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CHEST® Physician

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China News Service/CC BY 3.0

Medical workers screened thousands of travelers at Wuhan train stations for symptoms of 2019-nCoV infection until the Chinese government canceled planes and trains leaving the city.

2019 Novel Coronavirus: What clinicians need to know

BY M. ALEXANDER OTTO
MDedge News

As the 2019 Novel Coronavirus story unfolds, the most important thing for clinicians in the United States to do is ask patients who appear to have the flu if they, or someone they have been in contact with, recently returned from China, according to infectious disease experts.

"We are asking that of everyone with fever and respiratory symptoms who comes to our clinics, hospital, or emergency room. It's a powerful screening tool," said William Schaffner, MD, professor of preventive medicine and infectious diseases at Vanderbilt University Medical Center, Nashville, Tenn., and adviser to the Centers for Disease Control and Prevention (CDC).

In addition to fever, common signs of infection include cough, shortness of breath, and breathing difficulties. A few patients in Wuhan, China, the epicenter of the outbreak, have had diarrhea, vomiting, and other gastrointestinal symptoms. In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death. The incubation period appears to be up to 2 weeks, according to the World Health Organization (WHO).

If patients exhibit symptoms and either they or a close contact has returned from China recently, take standard airborne precautions and send specimens – a serum sample, oral and nasal pharyngeal swabs, and lower respiratory tract

CORONAVIRUS // *continued on page 7*

Fewer lung cancer deaths lead to record drop in overall cancer mortality

BY ANDREW D. BOWSER
MDedge News

Declines in death rates for lung cancer and melanoma have gained momentum in recent years, fueling a record drop in cancer mortality, the American Cancer Society says.

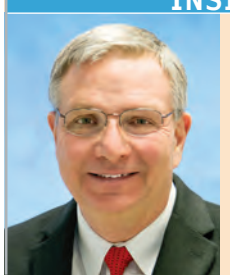
Lung cancer death rates, which were falling by 3% in men and 2% in women annually in 2008 through 2013, dropped by 5% in men and nearly 4% per year in women annually from 2013 to 2017, according to the society's 2020 statistical report.

Those accelerating reductions in death rates helped fuel the biggest-ever single-year decline in overall cancer mortality, of 2.2%, from 2016 to 2017, their report shows.

According to Rebecca L. Siegel and coauthors, the decline in melanoma death rates escalated to 6.9% per year among 20- to 49-year-olds over 2013-2017, compared with a decline of just 2.9% per year during 2006-2010. Likewise, the melanoma death rate decline was 7.2% annually

MORTALITY // *continued on page 6*

INSIDE HIGHLIGHT



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Indication

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

Select Important Safety Information

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

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

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

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

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

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

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

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

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.

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In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF[1–4]*

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More than 42,000 patients have taken pirfenidone worldwide[4§]

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

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

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

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

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

References: 1. Esbriet Prescribing Information. Genentech, Inc. July 2019. **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. 2019.

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

IPF=idiopathic pulmonary fibrosis.

*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).[1] In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide ($\%DL_{CO}$) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.[2] In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{CO}$ ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{CO}$ ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.[3] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[1,2] Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).[1,3,4] **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.[1,3]**

†Serious adverse reactions, including elevated liver enzymes and drug-induced liver injury, 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).[1]

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

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[1]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

NTM lung disease incidence, prevalence on the rise

BY STEVE CIMINO
MDedge News

A new study of claims-based data has found that the incidence and prevalence of nontuberculous mycobacterial (NTM) lung disease is increasing in most states.

To assess the NTM lung disease burden on a national level, Kevin L. Winthrop, MD, of Oregon Health & Science University, Portland, and associates analyzed patient data from a U.S. managed care claims database between 2008 and 2015. Their findings were published in the Annals of the American Thoracic Society.

A case of NTM lung disease was defined as a patient with at least two medical claims with the disease's diagnostic codes – 031.0 and A31.0 – that were at least 30 days apart. Of the 74,984,596 ben-

eficiaries in the database, 9,476 met the case definition for NTM lung disease; 69% (n = 6,530) were women.

From 2008 to 2015, the annual incidence of NTM lung disease increased from 3.13 (95% confidence interval, 2.88-3.40) to 4.73 (95% CI, 4.43-5.05) per 100,000 person-years, with the average rate of yearly change being +5.2% (95% CI, 4.0%-6.4%; *P* less than .01). The annual prevalence increased from 6.78 (95% CI, 6.45-7.14) to 11.70 (95% CI, 11.26-12.16) per 100,000 persons, with the average rate of yearly change being +7.5% (95% CI, 6.7-8.2%; *P* less than .01).

Dr. George Kubica/CDC

The majority of NTM lung disease in the United States is caused by *Mycobacterium avium* complex (17), although other species such as *M. abscessus*, *M. kansasii*, *M. xenopi*, and others contribute to this disease burden.

The authors acknowledged their study's limitations, including the lack of microbiologic or radiographic confirmation of the NTM infection and the inherent shortcomings of claims data–based studies overall. They did note a previous report, however, that "claims-based case identification has a high positive predictive value of approximately 82% for NTM lung disease."

The study was funded by Insmed; the Intramural Research Programs of the National Institute of Allergy and Infectious Diseases; and the National Heart, Lung, and Blood Institute. The authors reported no conflicts of interest.

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SOURCE: Winthrop KL et al. Ann Am Thorac Soc. 2019 Dec 13. doi: 10.1513/AnnalsATS.201804-236OC.

VIEW ON THE NEWS

Sachin Gupta, MD, FCCP, comments: It's a classic chicken-or-egg scenario in regard to the rising numbers. Increased awareness of NTM lung disease is, in part, why we're seeing prevalence and incidence go up. And yet the disease itself may also be growing in clusters and pockets, as the data show, in various places across the country. The worrisome aspect here is that future studies will likely show that, as incidence is increasing, mortality is increasing as well. That speaks to the challenges with these bugs: very hard to diagnose, very hard to treat.

LDCT scans key to mortality decline // *continued from page 1*

for the more recent time period, compared with just 1.3% annually in the earlier time period. The finding was even more remarkable for those 65 years of age and older, according to investigators, since the declines in melanoma death rates reached 6.2% annually, compared with a 0.9% annual increase in the years before immunotherapy.


Dr. Fontaine


Dr. Patel

Smoking cessation has been the main driver of progress in cutting lung cancer death rates, according to the report, while in melanoma, death rates have dropped after the introduction of immune checkpoint inhibitors and targeted therapies.

By contrast, reductions in death rates have slowed for colorectal cancers and female breast cancers, and have stabilized for prostate cancer, Ms. Siegel and coauthors stated, adding that racial and geographic disparities persist in preventable cancers, including those of the lung and cervix.

"Increased investment in both the equitable application of existing cancer control interventions and basic and clinical research to further advance treatment options would undoubtedly accelerate progress against cancer," said the investigators. The report appears in CA: A Cancer Journal for Clinicians.

While the decline in lung cancer death rates is good news, the disease remains a major killer, responsible for more deaths than breast, colorectal, and ovarian cancer combined, said Jacques P. Fontaine, MD, FCCP, a thoracic surgeon at Moffitt Cancer Center in Tampa.

"Five-year survival rates are still around the 18%-20% range, which is much lower than breast and prostate cancer," Dr. Fontaine said in an interview. "Nonetheless, we've made a little dent in that, and we're improving."

Two other factors that have helped spur that improvement, according to Dr. Fontaine, are the reduced incidence of squamous cell carcinomas, which are linked to smoking, and the increased use of lung cancer screening with low-dose computed tomography.

Squamous cell carcinomas tend to be central rather than peripheral, which makes the tumors harder to resect: "Surgery is sometimes not an option, and even to this day in 2020, the single most effective treatment for lung cancer remains surgical resection," said Dr. Fontaine.

Likewise, centrally located tumors may preclude giving high-dose radiation and may result in more "collateral damage" to healthy tissue, he added.

Landmark studies show that low-dose CT scans reduce lung cancer deaths by 20% or more; however, screening can have false-positive results that lead to unnecessary biopsies and other harms, suggesting that the procedures should be done in centers of excellence that provide high-quality, responsible screening for early lung cancer, Dr. Fontaine said.

While the drop in melanoma death rates is encouraging and, not surprising in light of new cutting-edge therapies, an ongoing unmet treatment need still exists, according to Vishal Anil Patel, MD, director of cutaneous oncology at the George Washington Cancer Center.

Response rates remain lower from other cancers, sparking interest in combining current immunotherapies with costimulatory molecules that may further improve survival rates, according to Dr. Patel.

In 2020, 606,000 cancer deaths are projected, according to the report. Of those deaths, nearly 136,000 are attributable to cancers of the lung and bronchus, while melanoma accounts for nearly 7,000 deaths.

The report notes that variation in cancer incidence reflects geographical differences in medical detection practices and the prevalence of risk factors, such as smoking, obesity, and other health behaviors. "For example, lung cancer incidence and mortality rates in Kentucky, where smoking prevalence was historically highest, are 3 to 4 times higher than those in Utah, where it was lowest," the investigators wrote.

Cancer mortality rates have fallen 29% since 1991, translating into 2.9 million fewer cancer deaths, the report says.

Ms. Siegel and coauthors are employed by the American Cancer Society, which receives grants from private and corporate foundations, and their salaries are solely funded through the American Cancer Society, according to the report.

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SOURCE: Siegel RL et al. CA Cancer J Clin. 2020;70(1):7-30. doi: 10.3322/caac.21590.

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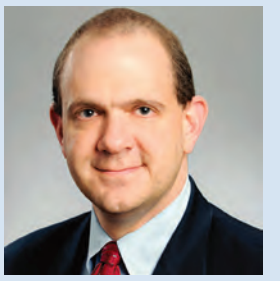
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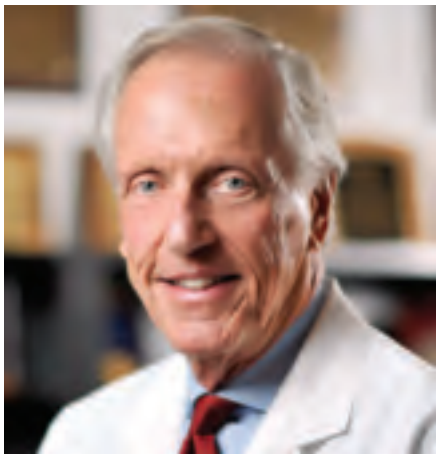
Clinicians should have a plan for responding to a coronavirus case // continued from page 1

specimens if available – to the local health department, which will forward them to the CDC for testing. Turnaround time is 24-48 hours.

The 2019 Novel Coronavirus (2019-nCoV), identified as the



Dr. William Shaffner

cause of an outbreak of respiratory illness first detected in December in association with a live-animal market in Wuhan, has been implicated in almost 2,000 cases and 56 deaths in that country. Cases have been reported in 13 countries besides China. Five cases of 2019-nCoV infection have been confirmed in the United States, all in people recently returned from Wuhan. As the virus spreads in China, however, it's almost certain more cases will show up in the United States. Travel history is key, Dr. Schaffner and others said.

Plan and rehearse

The first step to prepare is to use the CDC's Interim Guidance for Healthcare Professionals to make a written plan specific to your practice to respond to a potential case. The plan must include notifying the local health department, the CDC liaison for testing, and tracking down patient contacts.

"It's not good enough to just download CDC's guidance. Use it to make your own local plan and know what to do 24/7," said Daniel Lucey, MD, an infectious disease expert at Georgetown University Medical Center, Washington.

Know who is on call at the health department on weekends and nights, he recommended. Know where the patient is going to be isolated; figure out what to do if there's more than one, and tests come back positive. Have masks on hand, and rehearse the response. "Make a coronavirus team, and absolutely have the nurses involved," as well as other providers who may come into contact with a case, he added.

"You want to be able to do as well as your counterparts in Washington state and Chicago," where the two U.S. cases emerged. "They were prepared. They knew what to do," Dr. Lucey said.

Those first two U.S. patients – a man in Everett, Wash., and a Chicago woman – developed symptoms after returning from Wuhan, a city of 11 million just over 400 miles inland from the port city of Shanghai. On Jan. 26 three more cases were confirmed by the CDC, two in California and one in Arizona, and each had recently traveled to Wuhan. All five patients remain hospitalized, and there's no evidence they spread the infection further. There is also no evidence of human-to-human transmission of other cases exported from China to any other countries, according to the WHO.

What we know today might change tomorrow, so we have to keep tuned in to new information, but we learned a lot from SARS.

WHO declined to declare a global health emergency – a Public Health Emergency of International Concern, in its parlance – on Jan. 23. The step would have triggered travel and trade restrictions in member states, including the United States. For now, at least, the group said it wasn't warranted.

Fatality rates

The focus right now is China. The outbreak has spread beyond Wuhan to other parts of the country, and there's evidence of fourth-generation spread.

Transportation into and out of Wuhan and other cities has been curtailed, Lunar New Year festivals have been canceled, and the Shanghai Disneyland has been closed, among other measures taken by Chinese officials.

The government could be taking drastic measures in part to prevent the public criticism it took in the early 2000s for the delayed response and lack of transparency during the global outbreak of another wildlife-market coronavirus epidemic, severe acute respiratory syndrome (SARS). In a press conference Jan. 22, WHO officials commended the government's containment efforts but did not say they recommended them.

According to WHO, serious cases in China have mostly been in people over 40 years old with significant comorbidities and have skewed toward men. Spread seems to be limited to family members, health care providers, and other close contacts, probably by respiratory droplets. If that pattern holds, WHO officials said, the outbreak is containable.

Dr. Daniel Lucey

The fatality rate appears to be around 3%, a good deal lower than the 10% reported for SARS and much lower than the nearly 40% reported for Middle East respiratory syndrome (MERS), another recent coronavirus mutation from the animal trade.

The 2019-nCoV fatality rate might drop as milder cases are detected and added to the denominator. "It definitely appears to be less severe than SARS and MERS," said Amesh Adalja, MD, an infectious disease physician in Pittsburgh and emerging infectious disease researcher at Johns Hopkins University, Baltimore.

SARS: Lessons learned

In general, the world is much better equipped for coronavirus outbreaks than when SARS, in particular, emerged in 2003.

WHO officials in their press conference lauded China for it openness with the current outbreak, and for isolating and sequencing the virus immediately, which gave the world a diagnostic test in the first days of the outbreak, something that wasn't available for SARS. China and other countries also are cooperating and working closely to contain the 2019-nCoV.

Know who is on call at the health department on weekends and nights. Know where the patient is going to be isolated; figure out what to do if there's more than one.

"What we know today might change tomorrow, so we have to keep tuned in to new information, but we learned a lot from SARS," Dr. Shaffner said. Overall, it's likely "the impact on the United States of this new coronavirus is going to be trivial," he predicted.

Dr. Lucey, however, recalled that the SARS outbreak in Toronto in 2003 started with one missed case. A woman returned asymptomatic from Hong Kong and spread the infection to her family members before she died. Her cause of death wasn't immediately recognized, nor was the reason her family members were sick, since they hadn't been to Hong Kong recently.

The infection ultimately spread to more than 200 people, about half of them health care workers. A few people died.

If a virus is sufficiently contagious, "it just takes one. You don't want to be the one who misses that first patient," Dr. Lucey said.

Currently, there are no antivirals or vaccines for coronaviruses; researchers are working on both, but for now, care is supportive.

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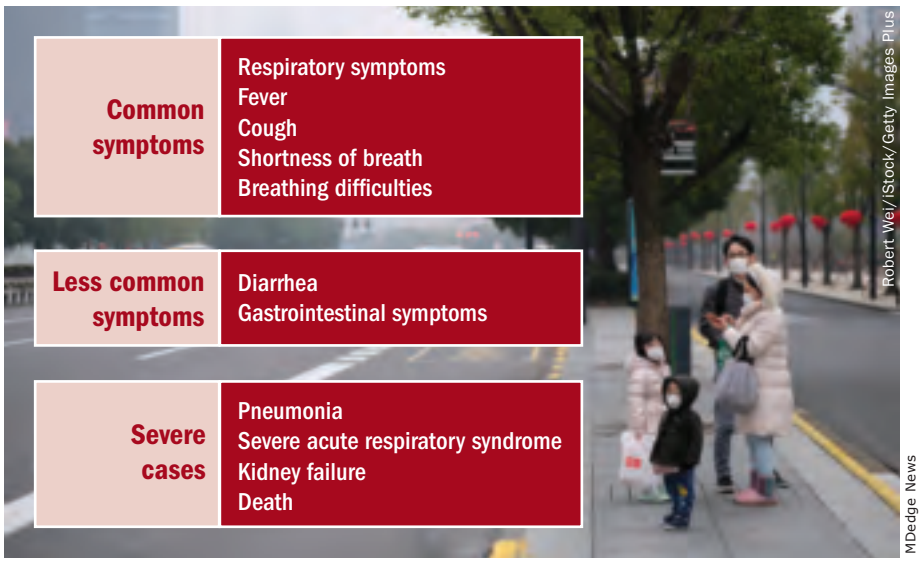
Symptoms of the 2019 Novel Coronavirus



Source: World Health Organization, Lancet 2020 Jan 24. doi: 10.1016/S0140-6736(20)30183-5

Dual e-cigarette and combustible tobacco use: Common, linked to extra respiratory disease risk

BY JEFF CRAVEN
MDedge News


AndreyPopov/Getty Images

E-cigarette use is significantly and independently associated with an increased risk of respiratory disease, according to a recent longitudinal analysis published in the American Journal of Preventive Medicine.

E-cigarettes have been promoted as a safer alternative to combustible tobacco, and until recently, there has been little and conflicting evidence by which to test this hypothesis. This study conducted by Dharma N. Bhatta, PhD, and Stanton A. Glantz, PhD, of the Center for Tobacco Control Research and Education at the University of California, San Francisco, is one of the first longitudinal examinations of e-cigarette use that controls for combustible tobacco use.

Dr. Bhatta and Dr. Glantz performed a multivariable, logistic regression analysis of adults enrolled in the nationally representative, population-based, longitudinal Population Assessment of Tobacco and Health study. The researchers analyzed the tobacco use of adults in the study in three waves, following them through wave 1 (September 2013 to December 2014), wave 2 (October 2014 to October 2015), and wave 3 (October 2015 to October 2016), analyzing the data between 2018 and 2019. Overall, wave 1 began with 32,320 participants, and 15.1% of adults reported respiratory disease at baseline.


Dr. Farber

Lung or respiratory disease was assessed by asking participants whether they had been told by a health professional that they had chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma. The researchers defined e-cigarette and combustible tobacco use as participants who never, currently, or formerly used e-cigarettes or smoked combustible tobacco. Participants who indicated they used e-cigarettes or combustible tobacco frequently or infrequently were placed in the current-user group, while past users were those participants who said they used to, but no longer use e-cigarettes or combustible tobacco.

The results showed former e-cigarette use (adjusted odds ratio, 1.34; 95% confidence interval, 1.23-1.46) and current e-cigarette use (aOR, 1.32; 95% CI, 1.17-1.49) were associated with an increased risk of having incident respiratory disease.

The data showed a not unexpected statistically significant association between former combustible tobacco use (aOR, 1.29; 95% CI, 1.14-1.47) as well as current combustible tobacco use (aOR, 1.61; 95% CI, 1.42-1.82) and incident respiratory disease risk.

There was a statistically significant association between respiratory disease and former or current e-cigarette use for adults who did not have respiratory disease at baseline, after adjusting for factors such as current combustible tobacco use, clinical variables, and demographic differences. Participants in wave 1 who reported former (aOR, 1.31; 95% CI, 1.07-1.60) or current (aOR, 1.29; 95% CI, 1.03-1.61) e-cigarette use had a significantly higher risk of developing incident respiratory disease in subsequent waves. There was also a statistically significant association between use of combustible tobacco and subsequent respiratory disease in later waves of the study (aOR, 2.56; 95% CI, 1.92-3.41), which the researchers noted was independent of the usual risks associated with combustible tobacco.

The investigators also looked at the link between dual use of e-cigarettes and combustible tobacco and respiratory disease risk. "The much more common pattern is dual use, in which an e-cigarette user continues to smoke combusted tobacco products at the same time (93.7% of e-cigarette users at wave 2 and 91.2% at wave 3 also used combustible tobacco; 73.3% of e-cigarette users at wave 2 and 64.9% at wave 3 also smoked cigarettes)," they wrote.

The odds of developing respiratory disease for participants who used both e-cigarettes and combustible tobacco were 3.30, compared with a participant who never used e-cigarettes, with similar results seen when comparing e-cigarettes and cigarettes.

"Although switching from combustible tobacco, including cigarettes, to e-cigarettes theoretically could reduce the risk of developing respiratory disease, current evidence indicates a high prevalence of dual use, which is associated with increased risk beyond combustible tobacco use," the investigators wrote.

Harold J. Farber, MD, FCCP, professor of pediatrics in the pulmonary section at Baylor College of Medicine and Texas Children's Hospital, both in Houston, said in an interview that the increased respiratory risk among dual users, who are likely using e-cigarettes and combustible tobacco together as a way to quit smoking, is particularly concerning.

"There is substantial reason to be concerned about efficacy of electronic cigarette products. Real-world observational studies have shown that, on average, tobacco smokers who use electronic cigarettes are less likely to stop smoking than those who do not use electronic cigarettes," he said. "People who have stopped tobacco smoking but use electronic cigarettes are more likely to relapse to tobacco smoking than those who do not use electronic cigarettes."

Dr. Farber noted that there are other Food and Drug Administration–approved medications for treating tobacco addiction. In addition, the World Health Organization, American Medical Association, Centers for Disease Control and Prevention, and FDA have all advised that e-cigarettes should not be used as smoking cessation aids, he said, especially in light of current outbreak of life-threatening e-cigarette and vaping lung injuries currently being investigated by the CDC and FDA.

"These study results suggest that the CDC reports of e-cigarette, or vaping, product use–associated lung injury are likely to be just the tip of the iceberg," he said. "Although the CDC has identified vitamin E acetate–containing products as an important culprit, it is unlikely to be the only one. There are many substances in the emissions of e-cigarettes that have known irritant and/or toxic effects on the airways."

Dr. Bhatta and Dr. Glantz acknowledged several limitations in their analysis, including the possibility of recall bias, not distinguishing between nondaily and daily e-cigarette or combustible tobacco use, and combining respiratory conditions together to achieve adequate power. The study shows an association, but the mechanism by which e-cigarettes may contribute to the development of lung disease remains under investigation.

This study was supported by grants from the National Institute on Drug Abuse; the National Cancer Institute; the FDA Center for Tobacco Products; the National Heart, Lung, and Blood Institute; and the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center Global Cancer Program. Dr. Bhatta and Dr. Glantz reported no relevant conflicts of interest.

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SOURCE: Bhatta DN, Glantz SA. Am J Prev Med. 2019 Dec 16. doi: 10.1016/j.amepre.2019.07.028.

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Cannabis users struggle to quit cigarettes

BY HEIDI SPLETE
MDedge News

Cigarette smokers who also use cannabis appear to face high hurdles to quit smoking, a large national survey has found.

"Over the past decade, there has been an increase in the use of cannabis among cigarette smokers and prevalence of cigarettes and cannabis co-use, suggesting that the negative consequences of cigarette–cannabis co-use may also become more prevalent over time," wrote Andrea H. Weinberger, PhD, of Yeshiva University, New York, and colleagues. They noted that the prevalence of cigarette smoking is nearly three times higher among persons who use cannabis and have cannabis use disorders relative to those who do not.

The 2019 National Survey of Drug Use and Health estimated that 15.9% of Americans aged 12 years or older used cannabis in the past year. This number has been rising throughout the 2000s.

In that same report, cannabis use disorder (or marijuana use disorder) was defined as when an individual experiences clinically significant impairment caused by the recurrent use of marijuana, including health problems, persistent or increasing use, and failure to meet major responsibilities at work, school, or home. The report stated that approximately 1.6% of Americans aged 12 or older in 2018 had marijuana use disorder.

In the study published in Tobacco Control, the researchers used the National Survey on Drug Use and Health data to analyze cigarette smoking quit ratios among U.S. adults with and without cannabis use and cannabis use disorders. "Quit ratio was calculated as the proportion of former smokers among lifetime smokers and is considered a measure of total cessation in a population," the researchers said.

In 2016, the quit ratios for adults with a history of cannabis use or cannabis use disorders were 23% and 15%, respectively, compared with 51% and 48%, respectively, in those with no cannabis use or cannabis use disorders.

Overall, quit ratios did not change significantly from 2002 to 2016 for individuals with cannabis use disorders after controlling for multiple demographic factors and other substance use disorders. However, during the same time period, quit ratios showed a nonlinear increase in cannabis users, nonusers, and individuals without cannabis use disorders.

The study findings were limited by several factors including the inability to generalize results to youth or individuals living outside the United States, the use of DSM-IV criteria to identify cannabis use disorder, the use of self-reports, and the inability to examine the timing of cannabis use as related to attempts to quit smoking, the researchers noted. However, the results highlight the need to consider offering smoking cessation treatment to individuals being treated for cannabis use disorders, and to include cannabis users in smoking cessation programs, the researchers noted.

KatarzynaBialasiewicz/Thinkstock

"Based on our results, both public health and clinical efforts to improve cigarette quit outcomes may benefit from including those with any cannabis use," they said. More research is needed to determine whether trends in the quit ratio change over time for cannabis users or those with cannabis use disorder, they added.

The study was funded by the National Institute on Drug Abuse. The researchers had no financial conflicts to disclose.

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SOURCE: Weinberger AH et al. Tob Control. 2020;29(1):74-80. doi: 10.1136/tobaccocontrol-2018-054590.

Screen for cannabis use in cardiovascular care settings

BY JENNIFER SMITH
MDedge New

Researchers are recommending routine screening of marijuana use in cardiovascular care settings.

A review of current evidence suggests an association between marijuana use and adverse cardiovascular effects, as well as interactions between marijuana and cardiovascular medications.

Although more research is needed, the review authors suggested patients may benefit from marijuana screening and testing as well as discussions about the potential risks of marijuana use in the setting of cardiovascular disease.

Ersilia M. DeFilippis, MD, of Columbia University Irving Medical Center in New York and colleagues conducted this review, which was published in the Journal of the American College of Cardiology.

The authors noted that research on marijuana use and cardiovascular disease is limited. The different forms of cannabis and various routes of administration have made it difficult to draw concrete conclusions about marijuana products. Additionally, there have been no randomized, controlled trials of marijuana products in the United States because such trials are illegal; however, there are observational studies linking marijuana use and adverse cardiovascular effects.

Snapshot of available evidence

One study showed that smoking marijuana produces many of the same cardiotoxic chemicals produced by smoking tobacco (BMJ. 2003 May 3;326[7396]:942-3). Another study suggested marijuana smokers may have greater exposure to harmful chemicals (J Psychoactive Drugs. 1988 Jan-Mar;20[1]:43-6).

More specifically, a meta-analysis suggested that smoking marijuana was one of the top three triggers of myocardial infarction (Lancet. 2011 Feb 26;377[9767]:732-40). And in a systematic analysis, 28 of 33 studies linked marijuana use to an increased risk of acute coronary syndromes (Clin Toxicol [Phila]. 2019 Oct;57[10]:831-41).

Furthermore, a study of 2.5 million marijuana users showed that 3% experienced arrhythmias (Int J Cardiol. 2018 Aug 1;264:91-2). A population survey showed that people who smoked marijuana in the past year experienced a 3.3-fold higher rate of cerebrovascular events (Aust N Z J Public Health. 2016 Jun;40[3]:226-30).

Studies have also indicated that cannabinoids can affect cardiovascular medications, including antiarrhythmics, calcium-channel blockers, isosorbide dinitrate/mononitrate, statins, beta-blockers, warfarin, theophylline, and nonsteroidal anti-inflammatory drugs (Medicines [Basel]. 2018 Dec 23;6[1] pii: E3; Curr Top Behav Neurosci. 2017;32:249-62; Pharmacogenet Genomics. 2009 Jul;19[7]:559-62; Ann Pharmacother. 2009 Jul;43[7]:1347-53; Pharmacol Ther. 2019 Sep;201:25-38).

Reviewer recommendations

Cardiovascular specialists should be informed about regulations governing marijuana products, as well as "potential health consequences of marijuana and its derivatives," according to Dr. DeFilippis and colleagues.

The authors recommend routinely screening patients for marijuana use, perhaps using the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory (PLoS One. 2017 May 26;12[5]:e0178194) or the Cannabis Abuse Screening Test (Int J Methods Psychiatr Res. 2018 Jun;27[2]:e1597).

The authors say urine toxicology "may be reasonable" for patients with myocardial infarction or new-onset heart failure. Such testing is required for patients undergoing a heart transplant because marijuana use may affect their candidacy.

Dr. DeFilippis and colleagues say cardiovascular specialists should inform patients about the risks associated with marijuana use. The authors recommend shared decision making for patients who use marijuana for symptom management or palliative purposes.

Three review authors disclosed relationships with many different pharmaceutical companies. One author disclosed relationships with Medscape Cardiology and WebMD, which are owned by the same parent company as MDedge.

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SOURCE: DeFilippis EM et al. J Am Coll Cardiol. 2020 Jan 20. doi: 10.1016/j.jacc.2019.11.025.

New heart failure trial data presage guideline revisions

BY MITCHEL L. ZOLER
MDedge News

PHILADELPHIA – The definition and treatment of heart failure with reduced ejection fraction should change based on recent findings and analyses from major trials, said a key heart failure leader at the American Heart Association scientific sessions.

The people charged with writing U.S. guidelines for heart failure management already have enough evidence to change the recommended way of using sacubitril/valsartan (Entresto) in patients with heart failure with reduced ejection fraction (HFrEF), said Clyde W. Yancy, MD, professor of medicine and chief of cardiology at Northwestern University, Chicago. Accumulated evidence from studies and more than 5 years of experience in routine practice with the angiotensin receptor neprilysin inhibitor (ARNI) combination sacubitril/valsartan for treating HFrEF patients justifies striking the existing recommendation to first start patients on an ACE inhibitor or angiotensin receptor blocker and only after that switching to sacubitril/valsartan, a sequence that has rankled some clinicians as an unnecessary delay and barrier to starting patients on the ARNI regimen.

U.S. guidelines should now suggest that ARNI treatment start immediately, suggested Dr. Yancy, who chaired the AHA/American College of Cardiology panel that updated U.S. guidelines for heart failure management in 2013 (Circulation. 2013 Oct 15;128[16]:e240-327), 2016 (J Am Coll Cardiol. 2016 Sep;68[13]:1476-88), and 2017 (Circulation. 2017 Aug 8; 136[6]:e137-61).

Mitchel L. Zoler/MDedge News

Dr. Clyde W. Yancy

Expanding the heart failure group for sacubitril/valsartan

Dr. Yancy also proposed a second major and immediate change to the existing heart failure guideline based on a new appreciation of a heart failure population that could benefit from ARNI treatment: patients with "mid-range" heart failure, defined by a left ventricular ejection fraction (LVEF) of 41%-49% that places them between patients with HFrEF with an ejection fraction of 40% or less, and those with heart failure with preserved ejection fraction (HFpEF) of 50% or more. As yet unchanged in the 2013 AHA/ACC heart failure guideline is the proposition that patients with heart failure and an ejection fraction of 41%-49% have "borderline" heart failure with characteristics, treatment patterns, and outcomes "similar to patients with HFpEF."

That premise should now go out the window, urged Dr. Yancy, based on a new analysis of data collected from both the recent PARAGON-HF trial of sacubitril/valsartan in patients with HFpEF and ejection fractions of 45% or higher (N Engl J Med. 2019 Oct 24;381[17]:1609-20) and the landmark PARADIGM-HF trial that established sacubitril/valsartan as a treatment for patients with HFrEF (N Engl J Med. 2014 Sep 11;371[11]:993-1004). A combined analysis of the more than 13,000 total patients in both studies suggested that "patients with ejection fraction lower than normal, which includes those with so-called heart failure with mid-range ejection fraction or borderline ejection fraction, would likely benefit from sacubitril/valsartan, compared with RAS inhibition," concluded the authors of

Continued on following page

ID consult for *Candida* bloodstream infections can reduce mortality risk

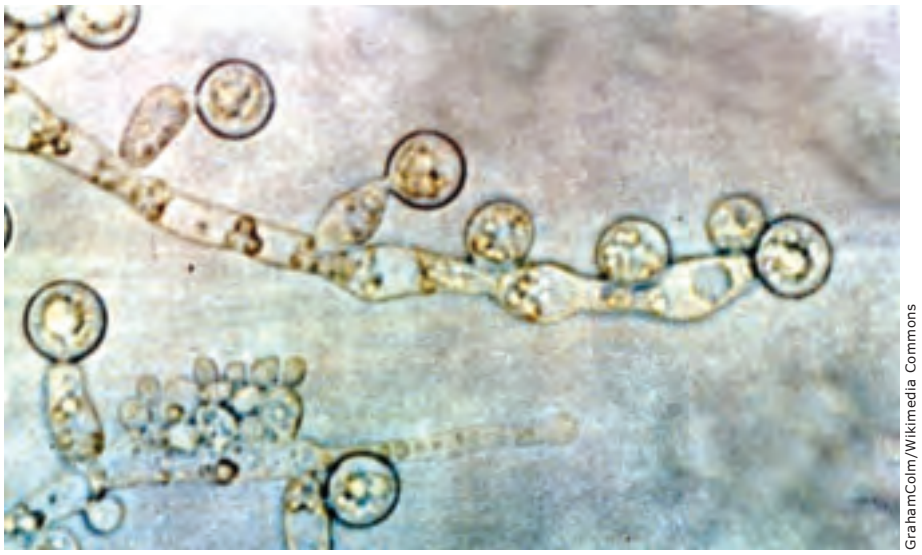
BY MARK S. LESNEY
MDedge News

Clinicians managing patients who have *Candida* bloodstream infection should consider an infectious disease (ID) consultation, findings from a large retrospective study suggest.

Mortality attributable to *Candida* bloodstream infection ranges between 15% and 47%, and delay in initiation of appropriate treatment has been associated with increased mortality. Previous small studies showed that ID consultation has conferred benefits to patients with *Candida* bloodstream infections. Carlos Mejia-Chew, MD, and colleagues from Washington University, St. Louis, sought to explore this further by performing a retrospective, single-center cohort study of 1,691 patients aged 18 years or older with *Candida* bloodstream infection from 2002 to 2015. They analyzed demographics, comorbidities, predisposing factors, all-cause mortality, antifungal use, central-line removal, and ophthalmological and echocardiographic evaluation in order to compare 90-day all-cause mortality between individuals with and without an ID consultation.

They found that those patients who received an ID consult for a *Candida* bloodstream infection had a significantly lower 90-day mortality rate than did those who did not (29% vs. 51%).

With a model using inverse weighting by the propensity score, they found that ID consultation was associated with a hazard ratio of 0.81 for mortality (95% confidence interval, 0.73-0.91; *P* less than .0001). In the ID consultation group, the median duration of antifungal therapy was significantly longer (18 vs. 14 days; *P* less than .0001); central-line removal was significantly more common (76% vs. 59%; *P* less than .0001); echocardiography use was more frequent (57% vs. 33%; *P* less than .0001); and ophthalmologic examinations were performed more often (53% vs. 17%; *P* less than .0001). Importantly, fewer patients in the ID consultation group were untreated (2% vs. 14%; *P* less than .0001).



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In an accompanying commentary, Katrien Lagrou, MD, and Eric Van Wijngaerden, MD, of the department of microbiology, immunology and transplantation, University Hospitals Leuven (Belgium) stated: "We think that the high proportion of patients (14%) with a *Candida* bloodstream infection who did not receive any antifungal treatment and did not have an infectious disease consultation is a particularly alarming finding. ... Ninety-day mortality in these untreated patients was high (67%)."

"We believe every hospital should have an expert management strategy addressing all individual cases of candidaemia. The need for such expert management should be incorporated in all future candidaemia management guidelines," they concluded.

The study was funded by the Astellas Global Development Pharma, the Washington University Institute of Clinical and Translational Sciences, and the Agency for Healthcare Research and Quality. Several of the authors had financial connections to Astellas Global Development or other pharmaceutical companies. Dr. Lagrou and Dr. Van Wijngaerden both reported receiving personal fees and nonfinancial support from a number of pharmaceutical companies, but all outside the scope of the study.

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SOURCE: Mejia-Chew C et al. Lancet Infect Dis. 2019;19:1336-44.

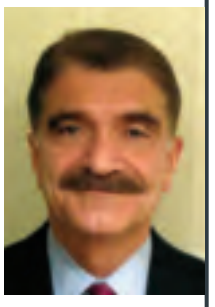
Continued from previous page

the new analysis (Circulation. 2019 Nov 17. doi: 10.1161/CIRCULATIONAHA.119.044586).

Dr. Yancy argued that, based on this new analysis, a further revision to the 2013 guideline should say that patients with heart failure with a LVEF of 41%-49% have characteristics, treatment responses, and outcomes that "appear similar to those of patient with HFrEF," a sharp departure from the existing text that lumps these patients with the HFpEF subgroup. "There appears to be a signal that extends the benefit of ARNI to patients with ejection fractions above the current threshold for HFrEF but below what is typically HFpEF," he said.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: Management of patients with heart failure and reduced ejection fraction is a challenge for the clinicians. The clinical evidence on the use of ARNI as the first-choice therapy in HFrEF and the DAPA-HF trial data confirming the positive impact of SGLT2 inhibitor dapagliflozin on reducing mortality and hospitalization and urgent visits due to heart failure in patients with and without type 2 diabetes are important findings which will lead to changes in guidelines for treating this group of patients.



Bringing SGLT2 inhibitors into heart failure management

Dr. Yancy also cited recently reported data from another landmark trial, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), as an impetus for both another immediate change to the guideline and for a potential second change pending a report of confirmatory evidence that may arrive in 2020.

The DAPA-HF results showed that the sodium -glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin (Farxiga) was just as effective for preventing all-cause death and heart failure hospitalizations and urgent visits in patients without type 2 diabetes as it is in patients with type 2 diabetes (N Engl J Med. 2019 Nov 21;381[21]:1995-2008), a remarkable finding for an agent that came onto the U.S. market as a diabetes drug specifically aimed at reducing levels of glycosylated hemoglobin.

Dr. Yancy proposed an immediate guideline change to acknowledge the proven protection against incident heart failure that treatment with a SGLT2 inhibitor gives patients with type 2 diabetes. There is now "a strong opportunity to use an SGLT2 inhibitor in patients with type 2 diabetes to reduce the incidence of heart failure," he said.

And he added that, if results from EMPEROR REDUCED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), studying the SGLT2 inhibitor empagliflozin (Jardiance) in HFrEF patients with and without type 2 diabetes, can confirm the efficacy of a second drug from this class in preventing heart failure events in patients with HFrEF but without diabetes, then the time will have arrived for another guideline change to establish the SGLT2 inhibitors as a new "foundational" drug for the management of all HFrEF patients, regardless of their level of glycemic control.

The SGLT2 inhibitors are a particularly attractive additional drug because they are taken once daily orally with no need for dosage adjustment, so far they have shown excellent safety in patients without diabetes with no episodes of hypoglycemia or ketoacidosis, and they have even shown evidence for heart failure benefit in patients older than 75 years, Dr. Yancy noted.

Dr. Yancy had no relevant disclosures.

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PCVs don't always protect children with asthma

BY MICHELE G. SULLIVAN
MDedge News

Even on-time pneumococcal vaccines don't completely protect children with asthma from developing invasive pneumococcal disease, a meta-analysis has determined.

Despite receiving pneumococcal valent 7, 10, or 13, children with asthma were still almost twice as likely to develop the disease as were children without asthma, Jose A. Castro-Rodriguez, MD, PhD, and colleagues reported in Pediatrics (2020 Jan. doi: 10.1542/peds.2019-1200). None of the studies included rates for those who received the pneumococcal polysaccharide vaccine (PPSV23).

"For the first time, this meta-analysis reveals 90% increased odds of invasive pneumococcal disease (IPD) among [vaccinated] children with asthma," said Dr. Castro-Rodriguez, of Pontificia Universidad Católica de Chile, Santiago, and colleagues. "If confirmed, these findings will bear clinical and public health importance," they noted, because guidelines now recommend PPSV23 after age 2 in children with asthma only if they're treated with prolonged high-dose oral corticosteroids.

However, because the analysis comprised only four studies, the authors cautioned that the results aren't enough to justify changes to practice recommendations.

Asthma treatment with inhaled corticosteroids (ICS) may be driving the increased risk, Dr. Castro-Rodriguez and his coauthors suggested. ICS deposition in the oropharynx could boost oropharyngeal candidiasis risk by weakening the mucosal immune response, the researchers noted. And that same process may be at work with *Streptococcus pneumoniae*.

A prior study found that children with asthma who received ICS for at least 1 month were almost four times more likely to have oropharyngeal colonization by *S. pneumoniae* as were those who didn't get the drugs. Thus, a higher carrier rate of *S. pneumoniae* in the oropharynx, along with asthma's impaired airway clearance, might increase the risk of pneumococcal diseases, the investigators explained.

Dr. Castro-Rodriguez and colleagues analyzed four studies with more than 4,000 cases and controls, and about 26 million person-years of follow-up.

Rates and risks of IPD in the four studies were as follows:

- Among those with IPD, 27% had asthma, compared with 18% of those without, an adjusted odds ratio of 1.8.
- In a European study of patients who received at least 3 doses of PCV7, IPD rates per 100,000 person-years for 5-year-olds were 11.6 for children with asthma and 7.3 for those without. For 5- to 17-year-olds with and without asthma, the rates were 2.3 and 1.6, respectively.

Continued on following page

President's report

BY STEPHANIE M. LEVINE, MD, FCCP
CHEST President

After an outstanding annual meeting in New Orleans, with the greatest number of attendees and a number of other firsts, and with the holidays rapidly approaching, you might think there would be a lull in activity, but your CHEST leadership and staff have been busy. Let's start with a CHEST 2019 recap.

This year's meeting had a total of 5,960 medical professionals and 8,593 total attendees. All were the highest in CHEST history! In addition, there were more international attendees, and CHEST 2019 saw the largest number of fellows-in-training and the largest number of advanced practice providers attending.

Since CHEST 2019, we have held five live learning sessions at headquarters in Glenview, with a total of 281 attendees, including: Extracorporeal Support for Respiratory and Cardiac Failure in Adults; Critical Care Ultrasound: Integration Into Clinical Practice; Comprehensive Pleural Procedures; Ultrasonography: Essentials in Critical Care; and the Advanced Critical Care Echocardiography Board Review Exam Course. In case you missed those opportunities, in the near future, CHEST will be holding the following 2020 courses: Comprehensive Bronchoscopy With Endobronchial Ultrasound February 20 – 22, Mechanical Ventilation: Advanced Critical Care Management February 27 - 29, Ultrasonography: Essentials in Critical Care March 5 - 7, Bronchoscopy and Chest Tubes in the ICU March 20 - 21, Advanced Clinical Training in Pulmonary Function Testing March 27 - 28, Critical Skills for Critical Care: A State-of-the-Art Update, and Procedures for ICU Providers April 30 - May 2. For additional information, check out the events at chestnet.org.

Internationally, the program for the Italian CHEST Congress, to be held with the Italian CHEST Chapter in Bologna in June (June 25-27), is finished. This meeting will be designed on a smaller scale of that of the annual CHEST meeting, with plenty of educational opportunities in the areas of pulmonary, critical care, and sleep medicine, and will also feature faculty from around the world. Come experience all the education, as well as the beauty of Italy in June! CHEST has continued other international activities with leadership attendance and lectures at the Asian Pacific Society of Respirology (APSR), where we engaged with multiple societies as CHEST continues to grow our international strategy to educate those who request further education in our fields. CHEST also sent selected young investigators to the APSR meeting.

Plans are well under way to hold another successful annual meeting in Chicago - CHEST 2020. The call for topics has ended, and proposal grading is ongoing. The call for abstracts has gone out and will close March 31. We encourage all, including our learners in training, to submit high quality abstracts and case reports, and we will offer suggestions for those needing editorial assistance. This is one of the many ways to get CHEST-involved. In addition to the innovations and experiences we offered last year, there will be continued social media presence and new exciting offerings at this year's annual meeting. Save the dates - October 17-21, in our home town of Chicago!

One of my goals for this year is to evaluate ways to increase engagement and leadership opportunities within the organization, with our CHEST NetWorks being one example. The work of the NetWorks task force is ongoing. Expect to see pilots of twitter handles, infographics, and e-bytes coming from some NetWorks in the near future.

Dr. Stephanie M. Levine

The editorial board for the next volume of SEEK Critical Care has been selected, and work is under way for delivery of the next print edition and library update at the summer Board Review Courses in August in Washington DC. Your *CHEST* journal editorial board has also been busy. The redesigned issue with the new content structure has hit mailboxes, and you can expect to see updated guidelines for "Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report" and "Chronic Cough Due to Stable Chronic Bronchitis: CHEST Expert Panel Report" out soon. Also, look for publications that CHEST has endorsed to include the College of American Pathologists' supplement "Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies" and the Society of Critical Care Medicine's algorithm and bundle for the "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children." CHEST had representatives to both of these writing groups. In addition, more podcasts will soon be on the horizon.

The CHEST Foundation gala, The Golden Era of EP (Erin Popovich) was held in early December at the AT & T center in San Antonio, with over 500 people in attendance, including many from the San Antonio community, current and former Spurs players and coaches, in addition to our leadership and staff. The Erin Popovich (EP) endowment is dedicated to empowerment and access for patients with interstitial lung disease, as well as research in this area. Over 3 million dollars have been raised to date to directly support this endowment. One of the early products from this endowment is the soon to be available Oxygen Access Toolkit, developed for use by provider offices, clinicians, DME suppliers, patients, and caregivers to answer some of the basic facts about access to oxygen that so many of our patients with ILD and other lung diseases need. Other resources will include the ILD Tree, Get a Second Opinion, You're Not Alone Patient Journey, Mnemonic for ILD Patients, the Patients' Bill of Rights, and a co-morbidities one–page information sheet.

After the next quarterly Board Meeting in January, I will update you on decisions regarding future strategy that emerge from that meeting. The agenda will include many of the topics mentioned above, in addition to a strategic discussion regarding CHEST's increased role in advocacy, which has been requested by many members.

Of course, all these events and activities could not be accomplished without the incredible effort by your CHEST staff and volunteer leadership. I look forward to many updates in my next report. As always, please reach out to me with any comments, questions, or suggestions, and if I am unable to respond, I will address it with the appropriate staff person. Thank you all for being the most important reason that CHEST exists. Have a great 2020!

Continued from previous page

- In 2001, a Korean study found an aOR of 2.08 for IPD in children with asthma, compared with those without. In 2010, the aOR was 3.26. No vaccine types were reported in the study.
- Rates of IPD were 3.7 per 100,000 person-years for children with asthma, compared with 2.5 for healthy controls – an adjusted relative risk of 1.5.

The pooled estimate of the four studies revealed an aOR of 1.9 for IPD among children with asthma, compared with those without, Dr. Castro-Rodriguez and his team concluded.

None of the studies reported hospital admissions, mortality, length of hospital stay, intensive care admission, invasive respiratory support, or additional medication use.

One, however, did find asthma severity was significantly associated with increasing IPD treatment costs per 100,000 person-years: $72,581 for healthy controls, compared with $100,020 for children with mild asthma, $172,002 for moderate asthma, and $638,452 for severe asthma.

In addition, treating all-cause pneumonia was more expensive in children with asthma. For all-cause pneumonia, the researchers found that estimated costs per 100,000 person-years for mild, moderate, and severe asthma were $7.5 million, $14.6 million, and $46.8 million, respectively, compared with $1.7 million for healthy controls.

The authors had no relevant financial disclosures.

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SOURCE: Castro-Rodriguez JA et al. Pediatrics. 2020 Jan. doi: 10.1542/peds.2019-1200.

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CHEST NETWORKS

Beta-blockers. Interstitial lung disease. Vaping. GL-ILD.

Clinical research

Nintedanib in progressive fibrosing interstitial lung diseases: Does one size really fit all?

Interstitial lung diseases (ILDs) include a variety of lung disorders, such as idiopathic interstitial pneumonias (IIPs), autoimmune diseases, granulomatous lung disease, and environmental diseases. They all have one thing in common—a progressive fibrosing phenotype that is almost universally fatal. It has been suggested that such diseases have a shared pathophysiologic mechanism irrespective of the cause and, hence, could respond to similar therapy. Nintedanib acts intracellularly by inhibiting multiple tyrosine kinases. Previous clinical trials have suggested that nintedanib inhibits the progression of lung fibrosis in patients with idiopathic pulmonary fibrosis (Richeldi, et al. *N Engl J Med*. 2014;370[22]:2071) and systemic sclerosis-associated ILD (Distler, et al. *N Engl J Med*. 2019;380[26]:2518). The INBUILD trial was conducted to study the efficacy and safety of nintedanib in patients with fibrosing interstitial lung diseases (Flaherty, et al. *N Engl J Med*. 2019;381[18]:1718).

Dr. Ijaz

Patients with a wide spectrum of progressive fibrosing ILD were enrolled in the INBUILD trial. This gave the phenotypic approach needed to study the effects of nintedanib in fibrosing ILDs. The authors reported an absolute difference of 107 mL in the annual rate of decline in forced vital capacity in the overall population, 128.2 mL (95% CI 65.4 to 148.5; *P* less than .001) in patients with UIP-like fibrotic pattern and 75.3 mL in patients with other fibrotic patterns, between patients who received nintedanib and those who received placebo. Earlier studies have shown similar results in patients with IPF. The most frequent adverse event was diarrhea (66.9% in the nintedanib group and 23.9% in placebo group). Liver enzymes derangement was more common in the nintedanib group. Nausea, vomiting, abdominal pain, decreased appetite, and weight decrease were also more frequent in the nintedanib group than in those in the placebo group. In conclusion, this study not only explored the effects of nintedanib on progressive fibrosing ILDs but also helped to enhance the understanding of their natural history, suggesting a final common pathway toward lung fibrosis.

Mohsin Ijaz, MD, FCCP
Steering Committee Member

Airway disorders

Beta-blockers in COPD: A settled debate?

Beta-blockers are the cornerstone in the management of patients with heart failure and myocardial infarction where they have shown to improve morbidity and mortality. Cardiovascular disease is common in patients with COPD. A 2014 meta-analysis of retrospective studies involving patients with COPD using a beta-blocker has shown lower death and lower exacerbation rate (Du Q, et al. *PLoS One*. 2014;9[11]:e113048). More recent studies continue to note underutilization of beta-blockers in patients with COPD due to concerns for adverse effects on pulmonary function (Lipworth B, et al. *Heart*. 2016;102[23]:1909).

Dr. Adrish

Dr. Ramesh

To further study these concerns, Dransfield and colleagues conducted a randomized controlled trial (BLOCK COPD) of 532 randomly assigned patients to receive either metoprolol or placebo (Dransfield, et al. *N Engl J Med*. 2019;381[24]:2304).

Primary outcome was time to first COPD exacerbation whereas

secondary outcomes included rate of exacerbation, mortality, hospitalization, symptoms, and spirometry data. Median time to exacerbation was similar between the two groups; however, metoprolol was associated with higher incidence of severe exacerbation requiring hospitalization (HR 1.91, 95% CI 1.29-2.83).

There was nonstatistical increase in deaths in metoprolol group, mainly contributed by fatal COPD events (seven in metoprolol vs one in placebo). The study results validated some of the concerns of worsening pulmonary function with beta-blocker use; however, in order to better understand the study results, we must pay attention to the study cohort.

In summary, patients did not have significant cardiac disease and, therefore, did not have an overt indication for beta-blocker use. Patients with COPD in this study were sicker than average patients. Lastly, there were more patients in the metoprolol group who had COPD exacerbations requiring ED visit or hospitalization in 12 months prior to study enrollment. For the above-mentioned reasons, the conclusion of this study should not discourage the use of beta-blockers in patients with COPD when underlying cardiac disease warrants their use, after careful consideration of benefits and risks.

Muhammad Adrish, MD, FCCP
Steering Committee Member
Navitha Ramesh, MD, FCCP
Steering Committee Member

Home-based mechanical ventilation and neuromuscular disease

Keeping up with the times: incorporating home mechanical ventilation education into pulmonary and critical care fellowship and clinical practice

Home mechanical ventilation (HMV) utilization for patients with chronic respiratory conditions is rapidly increasing in both pediatric and adult populations. By 2016, the estimated prevalence of HMV was 2.9-12.9/100,000 (3.1-18% via tracheotomy) (Rose, et al. *Respir Care*. 2015;60[5]:695; Valko, et al. *BMC Pulm Med.* 2018;18[1]:190). In 2012, limited regional US data were extrapolated to approximate a prevalence of 4.7-6.4/100,000 children utilizing HMV (King, A. *Respir Care*. 2012;57[6]921), but there is currently no comprehensive registry of HMV use in the United States. A US Department of Health and Human Services report in 2016 described an 85-fold increase in Medicare claims for home ventilators in 2015 compared with 2009 (OEI-12-15-00370; 9/22/2016).

With increasing demand, educating clinicians responsible for providing and managing HMV is paramount. Education specific to longitudinal management of the HMV is noticeably overlooked. The ACGME core competencies for PCCM fellowships include principles inherent to HMV, including modes/principles of ventilation, modalities/principles of oxygen supplementation, tracheostomy tube management, as well as the use of "masks for delivery of supplemental oxygen, humidifiers, nebulizers, and incentive spirometry" (ACGME Common Program Requirements 7/1/2019). However, training programs are not required to provide skills essential in HMV management, including: (1) appropriate patient selection for long-term HMV, (2) selection of well-matched home ventilators suited to patients' chronic conditions, (3) assessment/timing of transition to invasive ventilation, or (4) adjustments necessary to maintain optimal ventilator support. Life-sustaining ventilators used in ICUs differ from life-supporting HMV systems in modes, interface, cost, algorithms, circuitry, and available adjuncts.


Dr. Lussier

There is an opportunity (and responsibility) to improve current training guidelines to meet growing needs of the population and anticipate needs of trainees as they enter unsupervised practice. Although simulation initiatives at national CHEST meetings attempt to bridge education gaps, it is incumbent upon fellowship training programs to prepare pulmonologists with skills to manage HMV in order to maintain high standards of care in a safe, financially responsible, and evidence-based manner.

Bethany L. Lussier, MD, FCCP
NetWork Member
Won Y. Lee, MD, FCCP
Steering Committee Member

Critical care

Vaping-related acute lung injury: Where there's smoke, there's fire

E-cigarette or vaping product use–associated lung injury (EVALI) is a burgeoning public health problem in the United States. There have been more than 2,506 hospitalizations and 54 deaths from EVALI (cdc.gov). Unfortunately, the diagnosis is one of exclusion at present. The CDC defines EVALI as lung disease associated with e-cigarette or vaping exposure within 90 days, infiltrates, and absence of other causes (Layden, et al. *N Engl J Med.* 2019 Sep 6. doi: 10.1056/NEJMoa1911614).


Dr. Ouellette

As critical care providers, we are uniquely poised to detect and treat this illness, given that roughly one in three patients with EVALI require mechanical ventilation. Moreover, one-quarter of rehospitalizations and deaths occur 2 days after discharge from initial hospitalization (Mikosz, et al. *MMWR* 2020;68[5152]:1183). .

To better identify EVALI, the Centers for Disease Control and Prevention (CDC) recommends that health-care providers ask e-cigarette or vaping product users about respiratory, gastrointestinal, and constitutional symptoms, obtain chest imaging in those suspected of EVALI, consider outpatient management of stable patients, test for influenza, and use caution when prescribing steroids in the outpatient setting. Emphasizing cessation and advocating for annual influenza vaccination is also recommended (Update: Interim Guidance for Health Care Providers for Managing Patients with Suspected E-cigarette, or Vaping, Product Use–Associated Lung Injury. (*MMWR*. 2019;68[46]:1081).

So how can critical care providers assist in the understanding and treatment of EVALI? Critical care physicians treating patients with EVALI face unique challenges moving forward. We need to develop a better understanding of the triggers and pathophysiology of EVALI and learn to improve our recognition of the disease. We should study interventions that may improve outcomes such as corticosteroids. We know little about the long-term outcomes and sequalae of EVALI.

The best treatment for EVALI is prevention. Critical care physicians are experts at identifying and treating life-threatening conditions but as a community have less experience in the public health arena. If as physicians we are called upon to advocate for our patients, then perhaps there is a role for critical care physicians to advocate for a ban on vaping.

Matthew K. Hensley, MD, MPH
Fellow-in-Training Member
Daniel R. Ouellette, MD, MS, FCCP
NetWork Vice-Chair

Interstitial and diffuse lung disease

Granulomatous lymphocytic interstitial lung disease (GL-ILD)

Among the granulomatous lung diseases, Gl-ILD is hardly a new discovery, but for many reasons, it often goes undiagnosed for years. The relative rareness of the disease itself and, hence, the lack of awareness makes it an uncommon differential for granulomatous ILD. Patients with GL-ILD are often misdiagnosed with sarcoidosis, unspecified ILD, or lymphoid interstitial pneumonia, etc, before receiving a diagnosis of GL-ILD.

GL-ILD is seen in 5% to 22% of patients with common variable immunoglobulin deficiency (CVID). There are instances where patients are diagnosed with CVID based on a radiologic or histologic diagnosis of GL-ILD. Although GL-ILD suggests a pulmonary process, it actually encompasses a multisystemic granulomatous inflammatory disease that may affect the liver, spleen, bowels, lymphoid tissue, and conceivably any other organ system (Hartono, et al. *Ann Allergy Asthma Immunol.* 2017;118[5]:614. Pathogenesis of GL-ILD in CVID includes dysfunctional antigen handling (due to impaired T cell function) and aberrant immune response to viruses (Hurst, et al. *J Allergy Clin Immunol Pract.* 2017;5[4]:938).


Dr. Wynn

Patients with GL-ILD often present with progressive shortness of breath, restrictive lung functions with a background of CVID. Imaging findings are 5-30 mm lower lobe-predominant, nodules, ground glass opacities, and splenomegaly. Histopathology varies with predominant granulomas vs lymphocytic infiltrates. The process can be treated and often reversed with use of high dose immunoglobulin replacement, immunomodulatory therapy with agents like azathioprine, and rituximab. However, steroids are not helpful. Due to the lymphocytic dysregulation in GL-ILD, patients are at high risk of death from lymphoma. Part of the management is surveillance for malignancy and involvement of other organ systems.

A. Thanushi Wynn, MD
Fellow-in-Training Member

As add-on maintenance treatment for patients (12+ years) with moderate-to-severe asthma with an eosinophilic phenotype, or with OCS-dependent asthma regardless of phenotype

A PATH TO **ASTHMA CONTROL**

A NOVEL BIOLOGIC THAT INHIBITS IL-4 AND IL-13 SIGNALING, TWO OF THE SOURCES OF INFLAMMATION IN ASTHMA[1,a]

[a] **The mechanism of dupilumab action in asthma has not been established.**

INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

LIMITATION OF USE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with EGPA have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the chronic rhinosinusitis with nasal polyposis development program. A causal association between DUPIXENT and these conditions has not been established.

Acute Asthma Symptoms or Deteriorating Disease: Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

LEARN MORE AT *DUPIXENTASTHMAHCP.COM*

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **81%**

REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS through Week 24[1,b]

- **71% REDUCTION** with DUPIXENT 200 mg + SOC (n=65) vs placebo + SOC (n=68) (0.30 vs 1.04; rate ratio: 0.29 [95% CI: 0.11, 0.76])
- **81% REDUCTION** with DUPIXENT 300 mg + SOC (n=64) vs placebo + SOC (n=68) (0.20 vs 1.04; rate ratio: 0.19 [95% CI: 0.07, 0.56])

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

UP TO **430 mL**

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12[1]

- **430 mL IMPROVEMENT** with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL])
- **390 mL IMPROVEMENT** with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL])

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

TRIAL 1: 24-WEEK STUDY–776 adults (≥18 years) with moderate-to-severe asthma on a standard of care of medium- or high-dose ICS and a LABA were randomized to either DUPIXENT 200 mg Q2W[c] + SOC (n=150), DUPIXENT 300 mg Q2W[d] + SOC (n=157), or placebo + SOC (n=158). Subjects enrolled in Trial 1 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. DUPIXENT was administered as an add-on to background asthma treatment. **Primary endpoint:** Mean change from baseline to Week 12 in FEV_1 in patients with baseline eosinophils ≥300 cells/µL. **Other endpoint:** Annualized rate of severe exacerbation events during the 24-week treatment period.[e] **Selected baseline demographics:** Mean duration of asthma: 22 years; mean exacerbations in previous year: 2.2; high-dose ICS use: 50%; pre-dose FEV_1 at baseline: 1.84 L; mean FeNO: 39 ppb; mean total IgE: 435 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

[b] Severe exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
[c] With 400 mg loading dose.
[d] With 600 mg loading dose.
[e] Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LSM, least squares mean; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION WITH DUPIXENT[1]

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

430 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

TRIAL 1: BASELINE EOS ≥300 CELLS/µL

390 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1 from baseline at Week 12

with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL]) and sustained through 24 weeks (380 mL vs 220 mL)

~68% OF THE TOTAL IMPROVEMENT IN FEV_1 SEEN AT WEEK 2 WITH DUPIXENT 200 mg + SOC (Trial 1 ≥300 cells/µL)[2]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥1%) in patients with asthma are injection site reactions, oropharyngeal pain, and eosinophilia.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

MORE PATIENTS STOPPED USING OCS WITH DUPIXENT WHILE IMPROVING ASTHMA CONTROL[1,3]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

70%

REDUCTION IN OCS DOSE

(median 100%) from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) (95% CI: 60%, 80%) vs **42%** (median 50%) with placebo + SOC (n=107)

86% OF PATIENTS REDUCED OR ELIMINATED THEIR OCS DOSE with DUPIXENT 300 mg + SOC (n=103) vs **68%** with placebo + SOC (n=107)

IMPROVE LUNG FUNCTION AND REDUCE SEVERE EXACERBATIONS WITH THE ONLY BIOLOGIC INDICATED FOR OCS-DEPENDENT ASTHMA PATIENTS, REGARDLESS OF PHENOTYPE[b]

TRIAL 3: NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

59%
REDUCTION

IN ANNUALIZED RATE OF SEVERE EXACERBATIONS
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63])

220 mL
IMPROVEMENT

IN PRE-BRONCHODILATOR FEV_1
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **10 mL** with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL])

TRIAL 3: 24-WEEK STUDY–210 subjects (≥12 years) with asthma who required daily OCS in addition to regular use of standard of care of high-dose ICS plus an additional controller medication were randomized to either DUPIXENT 300 mg Q2W[c] + SOC + OCS (n=103) or placebo + SOC + OCS (n=107); the baseline mean OCS dose was 11 mg in the DUPIXENT group and 12 mg in the placebo group. **Primary endpoint:** Percent reduction from baseline in OCS dose at Week 24, while maintaining asthma control, in the overall population. **Additional secondary endpoints:** Annualized rate of severe exacerbation events during the 24-week treatment period; and mean change from baseline to Week 24 in FEV_1. **Selected baseline demographics:** Mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose FEV_1 at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/μL.

[a] Intention-to-treat (ITT) population was unrestricted by minimum baseline eosinophils or other Type 2 biomarkers (eg, FeNO or IgE).
[b] Asthma exacerbation was defined as a temporary increase in OCS dose for at least 3 days.
[c] With 600 mg loading dose.

Please see brief summary of full Prescribing Information on the following pages.

References: 1. DUPIXENT Prescribing Information. **2.** Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. **3.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485.

SANOFI GENZYME

REGENERON

DUP.19.08.0282

DUPIXENT® (dupilumab) injection, for subcutaneous use Rx Only
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

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

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program, as well as in adult patients with comorbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

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

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Warnings and Precautions (5.1)]*

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.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

In the 1-year placebo-controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, nonfatal myocardial infarctions [MI], and nonfatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described that follow, with the incidence of antibodies in other studies or to other products, may be misleading. Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had

neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level, which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

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PULMONARY PERSPECTIVES®

Resurgence of black lung among U.S. coal miners

BY CARA N. HALLDIN, PHD, MPH; AND A. SCOTT LANEY, PHD, MPH

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Dr. Halldin

Dr. Laney

Advances in technology over the last century, as well as the exportation of many high exposure jobs, nearly eliminated lung diseases caused by occupational exposure to respirable dust (the pneumoconioses) in the United States. One such example of this near elimination is black lung, or coal workers' pneumoconiosis (CWP), following the 1969 Federal Coal Mine Health and Safety Act.

The Act established permissible exposure limits to respirable dust, designed to prevent the most severe forms of CWP from occurring, and a national respiratory health screening program for underground coal miners. Between 1970 and the mid-1990s, disease prevalence plummeted from nearly 35% to less than 5% prevalence among longer tenured miners, and from 3% to less than 1% in miners with less than 10 years of mining tenure (Hall NB, et al. *Curr Environ Health Rep*. 2019;6[3]:137).

Many assumed that this was the last we'd hear of black lung – that the cases of disease existing in the 1990s were likely caused by exposures that occurred prior to the 1969 Act, and within a few years, no further cases would be detected.

This appeared to be an entirely reasonable assumption in the 1990s given the 30 years of declining prevalence and the continuous technological advances designed to continue reductions in dust exposures. In fact, the precipitous decline in black lung was briefly viewed as a public health triumph, as the most severe forms appeared to be near eradication in the United States just 2 decades ago (Attfield MD, et al. *Am J Public Health*. 1992;82[7]:971; Attfield MD, et al. *Am J Public Health.* 1992;82[7]:964).

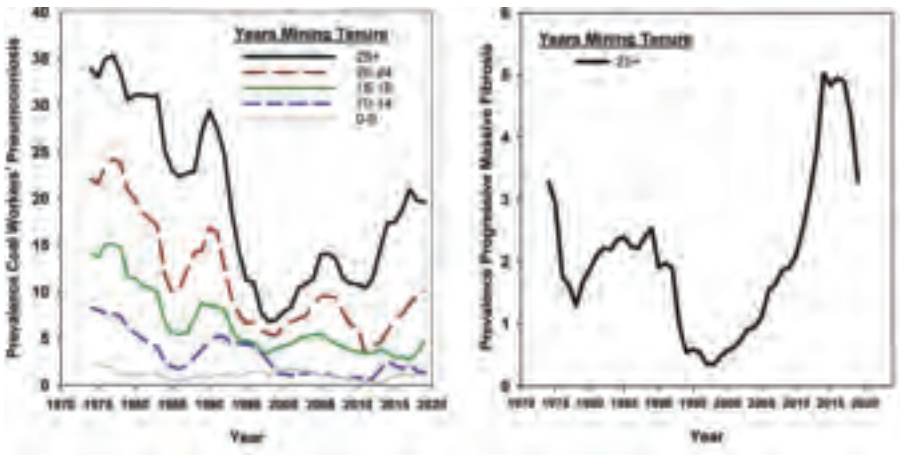

Figure 1. Prevalence of coal workers' pneumoconiosis and progressive massive fibrosis among working underground coal miners participating in the NIOSH Coal Workers' Health Surveillance Program, in Kentucky, Virginia, and West Virginia 1974-2019. Data are presented as the 5-year moving average percentage; surveillance is conducted on a 5-year national cycle (Data from NIOSH CWHSP [Coal Workers' Health Surveillance Program CWHSP Data Query System accessible: http://webappa.cdc.gov/ords/cwhsp-database.html]).

However, what has since been observed is a strong and ongoing resurgence of the potentially deadly fibrotic interstitial disease starting in the early 2000s (Figure 1), with the most striking increase observed in the Central Appalachian states of Kentucky, Virginia, and West Virginia (Blackley DJ, et al. *Am J Respir Crit Care Med.* 2014;190[6]:708; Blackley DJ, et al. *Am J Public Health.* 2018;108[9]:1220).

Of great concern is the resurgence of complicated Black Lung (progressive massive fibrosis [PMF]), which is completely disabling and leads to premature mortality. The prevalence of PMF is higher today than when NIOSH started formally tracking the disease in the 1970s, especially among specific populations. Since the mid-2000s, NIOSH and others have described the following(Hall NB, et al. *Curr Environ Health Rep.* 2019;6[3]:137):

- Increasing prevalence and severity of CWP both nationwide and specifically in Central Appalachia.
- Rapid progression of CWP.
- Increases in the frequency of lung transplantation for CWP.
- Severe disease among surface coal miners with no underground mining tenure.
- Increased severity of disease among former and retired miners.
- Hundreds of cases of PMF among coal miners seeking care at clinics in eastern Kentucky and southwestern Virginia.
- Increasing numbers of miners with PMF filing for federal black lung compensation.
- Radiologic and pathologic indications of increased respirable silica exposure among coal miners.
- Premature mortality in miners diagnosed with CWP.
- Underutilization of a secondary prevention worker removal program designed to reduce the exposure of miners with disease.
- Former miners with severe disease describing extreme pressure to operate. outside of applicable protective federal standards in order to increase productivity

In our surveillance work, we have talked to many miners who, after having months or years' worth of extensive workups for pneumonia, sarcoidosis, lung cancer, and/or diseases other than the pneumoconioses, have eventually learned that they actually had dust-induced lung disease attributable to their work. Additionally, through our evaluation of the transplantation data, it has become clear that dust-related lung disease is likely underreported or underrecognized among those receiving lung transplants.

Finally, through analysis of mortality data, it is apparent that CWP is also underreported as a cause of death among miners with black lung. We mention these points to emphasize how important it is to document

This month in the journal *CHEST*®

Editor's Picks

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

CHEST Reviews

Critically ill patients with the HIV: 30 years later.
By Dr. E. Azoulay, et al.

Phenotypic subtypes of obstructive sleep apnea: a challenge and opportunity for precision medicine.
By Drs. A. Zinchuk and H. K. Yaggi.

Basic primer for finances in academic adult and pediatric pulmonary divisions.
By Dr. L. Schnapp, et al.

Original Research

Eligibility for lung volume reduction surgery in chronic obstructive pulmonary disease patients identified in a UK primary care setting.
By Dr. H. Whittaker, et al.

Early life exposure to oral antibiotics and lung function into early adulthood.
By Dr. K. dos Santos, et al.

a full occupational history for proper diagnoses, early intervention, and improved public health information to inform primary and secondary disease prevention efforts.

Resources for clinicians

CWP is most commonly identified using plain posterior-anterior chest radiography and presence/severity of fibrotic change is described using an international standard established by the International Labour Office (International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconioses. Geneva: International Labour Office; 2011).

In the United States, NIOSH operates the B Reader Training and Certification Program, which offers a free self-study syllabus, https://www.cdc.gov/niosh/topics/chestradiography/breader.html, and in-person training courses on occasion, to assist physicians in learning and demonstrating continuous competency in classifying chest radiographs of dust-exposed workers according to the ILO Standards (Halldin CN, et al. *J Occup Environ Med.* 2019;61[12]:1045).

The B Reader Program and ILO Standards are currently undergoing a decade-long revision process where both will feature digitally acquired chest radiograph images. This process should be fully complete in the following months.

To educate miners, mine operators, and others about the risks of respirable dust, NIOSH produced an educational video, "Faces of Black Lung," in 2008 that featured two miners in their 50s and 60s who had complicated Black Lung. Because of the resurgence of disease and particularly severe cases being identified among much younger miners, NIOSH recently released an updated version of the video, "Faces of Black Lung II," where three Kentucky underground miners, ages 39, 42, and 48, describe the incredible disability and quality of life lost due to a disease caused by gross overexposure of respirable coal mine dust.

Unfortunately, the 42-year-old miner died from complications stemming from Black Lung less than a year after filming his part in the video, and the other two miners have been advised to be evaluated for lung transplantation.

Access the video here: https://www.cdc.gov/niosh/docs/video/2020-109d/default.html. We hope that these men's stories will help younger miners relate to the risks of respirable coal mine dust and help others understand the severity of disease as all three of these men struggled to breathe just describing their day to day tasks.

Parting message

No one should ever have to consider a lung transplant at the age of 40 because they went to work attempting to provide for their family. No one should ever be faced with end-of-life planning while their kids are in grade school because of a disease they acquired at work. Respirable coal mine dust is the only cause of black lung, and the coal mining industry has the necessary tech-

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nology and tools to prevent harmful exposures to respirable dust, and, together with miners, must successfully and consistently implement dust suppression controls. There is no cure for black lung; it's irreversible and can be first recognized and continue to progress even after a miner has left exposure. However, early identification and appropriate intervention can prevent progression to the most disabling manifestations.

The role of the clinician is to be part of the early identification of black lung through including CWP in the differential diagnosis for unusual or unexpected respiratory illness in otherwise healthy primarily working aged miners. The public health community must continue to monitor disease prevalence in working populations and implement policies and recommendations to support the efforts of those on the frontline – the miners, industry, and health-care workers.

The Energy Information Agency projects that coal will continue to be a substantial source of U.S. energy production and consumption well into the mid- to late-century. Unfortunately, Black Lung has made a resurgence and is killing miners, and each of us has a role to play in eliminating it once and for all.

We will continue to carry out our mandate to screen working coal miners for respiratory disease; however, given the continued contraction of the coal mining industry, it's much more likely for cases of disease to be recognized in the clinic setting. Therefore, we reiterate our previous plea to clinicians: when identifying an individual with interstitial fibrosis consider their full occupational history.

Dr. Halldin and Dr. Laney are from the Surveillance Branch, Respiratory Health Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV.

Join us in Italy

Bologna, Italy, will set a perfect backdrop for CHEST Congress 2020, hosted by CHEST and the CHEST Italian Delegates. This premier education event in pulmonary, critical care, and sleep medicine will give attendees access to world-renowned faculty from regional and international centers of excellence.

Whether you choose to attend sessions focusing on thoracic malignancies, airway disorders, chest infections, interventional pulmonary procedures, or sleep disorders, you can expect CHEST's expertise in simulation-based education, case- and problem-based sessions, and evidence-based medicine to shine through. We will be featuring innovative and diverse education opportunities incorporating the best of CHEST Annual Meeting, including lectures, recent advancements in clinical practice and science, guided poster presentations, and hands-on

simulation opportunities.

Additionally, look for CHEST Challenge to come to Italy! This international meeting will connect the best minds in chest medicine from Europe, the United States, and other countries around the world to help you and your team learn the latest and greatest in chest medicine.

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Italy attracts hundreds of thousands of people from all over the world each year, and it is easy to see why; Italy, a European country with a long Mediterranean coastline, has left a powerful mark on Western culture and cuisine. Bologna is the lively, historic capital of the Emilia-Romagna region in northern Italy. Piazza Maggiore is a sprawling plaza lined with arched colonnades;

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cafes; and medieval and Renaissance structures such as City Hall, the Fountain of Neptune, and the Basilica di San Petronio. Italy has easy rail transportation between cities, so plan to extend your stay and visit any number of the great Italian cities, including Rome: home of the Vatican, landmark art, and ancient ruins.

Make your plans soon for CHEST Congress 2020 in Bologna – June 25-27.

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The Piazza Maggiore in Bologna, Italy

CRITICAL CARE COMMENTARY

Neuromuscular blockade for ARDS in the ICU

BY ROBERT C. HYZY, MD, FCCP

The ability to control the delivery of ventilation to patients having the acute respiratory distress syndrome (ARDS) without encountering patient respiratory effort via the administration of neuromuscular blocking drugs has been a potentially appealing therapeutic option for decades (Light RW, et al. *Anesth Analg.* 1975;54[2]:219). This practice had been common in the late 20th century in order to avoid excessive tachypnea and appearance of patient discomfort with the collateral benefit of improving oxygenation and decreasing the fraction of inspired oxygen (Fio_2) (Hansen-Flaschen JH, et al. *JAMA*. 1991;26:2870).

Following the publication by the NIH-sponsored ARDS Network of the landmark low tidal volume lung protective ventilation trial, whereupon study subjects had been allowed to breathe up to 35 times per minute (ARDS Network, *N Engl J Med.* 2000;342[18]:1301) and additional concerns that neuromuscular blockade could potentially be associated with neuromuscular weakness, this practice fell out of favor.

Although the validity of using lung protective ventilation in ARDS, with a plateau pressure of less than 30 cm/H_2O via delivery of a low tidal volume, has withstood the test of time, subsequent attempts to utilize methods that would further protect the lung with additional "rescue" approaches to mechanical ventilation led to a partial renaissance of the neuromuscular blockade (NMB) approach. For example, high frequency oscillatory ventilation, with its idiosyncratic delivery of minute volumes of ventilator gas, requires NMB in order to be used. However, the publication of two negative trials, including one demonstrating an increased mortality, sidelined this approach (Ferguson ND, et al. *N Engl J Med.* 2013;368[9]:795).

More notably, the use of NMB in patients with ARDS has been advocated during conventional mechanical ventilation to avoid the generation of large tidal volumes via ventilator asynchrony occurring during patient-triggered breaths. Ostensibly, wiping out any patient effort via NMB eliminates manifestations of asynchrony, such as double triggering, which can generate areas of regional tidal hyperinflation in the injured lung and thereby worsen ventilator-induced lung injury. The utilization of NMB early in the course of ARDS (less than 48 hours) resulted in less lung inflammation (Forel JM, et al. *Crit Care Med.* 2006;34[11]:2749).

Subsequently, the ACURASYS trial found that patients with moderately severe or severe ARDS treated with NMB had a mortality benefit comparable to that seen in the original ARDS low tidal volume trial (Papazian L, et al. *N Engl J Med.* 2010;369:980).

Several criticisms of ACURASYS led to the desire for a larger confirmatory trial be undertaken. The NIH-sponsored successor to the ARDS Network, the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network, took this on straight away with its formation in 2014 (disclosure: the author is a Principal Investigator of one of the 13 PETAL Network Clinical Centers). This trial, called the Re-Evaluation of Systemic Early Neuromuscular Blockade, the ROSE trial, was published last year in the New England Journal of Medicine and failed to confirm a mortality benefit to NMB when used early in the course of ARDS, such as had been done earlier (Moss M, et al. *N Engl J Med.* 2019;380[21]:1997).

Dr. Hyzy

What then, should clinicians consider the proper use of NMB in ARDS to be?

There has been a recent spate of large negative trials of once-promising interventions in critical care medicine (Laffey. *Lancet Respir Med.* 2018;6[9]659). Among these were trials related to early mobility, vitamin D administration, transpulmonary pressure titrated positive end-expiratory pressure (PEEP), and of course, high frequency oscillatory ventilation, just to name a few disappointments. Recognition of heterogeneity of treatment effect (HTE), with some subgroups being more likely to respond to an intervention than others (Iwashyna. *Am J Respir Crit Care Med*. 2015;192[9]:1045), is cold comfort to the bedside clinician and all but the most dedicated health services researcher. At least to date, personalized medicine has fallen short of prospective validation in ARDS (Constantin et al. *Lancet Respir Med.* 2019;7[10]:870).

The failure of the ROSE trial to demonstrate a mortality benefit to ARDS patients with a P/F ratio of less than 150 on at least 8 cm H_2O treated with early NMB means the routine use of this approach in all such patients isn't warranted. In a prescient nod to HTE, "a foolish consistency," as Emerson said, "is the hobgoblin of little minds." Importantly, there were several subtle but not necessarily irrelevant differences between ACURASYS and ROSE. ROSE used a high PEEP algorithm to titrate PEEP to Fio_2, rather than the conventional low PEEP approach used in the original ARDS Network and ACURASYS trials. Potentially, the benefits of NMB on the injured lung in ARDS may have been mitigated by using higher PEEP levels. ROSE also failed to demonstrate a decrease in barotrauma as had been reported earlier. That said, it is difficult to ascribe the lack of benefit of NMB mechanistically to less asynchrony induced regional tidal hyperinflation in the NMB group at high PEEP, especially given the lighter sedation targets employed in both the NMB and the placebo group. Meanwhile, ROSE did confirm patients were not harmed by NMB by resulting in more neuromuscular weakness upon recovery.

Among patients with Berlin severe ARDS (ie. P/F less than 100 on at least 5 cm H_2O PEEP) evaluated between publication of ACURASYS and ROSE, clinicians were far more inclined to use NMB than other rescue modalities, including prone ventilation (Duan, *Ann Am Thorac Soc.* 2017;12:1818).

It seems unlikely the publication of ROSE will alter this. As rescue modalities go, NMB is relatively inexpensive, widely available and easily performed (Co, I and Hyzy RC, *Crit Care Med.* 2019 Dec 18. doi: 10.1097/CCM.0000000000004198).

Ultimately, though the question isn't whether NMB will be used in ARDS patients with refractory hypoxemia early or even later, but whether prone ventilation should be simultaneously initiated at the time of, or even before the institution of NMB.

As in ACURASYS, patients in the landmark PROSEVA prone ventilation trial were treated with a low PEEP algorithm (Guérin C et al. *N Engl J Med*. 2013;368[23]:2159).

Prone ventilation has many salutary physiologic benefits, not the least of which is recruitment of areas of collapsed lung. Patients who are recruitable with PEEP, i.e. whose PaO_2 increases with increasing PEEP in the face of an unchanged or minimally changed plateau pressure, may also demonstrate a mortality benefit (Goligher, EC et al. *Am J Respir Crit Care Med*. 2014;190[1]:70).

It remains unknown whether prone ventilation would remain of significant benefit should a high PEEP approach be employed.

Prone ventilation clearly has its adherents (Albert, RK, *Ann Am Thorac Soc.* 2020;17[1]:24), although underutilization remains prevalent perhaps due to its somewhat cumbersome nature. While it might have been interesting had ROSE performed a simultaneous assessment of prone ventilation along with NMB via a factorial trial design, clinicians remain at the crossroads of how to escalate ventilator support in the ARDS patient with worsening, if not refractory hypoxemia. The use of NMB with a high PEEP approach often allows for recruitment and a concomitant lowering of Fio_2 to acceptable levels in advance of the utilization of prone ventilation. Although some clinicians are able to successfully utilize prone ventilation without NMB, many are not, and NMB use was widespread in PROSEVA.

With no evidence of harm, the employment of NMB in the setting of Berlin severe ARDS is entirely justifiable, whether occurring early or late in the clinical course, regardless of, or potentially with the concomitant employment of prone ventilation. These two rescue modalities remain first line and, despite evidence to the contrary (Li, et al. *Am J Respir Crit Care Med*. 2018;197[8]:991) should be employed in advance of others, most notably extracorporeal support.

Dr. Hyzy is with the Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor.

Thank you to the CHEST 2020 Scientific Program Committee

The CHEST 2020 Scientific Program Committee has been working tirelessly to select the best and most clinically relevant sessions for the upcoming meeting. CHEST would like to extend a heartfelt thank you to all who actively participated in grading, curriculum group calls, the live meeting in February, and all the homework in between. We're not done, but your work has been instrumental in making the CHEST Annual Meeting 2020 a success.

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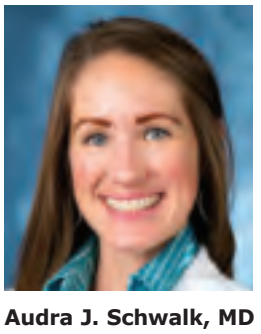

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Meet the 2019 FISH Bowl finalists

CHEST 2019 marked the inaugural FISH Bowl competition for attendees. Inspired by Shark Tank, our kinder, gentler, yet still competitive and cutting-edge FISH Bowl (**F**urthering **I**nnovation and **S**cience for **H**ealth) featured CHEST members disrupting our beliefs about how clinical care and education are performed. As health-care providers, they presented innovative ideas pertaining to education and clinical disease for pulmonary, critical care, and sleep medicine.

Six finalists were chosen from dozens of submissions, and three emerged winners! In this new Meet the FISH Bowl Finalists series, CHEST introduces you to many of them – including Education Category Finalist Dr. Bhavani.

Name: Siva Bhavani
Institution: University of Chicago
Position: Pulmonary Critical Care Fellow

Title: Quizomics
Brief summary: Quizomics is a cutting-edge mobile app that hosts trivia competitions for medical conferences. Quizomics is unlike any medical trivia competition you have ever seen, because the Quizomics app can host 20,000 medical professionals simultaneously competing in the world's largest medical trivia competition. Physicians compete among thousands of peers in their respective specialties to prepare for boards, obtain CME, and gain recognition in their fields as they fight their way to the top of the leaderboard!

1. What inspired your innovation? The average person checks their phone every 12 minutes, and this is no different at medical conferences. Whether you are in line for coffee, looking around at posters, or listening to a lecture - very little time passes before you are again checking your phone. The natural engagement we have with our phones can be leveraged for educational purposes by introducing gamified medical education platforms like Quizomics. I was inspired because the future of the medical conference demands digital engagement, gamified education, and large-scale social interaction. There is currently no platform that offers these services to prepare medical conferences for the digital education revolution that is coming.

2. Who do you think can benefit most from it, and why? The highest benefit is going to be to the physicians who are tired of the traditional CME options. Quizomics provides a high quality entertaining and educational platform for physicians to get CME while engaging and interacting with their peers. Further, physicians preparing for boards will find Quizomics an engaging alternative to the traditional textbooks. Finally, medical conferences will find that Quizomics can increase engagement, education, and attendance.

3. What do you see as challenges to your innovation gaining widespread acceptance? How can they be overcome? Content creation (trivia questions and explanations) is the biggest challenge to Quizomics. To overcome this, we plan to partner with tech-forward medical organizations that have high quality question banks in order to provide physicians with top-notch gamified education.

4. Why was it meaningful for you to emerge as a finalist in FISH Bowl 2019? FISH Bowl was an amazing opportunity to present Quizomics to others in the pulmonary/critical care specialty. Further, it was an opportunity to get direct feedback from leading educators in the field, and much of the resulting feedback has been incorporated into Quizomics.

5. What future do you envision for your innovation beyond FISH Bowl 2019? Quizomics is launching at a national neurosurgery board review course this winter. Following this pilot launch, Quizomics is scheduled for roll-out at Chicago area internal medicine residency programs through the summer of 2020. You can expect to see Quizomics at national conferences by 2021!

CHEST Foundation and Feldman Family Foundation Casino Night promises fun for a good cause

Keeping the momentum from our first-ever CHEST Foundation Reception and Casino Night at CHEST 2019, where champions in attendance raised more than $35,000 for pulmonary fibrosis research, the CHEST Foundation continues their long-standing partnership with the Feldman Family Foundation and invites you to the 7th Annual Irv Feldman Texas Hold 'Em Annual Tournament & Casino Night!

Funds raised at the event support the CHEST Foundation's mission-based programming and directly impact patients living with pulmonary fibrosis by providing them with access to chest medicine experts; assistance in securing medication and portable oxygen; and empowering the patients and their clinicians to better manage their disease.

Join us at 6:00 PM on Saturday, March 7, at Chevy Chase Country Club in Wheeling, Illinois, for an exciting evening of play. The grand prize winner of the poker tournament receives a coveted seat at the World Series of Poker Main Event – allowing them to test their mettle against the world's best players. We will also be hosting a plethora of other casino games like blackjack, craps, and roulette and an ever-expanding silent auction giving everyone a chance to join in on the fun and contribute to the fight against pulmonary fibrosis.

Interested in sponsoring the event, purchasing tickets, or receiving more information about the tournament? Contact Angela Perillo, Director of Development and Foundation Operations, at aperillo@chestnet.org.

Hope to see you March 7th!

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