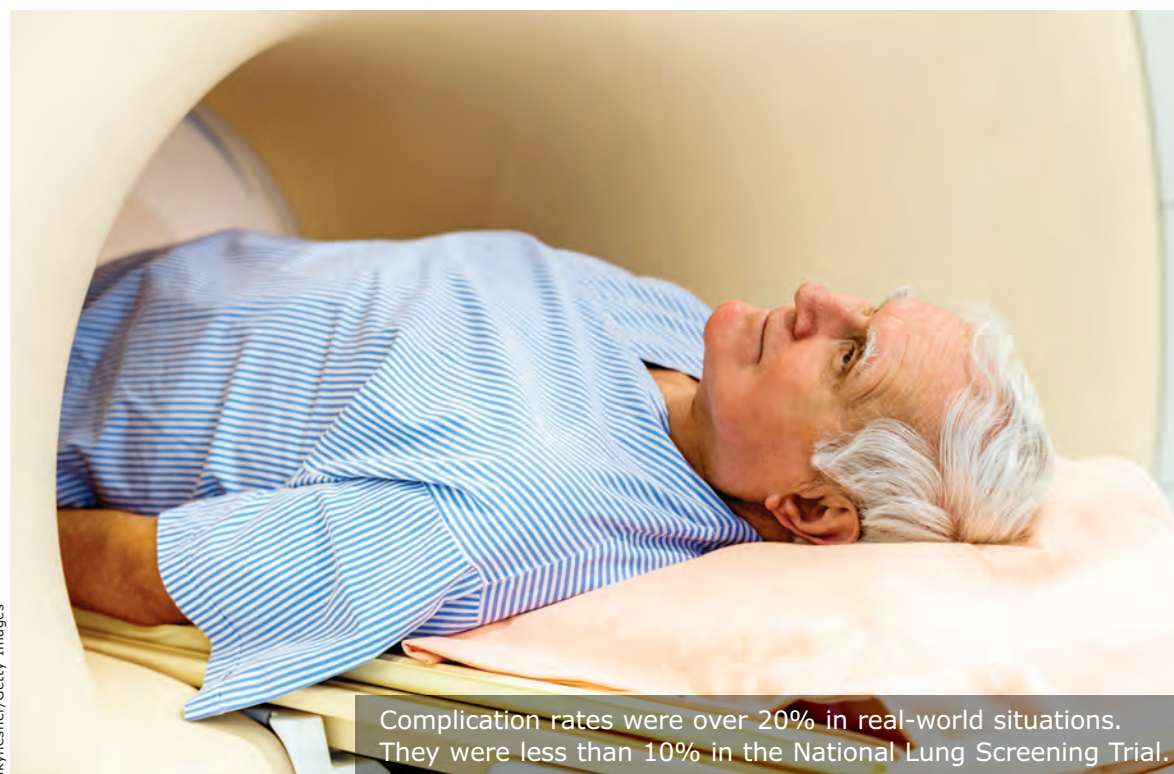




# CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

skynesher/Getty Images



Complication rates were over 20% in real-world situations. They were less than 10% in the National Lung Screening Trial.

## In real-world setting, LDCT screen is linked to high complication risk

BY ANDREW D. BOWSER

MDedge News

**T**he real-world rates of complications associated with diagnostic procedures that followed low-dose computed tomography (LDCT) for lung cancer screening were substantially higher, more than double, the rates that were seen in clinical trials of LDCT screening, a retrospective cohort study suggests.

Plus, those complications are potentially costly, based on the finding of the analysis of commercial and Medicare claims data for nearly 350,000 individuals.

The findings emphasize the importance of discussing the risk of adverse events and their

costs as part of the shared decision-making process between physicians and patients before LDCT screening, researchers said in a report on their study in JAMA Internal Medicine.

"As the number of individuals seeking lung cancer screening with LDCT increases, so too will the number of individuals undergoing invasive diagnostic procedures as a result of abnormal findings," that may be incidental or false positive, said Jinhai Huo, MD, PhD, of the department of health services research, management, and policy at the University of Florida, Gainesville.

The study included 174,702 individuals who underwent an invasive diagnostic procedure as a

LDCT SCREENING // continued on page 4

## More than 23% of antibiotic prescriptions 'inappropriate'

BY RICHARD FRANKI

MDedge News

**M**ore than 23% of all antibiotic prescriptions filled in 2016 were medically unnecessary, and another 36% were questionable, according to an analysis of prescribing data for 19.2 million children and nonelderly adults.

Based on the diagnosis codes for 15.5 million prescriptions filled that year, at least 3.6 million (23.2%) were "inappropriate" – prescribed for conditions for which an antibiotic is almost never recommended, such as acute upper respiratory conditions – and 5.5 million (35.5%) were "potentially inappropriate" – conditions such as acute sinusitis or otitis media, for which an antibiotic is only sometimes recommended, Kao-Ping Chua, MD, PhD, of the University of Michigan, Ann Arbor, and his associates reported in the BMJ.

Only 12.8% of filled prescriptions for the 39 oral antibiotics assessed were classified as "appropriate" under the investigators' scheme, which assigned an antibiotic appropriateness level to all 91,738 diagnostic codes in the 2016 ICD-10-CM. Finally, 28.5% of antibiotic fills were not associated with a recent diagnosis code, suggesting that they

ANTIBIOTIC PRESCRIBING // continued on page 6

### INSIDE HIGHLIGHT

#### NEWS FROM CHEST

Blood Test to Rule Out Lung Cancer in Patients with Low to Moderate Probability Nodules		
CLINICAL QUESTION	STUDY DESIGN	RESULTS
Can a blood test identify benign lung nodules?	Prospective Multicenter Observational Study	Integrated Classifier had Sensitivity 91% Specificity 44% Negative Predictive Value 91%
Used Integrated Classifier that combines: • Relative abundance of two Plasma Proteins • LIGBP • C163A • And 5 Clinical Risk Factors	178 patients with low to moderate risk nodules (<50% pretest probability of cancer)	With clinical use can expect: • 40% fewer procedures on benign nodules • 3% malignant nodules misclassified
Sivewright G et al. CHEST 2018; 154(3): 491-500 Visual Abstract by Rozemba Khan, DO, FCCP		

CHEST

Visual abstracts enhance reader experience

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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>**

<sup>†</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>

<sup>‡</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.

<sup>§</sup>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

result of abnormal findings on lung cancer screening and 169,808 control subjects.

All individuals studied were between 55 and 77 years old, the targeted age range for lung cancer screening specified by the Centers for Medicare & Medicaid Services.

Complication rates were about twice as high in the real-world study as they were in the landmark National Lung Screening Trial (NLST), both for a younger cohort of individuals aged 55-64 years, and an older Medicare age group of individuals aged 65-77 years, Dr. Huo

and his coinvestigators reported.

The estimated rate of complications was 22.0% (95% confidence interval, 21.7%-22.7%) in the younger age group, and even higher in the older age group, at 23.8% (95% CI, 23.0%-24.6%), according to investigators. By contrast, complication

rates in the NLST were 9.8% and 8.5% for younger and older age cohorts, respectively.

The cost of managing postprocedural complications was higher than the cost of the diagnostic procedures.

Mean costs ranged from \$6,320



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 × 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 ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × 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 ≥3 × 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 ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.		
<b>Table 2. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3</b>		
Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain¹	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%
¹ Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.		

Adverse reactions occurring in ≥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



for minor complications to \$56,845 for major complications, they reported.

The most common invasive diagnostic procedure in the study cohort was a cytology test or biopsy in 26.1%, followed by bronchoscopy in 25.6%, according to study data. Another 5.4% of study subjects underwent thoracic surgery.

In a previous Medicare advisory committee meeting, some experts had expressed concern that complication rates in settings outside of the NLST would likely be higher than what was reported in that study, Dr. Huo and coauthors noted. “Our findings echoed this concern,” the researchers wrote. The researchers reported no con-

flicts of interest. Their study was supported by the University of Texas MD Anderson Cancer Center, the University of Florida, the National Cancer Institute, and the National Institutes of Health. [chestphysiciannews@chestnet.org](mailto:chestphysiciannews@chestnet.org) **SOURCE:** Huo J et al. JAMA Intern Med. 2019 Jan 14.

ESBRIET® (pirfenidone)	ESBRIET® (pirfenidone)
<p>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 <i>[see Dosage and Administration section 2.4 in full Prescribing Information]</i>.</p> <p><u>Moderate CYP1A2 Inhibitors</u></p> <p>Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET <i>[see Clinical Pharmacology section 12.3 in full Prescribing Information]</i>. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended <i>[see Dosage and Administration section 2.4 in full Prescribing Information]</i>. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.</p> <p><u>Concomitant CYP1A2 and other CYP Inhibitors</u></p> <p>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.</p> <p><b>7.2 CYP1A2 Inducers</b></p> <p>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 <i>[see Clinical Pharmacology section 12.3 in full Prescribing Information]</i>.</p> <p><b>8 USE IN SPECIFIC POPULATIONS</b></p> <p><b>8.1 Pregnancy</b></p> <p><u>Risk Summary</u></p> <p>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 <i>[see Data]</i>.</p> <p>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.</p> <p><u>Data</u></p> <p><u>Animal Data</u></p> <p>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).</p> <p><b>8.2 Lactation</b></p> <p><u>Risk Summary</u></p> <p>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.</p> <p><u>Data</u></p> <p><u>Animal Data</u></p> <p>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.</p>	<p><b>8.4 Pediatric Use</b></p> <p>Safety and effectiveness of ESBRIET in pediatric patients have not been established.</p> <p><b>8.5 Geriatric Use</b></p> <p>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.</p> <p><b>8.6 Hepatic Impairment</b></p> <p>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 <i>[see Dosage and Administration section 2.3 in full Prescribing Information]</i>.</p> <p>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 <i>[see Clinical Pharmacology section 12.3 in full Prescribing Information]</i>.</p> <p><b>8.7 Renal Impairment</b></p> <p>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 <i>[see Clinical Pharmacology section 12.3 in full Prescribing Information]</i>. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed <i>[see Dosage and Administration section 2.3 in full Prescribing Information]</i>. 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.</p> <p><b>8.8 Smokers</b></p> <p>Smoking causes decreased exposure to ESBRIET <i>[see Clinical Pharmacology section 12.3 in full Prescribing Information]</i>, 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.</p> <p><b>10 OVERDOSAGE</b></p> <p>There is limited clinical experience with overdosage. 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.</p> <p>In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.</p> <p><b>17 PATIENT COUNSELING INFORMATION</b></p> <p>Advise the patient to read the FDA-approved patient labeling (Patient Information).</p> <p><u>Liver Enzyme Elevations</u></p> <p>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) <i>[see Warnings and Precautions (5.1)]</i>.</p> <p><u>Photosensitivity Reaction or Rash</u></p> <p>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 <i>[see Warnings and Precautions (5.2)]</i>.</p> <p><u>Gastrointestinal Events</u></p> <p>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 <i>[see Warnings and Precautions (5.3)]</i>.</p> <p><u>Smokers</u></p> <p>Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET <i>[see Clinical Pharmacology section 12.3 in full Prescribing Information]</i>.</p> <p><u>Take with Food</u></p> <p>Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.</p> <p>Distributed by: Genentech USA, Inc. A Member of the Roche Group 1 DNA Way, South San Francisco, CA 94080-4990</p> <p><b>Genentech</b> <i>A Member of the Roche Group</i></p> <p>ESBRIET® is a registered U.S. trademark of Genentech, Inc. © 2017 Genentech, Inc. All rights reserved. ESB/100115/0470(2)/2/17</p>

VIEW ON THE NEWS

Patients need briefing on harms vs. benefits


“The conversations that are occurring about lung cancer screening are woefully inadequate and do not discuss harms,” Rita F. Redberg, MD, wrote in an editorial note. Shared decision-making visits were made mandatory prior to lung cancer screening by the Centers for Medicare & Medicaid Services. That decision was made because of an evidence review suggesting a “low likelihood” that benefits of lung cancer screening would exceed harms in the Medicare population, Dr. Redberg wrote. Despite that, most Medicare beneficiaries are not having the required visit for shared decision making before they undergo the CT scan.

Of those Medicare beneficiaries who did have a shared decision-making visit, 40% opted out of screening, probably because they learned of the harms relative to the benefits during that visit, Dr. Redberg said.

“It is likely that patients’ decisions not to undergo low-dose computed tomography for lung cancer screening are driven by the high false-positive rate, high chance of incidental findings, and subsequent need for invasive procedures, and small chance of benefit,” she said in her comment.

Shared decision-making visits are also rarely happening in the privately insured population, as shown in previous research, Dr. Redberg noted.

She reported no conflicts of interest related to her Editor’s Note, which appears in JAMA Internal Medicine (2019 Jan 14).



Dr. Redberg is with the department of medicine, University of California, San Francisco.

# Greetings, readers!

BY DAVID A. SCHULMAN, MD, FCCP  
*CHEST Physician Editor in Chief*

One year ago, I wrote in these pages with regard to my two main goals for *CHEST Physician* for 2018, namely allowing more space in our pages for leaders and members to express their views, and improving interactivity between the staff here and our readership to help us better craft a publication that met your needs.

While I think we've met the first goal quite well, with a greater number of educational write-ups from our NetWork leadership and high-quality editorials and com-

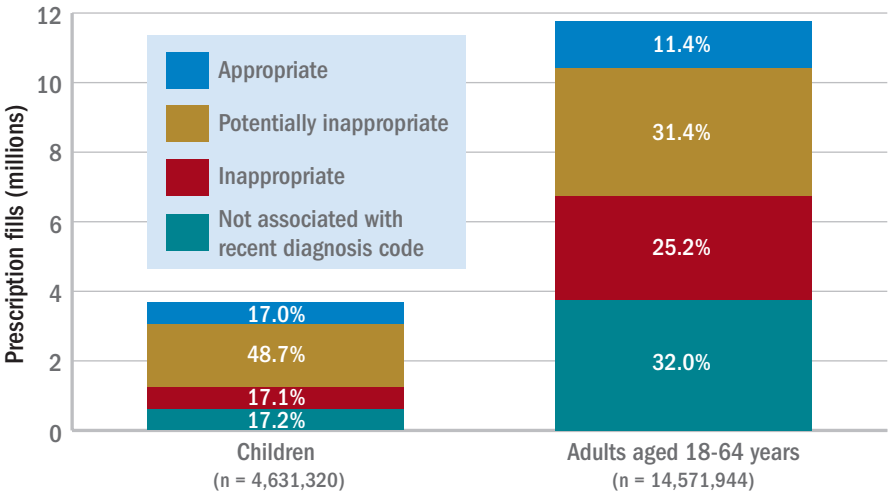
mentaries from other CHEST dignitaries, we have not yet heard much from the most important resource we have, our readers.

So for the coming year, I would welcome you to drop us a line every now and then. See something in our pages that you like, or with which you disagree? Is there something in the news relevant to pulmonary, critical care, or sleep medicine that you think we should have covered but did not?

Send us an email at [chestphysiciannews@chestnet.org](mailto:chestphysiciannews@chestnet.org). I look forward to closer contact with you over the coming year.

Let's make *CHEST Physician* even better together!

## Proportion of antibiotic prescription fills by appropriateness, 2016



Note: Based on data from the Truven MarketScan Commercial Claims and Encounters database.  
Source: BMJ. 2019;364:k5092. doi: 10.1136/bmj.k5092

## Antibiotic prescribing // continued from page 1

involved phone consultations that did not result in claims or visits that were paid out of pocket and did not make it into the Truven MarketScan Commercial Claims and Encounters database used in the study, the investigators said.

The three highest levels of inappropriate fills were 70.7% in office-based settings, 6.2% in urgent care centers, and 4.7% in emergency departments.

“The unacceptable scale of inappropriate antibiotic prescribing in the United States ... underscores the need to learn more about prescriptions that aren’t justified by a diagnosis – or are written after no diagnosis at all,” coinvestigator Jeffrey Linder, MD, of Northwestern University, Chicago, said in a written statement.

Prescriptions for children, who represented almost a quarter of all antibiotic fills, were less likely to be

inappropriate than those for adults aged 18-64 years. Proportions for children were 17.1% inappropriate, 48.7% potentially inappropriate, and 17.0% appropriate, compared with 25.2%, 31.4%, and 11.4%, respectively, for adults, Dr. Chua and his associates said.

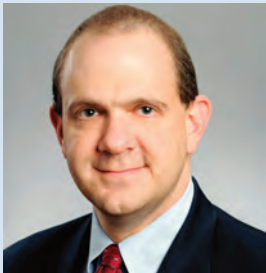
“This study shows how data and analytics can help us identify and understand important challenges facing the American health care system,” said Gopal Khanna, director of the Agency for Healthcare Research and Quality, which funded the study. “We now need to use these data to spur change in the prescribing of these very common medications.”

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**SOURCE:** Chua K-P et al. BMJ. 2019;364:k5092. doi: 10.1136/bmj.k5092.

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

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

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# Spending on medical marketing increased by \$12.2 billion over the last 2 decades

BY STEVE CIMINO

MDedge News

Total spending on medical marketing in the United States increased from \$17.7 billion in 1997 to \$29.9 billion in 2016, according to an analysis of direct-to-consumer (DTC) and professional marketing for prescription drugs, disease awareness campaigns, health services, and laboratory tests.

“Increased medical marketing reflects a convergence of scientific, economic, legal, and social forces,” wrote Lisa M. Schwartz, MD, and her coauthor, adding that, “although marketing expanded over 20 years, regulatory oversight remains relatively limited.” Dr. Schwartz, then codirector of the Center for Medicine and Media at The Dartmouth Institute in Lebanon, N.H., died in November of 2018, after her work was accepted for publication in JAMA.

Dr. Schwartz and her coauthor, David Woloshin, MD, also of Dartmouth, reviewed consumer advertising and professional marketing data, along with searches of medical literature and business journals, to ascertain the quantity and impact of spending. The most money was spent on marketing to medical professionals, which increased from \$15.6 billion in 1997 to \$20.3 billion in 2016. In terms of percentages, the biggest increase was seen in DTC advertising: \$2.1 billion in 1997 (11.9% of total spending) ballooned to \$9.6 billion

(32.1% of total spending). These increases were not accompanied by corresponding regulatory efforts to limit influence or protect patients and consumers. In 2016, the Food and Drug Administration’s Office of Prescription Drug Promotion received 97,252 promotional materials that drug companies submitted for review,

*Marketing saw a remarkable 430% increase (\$542 million to \$2.9 billion) over the 2 decades, while health services spending increased by 90% (\$1.2 trillion to \$2.2 trillion).*

compared with 34,182 in 1997, but violation letters for prescription drug advertising decreased from 156 to 11. In the same year, the FDA reviewed 41% of core materials – such as risk disclosures and key messages – for new drugs or indications prior to launch, a performance measure the coauthors called “critically important.”

In regard to disease awareness campaigns, 2004 guidance from the FDA on awareness advertising – including standards for unbranded campaigns and recommendations to avoid encouraging self-diagnosis and self-treatment – was withdrawn in 2015 and

never replaced. The Federal Trade Commission, which has jurisdiction over unbranded advertising, has not taken regulatory action of its own; any FDA requests for investigation are unknown. In addition, these 2 decades have not seen state attorneys general initiate any action against deceptive consumer advertising, nor has the FTC acted against misleading laboratory test promotion.

“The FDA and FTC should establish and enforce standards for responsible disease awareness campaigns,” the coauthors wrote, “including criteria to validate symptom quizzes (or banning them) and evidence-based strategies to minimize misconceptions that a drug can treat all symptoms of disease.”

Overall, spending on medical marketing actually increased faster than did spending on health services overall. Marketing saw a remarkable 430% increase (\$542 million to \$2.9 billion) over the 2 decades, while health services spending increased by 90% (\$1.2 trillion to \$2.2 trillion).

One of the rare similarities from 1997 to 2016 was spending on marketing prescription drugs to physicians, typically through face-to-face meetings and hospital visits; this held steady at approximately \$5 billion. However, spending on drug samples increased from \$8.9 billion to \$13.5 billion, while medical journal advertising declined drastically from \$744 million to \$119 million.

Spending on DTC marketing of prescription drugs increased across all therapeutic categories but three: cholesterol, allergy, and osteoporosis, each of which saw top-selling drugs either become over-the-counter or lose patent protection. Spending on drugs for diabetes/endocrine disease went from \$27 million in 1997 to a whopping \$725 million in 2016, followed by dermatology drugs (\$67 million to \$605 million) and pain/central nervous system drugs (\$56 million to \$542 million).

The coauthors shared potential limitations of their study, including the likelihood that they underestimated how much is actually spent on medical marketing. “Data on professional marketing (e.g., detailing) of laboratory tests, health services or devices, and pharmaceu-

## VIEW ON THE NEWS

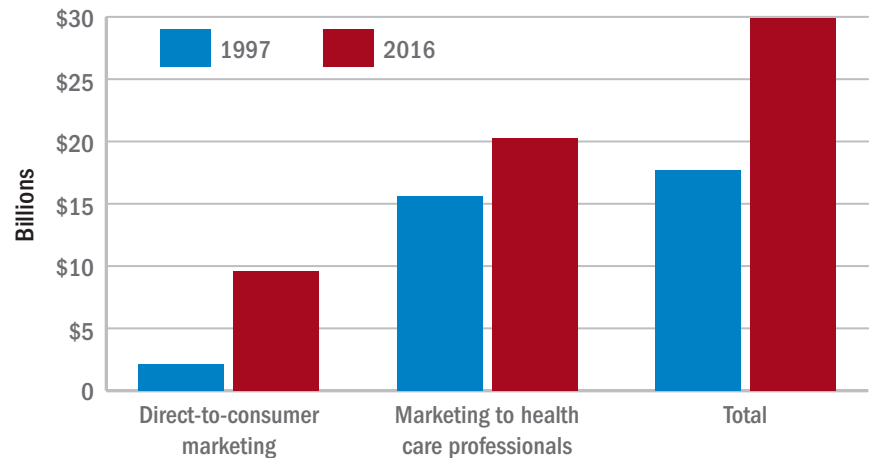
Michael E. Nelson, MD, FCCP,

comments: These data did not surprise me in the least.

I am certain that I am not the only health-care provider who has had to explain to patients why a drug or procedure that they saw on television or the internet is not indicated for their disease. Like many, I don’t spend a great deal of time reading the advertisements in medical journals, but it is more difficult to avoid the profusion of promotion in other forms of media, especially television. Effective advertising is not meant to educate, but rather to persuade one to purchase a product, often with hyperbole. Unfortunately, lack of oversight by the Food and Drug Administration and the Federal Trade Commission will make our jobs just that much more difficult. I long for the days of free pens and note pads with no TV commercials.



## Spending on U.S. medical marketing, 1997 and 2016



Note: Based on data from Kantar Media (DTC) and from IQVIA Institute for Human Data Science, Open Payments, and company websites (professionals).

Source: JAMA. Jan 8 2019;321(1):80-96. doi: 10.1001/jama.2018.19320

tical company spending on coupons or rebates, online promotion, and meetings and events could not be obtained,” they noted. In addition, company marketing budgets often do not include additional expenses that should count toward this total, and any published literature on medical marketing’s return on investment is largely based on observational data and cannot be fully relied upon.

The two coauthors previously served as medical experts in testosterone litigation and were cofounders of a company that provided data about the benefits and harms of prescription drugs, which ceased operations in December 2016. No other conflicts of interest were reported.

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SOURCE: Schwartz LM et al. JAMA. 2019 Jan 8. doi: 10.1001/jama.2018.19320.

# INPULSIS-ON: Long-term nintedanib safe for IPF

BY AMY KARON

MDedge News

**F**or patients with idiopathic pulmonary fibrosis, up to 68 months of treatment with nintedanib showed acceptable safety and tolerability and might have slowed disease progression, according to the results of the open-label INPULSIS-ON trial.

No new safety signals were identified among patients who continued nintedanib or who switched from placebo to the medication after completing one of the two 52-week phase 3 INPULSIS trials, reported Bruno Crestani, MD, of Hôpital Bichat, Paris, and his associates.

“Patients with idiopathic pulmonary fibrosis could use nintedanib over the long term to slow disease progression,” they wrote in *Lancet Respiratory Medicine*.

Idiopathic pulmonary fibrosis patients often die or deteriorate because of acute declines in respiratory function. Nintedanib (Ofev) is an intracellular tyrosine kinase inhibitor approved for idiopathic pulmonary fibrosis in the United States in 2014, based on the results of the replicate randomized, placebo-controlled, double-blind, phase 3 INPULSIS trials, in which nintedanib (150 mg twice daily) was tolerable, showed an acceptable overall toxicity profile, and lessened the annual rate of decline in forced vital capacity (FVC), compared with placebo.

Idiopathic pulmonary fibrosis has a chronic trajectory, so data on long-term safety and efficacy were clearly desirable. “Results from the open-label extension of the [founda-

tional] phase 2 TOMORROW trial [also] identified no new safety signals and suggested an effect of nintedanib on slowing the progression of idiopathic pulmonary fibrosis beyond 52 weeks; however, only 35 patients treated with nintedanib 150 mg twice daily entered the extension study,” the researchers wrote.

The open-label INPULSIS-ON trial included 734 patients, which was 91% of the population that completed the INPULSIS trials. A total of 59% patients in the open-label trial continued nintedanib while the rest switched to nintedanib from placebo. With both cohorts considered, the median duration of exposure to

nintedanib was 44.7 months.

Rates of major adverse cardiovascular events were 2.4 per 100 person-years of drug exposure among treatment initiators and 3.6 per 100 person-years among continuers. Rates of bleeding were 6.7 and 8.4 events per 100 person-years, respectively, while rates of myocardial infarction, using the broadest definition, were 0.7 and 1.3 events per 100 person-years, respectively. The most common adverse event was diarrhea, with 60.1 and 71.2 events per 100 person-years among treatment initiators and continuers, respectively. In all, 10% of treatment initiators and 5% of continuers stopped nintedanib because of diarrhea. A total

of 14% of treatment initiators and 12% of continuers stopped treatment because of disease progression.

The adjusted annual rate of decline in FVC was  $-135.1$  mL overall,  $-145$  mL in nintedanib continuers, and  $-119.7$  mL in nintedanib initiators, which resembled the findings of the INPULSIS trials.

Boehringer Ingelheim funded the study. Dr. Crestani disclosed grants and personal fees from Boehringer Ingelheim and other drug companies.

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**SOURCE:** Crestani B et al. *Lancet Respir Med*. 2018 Sep 14. doi: 10.1016/S2213-2600(18)30339-4.

## VIEW ON THE NEWS

### Bias may compromise efficacy data

**T**he study provides “invaluable safety data, including a very low incidence of cardiovascular events” among patients who received long-term nintedanib therapy for idiopathic pulmonary fibrosis, wrote Athol U. Wells, MD, in an editorial published alongside the study.

But the efficacy data were substantially more problematic, he said. “At first sight, the data seem to show that treatment benefits are sustained during long-term follow-up. However, this finding applied to patients completing 4 years of treatment. Approximately 70% of patients discontinued nintedanib [during the open-label extension trial].”

Death, probable treatment failure, or adverse events unrelated to idiopathic pulmonary fibrosis accounted for 62% of withdrawals from this study, and the investigators did not present FVC trends for these patients, he noted. This makes it difficult to know whether bias affected the efficacy results. Long-term stability or slow

progression was seen in 30%-40% of patients, exceeding results from previous IPF cohorts, but “this finding, although encouraging, is clearly non-definitive.”

The mortality data also were problematic because the trial excluded patients with major comorbidities and severe disease, and the researchers tracked vital status for only 6 weeks after patients withdrew from INPULSIS-ON, he said. “One cannot help but feel that a major opportunity was lost in this study and, equally, in the pirfenidone extension study. An intention-to-treat study design would have provided invaluable long-term efficacy data and should be prioritized in future.”

*Dr. Wells is with Royal Brompton Hospital in London. He disclosed personal fees from Boehringer Ingelheim, Intermune/Roche, Bayer, Actelion, and Raffo, outside the submitted work (Lancet Respir Med. 2018 Sep 14. doi: 10.1016/S2213-2600[18]30385-0).*

# In-hospital mortality higher in PAD patients with COPD

BY MARK S. LESNEY

MDedge News

**P**atients with peripheral arterial disease (PAD) and chronic obstructive pulmonary disease (COPD) have a 1.2-fold higher in-hospital mortality as do patients with PAD alone, Karsten Keller, MD, of the Johannes Gutenberg-University Mainz (Germany) and his colleagues wrote in *Respiratory Medicine*.

“Unexpectedly, this increase was not driven by [myocardial infarction] as the life-threatening acute presentation of [coronary artery disease], but rather was related to an increased risk for [pulmonary embolism] and a higher coprevalence of cancer.” The researchers recommended that PAD inpatients with COPD be monitored more intensively, especially for potential pulmo-

nary embolism and myocardial infarction.

Dr. Keller and his colleagues analyzed the German inpatient national database based on ICD codes. They identified 5,611,827 adult inpatients (64.8% men) diagnosed with PAD between January 2005 and December 2015, and of those, 13.6% also were coded for COPD. Overall, 277,894 PAD patients (5.0%) died in the hospital, Dr. Keller and his colleagues wrote.

The all-cause, in-hospital mortality was 6.5% in PAD patients with COPD, compared with 4.7% in patients with PAD alone ( $P$  less than .001). Cardiovascular events comprising pulmonary embolism, deep vein thrombosis, and myocardial infarction occurred more often in coprevalence with PAD and COPD.

In PAD patients, COPD was an independent predictor of in-hospital death (odds ratio, 1.16;

95% confidence interval, 1.15-1.17;  $P$  less than .001) as well as an independent predictor for PE (OR, 1.44; 95% CI, 1.40-1.49;  $P$  less than .001).

Coronary artery disease and heart failure were more common in PAD patients with COPD, as were cancer and renal insufficiency.

“Remarkably, PAD patients with COPD showed more frequently lower PAD stages than those without COPD. Especially, PAD stage IV was more prevalent in PAD patients without COPD (19.6% vs. 13.8%;  $P$  less than 0.001),” the authors wrote.

The German Federal Ministry of Education and Research funded the study, and the authors reported having no conflicts.

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**SOURCE:** Keller K et al. *Respir Med*. 2019 Feb;147:1-6.



# New CHEST expert panel advice on cough diagnosis

BY JIM KLING

MDedge News

**FROM THE JOURNAL CHEST®** ■ The CHEST Expert Cough Panel has released two new expert guidelines, one aimed at adult outpatients with a cough likely related to influenza or pneumonia and one for pertussis-associated cough in adults and children.

Upper and lower respiratory tract infections are a common reason for primary care visits. A cough caused by influenza or pneumonia represents an opportunity to intervene for a significant benefit. The recommendations were published in the journal *CHEST*®. The panel drafted recommendations based on available evidence and graded them using the CHEST grading system. The grading is based on the strength of the recommendation (either strong or weak) and a rating of the overall quality of the body of evidence. Where available evidence was weak, but guidance was still warranted, a weak suggestion was developed and graded 2C. Recommendations based on consensus in cases of insufficient clinical evidence are labeled “ungraded consensus-based statement.”

## Pneumonia or influenza?

In adult outpatients with acute cough, the clinical signs of pneumonia include cough, dyspnea, pleural pain, sweating/fevers/shivers, aches and pains, temperature greater than or equal to 38°C, tachypnea, and new and localizing chest examination signs. When pneumonia is suspected to cause acute cough, C-reactive protein (CRP) should be measured. A CRP value higher than 30 mg/L bolsters the case for pneumonia, whereas a CRP value of lower than 10 mg/L, or between 10 mg/L and 50 mg/L in the absence of dyspnea and daily fever, makes pneumonia less likely.

The guidelines recommend against routine measurement of procalcitonin for outpatient adults suspected to have pneumonia. For adults with acute cough and abnormal vital signs believed to be secondary to pneumonia, the guidelines call for a chest x-ray.

Routine microbiological testing need not be performed in suspected pneumonia, but it should be considered if the results could guide or lead to a change in therapy.

When pneumonia is suspected but imaging is unavailable, empiric antibiotics should be used in concordance

with local and national guidelines. If imaging turns up negative, antibiotics should not be used. However, if there is no clinical or radiographic evidence of pneumonia, antibiotics should not be used routinely.

Finally, adult patients with acute cough and suspected influenza should begin antiviral treatment within 48 hours of the start of symptoms.

## Pertussis

Pertussis has significant morbidity and mortality, with infants being particularly vulnerable, and it is highly contagious. Although antibiotics will not affect the course of the disease, they should be administered as quickly as possible in order to prevent further spread. This puts pressure on the clinician to make a treatment decision before further testing is available.

A prespecified meta-analysis found high sensitivity and low specificity for paroxysmal cough (sensitivity, 93.2%; specificity, 20.6%) and absence of fever (sensitivity, 81.8%; specificity, 18.8%). The study found low sensitivity and high specificity for inspiratory whoop (sensitivity, 29.8%; specificity, 79.5%) and posttussive vomiting (sensitivity, 32.5%; specificity, 77.7%). In children,

the review found that posttussive vomiting was moderately sensitive (60.0%) and specific (66.0%).

In adult patients with acute cough (less than 3 weeks' duration) or subacute cough (3-8 weeks), the new guidelines recommend that physicians consider four key characteristics: the presence of recurrent, prolonged coughing episodes with an inability to breathe during the spell (paroxysmal); posttussive vomiting; inspiratory whooping; and presence of fever.

In acute or subacute cough, if the patient has a fever (body temperature greater than 98.6° F or 37.6° C) or does not have a paroxysmal cough, pertussis is unlikely. On the other hand, posttussive vomiting or an associated inspiratory whooping sound suggests pertussis.

Children with a cough lasting fewer than 4 weeks (acute) should be assessed for paroxysmal cough, posttussive vomiting, and inspiratory whooping. A cough associated with any of these characteristics may be caused by pertussis.

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**SOURCES:** Moore A et al. *CHEST*. 2019 Jan;155:147-154; Hill A et al. *CHEST*. 2019 Jan;155:155-167.

# Prescribed opioids raise pneumonia risk

BY MARK S. LESNEY

MDedge News

**P**rescribed opioids were associated with an increase in community-acquired pneumonia in patients with and without HIV infection, according to results of a large database study.

People living with HIV (PLWH) appeared to have a greater community-acquired pneumonia (CAP) risk at lower opioid doses and particularly with immunosuppressive opioids compared with uninfected patients, although the difference was not significant, E. Jennifer Edelman, MD, of Yale University, New Haven, Conn., and her colleagues wrote in *JAMA Internal Medicine*.

The researchers performed a nested case-control study of 25,392 participants (98.9% men; mean age, 55 years) in the Veterans Aging Cohort Study from Jan. 1, 2000, through Dec. 31, 2012.

Dr. Edelman and her colleagues compared the characteristics of 4,246 CAP cases with those of 21,146 uninfected controls in the sample. They also compared cases and controls by HIV status, and ran models stratified by HIV status and formally checked for an interaction between prescribed opioid characteristics and HIV status.

In unadjusted logistic regression analysis, prescribed opioids were associated with increased odds of CAP, with the greatest risk observed with

currently prescribed opioids, compared with past prescribed opioids or no opioids.

Prescribed opioids remained associated with CAP in the adjusted models for past unknown or nonimmunosuppressive (adjusted odds ratio, 1.24; 95% confidence interval, 1.09-1.40) and past immunosuppressive opioid use (aOR, 1.42; 95% CI, 1.21-1.67). For currently prescribed opioids, nonimmunosuppressive or unknown, the aOR was 1.23 (95% CI, 1.03-1.48). For currently prescribed immunosuppressive opioids, the aOR was 3.18 (95% CI, 2.44-4.14).

Currently prescribed high-dose opioids were associated with the greatest CAP risk, followed by medium- and then by low-dose opioids, whether immunosuppressive or not.

With regard to the effect of HIV status in stratified, adjusted analyses, CAP risk tended to be greater among PLWH with current prescribed opioids, especially immunosuppressive opioids, compared with uninfected patients. However, the difference was not statistically significant.

Although the researchers stated that a limitation of their study was an inability to prove causality or rule out respiratory depression (vs. immunosuppression) as the cause of the increased CAP risk, “the observed effects of opioid immunosuppressive properties and CAP risk lend support to our hypothesis that opioids have clinically

relevant immunosuppressive properties.”

Dr. Edelman and her colleagues were not able to determine whether patients took their prescribed medications appropriately and to assess whether the patients took nonmedically prescribed opioids. Also, because men made up such a large portion of the study population, it is unclear whether the results are generalizable to women.

“Health care professionals should be aware of this additional CAP risk when they prescribe opioids, and future studies should investigate the effects of opioids prescribed for longer durations and on other immune-related outcomes,” wrote Dr. Edelman and her colleagues. “Understanding whether mitigating the risk of prescribed opioids for CAP is possible by using a lower dose and nonimmunosuppressive opioids awaits further study.”

They advised attempting to modify other factors known to affect CAP risk, including smoking and lack of vaccination.

Several U.S. government agencies and Yale University provided funding for the study. The authors reported that they had no conflicts.

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**SOURCE:** Edelman EJ et al. *JAMA Intern Med*. 2019 Jan 7. doi: 10.1001/jamainternmed.2018.6101.

# Leveraging CV, renal benefits of new diabetes drugs

BY MITCHEL L. ZOLER

MDedge News

CHICAGO – When the first results from a large trial that showed profound and unexpected benefits for preventing heart failure hospitalizations associated with use of the antihyperglycemic sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin came out – a little over 3 years ago – the general reaction from clinicians was some variant of “Could this be real?”



Dr. Braunwald

Since then, as results from some five other large, international trials have come out showing similar benefits from two other drugs in the same SGLT2-inhibitor class, canagliflozin and dapagliflozin, as well as results showing clear cardiovascular disease benefits from three drugs in a second class of antihyperglycemics, the glucagonlike peptide-1 receptor agonists (GLP-1 RAs), the consensus among cardiologists became: “The cardiovascular and renal benefits are real. How can we now best use these drugs to help patients?”

This change increasingly forces physicians to become more comfortable prescribing these two classes of antihyperglycemic drugs. During a talk at the American Heart Association scientific sessions, Eugene Braunwald, MD, arguably the top thought leader in cardiology, coined a new name for the medical subspecialty that he foresees navigating this overlap between diabetes care and cardiovascular disease prevention: diabetocardiology (although a more euphonic alternative might be cardiometabolism, while the more comprehensive name could be cardiometabolic).

“I was certainly surprised” by the report in 2015 from the EMPA-REG OUTCOME trial (N Engl J Med. 2015 Nov 26;373[22]:2117-28), said Dr. Braunwald, professor of medicine at Harvard Medical School in Boston. “Now we have three trials,” with the addition of the CANVAS trial for canagliflozin (N Engl J Med. 2017 Aug 17;377[7]:644-57) and the DECLARE-TIMI 58 trial (N Engl J Med. 2018 Nov 10. doi:10.1056/NEJMoa1812389) for dapagliflozin at the AHA meeting in November.

“We are in the midst of two pan-

demics: heart failure and type 2 diabetes. ... We have to learn how to deal with this,” said Dr. Braunwald, and the evidence now clearly shows that these drugs can help with that.

As another speaker at the meeting, Javed Butler, MD, a heart failure specialist, observed in a separate talk, “Heart failure is one of the most common, if not the most common, complications of patients with diabetes.” This tight link between heart failure and diabetes makes cardiovascular mortality “the number one cause of death” in patients with diabetes, said Dr. Butler, professor and chair of medicine at the University of Mississippi in Jackson.

“Thanks to the cardiovascular outcome trials, we now have a much broader and deeper appreciation of heart failure and renal disease as integral components of the cardiovascular-renal spectrum in people with diabetes,” said Subodh Verma, MD, a professor at the University of Toronto and cardiac surgeon at St. Michael’s Hospital in Toronto. Dr. Braunwald spelled out in his talk some of the interrelationships of diabetes, heart failure, and renal dysfunction that together produce a downward-spiraling vicious circle for patients, a pathophysiological process that clinicians can now short-circuit with a SGLT2 inhibitor.

## Outcome trials show the way

In the context of antihyperglycemic drugs, the “cardiovascular outcome trials” refers to a series of large trials mandated by the Food and Drug Administration in 2008 to assess the cardiovascular disease effects of new agents coming onto the U.S. market to treat type 2 diabetes mellitus (T2DM). By the time Dr. Verma spoke at the AHA meeting, he could cite reported results from 12 of these trials: 5 different drugs in the GLP-1 RA class, 4 drugs in the dipeptidyl peptidase-4 (DPP-4) inhibitor class, and 3 drugs from the SGLT2 inhibitor class. Dr. Verma summed what the findings have shown.

The four tested DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin) consistently showed neutrality for the primary outcome of major adverse cardiovascular disease events (MACE), constituted by cardiovascular disease death, MI, or stroke.

The five tested GLP-1 RAs (albiglutide, exenatide, liraglutide, lixisenatide, and semaglutide) showed a mixed pattern of MACE results that seemed to be linked with the

subclass the drug fell into. The two exenatide-based drugs, exenatide and lixisenatide, each showed a statistically neutral effect for MACE, as well as collectively in a combined analysis. In contrast, three human GLP-1-based drugs, albiglutide, liraglutide, and semaglutide, each showed a consistent, statistically significant MACE reduction in



Dr. Javed Butler

their respective outcome trials, and collectively they showed a highly significant 18% reduction in MACE, compared with placebo, Dr. Verma said. Further, recent analysis by Dr. Verma that used data from liraglutide treatment in the LEADER trial showed the MACE benefit occurred only among enrolled patients treated with liraglutide who had established atherosclerotic cardiovascular disease (ASCVD). Patients enrolled in the trial with only multiple risk factors (in addition to having T2DM) but without established ASCVD showed no significant benefit from liraglutide treatment for the MACE endpoint, compared with control patients.

Recently a press-release announcement of results from a sixth GLP-1 RA, dulaglutide, in the REWIND trial of MACE outcomes suggested that a drug in this class could have a broader effect. The majority, 69%, of the 9,901 patients with T2DM enrolled in REWIND had risk factors but not established ASCVD at enrollment. A Nov. 5, 2018, statement from the company developing this drug, Lilly, reported that the study overall produced a statistically significant reduction in MACE, although it provided no additional details. As the released noted, this made REWIND the first trial to show a MACE benefit from a drug in the GLP-1 RA class in patients without established ASCVD.

The MACE outcome results from the three SGLT2 inhibitor trials showed a similar pattern as liraglu-

tide: In patients with established ASCVD, the drugs individually each produced a MACE reduction, although dapagliflozin just missed having a statistically significant reduction. Collectively, the three drugs showed a statistically significant, 14% relative risk reduction for MACE, compared with control patients. But among patients with



Dr. Subodh Verma

multiple risk factors only, but without established ASCVD, included in two of the three trials (CANVAS and DECLARE-TIMI 58), the results showed both individually and collectively a neutral MACE effect.

But unlike the other antihyperglycemic drugs tested in the cardiovascular outcome trials, the SGLT2 inhibitors have shown two additional, highly important secondary outcomes: a consistent reduction in hospitalization for heart failure and a consistent reduction in renal-disease progression.

A meta-analysis of the three SGLT2 inhibitor trials published coincident with the release of the DECLARE-TIMI 58 results showed that, for the outcome of either cardiovascular death or hospitalization for heart failure, the SGLT2 inhibitors collectively showed a significant 29% relative decrease in this incidence among patients with a history of heart failure, and a significant 21% relative decrease among patients without history of heart failure (Lancet. 2018 Nov 10. doi: 10.1016/S0140-6736[18]32590-X). Among the subset of patients with established ASCVD, treatment with a SGLT2 inhibitor across all three trials showed a significant 16% relative risk reduction, and in the subset with multiple risk factors but no established ASCVD, the two SGLT2 inhibitors collectively produced a 16% relative cut in cardiovascular death or heart failure hospitalization with a *P* value of .06. Finally, the Lancet meta-analysis showed that,

PHOTOS: MITCHEL L. ZOLER/MDEDGE NEWS



for a combined endpoint that reflected renal worsening, the SGLT2 inhibitors showed a significant relative reduction of about 45% in both the subgroup of patients with established ASCVD and in the subgroup of those with just risk factors.

“This is a big step forward for patients with multiple risk factors and diabetes but without ASCVD, that both renal disease and hospitalization for heart failure are sensitive” to the SGLT2 inhibitors, Dr. Verma noted. “We see renal protection and reduction of heart failure hospitalization across both primary and secondary prevention patients, with no need to distinguish them based on ASCVD.” In contrast, he noted, the MACE benefit from the SGLT2 inhibitors seems limited to patients with ASCVD. The day before making this point in a talk during the meeting, Dr. Verma had published the same message in a commentary (Lancet. 2018 Nov 10. doi: 10.1016/S0140-6736[18]32824-1).

Although the “nomenclature of primary versus secondary prevention is appropriate for atherosclerotic outcomes, it is likely to be inappropriate for a person with type 2 diabetes who is at risk of hospitalization for heart failure and renal disease,” Dr. Verma wrote.

#### What it means for clinicians

The upshot of all of these cardiovascular outcome trial results from the past 3 years has been a new appreciation of how antihyperglycemic drugs can have cardiovascular and renal benefits that transcend their effects on glycemia. The evidence has put the SGLT2 inhibitors and GLP-1 RAs on track to challenge, and potentially displace, metformin as the top drug to prescribe for patients with T2DM.

Clinicians should realize that they should prescribe SGLT2 inhibitors and selected GLP-1 RAs “as early as metformin in patients with established ASCVD,” said Dr. Verma. “For patients with recalcitrant atherosclerotic disease and a history of MI and ischemia, I’d primarily treat with a GLP-1 RA. In a patient with left ventricular dysfunction or evidence of heart failure, I’d use an SGLT2 inhibitor. But it’s not a fight between these two. You could treat a patients with type 2 diabetes with both classes,” although the practicality of this approach is limited by the high cost of these drugs.

The SGLT2 inhibitors “should now be considered as first-line therapy after metformin in most people with type 2 diabetes, irrespective of whether or not they have established atherosclerotic vascular disease,

chronic kidney disease, or heart failure,” he and his associates wrote.

“What I struggle with the most is how we prioritize and individualize secondary-prevention therapies based on risk for ischemia and heart failure. Some therapies [the SGLT2 inhibitors] are predominantly for heart failure prevention, and some [the GLP-1 RAs] are primarily for

ischemia. How do we choose when a patient cannot afford to take both? Does a combination of a SGLT2 inhibitor and a GLP-1 RA offer the greatest CVD benefit? We need to test this in a trial. And will metformin be displaced as first-line treatment?” Dr. Verma asked.

“The day will probably come when, for maximal protection, you

treat with both classes. But right now we’re forced to choose because of the cost,” said John McMurray, MD, professor of cardiology at the University of Glasgow, at the meeting.

As to specifically which SGLT2 inhibitor to prescribe, “they all look pretty much the same” in the newly published meta-analysis, Dr. Mc-

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Murray said, although he noted that safety differences among agents in the class remain possible.

“For patients similar to those studied in the three SGLT2 inhibitor trials, clinicians should use one of these drugs to reduce the risk for



MITCHELL L. ZOLER/MDEDGE NEWS

Dr. John McMurray

incident heart failure, irrespective of their effect on MACE,” said Dr. Butler. Reducing the risk for incident heart failure and of progressive renal dysfunction are two new goals for antihyperglycemic therapy that now overlay the long-standing goals of controlling glycemia and reducing cardiovascular disease risk and the more recent goals of cutting cardiovascular disease mortality and cut-

ting the risk for a MACE event.

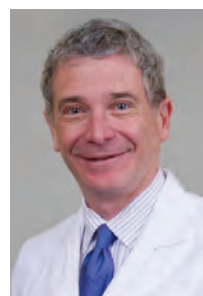
A current limitation for practice is that the none of the three drug companies that market the tested SGLT2-inhibitor drugs has sought regulatory approval for an indication of reducing the risk for heart failure hospitalization. Despite that, “these drugs should be used for renal protection and reducing heart failure hospitalizations,” Dr. Butler said. “We need to start thinking about this and not get lost thinking about only their MACE effect because, when you focus on MACE, there is a competition between the SGLT2 inhibitors and the GLP-1 RAs as drugs to prevent MACE, and SGLT2 inhibitors as drugs that primarily prevent heart failure and renal dysfunction, then there is no competition. Perhaps combined treatment is where we need to go,” he said in an interview.

But the enthusiasm that experts have for wider use of these drugs is not necessarily matched among many community physicians.

David J. Becker, MD, is an example of the clinicians who appreciate the growing evidence that supports wider use, but remain uneasy about applying this evidence in practice.

Dr. Becker, associate director of the Preventive and Integrative Heart Health Program of the Temple Heart

and Vascular Institute in Philadelphia, writes a column for the Philadelphia Inquirer on medical care. In a December 2018 piece, he said “like most cardiologists, I ‘don’t do diabetes’ – because it’s not my expertise.



Dr. Becker

The new drugs, however, mean I need to learn more” about treating these patients. “The problem: There are so many of these medications that they present a bewildering choice.”

Dr. Becker cited barriers to prescribing these drugs:

- High cost, with prices that run close to \$20/day for each drug.
- A thicket of names and choices that “lead to confusion and paralysis,” which has been exacerbated by “advertising wars.”
- Physicians usually defer to endocrinologists to prescribe these drugs, but most patients with T2DM aren’t seen by endocrinologists. The result: “Few doctors prescribe them.”

The cardiovascular disease benefits of these drugs have not been adequately promoted. Until that changes, “cardiologists like me will

not realize their importance,” Dr. Becker concluded.

Dr. Braunwald placed the onus for managing this emerging facet of diabetes largely outside the scope of endocrinology.

“We can’t call in a consultant every time we have a patient with diabetes,” he said. Training of cardiologists now needs to include treating patients with diabetes, Dr. Braunwald advised, just as 30 years ago when cardiologists had to become more familiar with blood clotting to better manage thrombotic disease.

Dr. Braunwald has been a consultant to Cardurion, Myokardia, and Sanofi; an adviser to Endcardia; and has received research funding from AstraZeneca, Daiichi Sankyo, and Novartis. Dr. Butler has been a consultant or adviser to Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Janssen, Merck, Novartis, Novo Nordisk, and Sanofi. Dr. Verma has received honoraria and research funding from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Merck, Novartis, NovoNordisk, Sanofi, and Valeant. Dr. McMurray has received research funding from 12 companies. Dr. Becker had no disclosures.

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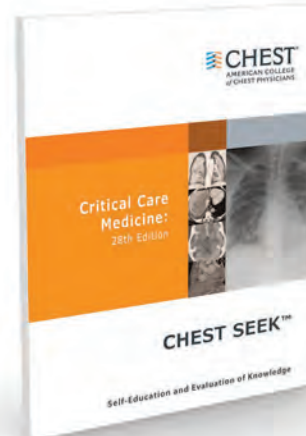
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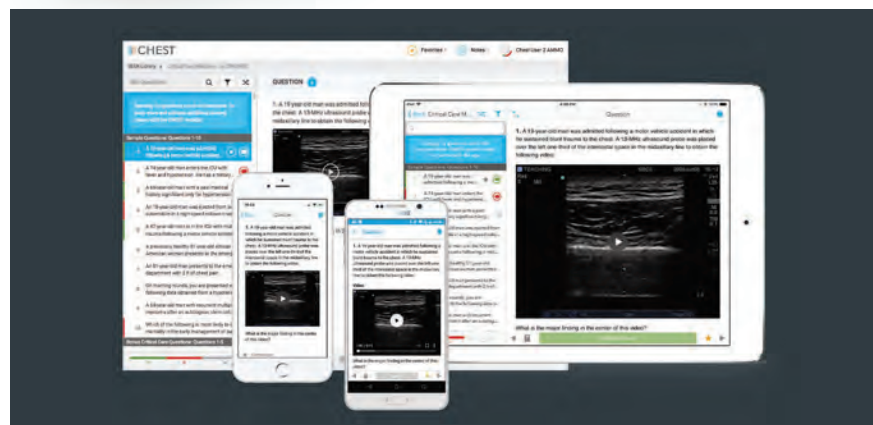


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# Secondhand vaping linked to asthma exacerbations

BY M. ALEXANDER OTTO

MDedge News

**FROM THE JOURNAL CHEST®** ■ Just like exposure to secondhand smoke, exposure to secondhand aerosols from e-cigarettes is associated with an increased risk of asthma exacerbations in children, according to a review of the 11,830 kids with asthma in the 2016 Florida Youth Tobacco survey.

Every year, the Florida Department of Health surveys public school children aged 11-17 years about various tobacco issues. In 2016, almost 12% of the asthmatic children in the survey said they vaped. Almost half were exposed to secondhand smoke, and a third reported exposure to secondhand vaping aerosols within the past 30 days. Overall, 21% reported an asthma attack in the past 12 months.

Using data from the Florida survey, the investigators crunched the numbers and found that second-hand aerosol exposure increased the odds of an asthma attack by 27%, independent of exposure to second-hand smoke and whether children smoked or vaped themselves (adjusted odds ratio, 1.27; 95% confidence interval, 1.11-1.47).

“Health professionals may wish to counsel asthmatic youth and their families regarding the potential risks of ENDS [electronic nicotine delivery system] use and exposure to ENDS aerosols.” Providers “may also consider including ENDS aerosol exposure as a possible trigger in asthma self-management/action plans and updating asthma home environment assessments to include exposure to ENDS aerosols,” said investigators led by medical student Jennifer Bayly, a research fellow at

the National Institute on Minority Health and Health Disparities in Bethesda, Md.

About 4% of adults in the United States and 11% of high school students vape, and almost 10% of U.S. adolescents reported living with an ENDS user in 2014. Given the data, “it is likely that a substantial number of asthmatic youth are exposed,” the investigators said.

The study adds to a growing body of evidence linking e-cigarettes to asthma. There’s moderate evidence for increased cough and wheezing in adolescents who use e-cigarettes, plus an association with e-cigarette use and increased asthma exacerbations. The new study, however, is likely the first to look specifically at secondhand exposure among asthmatic children. Ingredients in vaping aerosols, including flavorings, propylene

glycol, and vegetable glycerin, are physiologically active in the lungs, and may be lung irritants.

Overall, about half of the respondents were female, and two-thirds were 11-13 years old. About a third identified as Hispanic, a third as white, and just over a fifth as black. Three-quarters of the sample lived in large or mid-sized metropolitan areas, and close to two-thirds in stand-alone homes. Participants were considered exposed to secondhand aerosols if they reported that in the past month they were in a room or car with someone who was vaping.

The work was funded by the National Institutes of Health. The investigators had no disclosures.

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**SOURCE:** Bayly J et al. CHEST. 2018 Oct 22. doi: 10.1016/j.chest.2018.10.005.

## Off label drugs used for ADHD sleep problems common

BY THERESE BORDEN

MDedge News

**S**leep problems in children with attention-deficit/hyperactivity disorder are treated with a variety of medications, many off label for sleep and unstudied for safety and effectiveness in children, based on a study of Medicaid prescriptions.

“Sleep disorders coexist with attention-deficit/hyperactivity disorder (ADHD) for many children and are associated with neuropsychiatric, physiologic, and medication-related outcomes,” Tracy Klein, PhD, of Washington State University, Vancouver, and her colleagues wrote in the *Journal of Pediatric Health Care*.

These patients can have sleep-disordered breathing and behavioral issues occurring around bedtime. Adverse effects of the stimulant and nonstimulant medications used to treat ADHD can include sleep disturbance, delayed circadian rhythm, insomnia, and somnolence. Yet, research on sleep problems in children with ADHD and prescribing patterns is scanty, they said.

Dr. Klein and her colleagues used 5 years of pharmacy claims for children aged 3-18 years in Oregon insured through Medicaid and with a provider diagnosis of ADHD. The number of 30-day prescriptions was measured. The medications were classified as controlled or uncontrolled as determined by Title 21 of the U.S. Controlled Substances Act.

The data yielded 14,567 prescriptions for 2,518 children for a 30-day supply of medication known to potentiate sleep but off label for children. Children aged 3-11 years comprised about 38% of these patients. Some children were prescribed more than one of these medications. Medications specifically on label for sleep but not indicated for children were not included. Those

medications indicated for comorbid conditions and those indicated for ADHD that specifically cause somnolence were excluded.

The uncontrolled medications prescribed in this sample were amitriptyline, doxepin, hydroxyzine, low-dose quetiapine, and trazodone. The controlled medications identified were clonazepam and lorazepam, and phenobarbital.

Most of the prescriptions (63.8%) went to older children aged 12-18 years and most prescriptions (66.3%) went to males. The most commonly prescribed noncontrolled medication was trazodone (5,190 prescriptions), followed by hydroxyzine (2,539), and quetiapine (2,402). The most frequently prescribed controlled medication was clonazepam (2,145), followed by lorazepam (534).

Specialist prescribers wrote most of the prescriptions for this patient group, but no differences were found in prescribing patterns.

Dr. Klein and her colleagues noted that 871 unique children were prescribed 5,190 30-day-supply prescriptions for trazodone, including 23 children under age 5. Trazodone is a serotonin modulator indicated for the treatment of major depressive disorder, but has not been studied for safety and efficacy in children and has no Food and Drug Administration indication for children. “Hydroxyzine, quetiapine, and amitriptyline also were prescribed for a large number of children, including some for children as young as 3 years, despite lack of approval for use to induce to sleep and increased potential for significant adverse reactions in children,” they wrote.

Prescribers may receive pressure from families to “do something” for their children, who may be disruptive day and night. “Prescribers may be unaware that trazodone, which is commonly used in practice, has never been approved for treatment of insomnia in children or adults. Insurance may

### VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** ADD and ADHD are important problems to deal with, but pediatricians and family practice physicians frequently don’t have enough education on how to deal with sleep issues that may co-exist. Sleep hygiene can also be a problem that physicians may “medicate” instead of providing education on decreased screen time, for example. Pediatric pulmonologists who treat sleep-disordered breathing or board-certified pediatric sleep physicians are happy to receive referrals for these patients to help figure out how to treat sleep issues safely.



not adequately fund other options, such as extensive behavioral therapy,” she said in an interview.

These medications come with some risk for children, Dr. Klein noted. “Developmentally, [children] may be unable to verbally express the side effects they are feeling and may therefore be subject to a drug to treat a drug side effect, especially if their reaction to it is behavioral.” There is also potential for unanticipated drug interactions between off-label medications prescribed for sleep and drugs prescribed to treat ADHD.

The researchers reported having no disclosures. tborden@mdedge.com

**SOURCE:** Klein T et al. *J Pediatr Health Care*. 2018 Jan 8. doi: 10.1016/j.pedhc.2018.10.002.

# Guideline-concordant antibiotic treatment for pediatric CAP still unlikely in nonchildren's hospitals

BY LUCAS FRANKI

MDedge News

**G**uideline-concordant antibiotic treatment for pediatric community-acquired pneumonia (CAP) was significantly less likely in a nonchildren's hospital, according to new research.

"This gap is concerning because approximately 70% of children hospitalized with pneumonia receive care in nonchildren's hospitals," wrote Alison C. Tribble, MD, of C. S. Mott Children's Hospital, University of Michigan, Ann Arbor, and her associates. The report is in

JAMA Pediatrics.

Data were collected from the Pediatric Health Information System (children's hospitals) and Premier Perspectives (all hospitals) databases and included a total of 120,238 children aged 1-17 years diagnosed with CAP between Jan. 1, 2009, and Sept. 30, 2015. Before the publication of the new guideline in October 2011, the probability of receiving what would become guideline-concordant antibiotics was 0.25 in children's hospitals and 0.06 in nonchildren's hospitals.

By the end of the study period, the probability of receiving guideline-concordant antibiotics for pe-

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** I am obviously biased, since I am employed at a children's hospital. This is a robust study reported out of the University of Michigan that bears attention!

diatric CAP was 0.61 in children's hospitals and 0.27 in nonchildren's hospitals. Without the interventions, the probabilities would have been 0.31 and 0.08, respectively. The rate of growth over the 4-year postinter-

vention period was similar in both children's and nonchildren's hospitals.

"Studies in children's hospitals have suggested that local implementation efforts may be important in facilitating guideline uptake. Nonchildren's hospitals likely have fewer resources to lead pediatric-specific efforts, and care may be influenced by adult CAP guidelines," the authors noted.

No conflicts of interest were reported.

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**SOURCE:** Tribble AC et al. JAMA Pediatr. 2018 Dec 10. doi: 10.1001/jama-pediatrics.2018.4270.

## LAIV4 less effective against aggressive influenza virus strain

BY JEFF CRAVEN

MDedge News

**T**he quadrivalent live attenuated influenza vaccine (LAIV4) was less effective against the influenza A/H1N1pdm09 virus in children and adolescents across multiple influenza seasons between 2013 and 2016, compared with the inactivated influenza vaccine (IIV), according to research published in the journal Pediatrics.

With regard to other strains, there was similar effectiveness against influenza A/H3N2 and influenza B with LAIV4 and IIV vaccinations. "In contrast to findings of reduced LAIV4 effectiveness against influenza A/H1N1pdm09 viruses, our results suggest a possible but non-significant benefit of LAIV4 over IIV against influenza B viruses, which has been described previously," wrote Jessie R. Chung, MPH, from the influenza division at the Centers for Disease Control and Prevention in Atlanta, and her colleagues.

The researchers performed an analysis of five different studies where vaccine effectiveness was examined for LAIV4 and IIV in children and adolescents aged 2-17 years from 42 states.

The analysis included data from the U.S. Influenza Vaccine Effectiveness Network (6,793 patients), a study from the Louisiana State University Health Sciences Center (3,822 patients), the Influenza Clinical Investigation for Children (3,521 patients), Department of Defense Global, Laboratory-Based, Influenza Surveillance Program (1,935 patients), and the Influenza Incidence Surveillance Project (1,102 patients). The researchers sourced current and previous season vaccination history from electronic medical records and immunization registries.

Of patients vaccinated across all seasons, there was 67% effectiveness against influenza A/H1N1pdm09 (95% confidence interval, 62%-

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:**

The American Academy of Pediatrics (AAP) provides yearly updates for influenza vaccinations in the United States. For the 2018-2019 season, the AAP recommends inactivated influenza vaccine as the first choice, either in the inactivated trivalent form (IIV3) or the inactivated quadrivalent form (IIV4). The AAP is very specific in regards to usage of the live attenuated influenza vaccine, LAIV4, also called FluMist® Quadrivalent. The AAP states, "LAIV4 should be used for children who would not otherwise receive an influenza vaccine, if the child is at least 2 years old and healthy with no underlying chronic medical condition."<sup>1</sup>

## REFERENCE

1. AAP Red Book Updates 2018 "Recommendations for Prevention & Control of Influenza in Children 2018-2019.

72%) for those who received the IIV and 20% (95% CI, -6%-39%) for LAIV4. Among patients who received the LAIV4 vaccine, there was a significantly higher likelihood of influenza A/H1N1pdm09 (odds ratio, 2.66; 95% CI, 2.06-3.44) compared with patients who got the IIV vaccine.

The Influenza Clinical Investigation for Children was funded by MedImmune, a member of the AstraZeneca Group. Two of the researchers are employees of AstraZeneca. The other authors reported having no conflicts of interest.

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**SOURCE:** Chung JR et al. Pediatrics. 2018. doi: 10.1542/peds.2018-2094.

## Jet nebulizer beats breath-enhanced

BY JIM KLING

MDedge News

**I**n children with moderate to severe acute asthma, albuterol delivered by a conventional jet nebulizer led to more improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) than delivery via a breath-enhanced nebulizer.

One previous study has compared the two types of nebulizers in children with acute asthma. It showed that the new technology is noninferior to the older device, but it had a small sample size and did not examine spirometry data.

Mike Gardiner, MD, of the University of California, San Diego, and Matthew H. Wilkinson, MD, of the University of Texas Southwestern at Austin, conducted a randomized, observer-blind study of the effectiveness of the two nebulizers. The results were published in the Journal of Pediatrics.

At a large pediatric emergency department, researchers randomized 107 children (aged 6-18 years) with moderate to severe asthma exacerbations to one or the other nebulizer.

Children treated with the conventional jet nebulizer had a greater improvement in FEV<sub>1</sub> (+13.8% vs. +9.1% of predicted;  $P = .04$ ). The improvements were similar in a subgroup analysis of 57 subjects who met ATS/ERS (American Thoracic Society/ European Respiratory Society) spirometry guidelines (+14.5% vs. +8.5% of predicted;  $P = .03$ ). There were no significant differences in side effects, Pediatric Asthma Score, Pediatric Asthma Severity Score, ED length of stay, or admission rate.

The study was funded by the University of Texas Southwestern. The authors had no conflicts of interest.

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**SOURCE:** Gardiner M, Wilkinson MH. J Pediatr. 2019;204:245-9.



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# Synthetic opioids drive spike in fatal overdoses

BY RANDY DOTINGA

MDedge News

New federal statistics suggest that the opioid epidemic in the United States is evolving as physicians crack down on the use of prescription painkillers: Fatal drug overdose deaths rose by 12% from 2016 to 2017, boosted by a wave of fatalities linked to illicit synthetic opioids like fentanyl that are now linked to an estimated 60% of opioid-related deaths.

“Overall, the overdose epidemic continues to worsen, and it has grown increasingly complex by involvement of prescription and illicit drugs,” Lawrence Scholl, PhD, MPH, and his associates at the Centers for Disease Control & Prevention wrote in the Morbidity and Mortality Weekly Report.

The new statistics provide more evidence that 2017 marked “a sharp increase in what has characterized as the third wave of the opioid epidemic,” said drug and health policy researcher Stephen Crystal, PhD, of Rutgers University, New Brunswick, N.J., in an interview. He was referring to a wave that experts believe started in 2013 amid a spike in U.S. overdose deaths from fentanyl and other synthetic opioids.

The new report analyzes fatal drug overdose data from 2013 to 2017. According to the findings, the total number of those overdoses rose to 70,237 in 2017, up from 63,632 in 2016. The highest drug overdose death rates in 2017 were in West Virginia, followed by Ohio, Pennsylvania, and the District of Columbia.

Some statistics did not change much from 2016



to 2017: About two-thirds of the drug overdose deaths were linked to opioids in both years, and the death rate of cases linked to prescription drugs and heroin remained steady.

However, the percentage of fatal overdose cases linked to synthetic opioids grew 45% from 2016 to 2017. Overall, 60% of opioid-related fatal overdoses in 2017 involved synthetic opioids.

The report identifies increases in several areas from 2016 to 2017. Opioid-related drug overdose deaths among black people rose by 25%, and data

from 34 states and the District of Columbia found the highest increases in death rates in North Carolina (29%), Ohio (19%), and Maine (19%).

In regard to deaths linked to synthetic opioids specifically, the highest death rates in 2017 were in West Virginia (37 per 100,000), Ohio (32 per 100,000), and New Hampshire (30 per 100,000).

“Part of what we’re seeing in these increased numbers are individuals who have pain, can’t get prescribed opioids, and turn to street drugs,” Dr. Crystal said, adding that “abruptly cutting patients off is not good, and leaving patients with a lot of untreated pain is not good. If people are going to be discontinued [from opioids] or have their doses reduced, the taper needs to be done very slowly and carefully.”

Also, the death rates of cases linked to cocaine and psychostimulants (such as methamphetamine) jumped by more than a third in 2017.

The report had limitations, including that details about drug use were missing from 12% (2016) and 15% (2017) of death certificates in fatal overdose cases. By state, the percentages of those death certificates that included drug information ranged from as little as 55% to 99%.

The report points to early data from 2018 suggesting that the number of annual drug overdose deaths may be leveling off – although it says more analysis is needed to confirm the trend.

Dr. Crystal reported no relevant disclosures.

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**SOURCE:** Scholl L et al. MMWR. 2019 Jan 4;67(5152):1419-27.

## App aims to detect respiratory failure in opioid overdoses

BY RANDY DOTINGA

MDedge News

A smartphone app seeks to detect the first moments of an overdose-related respiratory crisis and summon help before it’s too late.

The ultimate goal is “to provide a harm reduction system that can automatically connect naloxone-equipped friends and family or emergency medical services to help prevent fatal overdose events,” Rajalakshmi Nandakumar, and her associates wrote in the study, published in Science Translational Medicine.

An estimated 70,000 people in the United States died from drug overdoses in 2017, according to a 2018 data brief from the Centers for Disease Control and Prevention.

“We’re hoping a device that most people carry around could be transformed into technology that could save your life in an overdose,” said anesthesiologist Jacob E. Sunshine, MD, of the University of Washington, Seattle, and coauthor of the study. The app, which builds on pre-

vious work aimed at detecting disordered breathing in sleep apnea, uses a “short-range active sonar system” to detect respiration in a person within the distance of about 3 feet.

The app’s microphone detects an “audio reflection” of the tone after it bounces off a nearby person’s body and then analyzes it to calculate the distance to the person’s chest. “We’re able to use those distances to measure when someone is taking a breath, and when they’re not taking a breath,” said Dr. Sunshine.

If a disordered breathing pattern is detected, the app is designed to send a text message with a GPS-pinpointed location to a prespecified contact. The app also could be set to call 911.

In the study, the investigators tested the app’s algorithm at a supervised injection facility – a space designed to allow users to inject illicit drugs safely – in Vancouver. They tested the app on 94 drug users as they injected themselves; half of the users “experienced clinically important respiratory depression,” and two needed to be treated by clinic staff

for overdose, the researchers wrote.

The app detected cessation of breathing for 10 seconds or longer 95.9% of the time (95% confidence interval, 86.0%-99.5%) with 97.7% specificity (95% CI, 88.2%-99.9%). However, the app was less adept at identifying respiratory depression (respiratory rate equal to or less than 7 breaths per minute): The investigators reported 87.2% sensitivity (95% CI, 74.2%-95.1%) and 89.3% specificity (95% CI, 76.9%-96.4%).

The app’s algorithm also was tested on patients undergoing anesthesia. It correctly detected disordered breathing in 19 of 20 patients.

It’s not clear how the app would work in environments full of breathing people and, potentially, pets. Since it needs to be able to bounce audio signals off a user’s chest, the app will not work if a phone is in a pocket or if a user is face down, turns around, or wanders off.

However, the app can detect sudden changes in motion, Dr. Sunshine said, and investigators are developing a way to require users to

check in with the app in certain situations that might signal trouble.

The next steps are to refine the app’s user interface and figure out how to connect it to the 911 emergency-response system, Dr. Sunshine said. Meanwhile, researchers have created a company to develop the product. “We’re going to do additional development through that entity and seek [Food and Drug Administration] approval,” Dr. Sunshine said. The investigators do not plan to charge users for the product.

The study was funded by the Foundation for Anesthesia Education and Research, the National Science Foundation, and the University of Washington’s Alcohol and Drug Abuse Institute. The researchers are inventors on a provisional patent application related to the project, and all have equity stakes in a company that is developing the technology.

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**SOURCE:** Nandakumar R et al. Sci Transl Med. 2019 Jan 9;11(474). doi: 10.1126/scitranslmed.aau8914.



# Topical mupirocin decolonizes *S aureus* in NICU infants

BY MARK S. LESNEY

MDedge News

**A**pplication of the topical antibiotic mupirocin to multiple body sites was reported to be safe and efficacious in eradicating *Staphylococcus aureus* (SA) colonization on infants in the neonatal intensive care unit (NICU), according to researchers at the University of Maryland, Baltimore.



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Karen L. Kotloff, MD, and her colleagues conducted a phase 2 multicenter, open-label, randomized trial to assess the safety and efficacy of intranasal plus topical mupirocin in eradicating SA colonization.

“*Staph aureus* is a leading cause of sepsis in young children admitted to the NICU. Sepsis, which is systemic infection, can be fatal in infants. Thus, preventing these infections is very important in managing risk for babies in the NICU who are fragile and struggling with multiple medical problems,” Dr. Kotloff said in a press release from the university.

Infants in the NICU at eight study centers who were less than 24 months old underwent serial screening for nasal SA. Infants colonized with SA were randomly assigned to receive 5 days of mupirocin versus no mupirocin to the intranasal, periumbilical, and perianal areas.

Treatment effects were assessed on day 8 (primary decolonization) and day 22 (persistent decolonization) for all three body areas.

Primary decolonization occurred in 62/66 (93.9%) of treated infants and 3/64 (4.7%) of the control infants (*P* less than .001).

Persistent decolonization was seen in 21/46 (45.7%) of treated infants compared with 1/48 (2.1%) of the controls (*P* less than .001).

“This multicenter trial supervised by Dr. Kotloff provides strong support for a safe strategy to minimize *Staphylococcus aureus* infections in some of the most at-risk patients in

any hospital, premature babies,” said E. Albert Reece, MD, who is dean of the University of Maryland School of Medicine.

He made his comments on the

study in a press release from the university.

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**SOURCE:** Kotloff KL et al. Pediatrics. 2019. doi: 10.1542/peds.2018-1565.

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 **CHEST**<sup>TM</sup> Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

# Alcohol, distress high with REM sleep behavior disorder

BY ERIK GREB

MDedge News

**A**lcohol consumption and psychological distress are associated with possible REM sleep behavior disorder (RBD), according to a population-based cohort study published in *Neurology*. In addition, the results replicate previous findings of an association between possible RBD and smoking, low education, and male sex.

The risk factors for RBD have been studied comparatively little. “While much is still unknown about RBD, it can be caused by medications or it may be an early sign of another neurologic condition like Parkinson’s disease, dementia with Lewy bodies, or multiple system atrophy,” according to Ronald B. Postuma, MD, an associate professor at McGill University, Montreal. “Identifying lifestyle and personal risk factors linked to this sleep disorder may lead to finding ways to reduce the chances of developing it.”

To assess sociodemographic, socioeconomic, and clinical correlates of possible RBD, Dr. Postuma and his colleagues examined baseline data collected between 2012 and 2015 in the Canadian Longitudinal Study on Aging (CLSA), which

included 30,097 participants. To screen for possible RBD, the CLSA researchers asked patients, “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep [e.g., punching, flailing your arms in the air, making running movements,

*“Identifying lifestyle and personal risk factors linked to this sleep disorder may lead to finding ways to reduce the chances of developing it.”*

etc.]?” Participants answered additional questions to rule out RBD mimics. Patients with symptom onset before age 20 years, positive apnea screen, or a diagnosis of dementia, Alzheimer’s disease, parkinsonism, or Parkinson’s disease were excluded from analysis.

In all, 3,271 participants screened positive for possible RBD. After the investigators excluded participants with potential mimics, 958 patients (about 3.2% of the total population) remained in the analysis. Approximately 59% of patients with possible RBD were male, compared with 42%

of controls. Patients with possible RBD were more likely to be married, in a common-law relationship, or widowed.

Participants with possible RBD had slightly less education (estimated mean, 13.2 years vs. 13.6 years) and lower income, compared with controls. Participants with possible RBD retired at a slightly younger age (57.5 years vs. 58.6 years) and were more likely to have retired because of health concerns (28.9% vs. 22.0%), compared with controls.

In addition, patients with possible RBD were more likely to drink more and to be moderate to heavy drinkers than controls; they were also more likely to be current or past smokers. Antidepressant use was more frequent and psychological distress was greater among participants with possible RBD.

When the investigators performed a multivariable logistic regression analysis, the associations between possible RBD and male sex and relationship status remained. Lower educational level, but not income level, also remained associated with possible RBD. Furthermore, retirement age and having reported retirement because of health concerns remained significantly associated with possible RBD, as did the amount of

alcohol consumed weekly and moderate to heavy drinking. Sensitivity analyses did not change the results significantly.

One of the study’s limitations is its reliance on self-report to identify participants with possible RBD, the authors wrote. The prevalence of possible RBD in the study was 3.2%, but research using polysomnography has found a prevalence of about 1%. Thus, the majority of cases in this study may have other disorders such as restless legs syndrome or periodic limb movements. Furthermore, many participants who enact their dreams (such as unmarried people) are likely unaware of it. Finally, the researchers did not measure several variables of interest, such as consumption of caffeinated products.

“The main advantages of our current study are the large sample size; the systematic population-based sampling; the capacity to adjust for diverse potential confounding variables, including mental illness; and the ability to screen out RBD mimics,” the authors concluded.

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**SOURCE:** Postuma RB et al. *Neurology*. 2018 Dec 26. doi: 10.1212/WNL.0000000000006849.

## PAP decreased levels of Alzheimer biomarker

BY MICHELE G. SULLIVAN

MDedge News

**S**oluble amyloid-beta in cerebrospinal fluid (CSF) decreased when subjects with obstructive sleep apnea used a positive airway pressure device with good adherence, suggesting that improving sleep could reduce the risk of Alzheimer disease in this population.

The small decrease in cerebrospinal amyloid-beta 40 (Ab40) and Ab42 hints at decreased neuronal release of the neurotoxic protein, wrote Yo-El S. Ju, MD, and her colleagues. The report was published online in *Annals of Neurology*.

Alzheimer disease (AD) biomarker studies typically find decreased CSF levels associated with increased Ab brain plaques. But before plaques form, increased soluble Ab in CSF is a risk factor for aggregation. Thus, higher soluble Ab levels in mid-life may suggest a risk of later Ab pathology, wrote Dr. Ju of Washington University, St. Louis.

“We tested individuals without any AD pathology as assessed by Ab42 [in CSF], a highly sensitive biomarker of amyloid plaques,” Dr. Ju and her coauthors wrote. “This means our study findings can be extrapolated to the large population of people with OSA [obstructive sleep apnea],

many of whom are middle-aged or younger, and have many years to accrue benefit from AD risk reduction. ... The effect of OSA on SWA [slow-wave activity], Ab, and possibly tau, is a probable proximal step in a cascade whereby OSA increases the risk of AD.”

The researchers recruited 35 subjects with mild to severe OSA and without abnormal Ab levels in CSF. Subjects used auto-titrating positive airway pressure (PAP) for 1-4 months; 18 were sufficiently compliant to be included in the analysis (more than 4 hours on more than 70% of 30 preceding nights as recorded by the machine). CSF was obtained after a baseline polysomnogram and after the treatment period lasting 1-4 months.

Of the 18 analyzed patients, 7 had mild OSA and 11 had moderate to severe OSA. They were an average of nearly 57 years old with a mean body mass index of 30.4 kg/m<sup>2</sup>; 7 patients had hypertension.

PAP treatment was effective, indicated by a normalized apnea-hypopnea index and decreased time in hypoxemia. Total sleep time and sleep efficiency were unchanged, but slow-wave activity did increase. As expected, hourly arousals and time in hypoxemia decreased, and hypoxic nadir shifted from an oxygen saturation of 82.5% to 91%.

“As a group, there was no significant change

in Ab with treatment,” the researchers wrote. But a correlational analysis found that “greater improvement in OSA was associated with greater decrease in Ab40 and Ab42. Additionally, we found that change in tau negatively correlated with OSA improvement.”

The team suggested a two-factor model to explain the relationship between OSA and Ab levels. “Due to decreased SWA, there would be relatively increased release of Ab into the [interstitial fluid]. However, as OSA severity worsens, pressure effects of obstructive respiratory events impede the clearance of Ab and tau out of the interstitial space, resulting in lower levels in the CSF and an inverse U-shaped curve. In this model, a small improvement in OSA may result in an increase in Ab or tau, whereas a larger improvement in OSA – that ameliorates both SWA and clearance mechanisms – will result in a decrease in Ab and tau.”

The project was funded in part by Philips-Respironics, which provided the devices, and by the National Institutes of Health. Philips-Respironics had no input or role in any other part of the study. The authors had no financial disclosures.

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**SOURCE:** Ju YS et al. *Ann Neurol*. 2018 Dec 31. doi: 10.1002/ana.25408.



# New hypopnea criteria ID unique OSA patient subset

BY ANDREW D. BOWSER

MDedge News

The latest recommended criteria for hypopnea define a distinct group of patients who report substantial daytime sleepiness but with no significant cardiovascular risk, investigators reported in a retrospective, cross-sectional analysis.



Dr. Won

The number of obstructive sleep apnea (OSA) diagnoses increased by nearly 13% when using the 2012 American Academy of Sleep Medicine (AASM) criteria of at least 3%

desaturation or arousal, instead of the 2007 criteria of at least 4% desaturation. While cardiovascular disease risk did not appear to be elevated in those with an OSA diagnosis based on the newer, more inclusive criteria, the OSA diagnosis remained a risk factor for arrhythmias in this group of patients, reported Christine H.J. Won, MD, of Yale University, New Haven, Conn., and her colleagues.

“Our findings suggest [that] a more inclusive hypopnea definition alters OSA severity categorization, identifies a new symptomatic group of patients with predominantly mild OSA without increased cardiovascular odds, and does not ameliorate the increased odds predicted by severe OSA for arrhythmias,” the investigators wrote in the *Journal of Clinical Sleep Medicine*.

The analysis by Dr. Won and her colleagues included 1,400 veterans

who had polysomnography for suspected sleep-disordered breathing. Of those veterans, two-thirds (932; 66%) had an OSA diagnosis based on at least 4% desaturation criteria. With the newer criteria of at least 3% desaturation or arousal, another 175 OSA diagnoses were captured out of the remaining 468 previously negative studies, meaning that more than 37% of those patients would be recategorized as having OSA, Dr. Won and her coauthors said.

Compared with individuals with OSA classified by the older, more restrictive criteria, the 175 individuals in this “new OSA” group were

younger and less likely to be obese. Compared to individuals without OSA, the new OSA group had more disrupted sleep architecture, worse oxygen saturations, and more self-reported sleepiness on the Epworth Sleepiness Scale.

Adding in the new OSA group redistributed disease severity, with a relative increase of 21.4% for mild and 21.3% for moderate OSA, but just 15.3% for severe OSA.

This is thought to be the first study to describe a unique group of patients who escape OSA diagnosis based on the at least 4% desaturation criteria but are captured with at least

3% desaturation or arousal criteria.

“It would also be important to assess whether treatment in any of these groups leads to improved cardiovascular health, or whether treatment of the [new OSA] group leads to improved daytime sleepiness or quality of life,” they said.

The researchers reported no conflicts of interest. Their work was performed at the Veterans Affairs Healthcare System in West Haven, Conn., Indianapolis, and Cleveland.

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**SOURCE:** Won CHJ et al. *J Clin Sleep Med*. 2018 Dec 15;14(12):1987-94.

## VIEW ON THE NEWS

### Useful take on varying hypopnea definitions

The study by Won and colleagues provides a “useful perspective” on how hypopnea is defined by including outcome data based on the two different scoring criteria, according to Kenneth R. Casey, MD, MPH, FCCP, and Rachna Tiwari, MBBS.

Results of the study suggest a rationale for using both the 2007 American Academy of Sleep Medicine hypopnea criteria based on  $\geq 4\%$  desaturation, and the updated 2012 AASM criteria based on  $\geq 3\%$  desaturation or arousal in the evaluation of polysomnography results, Dr. Casey and Dr. Tiwari said in a commentary accompanying the study.

“This perspective may ultimately be the solution to the confusion caused by competing functional definitions of hypopnea,” they said in the commentary published in the *Journal of Clinical Sleep Medicine*.

The 2007 recommended criteria of  $\geq 4\%$  desaturation seemed reasonable based on available evidence at the time, but was not rigorously based by today’s standards, the authors said.

At that time, they also proposed the new alter-

native criteria based on  $\geq 3\%$  desaturation or an arousal, which in 2012 became elevated to a recommended rule. However, the previous recommended rule was kept to accommodate patients who required Centers for Medicare & Medicaid Services reimbursement, according to Dr. Casey and Dr. Tiwari.

Subsequent studies demonstrated “significant differences” in apnea-hypopnea index results, depending on which scoring criteria were used, they added.

“This confusing, vacillating definition has created a rather bizarre, and perhaps unsettling, situation wherein the severity of the diagnosis of sleep-disordered breathing, and perhaps its presence or absence, is determined by the patient’s insurance coverage,” they said in the commentary.

*Dr. Casey and Dr. Tiwari are with the University of Wisconsin and William S. Middleton Memorial Veterans Hospital, both in Madison. They reported no conflicts of interest related to their editorial, which appears in the Journal of Clinical Sleep Medicine.*

# Data link severe sleep apnea and aggressive melanoma

BY HEIDI SPLETE

MDedge News

**FROM THE JOURNAL CHEST®** ■ Severe sleep-disordered breathing was significantly associated with more aggressive skin cancer in a study of 443 adults published in the journal *CHEST*.

Sleep-disordered breathing has been associated with cancer risk and mortality, but no large studies have examined the association in specific cancers, wrote Miguel Angel Martinez-Garcia, MD, of La Fe University and Polytechnic Hospital, Valencia, Spain, and his colleagues.

The researchers conducted a sleep study of 443 adults with melanoma within 6 months of their diagnoses. Overall, patients with more severe sleep apnea were nearly twice as likely to have

aggressive melanoma, defined as a Breslow index greater than 1 mm.

Patients with greater than 15.6 events per hour or in the DI4% tertile (more than 9.3 desaturations per hour) were approximately twice as likely (1.94 and 1.93 times, respectively) to have a more aggressive melanoma as were those with less severe sleep apnea, after adjustment for age, gender, body mass index, and melanoma location.

The average age of the patients was 60 years, 51% were male, and the average time between the melanoma diagnosis and the sleep study was 82 days.

Sleep symptoms were not significantly different between the patients with aggressive or less aggressive melanoma. However, in addition to more

severe sleep apnea, those with aggressive melanoma were significantly more likely to be older, male, and have a higher BMI than were those with less aggressive disease.

The association with sleep apnea was significant in patients younger than 55 years only if their Breslow index was greater than 2 mm, the researchers said.

The study was supported in part by Fondo de Investigación Sanitaria, SEPAR, Red Respira, and Sociedad Valenciana de Neumología.

The researchers had no financial conflicts to disclose.

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**SOURCE:** Martinez-Garcia MA et al. *Chest*. 2018. doi: 10.1016/j.chest.2018.07.015.

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# Poor-prognosis cancers linked to highest suicide risk in first year

BY ANDREW D. BOWSER

MDedge News

**S**uicide risk significantly increases within the first year of a cancer diagnosis, with risk varying by type of cancer, according to investigators who conducted a retrospective analysis representing nearly 4.7 million patients.

Risk of suicide in that first year after diagnosis was especially high in lung and pancreatic, while by contrast, breast and prostate cancer did not increase suicide risk, reported the researchers, led by Hesham Hamoda, MD, MPH, of Boston Children's Hospital/Harvard Medical School, and Ahmad Alfaar, MBBCh, MSc, of Charité–Universitätsmedizin Berlin.

That variation in suicide risk by cancer type suggests that prognosis and 5-year relative survival play a role in increasing suicide rates, according to Dr. Hamoda, Dr. Alfaar, and their coauthors.

“After the diagnosis, it is important that health-care providers be vigilant in screening for suicide and ensuring that patients have access to social and emotional support,” they wrote in a report published in *Cancer*.

Their analysis was based on 4,671,989 patients with a diagnosis

of cancer in the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2014. Out of 1,005,825 of those patients who died within the first year of diagnosis, the cause of death was suicide for 1,585, or 0.16%.

Overall, the risk of suicide in-

*“After the diagnosis, it is important that health-care providers be vigilant in screening for suicide and ensuring that patients have access to social and emotional support.”*

creased significantly among cancer patients versus the general population, with an observed-to-expected (O/E) ratio of 2.51 per 10,000 person-years, the investigators found. The risk was highest in the first 6 months, with an O/E mortality of 3.13 versus 1.8 in the latter 6 months.

The highest ratios were seen for lung cancer, with an O/E ratio of 6.05, and pancreatic cancer, with a ratio of 8.01, and the researchers found in further analysis.

Significant increases in suicide risk were also seen for colorectal

cancer (2.08) and melanoma (1.45), though rates were not significantly different versus the general population for breast (1.23) and prostate (0.99), according to the reported data.

Suicide risk was relatively high for any cancer with distant metastases (5.63), though still significantly higher at 1.65 in persons with localized/regional disease, the data show.

The increased suicide risk persisted more than 1 year after the cancer diagnosis, though not to the degree observed within that first year, they added.

Most patients with suicide as a cause of death were white (90.2%) and male (87%). Nearly 60% were between the ages of 65 and 84 at the time of suicide.

Social support plays an integral role in suicide prevention among cancer patients, the researchers noted.

Previous studies suggest that support programs may decrease suicide risk by making patients better aware of their prognosis, receptive to decreased social stigma, or less likely to have stress related to cost of care, they said.

“Discussing the quality of life after diagnosis, the effectiveness of therapy, and the prognosis of the disease

## VIEW ON THE NEWS

**Jacques-Pierre Fontaine, MD, FCCP, comments:** This article highlights the significantly increased risk of suicide in the first year after diagnosis in patients with generally poor prognosis cancers, such as lung and pancreatic cancer, as compared with the general population or even compared with patients with cancers associated with a better prognosis, such as breast and prostate cancers. Therefore, special emphasis must be placed on suicide prevention for this cohort of patients.

and maintaining a trusting relationship with health care professionals all decrease the likelihood of suicide immediately after a diagnosis of cancer,” they said.

Dr. Hamoda, Dr. Alfaar, and their coauthors reported no conflicts of interest. Funding for the study came in part from the German Academic Exchange Service (Dr. Alfaar).

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**SOURCE:** Saad AM et al. *Cancer*. 2019 Jan 7. doi: 10.1002/cncr.31876.

## Self-reporting extends lung cancer survival

BY WILL PASS

MDedge News

**P**atients with nonprogressive, metastatic lung cancer who report symptoms through a weekly, web-based monitoring system may survive longer than those who undergo standard imaging surveillance, according to a recent French study.

Self-reporting may notify care providers about adverse effects or recurrence earlier than imaging, suggested lead author, Fabrice Denis, MD, PhD, of Institut Inter-régional de Cancérologie Jean Bernard in Le Mans, France, and his colleagues. Findings were published in a letter in *JAMA*.

In 2017, a similar, single-center study showed that web-based symptom reporting could improve survival in patients undergoing chemotherapy. The lead investigator on that trial was Ethan Basch, MD, who coauthored the present publication.

The current, prospective study involved 121 patients treated at five centers in France between June 2014 and December 2017. Eligibility required a diagnosis of nonprogressive, metastatic



lung cancer, including stage III or IV non-small cell or small cell disease. Patients were treated with antiangiogenic therapy, chemotherapy, immunotherapy, or tyrosine kinase inhibitors.

Patients in the control group had standard follow-up with imaging every 3-6 months. In contrast, the patient-reported outcomes (PRO) group completed a weekly online survey of 13 common symptoms between follow-up visits. If patients reported symptoms that matched with predefined

criteria for severity or worsening, then the treating oncologist was notified.

When an 18-month interim analysis showed significant survival advantage in the PRO group, recruitment was stopped, and control patients were moved to the PRO group. After 2 years of follow-up, 40 patients (66.7%) in the control group had died, compared with 29 patients (47.5%) in the PRO group. Before censor for crossover, median overall survival (OS) was 22.5 months in the PRO group, compared with 14.9 months in the control group ( $P = .03$ ). Censoring for crossover widened the gap between groups by more than a month (22.5 vs. 13.5 months;  $P = .005$ ).

“A potential mechanism of action is that symptoms suggesting adverse events or recurrence were detected earlier,” the investigators concluded.

The study was funded by SIVAN Innovation. Investigators reported financial affiliations with AstraZeneca, SIVAN Innovation, Ipsen, Roche, the National Cancer Institute, Lilly, and others.

**SOURCE:** Denis F et al. *JAMA*. 2019 Jan 22;321(3):306-7.

# More benefit to chemoradiation in earlier SCLC

BY TED BOSWORTH

MDedge News

**I**n response to chemoradiation, patients with stage I or II small cell lung cancer (SCLC) have a significantly longer overall survival than do those with stage III disease, according to a post hoc analysis of a randomized trial of chemoradiation in patients with early stages of SCLC.

The fact that overall survival is better in stage I and II than in stage III SCLC isn't surprising. But the data confirm that stage I and II SCLC respond differently to chemoradiation than does stage III, providing a benchmark for safety and efficacy, according to the study authors.

The phase 3 CONVERT trial, from which the data were drawn, randomized patients with limited-stage SCLC to twice-daily (45 Gy in 30 fractions) or once-daily (66 Gy in 33 fractions) radiation after initiating cisplatin-etoposide chemotherapy (Lancet Oncol. 2017 Aug;18[8]:1116-25). Additional prophylactic cranial irradiation was permitted for those

with an indication.

Contrary to the researcher's hypothesis, once-daily radiation was not more effective for the primary outcome of overall survival in CONVERT, which limited enrollment to

*At 5 years, 49% of the stage I/II patients were alive, compared with 28% of the stage III patients.*

patients with local disease but did not stratify outcomes by SCLC stage. The purpose of the new post hoc analysis was to compare outcomes in those early-disease SCLC patients stratified by stage, which the authors noted is now recommended by several guidelines.

Because there were only four patients in CONVERT with stage I SCLC, those with either stage I or II SCLC, totaling 86 patients, were combined and then compared with the 423 with stage III SCLC.

At baseline, there were no significant differences between stage I/

II and III groups for median age, smoking history, Eastern Cooperative Oncology Group performance status, or dyspnea score at baseline. Similar proportions of patients completed the planned therapy.

However, the median survival was twice as long in the stage I/II group, compared with those with stage III SCLC (50 vs. 25 months), producing a hazard ratio for this outcome of 0.60 ( $P = .001$ ). At 5 years, 49% of the stage I/II patients were alive, compared with 28% of the stage III patients ( $P = .001$ ).

Other outcomes, such as progression-free survival at 5 years (47% vs. 26%;  $P = .003$ ) also favored those with earlier-stage disease.

The incidence of adverse events associated with chemoradiation was not significantly different for the two groups, with the exception of acute esophagitis, which was less frequent in patients with earlier-stage disease.

"The low incidence of severe toxic effects is a valid rationale to consider future radiotherapy dose intensification trials to improve outcomes"

in patients with stage I/II disease, according to study author Ahmed Salem, MB, ChB, of the University of Manchester (England), and his coinvestigators.

The data from the post hoc analysis support guideline recommendations to stage even early and local SCLC when evaluating response to therapy in clinical trials, noted Howard (Jack) West, MD, of Swedish Cancer Institute, Seattle, in an accompanying editorial (JAMA Oncol. 2018 Dec 6. doi: 10.1001/jamaoncol.2018.5187). Dr. West suggested that such staging information might be useful when counseling patients about treatment options.

"These results imply that we may do our patients a disservice by dispensing with clinically relevant staging information that can lead to a more refined assessment of prognosis and optimal treatment," Dr. West wrote.

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**SOURCE:** Salem A et al. JAMA Oncol. 2018 Dec 6:e185335. doi: 10.1001/jamaoncol.2018.5335.

# No link between sex and survival on checkpoint inhibitors in latest meta-analysis

BY ANDREW D. BOWSER

MDedge News

**M**en and women with cancer may derive a similar survival benefit from immune checkpoint inhibitor therapy, results of a recent meta-analysis suggest.

Both men and women had an overall survival benefit from immunotherapy versus standard of care therapy, with no significant difference between the sexes, according to authors of this meta-analysis, which included 23 randomized clinical trials comprising nearly 14,000 patients. Of the 23 trials, 13 were studies of non-small cell lung cancer and small cell lung cancer that included nearly 7,000 patients.

The findings, reported in JAMA Oncology, contrast with those of another recent analysis, which suggested that men had a greater advantage of receiving immunotherapy versus standard of care than women did.

"We found no evidence that sex should be considered when deciding whether to offer immunotherapy to patients with advanced cancers," said Christopher J.D. Wallis, MD, PhD, of the University of Toronto, and his coauthors said in their report.

The present meta-analysis was based on a "more contemporary and comprehensive" literature search strategy than the earlier one, accord-

ing to Dr. Wallis and his coinvestigators.

Specifically, they considered immunotherapy agents not included in the previous analysis, added seven new studies published since the previous analysis, and excluded three trials that compared immunotherapy agents, rather than comparing immunotherapy with standard of care, they explained in their report.

Their resulting meta-analysis included a total of 9,322 men and 4,399 women, most of whom were in their 70s. Overall, they found that immune checkpoint inhibitor therapy offered a statistically significant overall survival advantage versus standard systemic therapy, with a hazard ratio of 0.75 (95% confidence interval, 0.70-0.81;  $P$  less than .001).

That overall survival advantage was found for both men, with a hazard ratio of 0.75 (95% CI, 0.69-0.81;  $P$  less than .001) and women, at 0.77 (95% CI, 0.67-0.88;  $P = .002$ ), investigators further reported. There was no statistically significant difference in overall survival advantage between men and women, both overall ( $P = 0.60$ ) and in subgroup analyses that accounted for tumor type, line of treatment, and prevalence of women in the study.

The previous meta-analysis, published in the Lancet, found an overall survival hazard ratio of 0.72 for men receiving checkpoint inhibitors and 0.86 for women receiving checkpoint inhib-

## VIEW ON THE NEWS

**Jacques-Pierre Fontaine, MD, FCCP, comments:**

This more robust and updated meta-analysis disproves the previously accepted notion that immunotherapy with checkpoint inhibitors was more effective in men as compared with women. Although identifiable genetic mutations are more frequent in women, the immunotherapeutic approach and its expected efficacy is no different between men and women.

itors ( $P = .0019$ ), prompting those investigators to conclude that the magnitude of benefit was sex-dependent and that different immunotherapeutic approaches may be needed for men versus women.

Dr. Wallis reported no disclosures related to the study. Study coauthors provided disclosures related to Merck, AstraZeneca, Bristol-Myers Squibb, Illumina, Tempus, Novartis, Eli Lilly, Fate, Incyte, MedImmune, Pfizer, Roche/Genentech, Xcovery, Fate Therapeutics, Genocoea, and Iovance.

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**SOURCE:** Wallis CJD et al. JAMA Oncol. 2019 Jan 3. doi:10.1001/jamaoncol.2018.5904.



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# HIPAA compliance: Learn from these three cases

BY ALICIA GALLEGOS

MDedge News

Data security experts say three HIPAA violations that resulted in significant fines by the Office for Civil Rights (OCR) in 2018 hold important lessons for health professionals about safeguarding records and training staff in HIPAA compliance.

Read on to learn how the cases unfolded and what knowledge practices can gain from the common HIPAA mistakes.

**Who?** Allergy Associates of Hartford, Conn.

**What happened?** A patient contacted a local television station to complain about a dispute between herself and a physician at Allergy Associates. The disagreement stemmed from the office turning away the patient because she allegedly brought her service animal, according to a Nov. 26, 2018, announcement by the Department of Health & Human Services. The reporter contacted the doctor in question for a news story and, in responding, the physician disclosed protected patient information to the reporter.



Ms. Mitchell

**What else?** An OCR investigation determined that a privacy officer with Allergy Associates had instructed the physician not to respond to the media about the complaint or to respond with “no comment”; that advice was disregarded. The practice then failed to discipline the physician or take any corrective action following the disclosure, according to the OCR.

**How much?** The OCR imposed a \$125,000 fine on the practice and a corrective action plan that includes 2 years of OCR monitoring.

**Lessons learned:** Had the practice disciplined the physician or taken corrective action after the disclosure, the OCR may not have penalized the group so severely, according to Jennifer Mitchell, a Cincinnati-based health law attorney and vice chair of the American Bar Association eHealth, Privacy, & Security Interest Group.

“In my opinion, the government levied these penalties because the provider did not sanction the doctor,” Ms. Mitchell said in an interview. “Health care entities need to take proper steps to remediate and, at a minimum, hold their workforce responsible for their behavior and ensure that it won’t happen again.”

The case emphasizes the need to train team members on media protocols and to ensure that protected health information is not mistakenly released. In addition to implementing policies and procedures, practices must also be willing to discipline health professionals when violations occur.

“A health care provider’s natural inclination is to defend themselves if they are being accused by a patient,” she said. “However, under the HIPAA rules, health care providers have to understand that they are prohibited from making such public statements about any patient.”



MARKLEVANT/GETTY IMAGES

**Who?** Advanced Care Hospitalists of Lakeland, Fla.

**What happened?** Advanced Care Hospitalists (ACH) received billing services from an individual who represented himself to be affiliated with a Florida-based company named Doctor’s First Choice Billing. A local hospital later notified ACH that patient information, including names and Social Security numbers, were viewable on the First Choice website. ACH identified at least 400 patients affected by the breach and reported the breach to the OCR. However, ACH later determined that an additional 8,855 patients may have been affected and revised its OCR notification.

**What else?** During its investigation, the OCR found that the hospitalist group had never entered into a business associate agreement for billing services with First Choice, as required by HIPAA, and that the practice also failed to adopt any policies regarding business associate agreements until 2014, according to a Dec. 4, 2018, announcement from HHS.

**How much?** The OCR fined the practice \$500,000 and also imposed a robust corrective action plan that includes an enterprise-wide risk analysis and the adoption of business associate agreements. Roger Severino, OCR director, called the case especially troubling because “the practice allowed the names and Social Security numbers of thousands of patients to be exposed on the Internet after it failed to follow basic security requirements under HIPAA.”

**Lessons learned:** The case illustrates the importance of having a business associate agreement in place for all third parties that may have access to protected health information, said Clinton Mikel, a Farmington Hills, Mich., health law attorney specializing in HIPAA compliance.

Under HIPAA, a business associate is defined as a person or entity, other than a member of the workforce of a covered entity, who “performs functions or activities on behalf of, or provides certain services to, a covered entity that involve access by the business associate to protected health information.”

HIPAA requires that covered entities enter into contracts with business associates to ensure

appropriate safeguarding of protected health information.

“If your business associate has a breach, your practice must report the breach to OCR and your patients,” Mr. Mikel said in an interview. “The OCR will then investigate your practice and your relationship with the business associate. Just because the breach and fault clearly happened elsewhere, you will still be investigated, and could face a penalty if HIPAA requirements weren’t met.”

**Who?** Filefax of Northbrook, Ill.

**What happened?** The OCR opened an investigation after receiving an anonymous complaint that medical records obtained from Filefax, a company that provided storage, maintenance, and delivery of medical records for health professionals, were left unmonitored at a shredding and recycling facility. OCR’s investigation revealed that a person left the records of 2,150 patients at the recycling plant and that the records contained protected health information, according to an HHS announcement. It is unclear if the person worked for Filefax.

**What else?** The OCR discovered that, in a related incident, an individual who obtained medical records from Filefax left them unattended in an unlocked truck in the Filefax parking lot.

**How much?** The OCR imposed a \$100,000 fine on Filefax. The company is no longer in business; however, a court-appointed liquidator has agreed to properly store and dispose of the remaining records.

**Lessons learned:** Although the case did not involve a health provider, the circumstances are applicable to physicians, particularly when practices move or close, Mr. Mikel said. In some cases, a former patient may contact a shuttered practice only to learn their record cannot be located, or worse, that a breach has occurred.

“[Such a case is] ripe for a patient to complain to OCR,” he said. “OCR doesn’t care if you’re closed or retired, they’re going to look.”

HIPAA requires that covered entities apply appropriate administrative, technical, and physical safeguards to protect the privacy of protected health information in any form when moving or closing. The safeguards must prevent prohibited uses and disclosures of protected health information in connection with the disposal of such information, according to the rule. The HHS provides guidance for the disposing of medical records; further, the American Academy of Family Physicians has created a checklist on closing a practice that addresses the transferring of medical records.

Without taking the correct measures, doctors may end up drawing scrutiny from OCR and face a potential fine if violations are found, experts said.

“Covered entities and business associates need to be aware that OCR is committed to enforcing HIPAA regardless of whether a covered entity is opening its doors or closing them,” Mr. Severino of the OCR said in a statement. “HIPAA still applies.”

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# Hospital Readmissions Reduction Program may be doing more harm than good

BY GREGORY TWACHTMAN

MDedge News

**A** Medicare program aimed at lowering readmissions to hospitals could be having an adverse effect on mortality.

Results from a retrospective cohort study of hospitalizations for heart failure, acute myocardial infarction, and pneumonia in Medicare beneficiaries aged 65 years and older between April 1, 2005, and March 31, 2015 (covering the period before and after the Medicare Hospital Readmissions Reduction Program was announced in April 2010 and implemented in October 2012), found an increase in 30-day postdischarge mortality among heart failure and pneumonia patients.

“Most concerning, however, is the possibility that the relationship between the HRRP and postdischarge mortality for heart failure and pneumonia is causal, indicating that the HRRP led to changes in quality of care that adversely affected patients,” Rishi Wadhwa, MD, Harvard Med-

ical School, Boston, and his colleagues wrote in a report published Dec. 25, 2018, in JAMA.

They looked at 8.3 million hospitalizations for heart failure, acute MI, and pneumonia, among 7.9 million patients alive at the time of discharge. There were roughly 270,000 deaths within 30 days of discharge for heart failure; 128,000 for acute MI; and 246,000 for pneumonia.

For trends, the timing was divided into four periods: two prior to the announcement of the HRRP (April 2005–September 2007 and October 2007–March 2010); a third covering the time when the HRRP was announced (April 2010–September 2012); and the fourth when HRRP was implemented (October 2012–March 2015).

Among patients discharged with heart failure, 30-day mortality was rising even before the announcement of the HRRP, by 0.27% from the first period to the second period. That baseline trend continued when the HRRP was announced, by 0.49%, from the second period to the third. The difference in change between those periods was 0.22%. After implementation, 30-day mortality increased by 0.52%, with a difference in change from the third period of 0.25%.

In pneumonia patients, postdischarge mortality was stable before HRRP, but increased after HRRP, by 0.26%, with a difference in change from the second period to the third period of 0.22%. After implementation, the 30-day postdischarge mortality was 0.44%, with a difference in change of 0.40%.

Acute MI was a different story. Postdischarge mortality decreased significantly after the implementation of the HRRP, by 0.22%. The difference in change was –0.26%.

The authors suggested that, “although hospitals that reduce readmissions also appear to reduce mortality, this hospital-level concordance does not reflect the change in readmissions and mortality at the level of the patient population, which is arguably of greater importance to individual patients and to public health.”

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**SOURCE:** Wadhwa R et al. JAMA. 2018 Dec 25. doi: 10.1001/jama.2018.19232.

## 2019 Education Calendar



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



Calendar subject to change. For most current course list and more information, visit [livelearning.chestnet.org](http://livelearning.chestnet.org).

### VIEW ON THE NEWS Changes needed to hospital readmissions program

**E**vidence in this study shows that, while the Hospital Readmissions Reduction Program may be succeeding in reducing hospital admissions, little evidence is available to show that it is having a positive effect on patient outcomes.

The Centers for Medicare & Medicaid Services needs to reexamine the program and find alternative methods that are both effective at reducing hospital readmissions while at the same time protecting patients from unintentional harm, including death.

Gregg C. Fonarow, MD, University of California Medical Center, Los Angeles, in an editorial published in JAMA (Dec 25 2018. doi: 10.1001/jama.2018.19325).

## PULMONARY PERSPECTIVES®

# Chronic thromboembolic pulmonary hypertension: The “fixable” form of PH that you don’t want to miss

BY SONJA BARTOLOME, MD

**C**hronic thromboembolic pulmonary hypertension (CTEPH) is an elevation in pulmonary vascular resistance (PVR) resulting from chronic, “scarred-in” thromboembolic material partially occluding the pulmonary arteries. This vascular obstruction, over time, results in failure of the right ventricle and early mortality.

CTEPH was first characterized in an autopsy series from the Massachusetts General Hospital in 1931. On these postmortem examinations, it was noted that the affected patients had large pulmonary artery vascular obstruction, but also normal pulmonary parenchyma distal to this vascular obstruction and extensive bronchial collateral blood flow (Means J. *Ann Intern Med.* 1931;5:417). Although this observation set the groundwork for the theory that surgically removing the vascular obstruction to this preserved lung tissue could improve the condition of these patients, it would take until the mid-20th century until imaging and cardiac catheterization techniques allowed the recognition of the disease in real time.

CTEPH is thought to begin with an acute pulmonary embolus, but in approximately 3.4% of patients, rather than resolving over time, the thrombus will organize and incorporate into the pulmonary artery intimal layer (Simonneau G, et al. *Eur Respir Rev.* 2017;26:160112). A history of venous thromboembolism in a patient with persistent dyspnea should spur a screening evaluation for CTEPH; 75% of patients with CTEPH have a history of prior known acute pulmonary embolus, and 56% of patients report a prior diagnosis of deep venous thrombosis. An acute pulmonary embolus will fibrinolyse early with the vast majority of the vascular obstruction resolving by the third month. Therefore, if the patient continues to report a significant exercise limitation after 3 months of therapeutic anticoagulation therapy, or has concerning physical exam signs, a workup should be pursued.

The initial evaluation for CTEPH begins with a transthoracic echocardiogram (TTE) and ventilation/perfusion (V/Q) scintigraphy. A retrospective study comparing V/Q scan and multi-detector CT scan revealed that V/Q scanning had a sensitivity and specificity of 97% and 95% for CTEPH, while CTPA had good specificity at 99% but only 51% sensitivity (Tunariu N, et al. *J Nuc Med.* 2007;48[5]:680). If these are abnormal, then right-sided heart catheterization and invasive biplane digital subtraction pulmonary angiography are recommended.

These studies confirm the diagnosis, grade its severity, and allow an evaluation for surgically accessible vs distal disease. Some CTEPH centers utilize additional imaging techniques, such as magnetic resonance angiography, optical resonance imaging, spectral CT scanning with iodine perfusion images, and intravascular ultrasound.

These modalities and their place in the diagnostic algorithm are under investigation.

The goal of the initial evaluation process is to determine if the patient can undergo surgical pulmonary thromboendarterectomy (PTE), because



Dr. Bartolome

in experienced hands, this procedure ensures the best long-term outcome for the patient. The first pulmonary thromboendarterectomy was performed at the University of California San Diego in 1970. Because the disease involves the intimal layer of the pulmonary artery, the surgery had to involve not just removal of the intravascular obstruction but also a pulmonary artery intectomy. Surgical mortality rates were high in the initial experience. In 1984, a review of 85 worldwide cases reported an average mortality rate of 22%, and as high as 40% in some centers (Chitwood WR, Jr, et al. *Clin Chest Med.* 1984;5[3]:507).

Over the ensuing years, refinements in surgical technique, the utilization of deep hypothermia and cardiac arrest during the procedure, development of new surgical instruments, and standardization of surgical selection and postoperative care have improved surgical mortality to <5% in experienced centers. Long-term outcomes of successful PTE surgery remain good, with 90% 3-year survival vs 70% for those who do not undergo surgery and are medically treated. Importantly, 90% of postoperative patients report functional class I or II symptoms at 1 year (Condliffe R, et al. *Am J Respir Crit Care Med.* 2008;177[10]:1122). Because of this difference in early mortality and symptoms, PTE surgery remains the treatment of choice for CTEPH.

Despite the advances in PTE surgery, some patients are not operative candidates either due to surgically inaccessible disease or due to comorbidities. In 2001, Feinstein and colleagues described a series of 18 CTEPH cases treated with balloon pulmonary angioplasty (BPA). Promising hemodynamics effects were reported; however, the procedure had an unacceptable complication rate in which 11 patients developed reperfusion lung injury, 3 patients required mechanical ventilation, and 1 patient died.

In the ensuing years, Japanese and Norwegian groups have independently developed and improved techniques for BPA. The procedure is done in a series of sessions (average four to six), 1 to 4 weeks apart, where small (2-3 mm) balloons are directed toward distal, diseased pulmonary vessels. Common complications include reperfusion injury, vessel injury, hemoptysis, and, more rarely, respiratory failure. Still, early experience suggests this procedure decreases pulmonary vascular resistance over time, improves right ventricular

function, and improves patients’ symptoms (Andreassen A, et al. *Heart.* 2013;99[19]:1415). The experience with this procedure is limited but growing in the United States, with only a handful of centers currently performing BPAs and collecting data.

Lifelong anticoagulation, oxygen, and diuretics for right-sided heart failure are recommended for patients with CTEPH. The first successful large phase III medication study for CTEPH was the CHEST-1 trial published in 2013 (Ghofrani et al. *N Engl J Med.* 2013;369:310). This was a multicenter, randomized, placebo-controlled trial of the soluble guanylate cyclase stimulator riociguat. The study enrolled 261 patients with inoperable CTEPH or persistent pulmonary hypertension after surgery. The primary end point was 6-minute walk distance at 12 weeks. The treatment group showed a 46 m improvement ( $P<.001$ ). Secondary end points of pulmonary vascular resistance, NT-proBNP level, and functional class also improved. This pivotal trial led to the FDA approval of riociguat for inoperable or persistent postoperative CTEPH.

MERIT-1, a phase II, randomized placebo-controlled double trial of macitentan (an oral endothelin receptor antagonist) was recently completed. It enrolled 80 patients with inoperable CTEPH. The primary endpoint was pulmonary vascular resistance at week 16, expressed as a percentage of baseline. At week 16, the patients in the treatment arm had a PVR 73% of baseline vs 87.2% in the treatment group. This medication is not yet FDA-approved for the treatment of inoperable CTEPH (Ghofrani H, et al. *Lancet Respir Med.* 2017;5[10]:785-794).

Pulmonary hypertension medication has been postulated as a possible way to “pretreat” patients before pulmonary thromboendarterectomy surgery, perhaps lowering preoperative pulmonary vascular resistance and surgical risk. However, there are currently no convincing data to support this practice, and medical treatment has been associated with a possible counterproductive delay in surgery. A phase II study including CTEPH patients with high PVR for preoperative treatment with riociguat vs placebo is currently enrolling to determine if “induction” treatment with medication prior to surgery reduces risk or delays definitive surgery.

Occasionally, patients are found who have persistent thrombus but not pulmonary hypertension. Chronic thromboembolic disease (CTED) is a recently coined term describing patients who have chronic thromboembolism on imaging but have normal resting hemodynamics. Whether CTED represents simply unresolved clot that will never progress to CTEPH or is an early point on the continuum of disease not well-defined and a controversial topic among experts.

At many centers, patients with CTED and symptoms will undergo exercise testing to look

*Continued on following page*



# Visual abstracts enhance journal readers' experience

BY LISBETH MAXWELL

Managing Editor, CHEST

Physicians' time is decreasingly their own, and, yet, keeping abreast of clinical literature is increasingly more important. The journal *CHEST*® has introduced a new feature aimed at easing that task and broadening the reach of journal content: visual abstracts.

"It's become apparent that *CHEST* needs to make its content even more accessible, as well as available across many platforms," said Christopher Carroll, MD, FCCP, the journal's Web and Multimedia (WMM) Editor. "So we put together a Web and Multimedia team to take on that task.

At the direction of *CHEST* Editor in Chief Richard Irwin, MD, Master FCCP, Dr. Carroll assembled a team to help carry out an ambitious multimedia strategy (see box). Dr. Irwin charged the Web and Multimedia editorial team with not only extending the reach of journal content but also enhancing readers' engagement with and understanding of it.

"Our first project was the devel-

## Blood Test to Rule Out Lung Cancer in Patients with Low to Moderate Probability Nodules

CLINICAL QUESTION	STUDY DESIGN	RESULTS
<p><b>Can a blood test identify benign lung nodules?</b></p> <p>Used <b>Integrated Classifier</b> that combines:</p> <ul style="list-style-type: none"> <li>Relative abundance of two Plasma Proteins <b>LG3BP</b> <b>C163A</b></li> <li>And 5 Clinical Risk Factors</li> </ul>	<p>Prospective Multicenter Observational Study</p> <p><b>178 patients</b> with low to moderate risk nodules (&lt;50% pretest probability of cancer)</p> <p>29 (16%) malignant</p>	<p>Integrated Classifier had</p> <ul style="list-style-type: none"> <li>Sensitivity 97%</li> <li>Specificity 44%</li> <li><b>Negative Predictive Value 98%</b></li> </ul> <p>With clinical use can expect:</p> <ul style="list-style-type: none"> <li><b>40% fewer procedures on benign nodules</b></li> <li><b>3% malignant nodules misclassified</b></li> </ul>

Silvestri G et al. *CHEST* 2018; 154(3): 491-500

Visual Abstract by Roozehra Khan, DO, FCCP

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This is an example of the new infographics being introduced. A full gallery of all the visual abstracts so far is available at <https://journal.chestnet.org/infographics>.

opment of visual abstracts, a type of infographics used to distill the key points of a research abstract into an easily digested graphic form," says Dr. Carroll, who also is research director of pediatric critical care at Connecticut Children's Medical Center, Hartford, and a professor of pediatrics at the University of Connecticut School of

Medicine, Farmington.

The first visual abstracts were posted to accompany two articles in the July 2018 issue of *CHEST*. With the exception of August 2018, every issue since has been enhanced with infographics.

The visual abstracts are available through a number of vehicles: the journal's website (<https://journal.chestnet.org/>), the journal's mobile app (<https://journal.chestnet.org/content/mobileaccessinstructions>), and social media platforms such as Facebook (<https://www.facebook.com/acpcchest/>) and Twitter (<https://twitter.com/acpcchest>).

"Our goal with the infographics is to promote the exciting research *CHEST* publishes and to get readers to click through and read the entire article," says Dr. Carroll. "So far, we're happy with our results—and we're looking forward to even greater reach in 2019."

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Continued from previous page

for exercise induced pulmonary hypertension or an increase in dead space ventilation as a cause of their symptoms. A retrospective series of carefully chosen CTED patients who underwent PTE surgery reported improvements in symptoms and overall quality of life, without increased complications (Taboada D, et al. *Eur Respir J*. 2014 44[6]:1635). The operation carries risk, however, and further work into the epidemiology and prognosis of CTED is required before operative intervention can be recommended.

In conclusion, CTEPH is a disease that rarely occurs after an acute PE but when undiagnosed and untreated portends a poor prognosis. The definitive treatment for this disease is surgical PTE, but to achieve the best outcomes, this procedure needs to be performed at expert centers with multidisciplinary team experience. Patients who are poor operative candidates or with surgically inaccessible disease may be considered for balloon pulmonary angioplasty. For patients without more curative options, medication improves exercise tolerance. The field of CTEPH has been rapidly expanding over the last decade, leading to better patient outcomes and more treatment options.

Dr. Bartolome is Associate Professor, Pulmonary and Critical Care Medicine; Director, CTEPH Program; and Associate Director, PH Program; UT Southwestern Medical Center, Dallas, Texas.

## Meet the CHEST President-Designate

Steven Q. Simpson, MD, FCCP, is a pulmonologist and intensivist with an extensive background in sepsis and in critical care quality improvement. Dr. Simpson acts as a CHEST Regent-at-Large of the Board of Regents, board liaison for the Guidelines Oversight Committee, sits on numerous board task forces and subcommittees and is a member of the CHEST SEEK Critical Care Medicine Editorial Board. He will serve as CHEST President for the 2020-2021 term.

Dr. Simpson is Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the University of Kansas. He is also senior advisor to the Solving Sepsis initiative of the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services.

He has conducted research in all areas of severe sepsis, including molecular and cellular mechanisms, translational, quality improvement, and computer modeling studies.

He was a founder in 2005 of the Midwest Critical Care Collaborative, a multidisciplinary and interprofessional collaborative effort to improve the quality of critical care services throughout the Midwest.

In 2007, he initiated the Kansas Sepsis Project, a statewide program to improve severe sepsis care and outcomes via continuing education both in sepsis and in quality improvement principles

and via interprofessional collaborations. Dr. Simpson is an author of the 2016 and 2020 updates of the Surviving Sepsis Campaign Guidelines. He is a member of the board of directors



Dr. Simpson

and Chief Medical Officer of Sepsis Alliance, a nationwide patient information and advocacy organization.

During his tenure at the University of New Mexico, he contributed to the discovery of a particular form of sepsis, the hantavirus pulmonary syndrome, and published numerous papers on the clinical description, the he-

modynamic description, and the approach to supportive care for patients with the syndrome, including extracorporeal hemodynamic and oxygenation support.

Dr. Simpson has authored over 180 scientific articles, book chapters, editorials, abstracts and electronic media publications. He was awarded the 2009 Eli Lilly Distinguished Scholar in Critical Care Medicine Award of the American College of Chest Physicians and the 2013 Roger C. Bone Memorial Lecture in Critical Care Medicine, which recognizes career contributions to the field. He has also been recognized as a Distinguished CHEST Educator in 2017 and 2018.

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## CRITICAL CARE COMMENTARY

# Renal replacement therapy in the ICU: Vexing questions and team dynamics

BY JAVIER A. NEYRA, MD, MSCS; AND CAROLINE E. HAUSCHILD, RN, BSN

**M**ore than 5 million patients are admitted to ICUs each year in the United States, and approximately 2% to 10% of these patients develop acute kidney injury requiring renal replacement therapy (AKI-RRT). AKI-RRT carries high morbidity and mortality (Hoste EA, et al. *Intensive Care Med.* 2015;41:1411) and is associated with renal and



Dr. Neyra

systemic complications, such as cardiovascular disease. RRT, frequently provided by nephrologists and/or intensivists, is a supportive therapy that can be lifesaving when provided to the right patient at the right time. However, several questions related to the provision of RRT still remain, including the optimal timing of RRT initiation, the development of quality metrics for optimal RRT deliverables and monitoring, and the optimal strategy of RRT de-escalation and risk-stratification of renal recovery. Overall, there is paucity of randomized trials and standardized risk-stratification tools that can guide RRT in the ICU.

## Current vexing questions of RRT deliverables in the ICU

There is ongoing research aiming to answer critical questions that can potentially improve current standards of RRT.

## What is the optimal time of RRT initiation for critically ill patients with AKI?

Over the last 2 years, three randomized clinical trials have attempted to address this important question involving heterogeneous ICU populations and distinct research hypotheses and study designs.

Two of these studies, AKIKI (Gaudry S, et al. *N Engl J Med.* 2016;375:122) and IDEAL-ICU (Barbar SD, et al. *N Engl J Med.* 2018;379:1431) yielded no signif-

icant difference in the primary outcome of 60-day and 90-day all-cause mortality between the early vs delayed RRT initiation strategies, respectively (Table 1). Further, AKIKI showed no difference in RRT dependence at 60 days and higher catheter-related infections and hypophosphatemia in the early initiation arm. It is important to note that IDEAL-ICU was stopped early for futility after the second planned interim analysis with only 56% of patients enrolled (main hypothesis was that early



Ms. Hauschild

RRT initiation reduced 90-day all-cause mortality by 10%).

In contrast, the ELAIN trial (Zarbock A, et al. *JAMA.* 2016;315:2190) showed a significant 90-day mortality reduction (39% vs 55%), reduced RRT need (9 days vs 25 days), and reduced length of stay (51 days vs 82 days) favoring early RRT initiation strategy.

A larger study (STARRT-AKI) addressing this question with a more pragmatic approach (incorporating clinical judgment and equipoise among intensivists and nephrologists for patient eligibility) is underway. However, it is possible that STARRT-AKI will not provide a definitive answer for the inevitable search for implementing RRT initiation protocols in the ICU. Therefore, the scientific community may need to redirect the research focus to risk-stratification tools that can assist in the identification of patients who could benefit from early RRT initiation through an individualized approach rather than a standardized protocol.

## How can RRT deliverables in the ICU be effectively and systematically monitored?

The provision of RRT to ICU patients with AKI requires an iterative adjustment of the RRT prescription and goals of therapy to accommodate changes in the clinical status with emphasis in hemodynamics, multiorgan failure, and fluid

overload (Neyra JA. *Clin Nephrol.* 2018;90:1). The utilization of static and functional tests or point-of-care ultrasonography to assess hemodynamic variables can be useful. Furthermore, the implementation of customized and automated flowsheets in the electronic health record can facilitate remote monitoring. It is, therefore, essential that the multidisciplinary ICU team develops a process to monitor and ensure RRT deliverables. In this context, the standardization and monitoring of quality metrics (dose, modality, anticoagulation, filter life, downtime, etc) and the development of effective quality management systems are critically important. However, big multicenter data are direly needed to provide insight in this arena.

## How can renal recovery be assessed and RRT effectively de-escalated?

The continuous examination of renal recovery in ICU patients with

AKI-RRT is mostly based on urine output trend and, if feasible, interdi-alytic solute control. Sometimes, the transition from continuous RRT to intermittent modalities is necessary in the context of multiorgan recovery and de-escalation of care. However, clinical risk-prediction tools that identify patients who can potentially recover or already exhibit early signs of renal function recovery are needed. Current advances in clinical informatics can help to incorporate time-varying clinical parameters that may be informative for risk-prediction models. In addition, incorporating novel biomarkers of AKI repair and functional tests (eg, furosemide stress test, functional MRI) into these models may further inform these tools and aid the development of clinical decision support systems that enhance interventions to promote AKI recovery (Neyra JA, et al. *Nephron.* 2018;140:99).

*Continued on following page*

TABLE 1

## Comparison between recent randomized clinical trials addressing early vs delayed initiation of RRT in critically ill patients with AKI

Characteristics	AKIKI Trial	ELAIN Trial	IDEAL Trial
Participating sites	31 (France)	1 (Germany)	29 (France)
Total number of participants	620	231	488
Early RRT definition	KDIGO stage 3	KDIGO stage 2	KDIGO stage 3
Delayed RRT definition	BUN >112, K >6, pH <7.15, pulmonary edema, oliguria for >72 h	<12 h KDIGO stage 3 or absolute indications	>48 h KDIGO stage 3 or absolute indications
Timing from randomization to initiation of RRT, median	2 h (early) vs 57 h (delayed)	6 h (early) vs 25.5 h (delayed)	7.6 h (early) vs 51.5 h (delayed)
SOFA score, mean	11	16	12
CKD, %	10	41	15
Septic shock, %	67	32	100
Surgical intervention, %	21	97	-
RRT modality at initiation	HD, SLED, or CRRT	CRRT	HD, SLED, or CRRT
Primary endpoint	60-day mortality	90-day mortality	90-day mortality
Mortality – Early, %	49	39	58
Mortality – Delayed, %	50	55	54
Received RRT in delayed arm, %	51	91	62

Note: KDIGO = Kidney Disease: Improving Global Outcomes; HD = hemodialysis; SLED = sustained low efficiency dialysis.

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### Is post-AKI outpatient care beneficial for ICU survivors who suffered from AKI-RRT?

Specialized AKI survivor clinics have been implemented in some centers. In general, this outpatient follow-up model includes survivors who suffered from AKI stage 2 or 3, some of them requiring RRT, and tailors individualized interventions for post-AKI complications (preventing recurrent AKI, attenuating incident or progressive CKD). However, the value of this outpatient model needs to be further evaluated with emphasis on clinical outcomes (eg, recurrent AKI, CKD, readmissions, or death) and elements that impact quality of life. This is an area of evolving research and a great opportunity for the nephrology and critical care communities to integrate and enhance post-ICU outpatient care and research collaboration.

### Interdisciplinary communication among acute care team members

Two essential elements to provide effective RRT to ICU patients with AKI are: (1) the dynamics of the ICU team (intensivists, ne-

phrologists, pharmacists, nurses, nutritionists, physical therapists, etc) to enhance the delivery of personalized therapy (RRT candidacy, timing of initiation, goals for solute control and fluid removal/regu-

lation, renal recovery evaluation, RRT de-escalation, etc.) and (2) the frequent assessment and adjustment of RRT goals according to the clinical status of the patient. Therefore, effective RRT provision in the ICU requires the development of optimal channels of communication among all members of the acute care team and the systematic monitoring of the clinical status of the patient and RRT-specific goals and deliverables.

### Perspective from a nurse and quality improvement officer for the provision of RRT in the ICU

The provision of continuous RRT (CRRT) to critically ill patients

requires close communication between the bedside nurse and the rest of the ICU team. The physician typically prescribes CRRT and determines the specific goals of therapy. The pharmacist works

*Clinical risk-prediction tools that identify patients who can potentially recover or already exhibit early signs of renal function recovery are needed.*

closely with the nephrologist/intensivist and bedside nurse, especially in regards to customized CRRT solutions (when indicated) and medication dosing. Because CRRT can alter drug pharmacokinetics, the pharmacist closely and constantly monitors the patient's clinical status, CRRT prescription, and all active medications. CRRT can also affect the nutritional and metabolic status of critically ill patients; therefore, the input of the nutritionist is necessary. The syndrome of ICU-acquired weakness is commonly encountered in ICU patients and is related to physical immobility. While ICU patients with AKI are already at risk for

decreased mobility, the continuous connection to an immobile extracorporeal machine for the provision of CRRT may further contribute to immobilization and can also preclude the provision of optimal physical therapy. Therefore, the bedside nurse should assist the physical therapist for the timely and effective delivery of physical therapy according to the clinical status of the patient.

The clinical scenarios discussed above provide a small glimpse into the importance of developing an interdisciplinary ICU team caring for critically ill patients receiving CRRT. In the context of how integral the specific role of each team member is, it becomes clear that the bedside nurse's role is not only to deliver hands-on patient care but also the orchestration of collaborative communication among all health-care providers for the effective provision of CRRT to critically ill patients in the ICU.

*Dr. Neyra and Ms. Hauschild are with the Department of Internal Medicine; Division of Nephrology; Bone and Mineral Metabolism; University of Kentucky; Lexington, Kentucky.*

## 2019 GRANTS CYCLE

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# Secure a CHEST Foundation research award

In anticipation of the 2019 CHEST Foundation grants cycle, opening in late February, CHEST Foundation staff sat down with 2017 CHEST Foundation Community Service grant winner, Sharon Armstead, RRT, Director of



Clinical Education & Clinical Assistant Professor for the Department of Respiratory Care at Texas State University, to learn more about her project supporting respiratory asthma clinics in Guyana.

Ms. Armstead's program takes respiratory care students from her institution on a study abroad trip to Guyana with aims to educate Guyanese student populations about asthma and teach them self-management skills. Additionally, she and her students work alongside clinicians at Georgetown Public Hospital to host a mobile asthma clinic that provides asthma screenings and education for Guyanese students, the first of its kind at Texas State University.

This passion for supporting clinics in Guyana stems from a deeply personal place. "Guyana is my country of birth. I left when I was 14. I came back many years later realizing that I can give back to the county that gave me so much." Ms. Armstead shared.



Sharon Armstead, RRT (second from right), and her students with members of the Georgetown Public Hospital Corporation (GPHC) COPD/Asthma Team in Guyana.

"The CHEST Foundation grant opened doors for me that had never been opened before. Members of the community were very open to hearing what we had to say and receptive to the changes we suggested they make in their daily lives. The financial portion of the award allowed me to purchase additional spirometers for the asthma clinic, allowing for a whole new level of outpatient testing and outreach in the community."

In addition to the impact she and her students have in Georgetown, Ms. Armstead says opportunity provided to her students was life-changing for them. "To watch my students communicate with

people in a different country really helps build their confidence as future clinicians." Her study program received a significant growth in attendance over the past few years. "When we first started doing this study abroad in Guyana, I only had 2 students interested... We took 14 respiratory care students to Guyana in 2017. It's really elevated this study abroad pro-

gram at my institution."

The CHEST Foundation's grants cycle opens in late February. Visit our grants page (<https://foundation.chestnet.org/grants/apply-for-a-grant/>) to view the RFPs for our 2019 offerings and see a step-by-step walkthrough of how simple it is to apply for funding! Be a champion of lung health, and secure your research award today!

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## CHEST NETWORKS

# Five steering committees examine the literature

## Clinical Pulmonary Medicine Asthma-COPD overlap: An underappreciated phenotype of obstructive airway disease (OAD)

Asthma-COPD overlap (ACO) is a common yet underappreciated clinical entity within the complex OAD spectrum. Currently, there is no consensus criteria to define ACO; however, a roundtable consensus from an international group (Sin, et al. *Eur Respir J*. 2016; 48:664) suggests using major and minor criteria, with key features being airflow limitation, asthma history, and cigarette or biomass exposure. Several studies have shown that patients with ACO have severe disease, faster lung function decline, greater morbidity and mortality, and lower QoL (Alshabanat, et al. *PLoS One*. 2015;10:e0136065).

There is paucity of data on the pathophysiology, risk factors, and clinical management given exclusion of these patients from clinical trials of asthma and COPD. Indeed, clinicians and researchers now realize

that ACO is an umbrella term for multiple subphenotypes, including patients who have predominant asthma with some COPD features and others with predominant COPD with some asthma features. Overall, IgE level, FeNO, sputum, and blood eosinophils are usually higher in ACO than in COPD and relatively similar compared with asthma (Kobayashi, et al. *Int J Chron Obs Pulmon Dis*. 2016; 11:2117).

Most recently, a longitudinal study looked at predictors of ACO among NY firefighters exposed to WTC dust (Singh, et al. *CHEST*. 2018; 154[6]:1301). Pre-exposure low lung function and elevated blood eosinophils and IL4 (T2 inflammatory cytokine) increased risk of developing ACO among those exposed to WTC dust. Further research is required to better understand the interaction of environmental exposure and risk factors in the pathophysiology of ACO. It may be more pragmatic to use the unifying term OAD, as originally proposed in the Dutch hypothesis, and further delineate how



Dr. Luthra



Dr. D'Annunzio

several phenotypes of airway disease can be classified by combining traditional approaches with molecular and genomic analysis.

Munish Luthra, MD, FCCP  
Steering Committee Member

Samantha D'Annunzio, MD  
Steering Committee Member

## Airways Disorders Defining and treating early COPD: Can we make a difference?

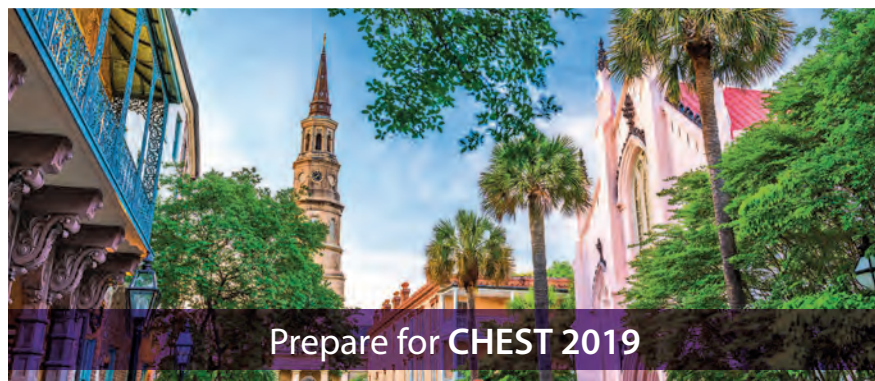
There is growing evidence that early COPD—before currently accepted spirometric or symptomatic criteria are present—may be an important

clinical entity. The primary pathobiologic mechanisms in early COPD development include both abnormal lung development and accelerated lung aging (Augustí. *Am J Respir Crit Care Med*. 2018;198[8]:987).

Martinez and colleagues recently proposed defining early COPD as age <50 with 10+ pack-year smoking history and at least one of the following: (1) early airflow limitation (postbronchodilator FEV<sub>1</sub>/FVC < lower limit of normal), (2) compatible CT scan abnormalities, (3) rapid decline in FEV<sub>1</sub> (≥60 mL/yr) that is accelerated relative to FVC (Martinez et al. *Am J Respir Crit Care Med*. 2018;197[12]:1540).

A novel multiresolution CT scan imaging protocol described by Koo and coworkers found that substantial loss of small airways—specifically the terminal and transitional bronchioles—occurs in patients with mild-to-moderate COPD even prior to the development of emphysema on CT scan. These findings show that significant destruction of the

*Continued on following page*



## Prepare for CHEST 2019

### Call for Abstracts, Case Reports, and Case Puzzlers

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Submit an abstract of original investigative work for consideration as a slide, poster, or poster discussion.

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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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Submit clinical case puzzlers that highlight an interesting teaching point in chest radiology for oral presentation during an interactive clinical case puzzler session.

For more information visit: [bit.ly/CallForAbstracts-CaseReports](http://bit.ly/CallForAbstracts-CaseReports)

### Call for Moderators and Graders

CHEST is currently calling for graders to review and grade the abstract and case report submissions for this year's annual meeting and requesting moderators to facilitate discussions, questions, and answers on-site at CHEST 2019 in New Orleans. Grading will take place March 18 to April 5. Moderators will be notified June to September of their acceptance as a moderator.

For more information, visit: [bit.ly/2019GradersAndModerators](http://bit.ly/2019GradersAndModerators)

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# This month in the journal **CHEST**®

## Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

**Giants in Chest Medicine – Atul C. Mehta, MBBS, FCCP**  
By Dr. J. K. Stoller

**Screening Heroin Smokers Attending Community Drug Services for COPD.**  
By Dr. H. Burhan, et al.

**The NHLBI LAM Registry: Prognostic Physiologic and Radiologic Biomarkers Emerge From a 15-Year Prospective Longitudinal Analysis.**  
By Dr. N. Gupta, et al.

**Indwelling Pleural Catheters in Hepatic Hydrothorax: A Single-Center Series of Outcomes and Complications.**  
By Dr. C. Kniese, et al.

**Implications of the Revised Common Rule for Human Participant Research.**  
By Dr. E. G. DeRenzo, et al.

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small airways has occurred prior to the development of mild COPD (Koo, et al. *Lancet Respir Med.* 2018;6:591).

Pharmacologic treatment for COPD is targeted at the reduction of symptoms and risk of exacerbation, as there remains no conclusive evidence that existing therapies modify long-term decline in lung function. It is unknown if pharmacotherapy for “early COPD” will alter the disease course. While not directly addressing this subset, information may be gleaned from trials on younger, more mild GOLD stage 1 or stage 2 patients.

The Tie-COPD trial, the largest powered study to date of mild-to-moderate COPD, found



Dr. Conroy



Dr. Blaivas

that among patients with GOLD stage 1 or 2 COPD treatment with tiotropium compared with placebo for 2 years resulted in significantly higher FEV<sub>1</sub> before bronchodilator use (between group difference of 157 mL) and slowed annual decline in FEV<sub>1</sub> after bronchodilator use (Zhou, et al. *N Engl J Med.* 2017;377[10]:923).

As our understanding of heterogeneity within COPD increases, striving for improved outcomes from our therapies—an impact on lung function in addition to symptom and exacerbation risk—may need to begin with the study of earlier treatment.

Megan Conroy, MD  
Steering Committee  
Fellow-in-Training

Allen J. Blaivas, DO, FCCP  
Steering Committee Vice-Chair

### Critical Care

#### Mechanical ventilation: One size fits all?

Mechanical ventilation (MV) is a life-saving intervention in the ICU, but it has been associated with numerous complications ranging from overuse of sedation, atelectasis, and baro or volutrauma. After 2000, it became well known that using a low tidal volume (VT) strategy (6 mL/kg predicted body weight, PBW) in patients

with ARDS produced lower mortality and more ventilator-free days (*N Engl J Med.* 2000;342[18]:1301). In addition, a meta-analysis in 2012 demonstrated a lower relative risk



Dr. Disselkamp



Dr. Megri

of new lung injury, mortality, and pulmonary infections with low VT in non-ARDS patients (*JAMA.* 2012;308[16]:1651). However, the included studies varied widely in their use of VT (9-12 mL/kg), duration of MV, and in mixed settings (ICU or operating room).

Recently, a large randomized clinical trial compared the effect of low (4-6 mL/kg, PBW) vs intermediate (8-10 mL/kg, PBW) VT ventilation strategy in non-ARDS ICU patients. Interestingly, the study concluded that there is no significant difference in ventilator-free days (21 days in each group), median length ICU and hospital stay, ICU mortality rates, and 28- and 90-day mortality. Also, there was no difference in new-onset ARDS, severe atelectasis, sedation use, and delirium (*JAMA.* 2018; 320[18]:1872). This study suggests that in non-ARDS patients, MV should be individualized according to each patient's clinical situation, the nature of the disease, and its effect on lung mechanics, especially in patients who cannot tolerate low tidal volumes.

Margaret A. Disselkamp, MD  
Steering Committee Member

Mohammed A. Megri, MD  
Steering Committee  
Fellow-in-Training

### Interstitial and Diffuse Lung Disease

#### Idiopathic pneumonias that are not all that idiopathic

Despite being defined as an individual entity for research purposes in 2015 (Fisher, et al. *Eur Respir J.* 2015;46:976), interstitial pneumonias with autoimmune features (IPAF) remain a heterogeneous group of interstitial lung diseases that puzzle the clinician. Since the introduction of the IPAF definition, there have been attempts to validate the diagnostic criteria

and study their prognostic implications. Some of these studies showed differential prognosis in patients who met the IPAF criteria (Oldham, et al. *Eur Respir J.* 2016;47:1767).

Although the implications of the presence of autoimmune antibodies in idiopathic interstitial pneumonias (IIPs) is not fully understood, the treatment often entails immunosuppression, especially in those with non-UIP patterns of disease and/or clinical features of autoimmune disease. The stakes are high when IIPs are associated with antibodies correlated with rapidly progressive disease, such as MDA-5 antibody or anti-synthetase antibodies.



Dr. Wynn

Pulmonologists often lack the clinical expertise to detect occult autoimmune disorders, though the role of the rheumatologist in facilitating the diagnosis and treatment of IPAF is not well delineated. Most health-care systems are not equipped with collaborative ILD-rheumatology clinics or even easy access to a rheumatologist. There is a need for real-world pragmatic studies to establish the optimal way to evaluate patients with ILD for autoimmune features and identify patients who would benefit most from an early referral to rheumatology to aid with diagnosis, treatment, and sometimes monitoring for extrapulmonary manifestations of autoimmune disorders.

Avanthika Thanushi Wynn, MD  
Steering Committee  
Fellow-in-Training

### Home-Based Mechanical Ventilation and Neuromuscular Disease Improving access to sleep medicine care for patients with NMD

Sleep-disordered breathing (SDB) occurs in up to 5% of children, with adverse implications for growth and development. Children with neuromuscular disease are at significantly higher risk than unaffected children (Chiang, et al. *Children.* 2018;5:e78). Respiratory dysfunction that may present as SDB before daytime impairment in gas exchange is evident. Diagnosing and treating

SDB (to include OSA, CSA, and hypoventilation syndromes) early can significantly improve morbidity and mortality.

Unfortunately, diagnostic sleep



Dr. Collen

medicine resources are limited. Children may wait up to a year or more for definitive testing with in-laboratory, attended polysomnography (PSG). Among children with neuromuscular disease, fewer than 10% may undergo a sleep clinic evaluation, and, of those who do, they may have only one visit over a 3-year period of care (Rose, et al. *Pediatr Pulmonol.* 2018;53:1378). Home sleep testing (HST) has been evaluated as an alternative to PSG given lower cost, availability, and advantage of the child sleeping in his/her own bed. Although HST is indicated in adults with a high pretest probability for moderate to severe OSA, it is not indicated in children, given the potential to underestimate disease severity or to miss the diagnosis entirely (Kirk, et al. *J Clin Sleep Med.* 2017;13[10]:1199). HST lacks electroencephalogram (EEG) and capnography. Technical recording mishaps are more common in children, but in-lab PSG has the advantage of on-site troubleshooting by a technologist. A recently published study by Fishman and colleagues attempted to compare gold standard in-lab PSG to HST with capnography (Fishman, et al. *J Clin Sleep Med.* 2018;14(12):2013). Despite a well-designed study with a carefully selected population, HST failed to reliably diagnose SDB. HST underestimated disease severity and, in some cases, missed the diagnosis of SDB entirely. The addition of end tidal CO<sub>2</sub> monitoring failed to improve diagnostic accuracy, and HST and PSG-ETCO<sub>2</sub> values were poorly correlated.

Although children with neuromuscular disease face long wait times for sleep evaluations, HST is clearly not the solution for now. It remains to be seen if innovations in HST with extended monitoring (and transcutaneous CO<sub>2</sub>) become viable. In the meantime, finding ways to improve access to sleep medicine care for children with neuromuscular disease is a must.

Jacob Collen, MD, FCCP  
Steering Committee Member

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*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

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