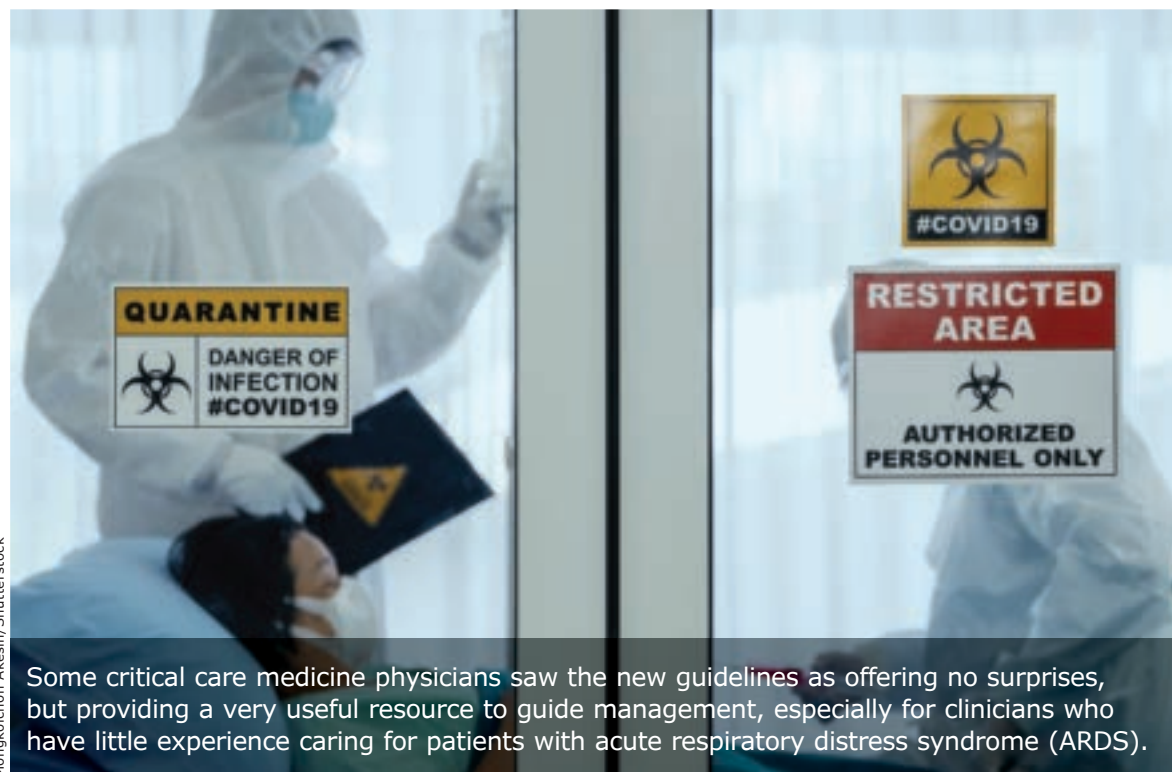




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Some critical care medicine physicians saw the new guidelines as offering no surprises, but providing a very useful resource to guide management, especially for clinicians who have little experience caring for patients with acute respiratory distress syndrome (ARDS).

COVID-19 critical care guidelines offer support to frontline clinicians

BY MITCHEL L. ZOLER

MDedge News

The Society of Critical Care Medicine released its first set of guidelines for managing critically ill patients with novel coronavirus disease (COVID-19) on March 20, 2020.

The 49 recommendations and statements it included are geared to “support hospital clinicians managing critically ill adults with COVID-19 in the ICU. The target users of this guideline are frontline clinicians, allied health professionals, and policy makers involved in the care of patients with COVID-19 in the ICU,” said the

document, written by a panel of 36 experts organized by the Surviving Sepsis Campaign, a joint program of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.

The document divides the recommendations into four categories: infection control, which includes 3 “best-practice” statements and 5 “weak” recommendations; hemodynamics, with 2 “strong” recommendations and 13 weak ones; ventilation, with 1 best-practice statement, 6 strong recommendations, and 12 weak recommendations; and therapy, with 7 weak recommendations. The guidelines also included five

COVID-19 // continued on page 7

E-cigarettes: Gateway to smoking regular cigarettes

BY JAKE REMALY

MDedge News

Youth who use e-cigarettes are five times more likely to become regular cigarette users 1 year later, according to a study published in the American Journal of Preventive Medicine. In addition, the number of days of e-cigarette use at baseline correlates with the number of days of cigarette smoking 1 year later, said Olatokunbo Osibogun, MBBS, PhD, a researcher in the department of epidemiology at Florida International University, Miami, and colleagues. “These results call for careful consideration of e-cigarettes’ harm reduction potential in the society and for strong policy and regulatory efforts to protect the American youth,” Dr. Osibogun and colleagues said.

E-cigarettes are the most common tobacco or nicotine product used by youth in the United States. Their popularity “is happening at a time when e-cigarettes are promoted as a tobacco harm reduction product that offers hope for adult smokers who could not quit otherwise,” the researchers said. “The balance between these

E-CIGARETTES // continued on page 4

INSIDE HIGHLIGHT



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Page 18


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two aspects of e-cigarettes’ role in society, that is, helping adult smokers versus recruiting youth to nicotine, has become a defining feature of the tobacco harm reduction debate and has policy and regulatory implications.”

Whether e-cigarette use among

youth is a risk factor for subsequent cigarette smoking is a contentious issue. Prior studies examining this question were cross-sectional, did not adjust for relevant covariates, or had small sample sizes or short follow-up durations, the researchers said.

Some looked at experimentation, not regular use.

Data from the Population Assessment of Tobacco and Health (PATH) cohort provide an opportunity to study the gateway question in a way that addresses limitations of previous studies, they said.

The PATH Study

The PATH Study is an ongoing, nationally representative, longitudinal cohort study of approximately 46,000 adults and youth aged 12 years and older in the United States. Study participants complete surveys related to tobacco use and health.

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For the present analyses, the investigators examined youth data from Wave 1 (2013-2014), Wave 2 (2014-2015), and Wave 3 (2015-2016). They defined current e-cigarette use as e-cigarette use in the past 30 days among cigarette nonsmokers (that is, those who did not report cigarette smoking in the past 30 days). They defined regular cigarette

smoking at Wave 2 and Wave 3 as reported cigarette smoking on 20 or more days in the past 30 days.

The researchers adjusted for covariates such as age, sex, race or ethnicity, parents' education, sensation-seeking behavior, other tobacco product use, alcohol use, marijuana use, prescription drug abuse, living with a tobacco user, susceptibility

to cigarette smoking, and noticing cigarette health warning labels. The researchers applied multivariable logistic regression models to evaluate associations between current e-cigarette use at baseline and regular cigarette smoking at follow-up.

Among 7,438 youth, 5.3% of current e-cigarette users at Wave 1 and Wave 2 reported regular cigarette

smoking 1 year later, compared with 0.3% of participants who were not using e-cigarettes. In the 2-year progression analysis, which included 7,185 participants, 8.2% of current e-cigarette users identified at Wave 1 reported regular cigarette smoking 2 years later, compared with 0.8% of participants who were not using e-cigarettes at baseline. In the multivariable logistic regression analyses, current e-cigarette users had five times higher odds of regular cigarette smoking in the 1-year progression model, compared with participants who were not current e-cigarette users. In the 2-year progression model, current e-cigarette users had 3.4 times higher odds of regular cigarette use, but this result was not statistically significant. "Additionally,

for every unit increase in the number of days of e-cigarette use at baseline, there was an increase in the number of days of cigarette smoking by 0.4 in the 1-year progression model," Dr.



Dr. Leone

Osibogun and colleagues reported.

Not all participants in the main analyses were naïve to cigarette use, but a sensitivity analysis that focused on participants who had never used cigarettes at baseline also found that e-cigarette users had higher odds of subsequent cigarette smoking.

The findings "offer strong support to e-cigarettes' potential to lead to regular cigarette smoking among youth," the researchers said. "By focusing on use patterns that are unlikely to reflect experimentation but rather represent robust transitions, this study shows that e-cigarette use precedes and strongly predicts regular cigarette smoking, even after adjusting for factors known to predispose to cigarette smoking."

Quantifying harms

The study provides one more significant piece of circumstantial evidence that e-cigarette smoking is associated with increased probability of cigarette smoking, said Frank T. Leone, MD, FCCP, commenting on the study. Dr. Leone is associate professor of medicine at University of Pennsylvania Medical Center and director of Penn Medicine's Comprehensive Smoking Treatment Program, both in Philadelphia. Various studies point in the direction that e-cigarette use causes nicotine dependence in "some substantial portion of the adolescent popula-

Continued on following page

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Funding failures: Tobacco prevention and cessation

BY RICHARD FRANKI

MDedge News

When it comes to state funding for tobacco prevention and cessation, the American Lung Association grades on a curve. It did not help.

The ALA gave failing grades to 43 states in its State of Tobacco Control report, along with three A's, one C, and four D's.

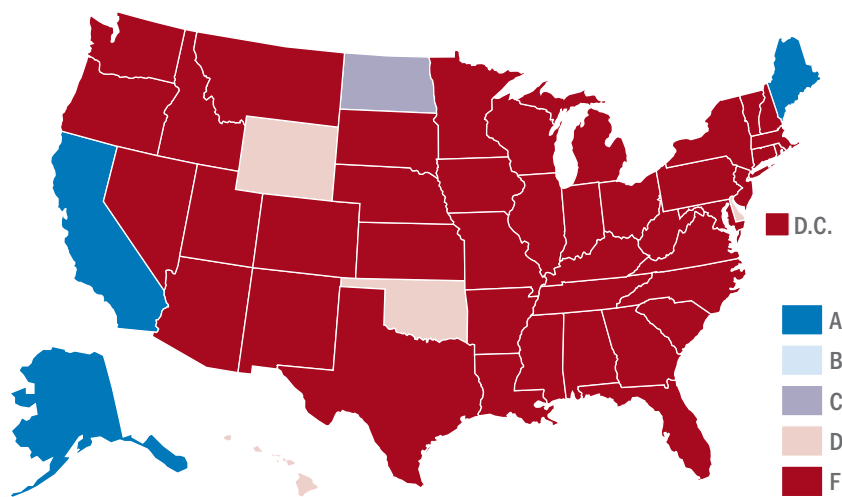
Each state's annual funding for tobacco prevention and cessation was calculated and then compared with the Centers for Disease Control and

Prevention's recommended spending level. That percentage became the grade, with any level of funding at 80% or more of the CDC's recommendation getting an A and anything below 50% getting an F.

The three A's went to Alaska – which spent \$10.14 million, or 99.4% of the CDC-recommended \$10.2 million – California (96.0%), and Maine (83.5%). The lowest levels of spending came from Georgia, which spend just 2.8% of the CDC's recommendation of \$106 million, and Missouri, which spent 3.0%,

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State grades: Tobacco prevention and cessation funding, 2020



MDedge News

Note: Grades based on the proportion of a state's total funding to the CDC's recommended level.

Source: American Lung Association

Continued from previous page

tion,” he said. “That has serious consequences.”

In adolescents, the central nervous system is highly plastic. E-cigarette use may cause structural changes to the brain that create “a perfect storm” where the development of tobacco dependence is far more likely, said Dr. Leone. E-cigarette use may not be deterministic, but “the chances are way higher.”

Whether e-cigarette use reduces harm relative to cigarettes remains an open question, and the harms of e-cigarettes are not well characterized, he said. Even assuming that e-cigarettes do benefit certain patients, does the benefit outweigh the harm of promoting nicotine dependence?

Physical harms such as lung cancer and emphysema may take decades to develop. “But what about doing well in school? Other addictions? Trouble with attention? Anxiety and depressive disorders? Those

kinds of harms are intrinsically difficult to capture,” Dr. Leone said. “Those are the harms that are most likely to affect this group of people.”

In addition, the wide range of e-cigarette products and modes of delivery means that the ability to calculate harm with “any kind of reliability ... goes right out the window,” he said. “There are lots of breadcrumbs that keep getting dropped that should give us pause, should make us take a step back, and think, ‘Things that I may have assumed to be true in the beginning may no longer be true and how should that affect my calculus?’”

The study authors disclosed support from the National Institute on Drug Abuse, the National Institutes of Health, and Florida International University.

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SOURCE: Osibogun O et al. Am J Prev Med. 2020 Mar 5. doi: 10.1016/j.amepre.2020.01.003

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

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Delaying cancer surgery during the COVID-19 outbreak

BY ROXANNE NELSON, RN, BSN

Cancer surgeries may need to be delayed as hospitals are forced to allocate resources to a surge of COVID-19 patients, says the American College of Surgeons, as it issues a new set of recommendations in reaction to the crisis.

Most surgeons have already curtailed or have ceased to perform elective operations, the ACS notes, and recommends that surgeons continue to do so in order to preserve the necessary resources for care of critically ill patients during the COVID-19 pandemic. The new clinical guidance for elective surgical case triage during the pandemic includes recommendations for cancer surgery as well as for procedures that are specific to certain cancer types.

First, decisions about whether to proceed with elective surgeries must consider the available resources of local facilities. The parties responsible for preparing the facility to manage coronavirus patients should be sharing information at regular intervals about constraints on local resources,

especially personal protective equipment (PPE), which is running low in many jurisdictions. For example, if an elective case has a high likelihood of needing postoperative ICU care, it is imperative to balance the risk of delay against the need of availability for patients with COVID-19.

Second, care coordination should use virtual technologies as much as possible, and facilities with tumor boards may find it helpful to locate multidisciplinary experts by virtual means, to assist with decision making and establishing triage criteria.

Three phases of pandemic

The ACS has also organized decision making into three phases that reflect the acuity of the local COVID-19 situation:

- Phase I. Semi-Urgent Setting (Preparation Phase) – few COVID-19 patients, hospital resources not exhausted, institution still has ICU ventilator capacity and COVID-19 trajectory not in rapid escalation phase
- Phase II. Urgent Setting – many COVID-19 patients, ICU and ven-

- tilator capacity limited, operating room supplies limited
- Phase III. Hospital resources are all routed to COVID-19 patients, no ventilator or ICU capacity, operating room supplies exhausted; patients in whom death is likely within hours if surgery is deferred

Thoracic cancer surgery

Thoracic cancer surgery guidelines follow those for breast cancer. Phase I should be restricted to patients whose survival may be impacted if surgery is not performed within next 3 months. These include:

- Cases with solid or predominantly solid (>50%) lung cancer or presumed lung cancer (>2 cm), clinical node negative
- Node-positive lung cancer
- Post-induction therapy cancer
- Esophageal cancer T1b or greater
- Chest wall tumors that are potentially aggressive and not manageable by alternative means
- Stenting for obstructing esophageal tumor
- Staging to start treatment (mediastinoscopy, diagnostic video-assisted thoracoscopic surgery for

- pleural dissemination)
- Symptomatic mediastinal tumors
- Patients who are enrolled in therapeutic clinical trials.

Phase II would permit surgery if survival will be impacted by a delay of a few days. These cases would include nonseptic perforated cancer of esophagus, a tumor-associated infection, and management of complications in a hemodynamically stable patient.

All thoracic procedures considered routine/elective would be deferred.

Phase III restricts surgery to patients whose survival will be compromised if they do not undergo surgery within the next few hours. This group includes perforated cancer of esophagus in a septic patient, a patient with a threatened airway, sepsis associated with the cancer, and management of surgical complications in an unstable patient (active bleeding that requires surgery, dehiscence of airway, anastomotic leak with sepsis).

The guidelines can be found at <https://bit.ly/2UjlnQj>.

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

Nonspecialists treating COVID-19 patients may need this guidance // continued from page 1

management questions considered by the writing panel without arriving at a recommendation because of insufficient evidence.

Useful guide for nonspecialists

Some critical care medicine physicians saw the new guidelines as offering no surprises, but providing a very useful resource to guide management, especially for clinicians who may become involved in caring for COVID-19 patients despite having little experience caring for patients with acute respiratory distress syndrome (ARDS).

“For those of us who manage ARDS patients all the time, this is not a lot of new information, but many critically ill COVID-19 patients are now being cared for by physicians who have not cared for these patients before,” commented Mangala Narasimhan, DO, FCCP, a critical care medicine physician at Long Island Jewish Medical Center in New Hyde Park, N.Y. In fact, Dr. Narasimhan and associates took the new guidelines soon after their release and used them to create a one-page summary sheet to give to all their colleagues who are now seeing COVID-19 patients, she said in an interview. “The guidelines are very important for clinicians who are suddenly taking care of a roomful of patients with ARDS.”



Dr. Narasimhan



Dr. Ferraro

“A lot of people want to know this information,” agreed David M. Ferraro, MD, FCCP, a pulmonologist and critical care medicine physician at National Jewish Health in Denver.

Perhaps the only potentially controversial aspect of the guidelines are a couple of weak recommendations that suggest using a high-flow nasal cannula (HFNC) rather than noninvasive positive pressure ventilation (NIPPV) in patients with acute hypoxemic respiratory failure who have not fully responded to conventional oxygen therapy. “This is controversial, and some of my colleagues are debating this,” said Dr. Narasimhan, but she noted that her clinic has decided to follow the recommended preference for HFNC, which seemed to have modest advantages over NIPPV in a recent meta-analysis (Intensive Care Med. 2019 May;45[5]:563-72).

Another issue with NIPPV is the higher risk for viral dispersion it seems to have, compared with a HFNC, said Dr. Ferraro. If a patient’s mask comes off during NIPPV, it creates a substantial risk for aerosolization of virus. That risk is likely lower with HFNC, especially a HFNC system that uses a small cannula without heating or humidification of the gas flow. “I’d recommend against NIPPV,” Dr. Ferraro said.

He also highlighted the value of quickly

forgoing continued use of either of these ventilatory approaches in a declining patient and having a low threshold to switch to intubation. “Many clinicians now favor erring on the side of early intubation,” he noted, an approach that the new guidelines endorsed in a best-practice statement: “In adults with COVID-19 receiving NIPPV or HFNC we recommend close monitoring for worsening respiratory status and early intubation in a controlled setting if worsening occurs.”

One aspect of the COVID-19 pandemic that the new guidelines don’t address are some of the challenges being faced from skyrocketing numbers of patients and inadequate supplies and manpower to meet their acute clinical needs. “We need recommendations on how systems should manage when they are overwhelmed,” commented Dr. Ferraro, an omission that he also saw in the COVID-19 management guidance released on March 13, 2020, by the World Health Organization.

“Neither document gets into this in depth, but that wasn’t in their scope,” Dr. Ferraro acknowledged. He said that recommendations on how to deal with scarce resources, inadequate staffing, and the health of clinicians are probably best handled on a state or local level rather than trying to create recommendations that are applicable to the entire U.S. health system.

Dr. Narasimhan and Dr. Ferraro reported that they had no disclosures.

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Delays of biologic prescriptions have consequences

BY RICHARD MARK KIRKNER

MDedge News

Insurance and specialty pharmacy delays in authorizing new biologic prescriptions for severe allergies leave waiting patients at risk of asthma attacks, hospitalizations, emergency department visits, and prednisone shots and their known side effects, according to a single-center study that was to have been presented at the annual meeting of the American Academy of Allergy, Asthma and Immunology.

The AAAAI canceled their annual meeting and provided abstracts and access to presenters for press coverage.

The study of 80 patients in State College, Pa., found that they waited an average of 44 days from when their doctor submitted the preauthorization request to the insurance company until the practice received the shipment for dispensing to the patient, investigator Faoud Ishmael, MD, PhD, of Mount Nittany Medical Group said in an interview. “The implication here is that these are really the most severe patients who, you would argue, need their medications the quickest, and it’s taking longer to get them than it would an inhaler,” Dr. Ishmael said.



Dr. Ishmael

The study focused on patients with severe asthma ($n = 60$) or urticaria ($n = 20$) who received a new prescription of monoclonal antibody therapy from March 2014 to August 2019. For asthma treatments, the average time was 45.8 days; for urticaria, 40.6 days ($P = .573$), Dr. Ishmael said. The researchers divided the total amount of time into two components: insurance plan review and approval ($P = .654$), and specialty pharmacy review and dispensing of the medicine, each of which averaged 22.8 days ($P = .384$), he said.

He also noted wide disparity in the range of approval times. “The shortest approval time was 1 day, and the longest 97 days,” Dr. Ishmael said. “It’s interesting that we had this really broad spread.”

What’s more, the study found no trend for the delays among insurers and specialty pharmacies, Dr.

Ishmael added. “When these prescriptions get submitted, it’s like a black box,” he said. “It really seems arbitrary why some of them take so long and some of them don’t.” The findings were independent of type of coverage, whether commercial or government, or even specific insurance plans. “It’s more the process that is flawed rather than one insurance company being the bad guy,” he said.

The study also looked at what happened to patients while they were waiting for their prescriptions to be delivered. “What we found is that over half of asthmatics had an exacerbation – 51% had at least one asthma attack where they needed prednisone,” Dr. Ishmael said ($P = .0015$), “and we had three patients admitted to the hospital over that time frame when they were waiting for the drugs.” One of those patients had been admitted



Dr. Craig

twice, making four total hospitalizations. Preliminary data analysis showed that about 40% of the patients who had attacks went to the emergency department.

For asthmatics who needed prednisone, the average dose was 480 mg ($P = .284$) – “a pretty substantial number,” in Dr. Ishmael’s words. He noted that a large portion of the study patients were obese, with a mean body mass index of 33 kg/m². Other comorbidities prevalent in the study population were hypertension and type 2 diabetes. “Prednisone is something that could worsen all of those conditions, so it’s not a trivial issue,” he said.

The study, however, didn’t evaluate costs of the interventions during the delay period vs. the costs of the medications themselves. Of the 80 prescriptions Dr. Ishmael and coauthors submitted, only one was rejected, that person being a smoker, he said. “I understand these are expensive medicines, but it’s counterproductive to delay them because in the long run the insurance company ends up paying for the hospitalization and the drug rather than just the drug,” he said.

Timothy Craig, DO, of Penn State Health Allergy, Asthma, and Immunology and professor of medicine and pediatrics at Penn State College

of Medicine, both in Hershey, said he was surprised at the brevity of the delays reported in Dr. Ishmael’s study. “They do much better than we do with preauthorization,” he said, noting that, in his experience, these approvals take much longer. He added that his own research has found faulty insurance plan algorithms are at the heart of these delays. “We need more studies to clarify how much this is interfering with patient care and how much risk they’re putting patients in,” he said.

The COVID-19 pandemic poses a double-edged sword for physicians managing patients with severe asthma, Dr. Craig noted. “Their asthma care is important, especially if they do test for COVID-19,” he said. On the other hand, doctors and nurses attending to COVID-19 patients will have less time to haggle with payers to expedite coverage for biologics for their severe asthma patients, he said. “I hope the flexibility is there, especially at this time to allow people to get on the biologics and stay on them,” he said.

Dr. Ishmael said these findings have serious implications because biologics are getting prescribed ever more frequently for asthma and hives. Steps his practice has taken to streamline the process include following the payer’s approval guidelines as closely as possible. This sometimes can mean making sure a patient with severe asthma has been maximized on controller medications before submitting the biologic prescription, he said. Another step is to use drug company programs to remove barriers to coverage.

Nonetheless, the approval process can be daunting even when taking those steps, he said. “Those guidelines that constitute approval may vary a lot from one insurer to another; and sometimes those guidelines are different from the criteria that studies may have used when these drugs were being evaluated in clinical trials,” he said. It would be helpful, he said, if payers used the National Heart, Lung, and Blood Institute and the Global Initiative for Asthma guidelines for biologics.

Dr. Ishmael has no relevant financial relationships to disclose.

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SOURCE: Ishmael F et al. AAAAI 2020, Session 809, Presentation 558

FDA broadens nintedanib ILD indication

BY MITCHEL L. ZOLER

MDedge News

A new indication for the tyrosine kinase inhibitor nintedanib approved by the Food and Drug Administration on March 9, 2020, broadened the drug’s targeted population to include patients with chronic fibrosing interstitial lung diseases with a progressive phenotype.

This new group of patients eligible for nintedanib treatment extends the drug’s labeling beyond patients with idiopathic pulmonary fibrosis (IPF) or interstitial lung disease (ILD) associated with systemic sclerosis or scleroder-

ma, and may come close to doubling the total number of eligible patients.

The new, expanded indication “helps to fulfill an unmet treatment need, as patients with these life-threatening lung diseases have not had an approved medication until now,” said Banu Karimi-Shah, MD, acting deputy director of the division of pulmonary, allergy, and rheumatology products in the FDA’s Center for Drug Evaluation and Research, in a written agency statement that announced the new indication.

The FDA first approved nintedanib (Ofev) for treating IPF in October 2014, and then granted a second indication in September 2019 for ILD as-

sociated with systemic sclerosis or scleroderma.

A recent assessment of 1,285 Canadian patients diagnosed with fibrotic ILD and entered into a national registry (CARE-PF) showed that IPF was the associated diagnosis for 25% of patients, and that the majority of patients had other primary diagnoses such as connective tissue disease ILD in 33% of enrolled patients, unclassifiable ILD in 22%, chronic sensitivity pneumonitis in about 8%, sarcoidosis in 3%, as well as other types (BMC Pulm Med. 2019 Nov 27. doi: 10.1186/s12890-019-0986-4).

It remains unclear right now what percentage

Continued on following page

Continued from previous page

of patients with fibrotic ILD have the progressive form that would make them eligible for nintedanib treatment under the new indication, but it's probably about another quarter of the entire ILD population, or roughly similar to the number of patients with an IPF etiology who are already eligible to get the drug, commented Martin Kolb, MD, a professor of respiratory at McMaster University, Hamilton, Ont., and a coinvestigator on the CARE-PF registry. A goal of the registry, which has now enrolled nearly 3,700 ILD patients, is to track them serially to get a better handle on the prevalence of progressive disease. The percentage of patients with ILD associated with systemic sclerosis or scleroderma is "relatively small," compared with these other two patients subgroups, Dr. Kolb said in an interview.

The evidence base for treating patients with progressive ILD is "really strong," he noted, and comes primarily from a major trial reported last year – the INBUILD study – that randomized 663 patients to treatment with either nintedanib or placebo and showed

that nintedanib treatment significantly cut the rate of decline in forced vital capacity during 1 year of treatment (New Engl J Med. 2019 Oct 31;381[18]:1718-27). "Conceptually, it makes so much sense" to treat the patients enrolled in INBUILD, the same patients who fit the new indication, with an agent like nintedanib that

slows fibrosis progression, and in some patients may bring progression to a virtual halt, said Dr. Kolb, a coinvestigator on the INBUILD study. The INBUILD study was sponsored by Boehringer Ingelheim, the company that markets nintedanib. Dr. Kolb has been a consultant to, received honoraria from, and received research fund-

ing from Boehringer Ingelheim. He has also received consulting fees or honoraria from Genoa, Gilead, GlaxoSmithKline, Indalo, Prometic, Roche, and Third Pole, and he has received research funding from Actelion, Alkermes, Gilead, GlaxoSmithKline, Pharmaxis, Prometic, RespiVert, and Roche.

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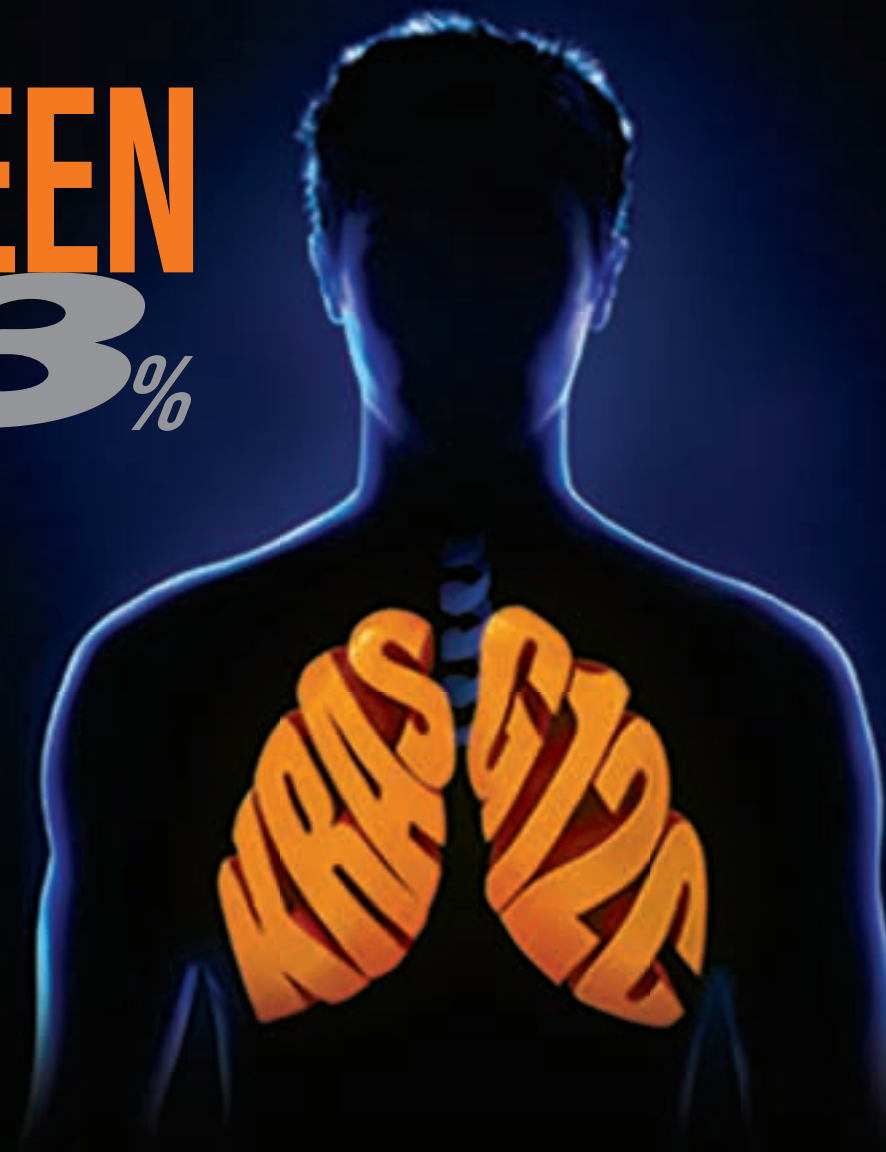
VIEW ON THE NEWS

Megan Conroy, MD, comments:

In treating patients with interstitial lung disease, the classification of disease into a clearly differentiated etiology is often difficult. Interstitial lung disease with autoimmune features may show progressive loss of lung function even before the underlying autoimmune disorder has declared itself within diagnostic criteria. The expansion of labeling for nintedanib to include a broader population of patients with progressive, fibrosing ILD including chronic hypersensitivity pneumonitis, ILD with autoimmune features, and idiopathic nonspecific interstitial pneumonia provides an option for slowing of disease progression even in the absence of cleanly differentiated disease etiology, adding an important therapeutic option for this patient population.



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EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer.

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PULMONOLOGY

GLP-1R agonists linked to lower inflammatory biomarker levels

BY RICHARD MARK KIRKNER

MDedge News

Patients with both type 2 diabetes and asthma who were on glucagon-like peptide receptor-1 (GLP-1R) agonists for glucose control had lower levels of a key biomarker of airway inflammation than similar patients on other types of glucose-control medications, according to results of a study to have

“At this point, further study is needed to understand the clinical impact of GPL-1R [agonists] in asthma...for patients with type 2 diabetes.”

been presented at the annual meeting of the American Academy of Asthma, Allergy, and Immunology. The AAAAI canceled their annual meeting and provided abstracts and access to presenters for press coverage.

The findings from this study potentially replicated findings in humans that have been reported in preclinical trials.

“Our work showed that type 2 diabetics with asthma who were treated with GLP-1 receptor agonists had lower levels of periostin, and this provides really one of the first human data to show that these drugs may impact key inflammation pathways in the airway,” Dinah Foer, MD, of Brigham and Women’s Hospital, Boston, said in an interview. She described periostin as “a known critical inducer of airway mucus production and airway responsiveness.”

The study retrospectively evaluated serum samples from the Partners HealthCare Biobank of 161 adults with both asthma and type 2 diabetes, 42 of whom were on GLP-1R agonists and 119 of whom were taking non-GLP-1R agonist diabetes medications. The study used the Partners Healthcare EHR to identify eligible patients.

The study found that periostin levels were significantly decreased in GLP-1R agonist users: 19.1 ng/mL (standard deviation, +8.7) versus 27.4 ng/mL (SD, +14) in the non-GLP-1R agonist group ($P = .001$), Dr. Foer said. The other known

mediators of asthma inflammatory pathways that were measured – interleukin-6, IL-8, sCD163, total IgE, and sST2 (soluble suppression of tumorigenesis-2) – showed no differences between the two groups, Dr. Foer said.

She said that this was the first human study to show similar results to preclinical models of asthma pathways. “What was interesting to us was that our findings were robust even when we controlled for covariates,” she added.

These findings lay the groundwork for further research into the potential therapeutic role GLP-1R agonists in asthma, Dr. Foer said. “This supports using periostin as a biomarker for novel therapeutic use of GLP-1R [agonists] in asthma,” she said. “At this point, further study is needed to understand the clinical impact of GPL-1R [agonists] in asthma both for patients with type 2 diabetes and potentially in the future for patients who don’t have type 2 diabetes or metabolic disease.”

She added: “I don’t think we’re there yet; this is just one foot forward.”

The next step for researchers involves analyzing outcomes in asthmatics with type 2 diabetes on GLP-1R agonist therapy using a larger sample size as well as patients with asthma and metabolic disease, Dr. Foer said. The goal would be to identify corresponding biomarkers.

“There’s a terrific conversation in the field about the relationships between metabolism and asthma,” she said. “What our data contributes to that is, it suggests a role for metabolic pathways, specifically as it’s related GLP-1R [agonist] signaling pathways in regulating airway inflammation.”

Mark Moss, MD, associate professor of allergy & immunology at the University of Wisconsin–Madison, who was to serve as the moderator of the session, was positive about the GLP-1R agonist findings. He said in an interview: “This is promising research that provides a possible new target for the treatment of asthma.”

Dr. Foer disclosed that she has no relevant financial relationships.

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SOURCE: Foer D et al. AAAAI, Session 462, Abstract 8.

Airway anomalies may raise adenotonsillectomy risk

BY MITCHEL L. ZOLER

MDedge News

Underlying cardiac disease, airway anomalies, and younger age each independently boosted the risk of severe perioperative respiratory adverse events (PRAE) in children undergoing adenotonsillectomy to treat obstructive sleep apnea, in a review of 374 patients treated at a single Canadian tertiary referral center.

In contrast, the analysis failed to show independent, significant effects from any assessed polysomnography or oximetry parameters on the rate of postoperative respiratory complications. The utility of preoperative polysomnography or oximetry for risk stratification is questionable for pediatric patients scheduled to adenotonsillectomy to treat obstructive sleep apnea, wrote Sherri L. Katz, MD, of the University of Ottawa, and associates in a recent report published in the *Journal of Clinical Sleep Medicine*, although they also added that making these assessments may be “unavoidable” because of their need for diagnosing obstructive sleep apnea and determining the need for surgery.

Despite this caveat, “overall our study results highlight the need to better define the complex interaction between comorbidities, age, nocturnal respiratory events, and gas exchange abnormalities in predicting risk for PRAE” after adenotonsillectomy, the researchers wrote. These findings “are consistent



Patients with an airway anomaly had a 219% increased rate of perioperative respiratory adverse events, compared with those with no anomaly; patients with underlying cardiac disease had a 109% increased rate, compared with those without cardiac disease.

with existing clinical care guidelines” and “cardiac and craniofacial conditions have been associated with risk of postoperative complications in other studies.” The analysis used data collected from all children aged 0-18 years who underwent polysomnography assessment followed by adenotonsillectomy at one Canadian tertiary referral center, Children’s Hospital of Eastern On-

tario in Ottawa, during 2010-2016. Their median age was just over 6 years, and 39 patients (10%) were younger than 3 years at the time of their surgery. More than three-quarters of the patients, 286, had at least one identified comorbidity, and nearly half had at least two comorbidities. Polysomnography identified sleep-disordered breathing in 344 of the children (92%), and diag-

nosed obstructive sleep apnea in 256 (68%), including 148 (43% of the full cohort) with a severe apnea-hypopnea index.

Sixty-six of the children (18%) had at least one severe PRAE that required intervention. Specifically these were either oxygen desaturations requiring intervention or need for airway or ventilatory support with interventions such as jaw thrust, oral or nasal airway placement, bag and mask ventilation, or endotracheal intubation.

A multivariate regression analysis of the measured comorbidity, polysomnography, and oximetry parameters, as well as age, identified three factors that independently linked with a statistically significant increase in the rate of severe PRAE: airway anomaly, underlying cardiac disease, and young age. Patients with an airway anomaly had a 219% increased rate of PRAE, compared with those with no anomaly; patients with underlying cardiac disease had a 109% increased rate, compared with those without cardiac disease; and patients aged younger than 3 years had a 310% higher rate of PRAE, compared with the children aged 6 years or older, while children aged 3-5 years had a 121% higher rate of PRAE, compared with older children.

The study received no commercial funding. Dr. Katz has received honoraria for speaking from Biogen that had no relevance to the study.

mzoler@mdedge.com

SOURCE: Katz S et al. *J Clin Sleep Med*. 2020 Jan 15;16(1):41-8

VIEW ON THE NEWS

Mary Cataletto, MD, FCCP, comments:

There are a number of syndromes, for example, Down syndrome (DS), Beckwith Wiedemann syndrome, and Prader Willi syndrome, that are associated with higher prevalence of obstructive sleep apnea. The craniofacial and airway features are different in each of them and knowledge about the syndrome and the child’s exam will influence decision making. Children with DS, for example, are known to have a higher incidence of OSA with a prevalence estimated at about 70%. OSA in DS is classified as severe in almost 50%. Adenotonsillectomy remains the most common intervention for OSA in children with DS although evidence suggests that there is often residual apnea despite AT. Other therapies are often needed. Factors that may influence the presence and severity of OSA in DS include generalized hypotonia, large tongue, midfacial hy-

poplasia, small mouth, small airway caliber, and lingual tonsillar hypertrophy. Children with DS also they have a higher incidence of other airway anomalies – laryngomalacia, subglottic stenosis, and tracheomalacia.

In each child referred for adenotonsillectomy, careful consideration must be given to potential risks and benefits. Team selection, location and timing of the procedure, preoperative preparations, management of comorbid conditions, and arrangements for postoperative monitoring and management are considered in those selected as surgical candidates. For children who are not deemed to be appropriate surgical candidates, alternatives are available and individualized to the child’s needs.

There is clearly more work to be done. While this study is limited by its retrospective nature and potential referral bias, it adds to our medical knowledge by presenting a detailed simultaneous

analysis polysomnography and clinical data in a large cohort of children with obstructive sleep apnea who underwent adenotonsillectomy. Notably approximately three-quarters of these children had at least one comorbid condition. Underlying cardiac disease, airway anomalies, and young age were identified as independent predictors of perioperative risks for respiratory adverse events. These findings contrast with previous studies where polysomnography metrics were found to be independent predictors of postoperative respiratory adverse events. This paper is an important addition to medical knowledge and highlights the need to better define the complex interactions among comorbid conditions.



Cardiac arrest: Targeted temperature management may be a game changer

BY BRUCE JANCIN

MDedge News

SNOWMASS, COLO. – Targeted temperature management maintained at 32-36 degrees Celsius is now a strong class I recommendation for all comatose patients who experience return of spontaneous circulation after out-of-hospital cardiac arrest, including those with nonshockable rhythms, Erin A. Bohula, MD, PhD, said at the annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.

“Our practice is that there are no absolute contraindications to targeted temperature management at the Brigham. Everybody gets cooled,” said Dr. Bohula, a cardiologist and critical care specialist at Brigham and Women’s Hospital and Harvard Medical School, Boston.

The current ACC/AHA guidelines declare: “There are essentially no patients for whom temperature control somewhere in the range between



BRUCE JANCIN/MDEDGE NEWS

“Our practice is that there are no absolute contraindications to targeted temperature management at the Brigham. Everybody gets cooled,” said Dr. Erin A. Bohula.

32 degrees C [89.6 F] and 36 degrees C [96.8 F] is contraindicated.” The writing committee cited “recent clinical trial data enrolling patients with all rhythms, the rarity of adverse effects in trials, the high neurologic morbidity and mortality without any specific interventions, and the preponderance of data suggesting that temperature is an important variable for neurologic recovery” (Circulation. 2015 Nov 3;132[18 Suppl 2]:S465-82).

“That’s a pretty strong statement,” Dr. Bohula observed.

The current guidelines, which date back to 2015, give a class I, level of evidence B recommendation for targeted temperature management (TTM) in patients who are comatose with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest involving ventricular fibrillation or pulseless ventricular fibrillation. The bedside definition of comatose is lack of meaningful response to verbal commands to squeeze hands, blink, or move toes.

The current recommendation for TTM in patients resuscitated from out-of-hospital cardiac arrest with a nonshockable rhythm is class I, level of evidence C, meaning it’s based on expert consensus. However, that recommendation is now out of date and due for a level-of-evidence upgrade in light of the recent results of the French HYPERION trial, an open-label randomized trial of 584 patients resuscitated from cardiac arrest with a nonshockable rhythm. Although 90-day mortality was similarly high in the TTM and targeted normothermia groups, the rate of favorable neurologic outcome as assessed by a Cerebral Performance Category scale score of 1 or 2 was 10.2% in the TTM group, significantly better than the 5.7% rate in controls (N Engl J Med. 2019 Dec 12;381[24]:2327-37).

The 2010, ACC/AHA guidelines recommended a TTM range of 32-34 degrees C, but on the basis of subsequent persuasive randomized trial data, that range was broadened to 32-36 degrees C in the 2015 guidelines, with a class IB recommendation. Maintenance of TTM for at least 24 hours has a IIa, level of evidence C recommendation in the current guidelines.

The guidelines emphasize that specific features may favor selection of one temperature for TTM over another. For example, patients with seizures or cerebral edema might be better off with TTM at a lower temperature, while a higher temperature may be best for those with bleeding or severe bradycardia. At Brigham and Women’s Hospital, the default temperature is 33 degrees C. However, TTM with a goal of 36 degrees C is seriously considered in patients with recent head trauma, major surgery within the past 2 weeks, refractory hypotension, severe sepsis, pregnancy, or high bleeding risk. Rewarming is done at a rate of 0.25 degrees C per hour, with sedation maintained until the patient has been returned to 98.6 degrees F, according to Dr. Bohula.

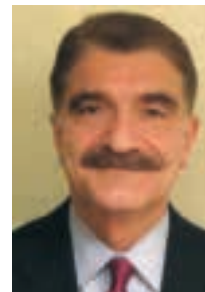
Based on several negative studies of TTM using rapid infusion of chilled fluids in the ambulance en route to the hospital, the guidelines rate that practice class IIIA, meaning don’t do it. Avoidance of a systolic blood pressure below 90 mm Hg and a mean arterial pressure of less than 65 mm Hg gets a class IIb level of evidence C recommendation to lessen the risk of cerebral hypoxia.

TTM a major breakthrough

Prior to the introduction of TTM, comatose patients with ROSC after out-of-hospital cardiac arrest had a dreadful prognosis, with survival rates of 1%-10% in registry studies. In contrast, the survival rate in the landmark TTM clinical trials was 50%-60%. And while that’s a dramatic improvement, ROSC after cardiac arrest remains a high-mortality condition. Dr. Bohula was first author of a report by the Critical Care Cardiology Trials Network, composed of 16 tertiary cardiac intensive care units in the United States and Canada. Cardiac arrest was the primary indication for 8.7% of 3,049 consecutive admissions, and its

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The strategy of using systemic hypothermia (temp. 32° C) for protection of the heart is well known to cardiac surgeons in their daily work. Deep Hypothermic Circulatory Arrest (DHCA, body temperature ≤ 20° C), with or without hypothermic antegrade or retrograde cerebral perfusion, is a well-established practice for operations involving the aortic arch pathologies of varying complexity. The French HYPERION trial and other published work cited in this report are encouraging for application of TTM in the care of patients with out-of-hospital cardiac arrest and return of spontaneous circulation.



38% mortality rate was the highest of all cardiac critical care indications (JAMA Cardiol. 2019 Jul 24;4[9]:928-35).

TTM was developed in response to a recognition that two-thirds of deaths in patients who make it to the hospital after out-of-hospital cardiac arrest are neurologic – the result of brain anoxia – rather than being due to the myocardial ischemia that may have initially brought them to medical attention.

“Time is brain cells, the same way we think of time as cardiac muscle,” Dr. Bohula observed.

The main idea behind therapeutic hypothermia is that it lowers the cerebral metabolic rate of oxygen to reduce the consequences of ongoing anoxia. The brain doesn’t require as much perfusion when cooled.

TTM has other beneficial neurologic effects as well: It reduces cerebral blood volume via autoregulation, decreases intracranial pressure, and blunts the inflammatory response involved in the postcardiac arrest syndrome. In addition, TTM has anticonvulsant properties, an important effect because seizures and/or myoclonus occur in up to 15% of adults who achieve ROSC after cardiac arrest – and in even more of those who are comatose after doing so. And seizures increase the brain’s metabolic rate threefold, resulting in more cerebral ischemic injury, she explained.

Seizure activity can be difficult to distinguish from shivering in a patient on TTM. For this reason Dr. Bohula recommends putting patients on continuous EEG monitoring from the time of admission, as is the routine practice at the Brigham.

She reported serving as a consultant to Daiichi Sankyo, Servier, Lexicon, Kowa, Merck, Novartis, Novo Nordisk, and the National Institutes of Health. In addition, she generates institutional research grants provided by a half-dozen pharmaceutical companies.

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SARS-CoV-2 survival on surfaces similar to SARS-CoV-1

BY RICKI LEWIS, PHD

The novel coronavirus, SARS-CoV-2, remains viable in aerosols for hours and on surfaces for days, according to a new study.

The data indicate that the stability of the new virus is similar to that of SARS-CoV-1, which caused the SARS epidemic, researchers report in an article published on the medRxiv preprint server (medRxiv. 2020. doi: 10.1101/2020.03.09.20033217). The study has since been published in the New England Journal of Medicine (2020 Mar 17. doi/10.1056/NEJMc200497).

Transmission of SARS-CoV-2, which causes COVID-19, has quickly outstripped the pace of the 2003 SARS epidemic. “Superspread” of the earlier disease arose from infection during medical procedures, in which a single infected individual seeded many secondary cases. In contrast, the novel coronavirus appears to be spread more through human-to-human transmission in a variety of settings.

However, it’s not yet known the extent to which asymptomatic or presymptomatic individuals spread the new virus through daily routine.

To investigate how long SARS-CoV-2 remains infective in the environment, Neeltje van Doremalen, PhD, of the Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, in Hamilton, Mont., and colleagues conducted simulation experiments in which they compared the viability of SARS-CoV-2 with that of SARS-CoV-1 in aerosols and on surfaces.

Among patients infected with SARS-CoV-2, viral loads in the upper respiratory tract are high;

as a consequence, respiratory secretion in the form of aerosols (<5 mcm) or droplets (>5 mcm) is likely, the authors note.

van Doremalen and colleagues used nebulizers to generate aerosols. Samples of SARS-CoV-1 and SARS-CoV-2 were collecting at 0, 30, 60, 120, and 180 minutes on a gelatin filter. The researchers then tested the infectivity of the viruses on

“Taken together, our results indicate that aerosol and fomite transmission of HCoV-19 [SARS-CoV-2] is plausible, as the virus can remain viable in aerosols for multiple hours and on surfaces up to days.”

Vero cells grown in culture.

They found that SARS-CoV-2 was largely stable through the full 180-minute test, with only a slight decline at 3 hours. This time course is similar to that of SARS-CoV-1; both viruses have a median half-life in aerosols of 2.7 hours (range, 1.65 hr for SARS-CoV-1, vs. 7.24 hr for SARS-CoV-2).

The researchers then tested the viruses on a variety of surfaces for up to 7 days, using humidity values and temperatures designed to mimic “a variety of household and hospital situations.” The volumes of viral exposures that the team used were consistent with amounts found in the human upper and lower respiratory tracts.

For example, they applied 50 mL of virus-containing solution to a piece of cardboard and then swabbed the surface, at different times, with an additional 1 mL of medium. Each surface assay

was replicated three times.

The novel coronavirus was most stable on plastic and stainless steel, with some virus remaining viable up to 72 hours. However, by that time the viral load had fallen by about three orders of magnitude, indicating exponential decay. This profile was remarkably similar to that of SARS-CoV-1, according to the authors.

However, the two viruses differed in staying power on copper and cardboard. No viable SARS-CoV-2 was detectable on copper after 4 hours or on cardboard after 24 hours. In contrast, SARS-CoV-1 was not viable beyond 8 hours for either copper or cardboard.

“Taken together, our results indicate that aerosol and fomite transmission of HCoV-19 [SARS-CoV-2] is plausible, as the virus can remain viable in aerosols for multiple hours and on surfaces up to days,” the authors conclude.

Andrew Pekosz, PhD, codirector of the Center of Excellence in Influenza Research and Surveillance and director of the Center for Emerging Viruses and Infectious Diseases at the Johns Hopkins Center for Global Health, Baltimore, Maryland, applauds the real-world value of the experiments.

“The PCR [polymerase chain reaction] test used [in other studies] to detect SARS-CoV-2 just detects the virus genome. It doesn’t tell you if the virus was still infectious, or ‘viable.’ That’s why this study is interesting,” Pekosz said. “The investigators and Pekosz have disclosed no relevant financial relationships.

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

Coronavirus may contaminate surfaces via fecal shedding

BY ANDREW D. BOWSER

MDedge News

The toilet bowl, sink, and bathroom door handle of an isolation room housing a patient with the novel coronavirus tested positive for the virus, raising the possibility that viral shedding in the stool could represent another route of transmission, investigators reported.

Air outlet fans and other room sites also tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), though an anteroom, a corridor, and most personal protective equipment (PPE) worn by health care providers tested negative, according to the researchers, led by Sean Wei Xiang Ong, MBBS, of the National Centre for Infectious Diseases, Singapore.

Taken together, these findings suggest a “need for strict adherence to environmental and hand hygiene” to combat significant environmental

contamination through respiratory droplets and fecal shedding, Dr. Ong and colleagues wrote in JAMA.

Aaron Eli Glatt, MD, chair of medicine at Mount Sinai South Nassau in New York, said these results demonstrate that SARS-CoV-2 is “clearly capable” of contaminating bathroom sinks and toilets.

“That wouldn’t have been the first place I would have thought of, before this study,” he said in an interview. “You need to pay attention to cleaning the bathrooms, which we obviously do, but that’s an important reminder.”

The report by Dr. Ong and co-authors included a total of three patients housed in airborne infection isolation rooms in a dedicated SARS-CoV-2 outbreak center in Singapore. For each patient, surface samples were taken from 26 sites in the isolation room, an anteroom, and a bathroom. Samples were also taken from PPE on physicians as they left the patient rooms.

Samples for the first patient, taken right after routine cleaning, were all negative, according to researchers. That room was sampled twice, on days 4 and 10 of the illness, while the patient was still symptomatic. Likewise, for the second patient, postcleaning samples were negative; those samples were taken 2 days after cleaning.

However, for the third patient, samples were taken before routine cleaning. In this case, Dr. Ong and colleagues said 13 of 15 room sites (87%) were positive, including air outlet fans, while 3 of 5 toilet sites (60%) were positive as well, though no contamination was found in the anteroom, in the corridor, or in air samples.

That patient had two stool samples that were positive for SARS-CoV-2, but no diarrhea, authors said, and had upper respiratory tract involvement without pneumonia.

The fact that swabs of the air exhaust outlets tested positive suggests

that virus-laden droplets could be “displaced by airflows” and end up on vents or other equipment, Dr. Ong and coauthors reported.

All PPE samples tested negative, except for the front of one shoe.

“The risk of transmission from contaminated footwear is likely low, as evidenced by negative results in the anteroom and corridor,” they wrote.

While this study included only a small number of patients, Dr. Glatt said the findings represent an important and useful contribution to the literature on coronavirus disease 2019 (COVID-19).

Funding for the study came from the National Medical Research Council in Singapore and DSO National Laboratories. Dr. Ong and colleagues reported no conflicts of interest.

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SOURCE: Ong W, X et al. JAMA. 2020 Mar 4. doi: 10.1001/jama.2020.327

Guidance defines vaping-related respiratory syndrome

BY ANDREW D. BOWSER

MDedge News

ORLANDO – Knowledge of vaping devices, familiarity with terminology, and the ability to quickly pinpoint individuals at risk of lung injury are just a few skills that can help critical care professionals confronted with patients who may have vaping-associated lung disease, according to a new guidance.

The guidance offers a risk-stratification system that classifies patients into groups based on exposure, symptoms, and imaging results, and provides specific evaluation needs and management strategies for each. The guidance is designed to help critical care professionals efficiently identify those at high risk of respiratory failure (Crit Care Explor. 2020;2[2]:e0081).

Physicians also need to communicate with patients to identify what substances are being vaped and develop effective methods to encourage abstinence, according to the authors, led by Craig M. Lilly, MD, FCCP, professor of medicine, anesthesiology, and surgery at the University of Massachusetts, Worcester.

“I would encourage every intensivist, when they leave their intensive care unit at night, [to ask], ‘have I advised against vaping today?’” Dr. Lilly said at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

The guidelines, concurrently published as a review article in Critical Care Explorations, propose the term vaping-associated respiratory distress syndrome (VARDS), which the authors say constitutes an acute and progressive respiratory syndrome marked by pathologic changes of lung injury and potentially life-threatening hypoxemic respiratory failure.

They also introduce the three-group Worcester classification system, which is intended to triage vaping-exposed individuals for risk of VARDS based on the presence or absence of vaping-related symptoms and infiltrates, and normal or abnormal oxygen saturation.

“It’s very simple,” said Dr. Lilly, who added that the risk-stratification model was developed at the request of Massachusetts public health officials.

Patients with vaping exposure but no symptoms attributable to vaping, such as cough, chest pain, or weight loss, are classified as Worcester Low Risk and testing is not recommended, he said.

By contrast, individuals are considered Worcester Medium Risk if they have vaping exposure, symptoms, and a vaping-associated abnormal pattern on imaging, but



Dr. Lilly

no hypoxemia; the presence of hypoxemia would tip the scale toward Worcester High Risk.

“Most patients that have died from vaping have been sent out of emergency rooms when they were noted to be hypoxic,” Dr. Lilly told meeting attendees.

Louella B. Amos, MD, a pediatric pulmonologist at Children’s Hospital of Wisconsin in Milwaukee, said she expects the guidance and risk-stratification system will be useful not only for critical care specialists, but for other health care providers as well.

“It’s important to make decisions relatively quickly, depending on the severity of symptoms, and I think this is nice and simple,” Dr. Amos said in an interview.

“We always triage when we see patients, either at the door or in our clinic, or behind that, even in the hospital,” she said. “So I think this can be a great tool for everybody, not only the intensivist, but people who are triaging at the front.”

Management of individuals at low risk of VARDS begins with encouragement of abstinence. “We think that every vaping patient should be advised to quit vaping,” Dr. Lilly said. Patients who are interested in quitting who have not yet worked with someone in their health care team whom they trust can be referred to their primary care physicians for counseling, he added, while those struggling with addiction, unable to quit, and unable to

partner with a primary care physician can be referred to an addiction medicine specialist.

For moderate-risk patients, vaping cessation is “absolutely mandatory,” said Dr. Lilly, who recommended monitoring of vaping abstinence, outpatient evaluation based on imaging studies, and adequate follow-up to ensure symptoms resolve, tests normalize, and daily activities bounce back to baseline levels.

The guidance offers more extensive recommendations for the VARDS high-risk group, including supervised vaping abstinence, continuous pulse oximetry, and early intervention with noninvasive ventilation, and mechanical ventilation if required, Dr. Lilly said.

Judging vaping exposure is challenging, requiring clinicians to have a familiarity with the many different devices that are available.

Beyond device type, he added, it’s important to know the various terms for devices and lingo that patients may use to describe them, what solutions are vaped, whether those solutions are commercially prepared or off the street, the dose

the device delivers, and a number of other factors, he said.

Clinical evaluation typically comes down to unexplained cough, chest pain, weight loss, fatigue, or

The guidance offers a risk-stratification system that classifies patients into groups based on exposure, symptoms, and imaging results, and provides specific evaluation needs and management strategies for each.

dyspnea, though one other clue is whether there are gastrointestinal symptoms: “The same way that aerosols can go down to the lungs, they also go into the GI tract, and when nausea, vomiting, or cramping abdominal pain is tightly associated with vaping exposure, one should assume that the patient has been toxin exposed,” he explained.

Dr. Lilly said he had no financial relationships to disclose.

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Varied nightly sleep duration linked to CVD risk

BY PATRICE WENDLING

People who frequently alter the amount of sleep and time they go to bed each night are twofold more likely to develop cardiovascular disease, independent of traditional CVD risk factors, new research suggests.

Prior studies have focused on shift workers because night shift work will influence circadian rhythm and increase CVD risk. But it is increasingly recognized that circadian disruption may occur outside of shift work and accumulate over time, particularly given modern lifestyle factors such as increased use of mobile devices and television at night, said study coauthor Tianyi Huang, ScD, MSc, of Brigham and Women's Hospital and Harvard Medical School in Boston.

"Even if they tend to go to sleep at certain times, by following that lifestyle or behavior, it can interfere with their planned sleep timing," he said.

"One thing that surprised me in this sample is that about one third of participants have irregular sleep patterns that can put them at increased risk of cardiovascular disease. So I think the prevalence is higher than expected," Dr. Huang added.

As reported today in the *Journal of the American College of Cardiology*, the investigators used data from 7-day wrist actigraphy, 1 night of at-home polysomnography, and sleep questionnaires to assess sleep duration and sleep-onset timing among 1,992 Multi-Ethnic Study of Atherosclerosis participants, aged 45 to 84 years, who were free of CVD and prospectively followed for a median of 4.9 years.

A total of 786 patients (39.5%) had sleep duration standard deviation (SD) > 90 minutes and 510 (25.6%) had sleep-onset timing SD > 90 minutes.

During follow-up, there were 111 incident CVD events, including myocardial infarction, coronary heart disease death, stroke, and other coronary events.

Compared with people who had less than 1 hour of variation in sleep duration, the risk for incident CVD was 9% higher for people whose sleep duration varied 61 to 90 minutes (hazard ratio, 1.09; 95% confidence interval, 0.62-1.92), even after controlling for a variety of cardiovascular and sleep-related risk factors such as body mass index, systolic blood pressure, smoking status, total cholesterol, average sleep duration, insomnia symptoms, and sleep apnea.

Moreover, the adjusted CVD risk was substantially increased with 91 to 120 minutes of variation (HR, 1.59; 95% CI, 0.91-2.76) and more than 120 minutes of variation in sleep du-



Dr. Krumholz

ration (HR, 2.14; 95% CI, 1.24-3.68).

Every 1-hour increase in sleep duration SD was associated with 36% higher CVD risk (95% CI; 1.07 - 1.73).

Compared with people with no more than a half hour of variation in nightly bedtimes, the adjusted hazard ratios for CVD were 1.16 (95% CI, 0.64-2.13), 1.52 (95% CI, 0.81-2.88), and 2.11 (95% CI, 1.13-3.91) when bedtimes varied by 31 to 60 minutes, 61 to 90 minutes, and more than 90 minutes.

For every 1-hour increase in sleep-onset timing SD, the risk of CVD was 18% higher (95% CI; 1.06-1.31).

"The results are similar for the regularity of sleep timing and the regularity of sleep duration, which means that both can contribute to circadian disruption and then lead to development of cardiovascular disease," Dr. Huang said.

This is an important article and signals how sleep is an important marker and possibly a mediator of cardiovascular risk, said Harlan Krumholz, MD, of Yale School of Medicine in New Haven, Connecticut, who was not involved with the study.

"What I like about this is it's a nice longitudinal, epidemiologic study with not just self-report, but sensor-detected sleep, that has been correlated with well-curated and adjudicated outcomes to give us a strong sense of this association," he told this news organization. "And also, that it goes beyond just the duration – they combine the duration and timing in order to give a fuller picture of sleep."

Nevertheless, Dr. Krumholz said researchers are only at the beginning of being able to quantify the various dimensions of sleep and the degree to which sleep is a reflection of underlying physiologic issues, or whether patients are having erratic sleep patterns that are having a toxic effect on their overall health.

Questions also remain about the mechanism behind the association, whether the increased risk is universal or more harmful for some people, and the best way to measure factors

during sleep that can most comprehensively and precisely predict risk.

"As we get more information flowing in from sensors, I think we will begin to develop more sophisticated approaches toward understanding risk, and it will be accompanied by other studies that will help us understand whether, again, this is a reflection of other processes that we should be paying attention to or whether it is a cause of disease and risk," Dr. Krumholz said.

Subgroup analyses suggested positive associations between irregular sleep and CVD in African Americans, Hispanics, and Chinese Americans but not in whites. This could be because sleep irregularity,

"One thing that surprised me in this sample is that about one third of participants have irregular sleep patterns that can put them at increased risk of cardiovascular disease."

both timing and duration, was substantially higher in minorities, especially African Americans, but may also be as a result of chance because the study sample is relatively small, Huang explained.

The authors note that the overall findings are biologically plausible because of their previous work linking sleep irregularity with metabolic risk factors that predispose to atherosclerosis, such as obesity, diabetes, and hypertension. Participants with irregular sleep tended to have worse baseline cardiometabolic profiles, but this only explained a small portion of the associations between sleep irregularity and CVD, they note.

Other possible explanations include circadian clock genes, such as clock, per2, and bmal1, which have been shown experimentally to control a broad range of cardiovascular functions, from blood pressure and endothelial functions to vascular thrombosis and cardiac remodeling. Irregular sleep may also influence the rhythms of the autonomic nervous system, and behavioral rhythms with regard to timing and/or amount of eating or exercise.

Further research is needed to understand the mechanisms driving the associations, the impact of sleep irregularity on individual CVD outcomes, and to determine whether a 7-day SD of more than 90 minutes for either sleep duration or sleep-onset timing can be used clinically as a threshold

target for promoting cardiometabolically healthy sleep, Dr. Huang said.

"When providers communicate with their patients regarding strategies for CVD prevention, usually they focus on healthy diet and physical activity; and even when they talk about sleep, they talk about whether they have good sleep quality or sufficient sleep," he said.

In a related editorial, Olaf Oldenburg, MD, Luderus-Kliniken Münster, Clemenshospital, Münster, Germany, and Jens Spiesshoefer, MD, Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy, write that the observed independent association between sleep irregularity and CVD "is a particularly striking finding given that impaired circadian rhythm is likely to be much more prevalent than the extreme example of shift work."

They call on researchers to utilize big data to facilitate understanding of the association and say it is essential to test whether experimental data support the hypothesis that altered circadian rhythms would translate into unfavorable changes in 24-hour sympathovagal and neurohormonal balance, and ultimately CVD.

The present study "will, and should, stimulate much needed additional research on the association between sleep and CVD that may offer novel approaches to help improve the prognosis and daily symptom burden of patients with CVD, and might make sleep itself a therapeutic target in CVD," the editorialists conclude.

This research was supported by contracts from the National Heart, Lung, and Blood Institute, and by grants from the National Center for Advancing Translational Sciences. The MESA Sleep Study was supported by an NHLBI grant.

Drs. Krumholz and Oldenburg have disclosed no relevant financial relationships. Dr. Spiesshoefer is supported by grants from the Else-Kröner-Fresenius Stiftung, the Innovative Medical Research program at the University of Münster, and Deutsche Herzstiftung; and by young investigator research support from Scuola Superiore Sant'Anna Pisa. He also has received travel grants and lecture honoraria from Boehringer Ingelheim and Chiesi.

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

SOURCE: Huang T. *J Am Coll Cardiol*. 2020 Mar 2. doi: 10.1016/j.jacc.2019.12.054.

Disruptions in cancer care in the era of COVID-19

BY ROXANNE NELSON, RN, BSN

Even in the midst of the COVID-19 pandemic, cancer care must go on, but changes may need to be made in the way some care is delivered.

“We’re headed for a time when there will be significant disruptions in the care of patients with cancer,” said Len Lichtenfeld, MD, deputy chief medical officer of the American Cancer Society, in a statement. “For some it may be as straightforward as a delay in having elective surgery. For others it may be delaying preventive care or adjuvant chemotherapy that’s meant to keep cancer from returning or rescheduling appointments.”

Dr. Lichtenfeld emphasized that cancer care teams are going to do the best they can to deliver care to those most in need. However, even in those circumstances, it won’t be life as usual. “It will require patience on everyone’s part as we go through this pandemic,” he said.

“The way we treat cancer over the next few months will change enormously,” writes a British oncologist in an article published in the *Guardian*.

“As oncologists, we will have to find a tenuous balance between undertreating people with cancer, resulting in more deaths from the disease in the medium to long term, and increasing deaths from COVID-19 in a vulnerable patient population. Alongside our patients we will have to make difficult decisions regarding treatments, with only

“As oncologists, we will have to find a tenuous balance between undertreating people with cancer, resulting in more deaths from the disease in the medium to long term, and increasing deaths from COVID-19 in a vulnerable patient population.”

low-quality evidence to guide us,” writes Lucy Gossage, MD, consultant oncologist at Nottingham (England) University Hospital.

The evidence to date (from reports from China in the *Lancet Oncology*) suggests that people with cancer have a significantly higher risk of severe illness resulting in intensive care admissions or death when infected with COVID-19, particularly if they recently had chemotherapy or surgery.

“Many of the oncology treatments we currently use, especially those given after surgery to reduce risk of cancer recurrence, have relatively small benefits,” she writes.

“In the current climate, the balance of offering these treatments may shift; a small reduction in risk of cancer recurrence over the next 5 years may be outweighed by the potential for a short-term increase in risk of death from COVID-19. In the long term, more people’s cancer will return if we aren’t able to offer these treatments,” she adds.

Postpone routine screening

One thing that can go on the back burner for now is routine cancer screening, which can be



Dr. Lichtenfeld

postponed for now in order to conserve health system resources and reduce contact with health-care facilities, says the ACS.

“Patients seeking routine cancer screenings should delay those until further notice,” said Dr. Lichtenfeld. “While timely screening is important, the need to prevent the spread of coronavirus and to reduce the strain on the medical system is more important right now.”

But as soon as restrictions to slow the spread of COVID-19 are lifted and routine visits to health facilities are safe, regular screening tests should be rescheduled.

Guidance from ASCO

The American Society of Clinical Oncology (ASCO) has issued new guidance on caring for patients with cancer during the COVID-19 outbreak.

First and foremost, ASCO encourages providers, facilities, and anyone caring for patients with cancer to follow the existing guidelines from the Center for Disease Control and Prevention when possible.

ASCO highlights the CDC’s general recommendation for healthcare facilities that suggests “elective surgeries” at inpatient facilities be rescheduled if possible, which has also been recommended by the American College of Surgeons.

However, in many cases, cancer surgery is not elective but essential, it points out. So this is largely an individual determination that clinicians and patients will need to make, taking into account the potential harms of delaying needed cancer-related surgery.

Systemic treatments, including chemotherapy and immunotherapy, leave cancer patients vulnerable to infection, but ASCO says there is no direct evidence to support changes in regimens during the pandemic. Therefore, routinely stopping anticancer or immunosuppressive therapy is not recommended, as the balance of potential

harms that may result from delaying or interrupting treatment versus the potential benefits of possibly preventing or delaying COVID-19 infection remains very unclear.

Clinical decisions must be individualized, ASCO emphasized, and suggested the following practice points be considered:

- For patients already in deep remission who are receiving maintenance therapy, stopping treatment may be an option.
- Some patients may be able to switch from IV to oral therapies, which would decrease the frequency of clinic visits.
- Decisions on modifying or withholding chemotherapy need to consider both the indication and goals of care, as well as where the patient is in the treatment regimen and tolerance to the therapy. As an example, the risk-benefit assessment for proceeding with chemotherapy in patients with untreated extensive small-cell lung cancer is quite different than proceeding with maintenance pemetrexed for metastatic non-small cell lung cancer.
- If local coronavirus transmission is an issue at a particular cancer center, reasonable options may include taking a 2-week treatment break or arranging treatment at a different facility.
- Evaluate if home infusion is medically and logistically feasible.
- In some settings, delaying or modifying adjuvant treatment presents a higher risk of

“While timely screening is important, the need to prevent the spread of coronavirus and to reduce the strain on the medical system is more important right now.”

compromised disease control and long-term survival than in others, but in cases where the absolute benefit of adjuvant chemotherapy may be quite small and other options are available, the risk of COVID-19 may be considered an additional factor when evaluating care.

Delay stem cell transplants

For patients who are candidates for allogeneic stem cell transplantation, a delay may be reasonable if the patient is currently well controlled with conventional treatment, ASCO comments. It also directs clinicians to follow the recommendations provided by the American Society of Transplantation and Cellular Therapy and from the European Society for Blood and Marrow Transplantation regarding this issue.

Finally, there is also the question of prophylactic antiviral therapy: Should it be considered for cancer patients undergoing active therapy?

The answer to that question is currently unknown, says ASCO, but “this is an active area of research and evidence may be available at any time.”

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

CRITICAL CARE COMMENTARY

Hyperoxia in the ICU: Is less more?

BY SAID CHAABAN, MD; AND
PARIJA SEN, MD

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous." Paracelsus once said.

A bit of history

Oxygen was discovered in 1775 and was since noted to be both vital and poisonous. It was much later in 1899 that it was demonstrated that partial pressures of oxygen up to 75% led to both severe lung injury and death as compared with levels of 40% to 50%. While the administration of oxygen in hypoxic patients is beneficial, this intervention in healthy subjects leads to a reduction in heart rate, cardiac index, and an increase in mean arterial pressure, systemic vascular resistance, and large artery stiffness.

While oxygen itself is not toxic, the reactive oxygen species that form as a result of oxygen metabolism are. A study showed that supplementation of oxygen in patients with COPD, or in women undergoing C-section with the use of spinal anesthesia, leads to an increase in reactive oxygen species (Winslow RM. *Transfusion*. 2013;53[2]:424).

Hyperoxia has multiple clinical effects on lung physiology and gas exchange that include worsening hypoxemia secondary to absorptive atelectasis and damage to the airways and lung parenchyma (Sackner MA, et al. *Ann Intern Med*. 1975;82[1]:40).

High levels of inspired oxygen could also lead to accentuation of hypercapnia as explained by the Haldane effect; a reduction of the affinity for carbon dioxide leading to an increase in PaCO_2 . High oxygen levels can also decrease the hypoxic drive for ventilation leading to worsening hypercapnia.

Hyperoxia is a situation routinely encountered in clinical practice, as well, often resulting from an overzealous attempt to prevent or reverse hypoxia. ICU physicians, though aware of potential threats of hyperoxia, often fail to translate such concerns in their clinical practice (Helmerhorst HJ, et al. *Ann Intensive Care*. 2014;4:23).

Effects of hyperoxia in CNS and cardiovascular disease

The last 2 decades have seen several studies looking into the effects of hyperoxia in specific clinical scenarios. Arterial hyperoxia was found to be independently associated with in-hospital death in ventilated stroke patients in the ICU, as compared with either arterial normoxia or hypoxia (Rincon F, et al. *Crit Care Med*. 2014;42[2]:387). The AVOID trial showed that supplemental oxygen therapy in patients with ST-elevation myocardial infarction, but without hypoxia, increased early myocardial injury with risk of larger myo-

cardial infarct size at 6 months. (Stub D, et al. *Circulation*. 2015;131[24]:2143).

Hyperoxia in the ICU

Although the potential risks of hyperoxia in conditions such as stroke and cardiac arrest had been observed, the jury was still out on its effects on a critically ill, mixed population, as routinely encountered in the ICU. Oxygen-ICU, a single center trial published in 2016, was one of the first looking at a mixed ICU population, while assessing the effects of a conservative oxygen delivery strategy against a conventional one (Girardis M, et al. *JAMA*. 2016;316[15]:1583). The researchers noted a significant mortality difference favoring conservative oxygen therapy, particularly in intubated patients. The IOTA group's systematic

review and meta-analysis of 16,000 patients showed an increased relative risk of death in-hospital with hyperoxia, that persisted over a prolonged period while conferring no obvious advantages (Chu DK, et al. *Lancet*. 2018;391[10131]:1693).

With the growing body of evidence, the need of the hour was an ICU-based ran-

domized trial that may settle the debate. The 21 center, 1,000 patient ICU-ROX trial promised to deliver on that (Mackle D, et al. *N Engl J Med*. 2019 Oct 14. doi: 10.1056/NEJMoa1903297). The study design was more reflective of real-life clinical scenarios than some of its predecessors, with the control group exposed to usual-oxygen therapy instead of liberal hyperoxia. Both groups had a lower saturation threshold of 91% while the conservative-oxygen group had an upper limit of 97% along with a conscious effort made to drop the FiO_2 to 21%. Though both groups had similar median PaO_2 levels, the conservative group spent much greater time (median 29 hours) at 21% FiO_2 than the usual group (median 1 hour). SpO_2 targets also allowed frequent changes to oxygen delivery without the need for blood gases.

Presuming the primary effect of oxygen toxicity would be on the lungs, the study was powered for a primary outcome of ventilator-free-days, which showed no significant difference among the groups. No significant differences in mortality or other secondary outcomes were observed.

The ICU-ROX trial leaves us with a few questions, the most important follow:

Are the detrimental effects of hyperoxia limited to certain disease-specific groups or generally applicable?

The evidence is substantial in patients with cardiac arrest/myocardial injury. A prespecified subgroup analysis in ICU-ROX indicated a higher number of ventilator-free days with conservative oxygen therapy in patients with hypoxic ischemic encephalopathy. When asked, Dr. Paul Young, one of the investigators of the ICU-ROX group, states, "These

are actually pretty small subgroups, and the number of mortality events is quite small. My belief is that these data are best viewed as hypothesis-generating rather than practice-changing"

Where do we stand?

While we look for further answers regarding the consequences of hyperoxia, it is established that conservative oxygen therapy aimed at reducing delivered FiO_2 is a safe practice without any adverse outcomes. The conservative oxygen group in ICU-ROX allowed SpO_2 levels as low as 91% with no serious hypoxic events. On the other hand, the IOTA group in their data analysis suggested a possible increase in mortality risk, which was dose-dependent on the magnitude of increase in SpO_2 , in the range of 94% to 96%. Based on the available evidence, it is reasonable to encourage targeting lowest FiO_2 values needed to maintain SpO_2 between 91% and 96% in our ICU patients. There would always be a small fraction of patients, such as those with ARDS or severe hypoxic respiratory failure, in whom this may not be achievable given fluctuating and unreliable SpO_2 levels in the setting of profound hypoxia.

What lies ahead?

As the debate rages on, in an effort to answer this question for once and for all, the researchers of ICU-ROX are planning to conduct a multinational, multicenter RCT, the MEGA-ROX.

Hyperoxia has multiple clinical effects on lung physiology and gas exchange that include worsening hypoxemia secondary to absorptive atelectasis and damage to the airways and lung parenchyma.

An ICU trial of this size has not been attempted before and, given the sample size, Dr. Young feels the MEGA-ROX will be powered to detect an absolute mortality difference as low as 1.5%, if it does exist. There is a distinct possibility that conservative oxygen therapy will be best for patients with some diagnoses while liberal oxygen will be best for patients with other diagnoses. "We are conducting a number of parallel nested trials within the overall 40,000 participant trial sample. Each of these nested trials will evaluate a prespecified hypothesis in a specific cohort of critically ill patients and is accompanied by an appropriate power calculation. This will be able to address any heterogeneity of treatment effect among the different subgroups," he concluded. As we eagerly await the results of MEGA-ROX, there may be a growing belief among intensivists that when it comes to oxygen in the ICU, less may be truly more.

Dr. Chaaban and Dr. Sen are with the University of Kentucky College of Medicine, Lexington, Kentucky.



Dr. Chaaban



Dr. Sen

The “Windy City” waits for you!

CHEST Annual Meeting 2020 will be here before you know it and we're here to guide you through our Second City home, Chicago, Illinois. We're so excited to be hosting CHEST 2020 in our backyard this year and want to help you experience everything that the city has to offer when you aren't taking in the latest education in clinical chest medicine.

Whether you're looking to embrace the culture, discover new shops, seeking entertainment, or just looking for a photo opportunity, we've got you covered. There's something for everyone! Here are a few suggestions to keep you busy after your courses and sessions end.

Millennium Park campus

Located in the heart of the city, Millennium Park is home to the Art Institute of Chicago, Cloud Gate (“The Bean”), Maggie Daley Park, Crown Fountain, Park Grill restaurant, and more. This is the perfect place to take a fall stroll this October.

Cloud Gate (the bean)

Undoubtedly, one of Chicago's most popular attractions, this reflective sculpture opposite of Millennium Park is a must for the perfect selfie. Don't forget to bring your selfie stick to optimize your angles!

Field Museum

One of the largest history museums in the world, this space is filled with an extensive collection of artifacts and scientific-specimens, along with educational programs. Whether you're interested in browsing through photo archives, taking a public tour, or strolling through the library of over 275,000 books, it would be easy to spend a few hours here during your breaks. (Kids will love it too!)

Wrigley Field tours

The World Series is set to start during the meeting, fingers crossed the Cubs will be making a return to Wrigley Field. Regardless, you can still attend an off-season tour allowing you to visit the Visitors' clubhouse, Cubs' dugout, field, American Airlines 1914 Club, Maker's Mark Barrel Room, and The W Club at the home of the Chicago Cubs.

Starbucks Reserve Roastery

While you're strolling on Michigan Avenue, be sure to stop by the world's largest Starbucks. Enjoy a latte while you take a tour of the roastery or even experience a master tasting.

Take a river boat tour

Embrace the outdoors by taking a scenic cruise on the Chicago River during a boat tour. Choose from tours that highlight architecture, classic Chicago spots, a dinner cruise, and more.

Skydeck Chicago

Take a step out on the Ledge during your stay in Chicago. Test your limits on the 103rd floor of the Willis Tower by stepping onto a glass platform 1,353 feet in the air. Skydeck Chicago also features museum-quality exhibits and theater presentation, Reaching For The Sky.

Navy Pier

Stretching more than 3,000 feet along the shoreline of Lake Michigan, Navy Pier offers access to parks, gardens, shops, dining experiences, live entertainment, and more. If you're looking for an engaging experience for kids, Navy Pier is also home to the Chicago Children's Museum.

Frank Lloyd Wright tours

Wrap up your time in Chicago with the *Wright Along the Lake* tour, a half-day guided bus tour featuring some of Wright's most iconic sites in Chicago. Tours are also available for select sites including the Frederick C. Robie House and the Rookery Light Court.

The Magnificent Mile

One of the most iconic shopping centers in the world, The Magnificent Mile stretches across downtown Michigan Avenue and features historic landmarks, more than 460 retailers, and more than 275 restaurants.

Don't forget to bring your jacket for outdoor activities! They don't call Chicago the Windy City for nothing.

We look forward to exploring clinical chest medicine and the city of Chicago with you at CHEST Annual Meeting 2020 in October. See you there!

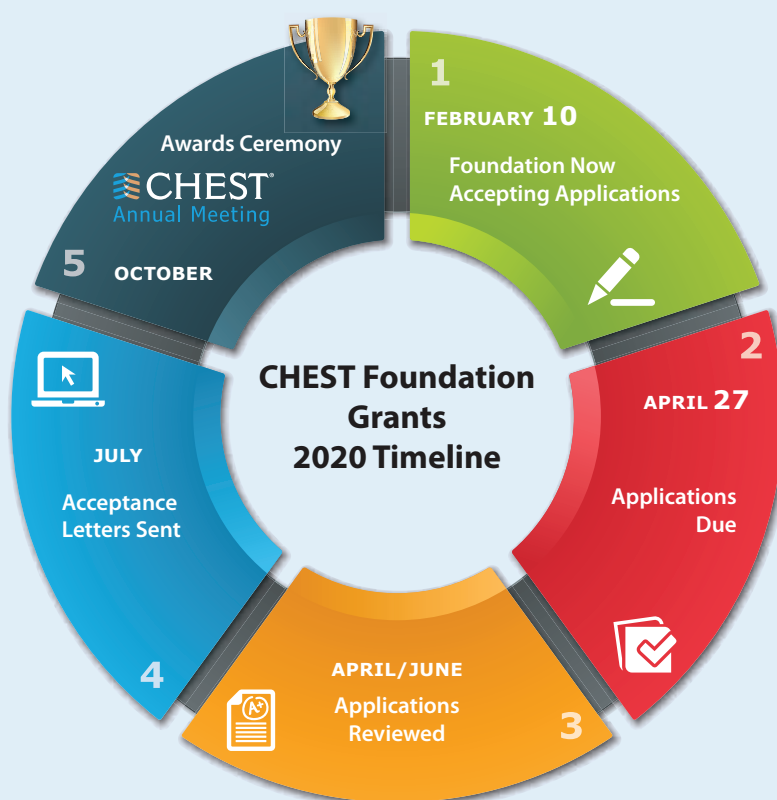


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PULMONARY PERSPECTIVES®

Expansion of the donor pool in lung transplantation

BY MARC A. SALA, MD; AND
RADE TOMIC, MD, FCCP

Lung transplants are increasing, with 2,562 performed in the United States in 2018 – a 31% increase over the preceding 5 years. With this increased demand for donor lungs, waitlist mortality in the United States is 9.4 deaths per 100 waitlist-years for obstructive lung diseases and as high as 29.7 deaths per 100 waitlist-years for restrictive lung diseases (Valapour M, et al. *Lung. Am J Transplant.* 2020;20[suppl s1]:427). Conversely, lungs are utilized from eligible multiorgan donors only 15% to 20% of the time, usually due to concerns over donor history or organ quality (Young KA, et al. *Chest.* 2019;155[3]:465). In light of this imbalance of supply and demand, lung transplant specialists are making significant efforts to expand the donor pool of available organs. Three of these strategies include: (1) applications of ex-vivo lung perfusion (EVLP) technology; (2) use of lungs from hepatitis C-positive donors for hep C-negative recipients; and (3) increasing utilization of donation after cardiac death.



Dr. Sala

Normothermic ex-vivo lung perfusion is a technology that allows donor lungs to be perfused and ventilated after removal from the donor but before transplant into the recipient. This is in contrast to the traditional method of cold static preservation. The proposed advantage of using this technology is to allow time for a more thorough assessment of graft quality and to improve function of grafts not meeting established criteria for transplant, all-the-while decreasing organ ischemia despite an increased cross-clamp time. There are currently four commercial systems available capable of EVLP. Broadly speaking, three EVLP management protocols exist (Toronto, Lund, and OCS), which differ in perfusate composition, target flow, pulmonary arterial pressure, left atrial pressure, and ventilatory settings. Notably, the Toronto protocol uses a closed left atrium, whereas the Lund and OCS protocol use an open left atrium. There are excellent published reviews of the different systems (Possoz J, et al. *J Thorac Dis.* 2019;11[4]:1635). EVLP has now been studied for two different goals: (1) to allow an extended evaluation of lungs of questionable quality before transplant; or (2) for routine use in all lung transplantations in place of cold static preservation.

In most studies concerning the use of EVLP for reconditioning of donor lungs, “high risk” or “extended criteria” refers to one or more of the following: P/F ratios < 300 on arterial blood gas, macroscopic abnormalities (eg, pulmonary edema, poor lung compliance), donation after circulatory death, or high-risk history (eg, aspiration).

The largest cohort with the longest follow-up addressing the role of EVLP for donation of lungs with extended criteria was published from the Toronto Lung Transplant Group. Their results have demonstrated equivalent graft survival and rates of chronic lung allograft dysfunction (CLAD) up to 9 years posttransplant compared with standard criteria donor lungs, despite utilizing lower quality lungs and having a longer median preservation (Divithotawela C, et al. *JAMA Surg.* 2019;154[12]:1143). The group’s subsequent lung transplant rates have increased over the past decade.



Dr. Tomic

Among these, 87% of eligible lungs were transplanted, and outcomes were excellent, albeit shorter in follow-up compared with the Toronto cohort (eg, primary graft dysfunction grade 3 (PGD3) within 72 hours was 44% and 1-year survival was 91%). Based on these trials and many other retrospective reports, it has been concluded by many experts in the field that EVLP-treated extended criteria donor lungs perform equally well to standard criteria donor lungs.

Two RCTs have been conducted to evaluate whether EVLP is noninferior to static cold storage with donor lungs meeting “standard criteria” for transplant. The first was a single center study at the Medical University of Vienna, that looked at 80 recipient/donor pairs. Lungs in the EVLP arm underwent 4 hours of perfusion with frequent reassessment of quality before transplant, whereas the lungs in the control arm went directly to transplant. This study met noninferiority criteria looking at primary outcomes of PGD grade >1 and 30-day survival (Slama A, et al. *J Heart Lung Transplant.* 2017;36[7]:744). The second study was a phase 3, multicenter, international trial that included 320 recipient/donor pairs randomized to either EVLP (without a pre-specified time on the EVLP system) or static cold storage. This trial met noninferiority for safety endpoints (lung graft-related adverse events within 30 days) and a composite primary outcome of PGD grade 3 incidence within 72 hours and 30-day survival (Warnecke G, et al. *Lancet Respir Med.* 2018;6[5]:357). The authors also tested and found superiority of EVLP in lower PGD grade 3 frequency compared with control. While these RCTs may suggest a role for EVLP in the procurement process of standard criteria organs in addition to extended criteria organs in the future, major criticisms for these trials include the lack of a demonstrable clinical benefit over cold storage beyond the lower PGD3 rates.

In the era of direct-acting antiviral agents available to treat HCV infection, there have been efforts to study the early use of anti-HCV medications to prevent infection as a result of heart or lung transplant from HCV viremic donors to HCV-negative recipients. In one major trial on efficacy, it was found that 4 weeks of sofosbuvir and velpatasvir, when started within a few hours of transplant, was sufficient to achieve a sustained (undetectable) virologic response at 12 weeks after completion of the antiviral regimen (Woolley AE, et al. *N Engl J Med.* 2019;380[17]:1606). Therefore, many transplant centers have adopted protocols to increase the donor pool (by CDC estimates about 4% of solid organ donors are HCV-positive) by accepting HCV nucleic acid amplification test (NAT)-positive donors for HCV-negative recipients, after appropriate informed consent.

Donation after cardiac death (DCD), which is alternatively known as donation after circulatory determination of death (DCDD), generally

Three strategies to expand the pool of available organs include: (1) applications of ex-vivo lung perfusion (EVLP) technology; (2) use of lungs from hepatitis C-positive donors for hep C-negative recipients; and (3) increasing utilization of donation after cardiac death.

refers to organ procurement taking place after cessation of circulation, often after inpatient withdrawal of support. This is in contrast to the much more common practice of donation after brain death (DBD). Addressing concerns over the quality of lungs donated in the context of DCD compared with DBD, analyses of ISHLT registry data have demonstrated no differences in hospital length of stay or survival at 1 or 5 years (Van Raemdonck D, et al. *J Heart Lung Transplant.* 2019;38[12]:1235). Outcomes comparing specific mechanisms of donor death in DCD remain relatively unknown, such as outcomes from donors withdrawn from life support vs donors who had an uncontrolled cardiac death.

These methods for expanding the donor pool are not mutually exclusive, and, in fact, application of EVLP for lungs obtained in the context of DCD seems to be increasingly common. Optimization of protocols with collaboration between lung transplant centers will be paramount as we move forward in advancing this field. As we do so, efforts to successfully increase the donor pool will serve to provide a life-saving therapy to an ever-growing number of patients with end-stage lung disease.

Dr. Sala and Dr. Tomic are with the Division of Pulmonary and Critical Care Medicine, Northwestern University, Chicago, Illinois.

CHEST NETWORKS

Silicosis epidemic. Specialist palliative care. Respiratory therapy. Tongue fat and OSA. Immunotherapy and NSCLC.

Occupational and Environmental Health

Severe silicosis in engineered stone fabrication workers: An emerging epidemic

Silicosis is an irreversible fibrotic lung disease caused by inhalation of respirable forms of crystalline silica. Silica exposure is also associated with increased risk for mycobacterial infections, lung cancer, emphysema, autoimmune diseases, and kidney disease (Leung CC, et al. *Lancet*. 2012;379[9830]:2008; Bang KM, et al. *MMWR*. 2015;64[5]:117). Engineered stone is a manufactured quartz-based composite increasingly used for countertops in the United States where imports of engineered stone for this use have increased around 800% from 2010 to 2018. With this, reported silicosis cases among engineered stone fabrication workers have risen. Silica content in different stones varies from up to 45% in natural stones (granite)

to >90% in engineered stone and quartz. The act of cutting, grinding, sanding, drilling, polishing, and installing this stone puts workers with direct and indirect contact with these tasks at risk for hazardous levels of inhaled silica exposure (OSHA et al. <https://www.osha.gov/Publications/OSHA3768.pdf>. 2015).

A growing number of cases associated with stone fabrication have been reported worldwide (Kramer MR, et al. *Chest*. 2012;142[2]:419; Kirby T. *Lancet*. 2019;393:861). The CDC recently published a report of 18 cases of accelerated silicosis over a 2-year period among engineered stone fabrication workers. The majority of patients were aged <50 years, five patients had autoimmune disease, two patients had latent TB, and two died (Rose C, et al. *MMWR*. 2019;68[38]:813). Thus, the experience of engineered stone fabrication workers appears to parallel that of patients exposed



Dr. Cherian



Dr. Rokadia

to silica in other occupations.

Control measures (see resources below) for silica exposure, prevention, and medical surveillance have been updated since 2016 at the federal level prompting a recent revision of OSHA's National Emphasis Program for respirable crystalline silica as of February 2020 (OSHA, <https://www.osha.gov/news/newsreleases/trade/02052020>, published February 5, 2020). Despite these measures, enforcement within the stone fabrication industry remains challenging. Small-scale

operations with limited expertise in exposure control combined with high density of immigrant workers with limited health-care access and potential threat of retaliation have limited compliance with updated standards (Rose C, et al. *MMWR*. 2019;68[38]:813).

Silicosis is preventable, and efforts to minimize workplace exposure and enhance medical surveillance of stone fabrication workers should be prioritized.

Useful resources for silica workplace control measures:

<https://www.cdph.ca.gov/silica-stonefabricators>

<https://www.cdc.gov/niosh/topics/silica/>

https://www.osha.gov/sites/default/files/enforcement/directives/CPL_03-00-023.pdf

Sujith Cherian, MD, FCCP

Haala Rokadia, MD, FCCP

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NetWorks continued on following page



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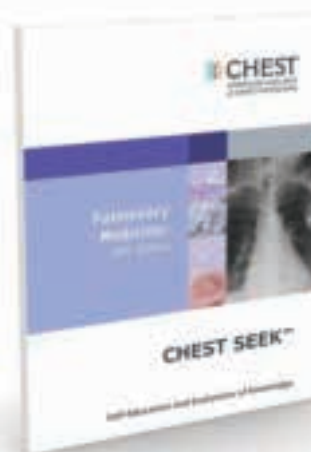
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NetWorks continued from previous page

Palliative and End-of-Life Care

Building primary palliative care competencies in the CHEST community

The CHEST community cares for many patients with serious illnesses characterized by a high risk of mortality, burdensome symptoms or treatments, and caregiver distress, which negatively impact quality of life (QOL) (Kelly, et al. *J Palliat Med.* 2018;21[S2]:S7). Specialist palliative care (PC) clinicians work in partnership with other specialties to optimize QOL and alleviate suffering for seriously ill patients (ie, advanced or chronic respiratory disease and/or critical illness).

Referral for specialist PC integration should be based on the complex needs of patients and not prognosis. PC can and should be delivered alongside disease-directed and life-prolonging therapies. Early PC referral in serious illness has been associated with improved QOL, better prognostic awareness, and, in some instances, increased survival. Additionally, reductions in medical costs at the end-of-life have been observed with early PC integration (Parikh, et al. *N Engl J Med.* 2013;369[24]:2347). However, patients with chronic or advanced respiratory diseases often receive PC late, if at all (Brown, et al. *Ann Am Thorac Soc.* 2016;13[5]:684). This might be explained by significant shortages within the PC workforce, misconceptions that PC is only delivered at the end of life, and limited proficiency or comfort



Dr. Khateeb



Dr. Markos

in primary PC delivery. Primary PC competencies have already been defined for pulmonary and critical care clinicians (Lanken, et al. *Am J Respir Crit Care Med.* 2008;177:912). The Palliative and End-of-Life Care NetWork is focused on promoting awareness of specialty PC while providing education and resources to support primary PC competencies within the CHEST community. Look for NetWork-sponsored sessions at the annual meeting and follow conversations on social media using the hashtag #CHESTPalCare. *Dina Khateeb, DO*
Fellow-in-Training Member

Respiratory Care

I am a new respiratory therapist and a team member

It's 11:00 pm and relatively quiet in the ICU. Then, that all too familiar sound, Code Blue. I rush to the room and assess the situation. As a new grad, this is one of the skills I am still developing; balancing my adrenaline with critical thinking in order to help manage the situation. Whether it is an unplanned extubation, acute respiratory failure, or cardiac arrest, as

the respiratory therapist, I am there to bring an expertise to the assessment and management of airway and breathing. Once the crisis is resolved, my work is not done. I remain at the bedside to ensure ventilator management, explain to the family the respiratory interventions, and work with the medical team to implement the best plan of care.

As the bedside RT, I have unique perspective and training. My education prepared me with the knowledge base to work in this arena, but I still have so much to learn. And, as a new grad, one of the biggest lessons I have learned so far is to speak up. Whether it is during rounds, a code situation, or just conversations with the team. I owe it to my patients to advocate for their care and provide the expertise that I bring to the team. To the doctor or nurse, I hope you will give me that opportunity to help care for our patients; to learn; and even teach, to improve that care. *Bethlehem Markos*
Fellow-in-Training Member

Sleep Medicine

What's new in the sleep apnea treatment pipeline?

While weight loss in obese patients with sleep apnea is an effective treatment strategy, researchers honed in on a particular site of impact – the tongue fat (Wang SH, et al. *Am J Respir Crit Care Med.* 2020;201[6]:718). After a weight loss program, they studied the changes in the tongue, pterygoid, lateral pharyngeal wall, and abdominal fat volumes using MRI. It turned out that reduced tongue fat volume was the primary mediator associated with AHI improvement. The authors suggested a reduction in tongue fat volume may be a potential OSA treatment strategy. Future studies will tell whether this is feasible and effective.

Recently, the FDA approved a new medication to treat residual daytime sleepiness in patients with sleep apnea – solriamfetol. Like other wake-promoting agents, it acts on the central nervous system and im-

NetWorks continued on following page

This month in the journal CHEST®

Editor's Picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editor in Chief

Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR).

By Dr. D. B. Price, et al.

Validation of the COPD Assessment Test (CAT) as an outcome measure in bronchiectasis.

By Dr. J. D. Chalmers, et al.

Comparative effects of LAMA-



LABA-ICS versus LAMA-LABA for COPD: Cohort study in real world clinical practice.

By Dr. S. Suissa, et al.

Airway management in critical illness: An update.

By Dr. J. Scott, et al.

Extremes of age decrease survival in adults after lung transplant.

By Dr. M. Valapour, et al.

CHEST strengthens advocacy presence with NAMDRC integration

BY STEPHANIE M. LEVINE, MD, FCCP, AND JAMES P. LAMBERTI, MD, FCCP

On Thursday, March 12, the American College of Chest Physicians (CHEST) and the National Association for Medical Direction of Respiratory Care (NAMDRC) announced publicly our official intent to come together as one association, integrating all NAMDRC activities and operations into CHEST.

This integration launch followed months of discussion between CHEST and NAMDRC leadership. Our respective Boards agreed that united efforts will amplify our individual involvement in patient advocacy and policy.

CHEST and NAMDRC have an intertwined purpose of delivering the highest standard of care for our patients. For this reason, our likeminded advocacy agendas can be even better fulfilled when we can leverage strengths from both associations.

CHEST and NAMDRC have shared an overlapping membership and collaborative history of empowering patients through the



Dr. Levine



Dr. Lamberti

advancement of public policy and clinical education for decades. In addition to our individual efforts, our associations historically leveraged a combined advocacy presence in Washington DC to advance legislation against major tobacco corporations.

Coming together as a joint advocacy-focused organization, the initiation of CHEST's Health Policy and Advocacy Committee, which will be comprised of an equal selection of CHEST and NAMDRC leadership, will drive CHEST's advocacy agenda. The committee will work directly with policymakers, and target legislative and regulatory

CHEST and NAMDRC continued on following page

NetWorks continued from previous page

proves the reuptake of dopamine and norepinephrine. We look forward to head-to-head studies with current agents (modafinil or armodafinil).

Though not entirely new, two devices have been gaining popularity for sleep apnea treatment. Both are nerve stimulators: one designed for obstructive sleep apnea, is a hypoglossal nerve stimulator; the other, a treatment for central sleep apnea, is a phrenic nerve stimulator. They are slowly gaining popularity, though their invasive nature, patient selection criteria, and cost may limit their widespread adoption. More importantly, data on long-term outcomes and impact on hard endpoints such as mortality and reduction in cardiovascular morbidity are sparse. *Ritwick Agrawal, MD, MS, FCCP Steering Committee Member*

Thoracic Oncology

The long and winding treatment road of advanced lung cancer: Long-term outcomes with immunotherapy
Immune checkpoint inhibitors

CHEST and NAMDRRC continued from previous page

issues impacting pulmonary, critical care, and sleep medicine.

A committee of this kind, dedicated strictly to advocacy efforts, will be absolutely invaluable to our united organization. This group will be a true asset for membership to turn, to voice concerns within our practice, and to direct action on policies that matter to our patients.

Members of both organizations were notified of the integration by email on Wednesday, March 11. Along with email notification, NAMDRRC members also received a voting ballot, as the dissolution of a nonprofit organization for Virginia-based organizations requires a vote of approval by membership within a 25-day waiting period.

NAMDRRC's long regarded monthly publication, *Washington Watchline*, will continue through CHEST, as will the NAMDRRC Annual Meeting, slated for next March 18-20, 2021 in Sonoma, California, in conjunction with the CHEST Spring Leadership Meeting.

Concentrating our efforts under one organization allows us to offer the best possible opportunities to our membership, patients, and far-reaching network. This is an exciting time for everyone involved, and we are looking forward to seeing all we can accomplish together.



Dr. Agrawal



Dr. Mehta

(ICIs) have transformed the landscape in advanced non-small cell lung cancer (NSCLC) treatment, extending progression-free survival (PFS) and overall survival (OS).

Pembrolizumab is approved in advanced NSCLC with $\geq 50\%$ PD-L1 expression based on KEYNOTE-024 trial.¹ Recent updated analysis of KEYNOTE 024 trial² showed that patients with advanced NSCLC treated with pembrolizumab had a median OS of 30.0 months compared with 14.2 months for those treated with chemotherapy. More recently, 5-year outcomes of KEYNOTE-001 trial³ showed that OS was 23.2% for treatment-naïve patients and 15.5% for previously treated patients with no grade 4 or 5 treatment-related adverse events.

Nivolumab is approved for the treatment of patients with advanced NSCLC with progression of disease after standard chemotherapy (regardless of PD-L1 expression) based on CHECKMATE 017/057 trials.^{4,5} OS at 5 years in recently presented pooled analysis of these trials was 13.4% in nivolumab arm compared with 2.6% in docetaxel arm with a PFS of 8% and 0%, respectively.^{6,7} Median duration of response was 19.9 months vs 5.6 months. At 5 years, almost one-third of patients who responded to the nivolumab were without disease progression. Similarly, a recent 5-year analysis of patients with advanced NSCLC treated with nivolumab showed OS of 16%, identical for squamous and nonsquamous histology; 75% of 5-year survivors were without disease progression.⁸

Treatment with immunotherapy in advanced NSCLC has resulted in a dramatic change in outcomes with a small percentage of patients able to achieve durable responses.

Hiren Mehta, MD, FCCP Steering Committee Member

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Meet the 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 (Furthering Innovation and Science for Health) featured CHEST members disrupting our beliefs about



Dr. Cota

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. Cota.

Name: Donna Cota, DO

Institutional Affiliation: Bay-state Medical Center, PGY5 Critical Care

Position: 2nd Year Fellow in PGY5 Critical Care

Title: Time to Vent: A Blended Learning Experience

Brief Summary of Submission: Time to Vent is a blended learning experience focused on ventilator management that incorporates modalities for all learning types. It includes a hand-out, audio/visual presentation, and practice case scenarios.

1. What inspired your innovation? I remembered that as a resident, I had a very difficult time understanding ventilators and worked hard to try to understand them on my own. When I started fellowship, I thought I understood ventilator management and then realized I was still wrong. I have focused my training on education, and I wanted to create a concise resource geared toward the fundamentals of ventilators for the benefit of educational levels.

2. Who do you think can benefit most from it, and why?

Right now, I have focused the project on teaching residents of varying specialties, such as internal medicine and emergency medicine. They are still in training and rotate through ICUs, needing to understand ventilators for effective patient care and questions are present on their board examinations.

3. What do you see as challenges to your innovation gaining widespread acceptance?

How can they be overcome? The biggest challenge is making the website able to be found on Google. This is a work in progress. However, right now, the link is sent via email to interested parties.

4. Why was it meaningful for you to emerge as a finalist in FISH Bowl 2019? It built confidence that my lifelong project is important and has merit to

Our kinder, gentler, yet still competitive and cutting-edge FISH Bowl featured CHEST members disrupting our beliefs about how clinical care and education are performed.

it. And, it ended up becoming a way for people to learn about the project and ask me for the link.

5. What future do you envision for your innovation beyond FISH Bowl 2019? I am still going to continue to improve the project with current endeavors to include a piece on waveforms and dyssynchrony of the ventilator. My ultimate goal is to create a free virtual ventilator simulator with practice cases.

INDEX OF ADVERTISERS

Amgen Corporate	9
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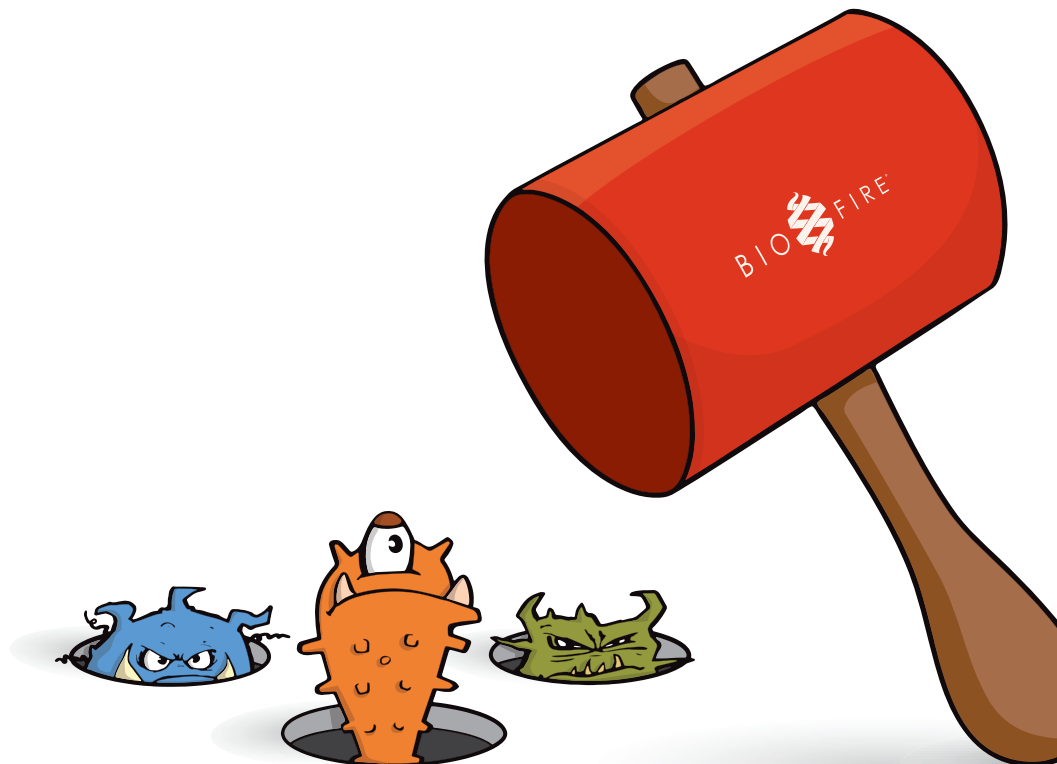
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