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Guidelines updated for treating community-acquired pneumonia

BY MARK S. LESNEY
MDedge News

An update to the 2007 guidelines on the treatment of community-acquired pneumonia (CAP) was published by two medical societies, based upon the work of a multidisciplinary panel that "conducted pragmatic systematic reviews of the relevant research and applied Grading of Recommendations, Assessment, Development, and Evaluation methodology for clinical recommendations."

The panel addressed 16 questions in the areas including diagnostic testing, determination of site of care, selection of initial empiric antibiotic therapy, and subsequent management decisions. Some of their recommendations remained unchanged from the 2007 guidelines, but others were updated based upon more-recent clinical trials and epidemiological studies, according to Joshua P. Metlay, MD, of Massachusetts General and colleagues on behalf of the Infectious Diseases Society of America and the American Thoracic Society.

Among the key recommendations differing from the previous guidelines, the 2019 guidelines include the following:

- Sputum and blood culture samples are recommended in patients with severe disease, as well as in all inpatients empirically treated for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*.

GUIDELINES // *continued on page 6*

CDC, FDA in hot pursuit of vaping lung injuries' source

BY THERESE BORDEN
MDedge News

The national outbreak of vaping-associated lung injuries is ongoing, and the number of cases and deaths continues to rise.

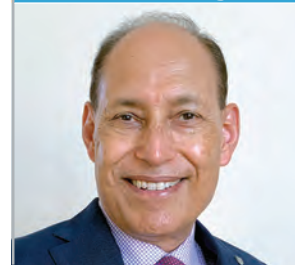
The Centers for Disease Control and Prevention is providing frequent updates of the wide-ranging and aggressive investigation of the cases and deaths linked to vaping, and although a definitive cause remains unknown, evidence is accumulating to implicate tetrahydrocannabinol (THC)-containing devices.

The investigation is being conducted in concert with the Food and Drug Administration, state and local health departments, and public health and clinical partners.

The acronym EVALI has been developed by CDC to refer to e-cigarette, or vaping products use–associated lung injury. In a report summarizing data up to Oct. 31, CDC reported 1,888 EVALI cases and 37 deaths. These cases have occurred in all U.S. states (except Alaska), the District of Columbia, and the U.S. Virgin Islands. The CDC also published a report in the Morbidity

VAPING // *continued on page 7*

INSIDE HIGHLIGHT



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ACIP approves 2020 adult vaccination schedule

BY HEIDI SPLETE
MDedge News

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices voted unanimously to approve the adult immunization schedule for 2020, although some fine-tuning may occur before publication.

"Some of the wordsmithing may be done later," ACIP executive secretary Amanda Cohn, MD, said at the ACIP October meeting.

These small changes revolved mainly around how much wording to include in the current color block tables versus including the information in the notes section.

Key updates to the schedule included a change in wording for the definition of the red bars on the table to include "not recommend-

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ed or contraindicated" instead of only the word "contraindicated." Committee members were especially interested in changing this wording to guide clinicians in use of the live attenuated influenza vaccine because of its potential value in vaccinating health care personnel.

Other updates include language that vaccination of young adults aged 16-23 years who are not at increased risk for meningococcal disease should be vaccinated as follows: "Based on shared clinical decision making, 2-dose series MenB-4C at least 1 month apart or 2-dose series MenB-FHbp at 0, 6 months."

Similarly, clinical decision-making language was added to the notes for the pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13).

The routine vaccination calls for only one dose of PPSV23 given on or after the individual's 65th birthday. Then, based on shared clinical decision making, a dose of PCV13 is recommended for immunocompetent individuals aged 65 years and older. The notes also state that, based on shared clinical decision making, PCV13 and PPSV23 should not be given in the same visit and, if both will be given, PCV13 should be first and should be given 1 year before PPSV23. In addition, "PPSV23 should be given at least 5 years after any previous PPSV23 dose."

"We can't let the perfect be the enemy of the good," said Jason Goldman, MD, liaison representing the ACP. "Those who want to learn the schedule will learn it."

The schedule also adds shared clinical decision making to the notes on human papillomavirus vaccination for adults aged 27-45 years.

The committee members acknowledged the increasing complexity of the adult vaccination schedule, but several members agreed that it is accessible to many clinicians.

"We can't let the perfect be the enemy of the good" said Jason Goldman, MD, liaison representing the American College of Physicians. "Those who want to learn the schedule will learn it; the health system will learn it," even if not every specialist does.

The table "is something to draw you in," said Sandra Fryhofer, MD, an internist who is liaison for the American Medical Association.

More specific information about contraindications for patients with cochlear implants, which also came up in the discussion, may be added to the schedule at a later date.

The ACIP members had no financial conflicts to disclose.

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Guidelines have some weak spots // continued from page 1

- Macrolide monotherapy is only conditionally recommended for outpatients based on resistance levels.
- Procalcitonin assessment, not covered in the 2007 guidelines, is not recommended in order to determine initial antibiotic therapy.
- Corticosteroid use, not covered in the 2007 guidelines, is not recommended, though it may be considered in patients with refractory septic shock.
- The use of health care–associated pneumonia (HCAP) as a category should be dropped, with a switch to an emphasis on local epidemiology and validated risk factors to determine the need for MRSA or *P. aeruginosa* treatment.
- Standard empiric therapy for severe CAP should be beta-lactam/macrolide and beta-lactam/fluoroquinolone combinations, but with stronger evidence in favor of the beta-lactam/macrolide combination.

The updated guidelines include recommendations dealing with the management of patients with comorbidities, and were published in the American Journal of Respiratory and Critical Care Medicine.

"A difference between this guideline and previous ones is that we have significantly increased the proportion of patients in whom we recommend routinely obtaining respiratory tract samples for microbiologic studies. This decision is largely based on a desire to correct the overuse of anti-MRSA and antipseudomonal therapy that has occurred since the introduction of the HCAP classification (which we recommend abandoning) rather than high-quality evidence," the authors concluded. They "expect our move against endorsing monotherapy with macrolides, which is based on population resistance data rather than high-quality clinical studies, will generate future outcomes studies comparing different treatment strategies."Authors reported relationships with pharmaceutical companies; full disclosures are detailed at the end of the guidelines publication.

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SOURCE: Metlay JP et al. Am J Respir Crit Med. 2019;200(7):e45-67.

VIEW ON THE NEWS

From IDWeek 2019: "Ever since we wrote the first CAP [community-acquired pneumonia] guidelines in 1993, we've heard good and bad things, and I agree with both," Michael S. Niederman, MD, FCCP, said in a presentation at IDWeek 2019. "For good or for bad, [guidelines] are a standard against which care can be evaluated." He discussed how, as guidelines have become more evidence based, they have often become "more wishy washy," that when the evidence is weak, the recommendation is weak, and the guidelines merely advise doctors: "You figure it out."

However, he pointed out that, since CAP guidelines were developed, there have been overall improvements in patient care and antibiotic stewardship. But he saw several weaknesses in the new guidelines, including the fact that they did not update minor criteria for determining severe CAP from the 2007 guidelines, despite several studies indicating that there were other criteria to consider. The updated guidelines held a negative view of the use of serum procalcitonin to guide site-of-care decisions, which Dr. Niederman argued went against an analysis of the Etiology of Pneumonia in the Community (EPIC) study.

Dr. Niederman is clinical director of the division of pulmonary and critical care medicine at New York Presbyterian Hospital/Weill Cornell Medical Center, and professor of clinical medicine at Weill Cornell Medical College.

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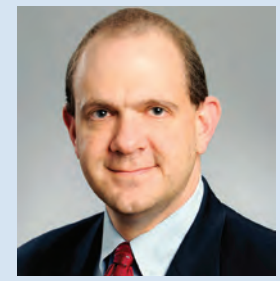

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THC identified as probable culprit in vaping injuries, but investigation continues // continued from page 1

and Mortality Weekly report on characteristics of those patients who have died from EVALI-based symptoms as of Oct. 15, 2019.

With data available for more than 867 patients with EVALI, about 86% had a history of using e-cigarette or vaping products that contained THC in the previous 90 days; 64% reported using nicotine-containing products; 34% reported exclusive use of THC-containing products, and 11% reported exclusive use of nicotine-containing products; 52% reported use of both.

In a telebriefing on Oct. 25, Anne Schuchat, MD, CDC principal deputy director, said, "The data do continue to point towards THC-containing products as the source of the vast majority of individuals' lung injury. There are continuing cases that do not report that history. But I'd like to stress that we don't know what the risky material or substance is. THC may be a marker for a way that cartridges were prepared or the way that the devices are producing harm."

EVALI deaths

Among the 29 deaths reported as of Oct. 15, 59% (17) were male. The median age was 45 years (range, 17-75 years), 55 years (range, 17-71 years) among males, and 43 years (range, 27-75 years) among females; the age difference between males and females was not statistically significant. Patients who died tended to be older than patients who survived. Among 19 EVALI patients who died and for whom data on substance use were available, the use of any THC-containing products was reported by patients or proxies for 84% (16), including 63% (12) who exclusively used THC-containing products. Use of any nicotine-containing products was reported for 37% (7), including 16% (3) who exclusively used nicotine-containing products. Use of both THC- and nicotine-containing products was reported in four of those who died.

Investigation update

Mitch Zeller, JD, director, Center for Tobacco Products at the Food and Drug Administration, participated in the telebriefing and provided an update on the ongoing investigation. He said, "FDA has received or collected over 900 samples from 25 states to date. Those numbers continue to increase. The samples [were] collected directly from consumers, hospitals, and from state offices include vaping devices and products that contain liquid as well as packaging and some nearly empty containers." He also noted that the self-reports of THC and/or nicotine use could mean that there are misreported data, because reports in many cases are coming from teens and from jurisdictions in which THC is not legal (see related story on 15).

Dr. Schuchat noted, "We are aware of older cases that look similar to what we are seeing now. But we do not believe that this outbreak or surge in cases is due to better recognition." She suggested that unknown substances may have been introduced into the supply chain.

A "handful" of cases of readmission have been reported, and the CDC is currently investigating whether these cases included patients who took up vaping again or had some other possible contributing factor. Dr. Schuchat cautioned recovering patients not to resume vaping because of the risk of readmission and the probability that their lungs remain in a weakened state.

Clinical guidance update

The CDC provided detailed interim clinical guidance on evaluating and caring for patients with EVALI. The recommendations focus on patient history, lab testing, criteria for hospitalization, and follow-up for these patients.

Obtaining a detailed history of patients presenting with suspected EVALI is especially important for this patient population, given the many unknowns surrounding this condition, according to the CDC. The updated guidance states, "All health care providers evaluating patients for EVALI should ask about the use of e-cigarette or vaping products, and ideally should ask about types of substances used (e.g., THC, cannabis [oil, dabs], nicotine, modified products or the addition of substances not intended by the manufacturer); product source, specific product brand and name; duration and frequency of use, time of last use; product delivery system and method of use (aerosolization, dabbing, or dripping)." The approach recommended for soliciting accurate information is "empathetic, nonjudgmental" and, the guidelines say, patients should be questioned in private regarding sensitive information to ensure confidentiality.

A respiratory virus panel is recommended for all suspected EVALI patients, although at this time, these tests cannot be used to distinguish EVALI from infectious etiologies. All patients should be considered for urine toxicology testing, including testing for THC.

Imaging guidance for suspected EVALI patients includes chest x-ray, with additional CT scan when the x-ray result does not correlate with clinical findings or to evaluate severe or worsening disease.

Recommended criteria for hospitalization of patients with suspected EVALI are those patients with decreased O_2 saturation (less than 95%) on room air, in respiratory distress, or with comorbidities that compromise pulmonary reserve. As of Oct. 8, 96% of patients with suspected EVALI reported to the CDC have been hospitalized.

VCHAL/GETTY IMAGES

As for medical treatment of these patients, corticosteroids have been found to be helpful. The statement noted, "Among 140 cases reported nationally to CDC that received corticosteroids, 82% of patients improved."

The natural progression of this injury is not known, however, and it is possible that patients might recover without corticosteroids. Given the unknown etiology of the disease and "because the diagnosis remains one of exclusion, aggressive empiric therapy with corticosteroids, antimicrobial, and antiviral therapy might be warranted for patients with severe illness. A range of corticosteroid doses, durations, and taper plans might be considered on a case-by-case basis."

The report concluded with a strong recommendation that patients hospitalized with EVALI are followed closely with a visit 1-2 weeks after discharge and again with additional testing 1-2 months later. Health care providers are also advised to consult medical specialists, in particular pulmonologists, who can offer further evaluation, recommend empiric treatment, and review indications for bronchoscopy.

Coding guidance

CDC has issued coding guidance to help track EVALI. The document was posted on the CDC website. The following conditions associated with EVALI are covered in the new coding guidance:

- Bronchitis and pneumonitis caused by chemicals, gases, and fumes; including chemical pneumonitis; J68.0.
- Pneumonitis caused by inhalation of oils and essences; including lipoid pneumonia; J69.1.
- Acute respiratory distress syndrome; J80.
- Pulmonary eosinophilia, not elsewhere classified; J82.
- Acute interstitial pneumonitis; J84.114.

The document notes that the coding guidance has been approved by the National Center for Health Statistics, the American Health Information Management Association, the American Hospital Association, and the Centers for Medicare & Medicaid Services.

The search continues

Mr. Zeller cautioned that this investigation will not be concluded in the near future. He noted, "We are committed to working to [solve the mystery] just as quickly as we can, but we also recognize that it will likely take some time. Importantly, the diversity of the patients and the products or substances they have reported using and the samples being tested may mean ultimately that there are multiple causes of these injuries."

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Richard Franki and Gregory Twachtman contributed to this story.

INNOVATIVE MEDICINE Best Practices

Treatment of Unresectable Stage III Non-small Cell Lung Cancer

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Introduction

With a recent renaissance in cancer diagnostics and treatment, there is renewed promise for many who previously held little hope. Lung cancer represents the second most frequently diagnosed cancer, a close second to breast cancer, at 12.9% of expected new cancer cases in 2019.[1] However, the 23.5% death rate predicted for lung cancer outranks breast, prostate, colorectal, and skin melanomas combined.[1] Five-year lung cancer survival rates have increased from 11% in 1975 to more than 20% in 2016.[1] This relatively low rate of survival can probably be explained by the fact that the majority of patients are diagnosed with locally advanced disease (Stage III, disease metastatic to mediastinal or supraclavicular nodes) or advanced disease (Stage IV, disease metastatic to other organs).[2-4] Recent advancements in treatment are proving effective in improving patient outcomes[5,6]; combined with adherence to screening recommendations and immediate referral to appropriate specialists, earlier diagnosis and staging can help lead to improved outcomes.[7-9]

Non-small cell lung cancer (NSCLC) constitutes 80% to 85% of lung cancer diagnoses, including histological identification of adenocarcinoma, squamous cell, large cell, and undifferentiated carcinomas.[10-12] Approximately 25% to 30% of patients with NSCLC are diagnosed with locally advanced or Stage III disease.[12] A proportion of these patients may experience the curative benefits of combined chemotherapy and surgery or concurrent chemotherapy and radiation therapy.[5,13] About 40% of patients with NSCLC are diagnosed with Stage IV disease, and the treatment goal in these patients is to manage symptoms, improve quality of life, and extend survival.[13,14] Treatment options include systemic chemotherapy, targeted mutation therapies, radiation, immunotherapy, and on occasion surgery.[7] It is vital that we increase early diagnosis, accurate staging, and referral to the appropriate specialists in lung cancer to ensure that treatment is optimized and more lives are potentially saved.[7]

Screening and Diagnosis

Unlike with breast, prostate, and colorectal cancers, systematic screening for lung cancer is not a well-established population-based practice, and its role is not fully grasped by primary caregivers.[15] Risk factors such as history of tobacco use and exposure to second-hand smoke are common knowledge, but other environmental exposures (diesel smoke, pollution, and other cancer-causing agents) are difficult to quantify.[16,17] Populations with lifestyles with higher exposure to these factors are generally more reticent to intervention and skeptical of the benefits of treatment, while others may be concerned that radiation-based screening techniques contribute to the risk.[15] In addition to patient perceptions that defer intervention, presenting symptoms of cough and dyspnea are frequently confounded with other respiratory conditions, creating a delay in early detection and staging.[9] Even further delays have been seen when patients present with more generalized symptoms like fatigue or bone or joint pain.[9]

Based on the National Lung Screening Trial (NLST),[18] the American College of Chest Physicians (ACCP) has published recommendations that low-dose computerized tomography (LDCT) scans be performed annually on patients meeting the following criteria: (1) 30 pack-year current smoker or former smoker between the ages of 55 and 74 years, (2) former smokers who have quit within the past 15 years, and (3) no comorbidities that potentially preclude curative treatment benefit.[15] The National Comprehensive Cancer Network® (NCCN®) also encourages patients to seek yearly screening if they are 50 years or older, have a 20 or more pack-year smoking history, and have other known risk factors besides second-hand smoke exposure, such as radon exposure.[19] Screening with LDCT, in select patients at high risk for lung cancer, decreased the relative risk of death from lung cancer by 20% when compared with chest radiography.[18] As such, efforts are being made to educate general practitioners and the public about this tremendous benefit.[15,19,20]

The goal of screening is to identify a lung cancer in the earliest possible stage, which, as **Table 1** demonstrates, directly improves survivability.[19] However, imaging alone does not provide accurate staging, and once lung cancer is suspected, time is of the essence in ensuring no further progression. Various target time recommendations have been published advocating for improved wait times across the care spectrum, ranging from 30 to 52 days of median wait time from diagnosis to first treatment.[23,24] Yet one Canadian study showed that despite the recommended time of 2 weeks between symptom onset and diagnosis, the actual median time to diagnosis was 4.5 months.[9] It has been estimated that every 4 weeks between scans represents the potential for a 13% progression.[25] Kasymjanova et al describe 2 studies and a meta-analysis demonstrating that increased wait times impart a negative effect on recurrence and survival.[23] In their own study, it was noted that reduced wait times particularly benefited Stage III NSCLC survival.[23]

Because pulmonologists may be the first specialist a patient sees, they are relied upon to diagnose, stage, and coordinate care for many patients with lung cancer.[26] Because Stage III NSCLC is a curative intent setting,[13,27] it is of particular importance to coordinate more complicated surgical, radiation, and chemotherapy care for these patients as soon as the diagnosis and stage have been ascertained.[7] While initial chest computed tomography or positron emission tomography (PET) scans often determine tumor size(s) and location(s), and presence of hilar or mediastinal nodes and extrathoracic lesions (excluding the brain), these studies cannot be the sole factors used in staging, and they falsely overstage 19% of the time and understage 13% of the time.[28] The ACCP guidelines recommend magnetic resonance imaging (MRI) of the brain for patients with clinical Stage III or IV disease with or without symptoms of intracranial disease,[29] whereas NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend staging brain MRI in patients with clinical Stage IB (optional), IIA/B, IIIA/B/C and IV.[30]

Diagnostic procedures to obtain accurate histological diagnosis and staging and adequate tissue samples for molecular testing must be considered, ideally with input from a multidisciplinary team (MDT) composed of pulmonologists, thoracic surgeons, and radiology specialists who are board certified and have expertise in thoracic oncology whenever any stage of NSCLC is suspected.[30] PET imaging can be used to identify the optimal biopsy site that produces the highest yield, is minimally invasive, and is most likely to confer the highest staging.[30] Whenever possible, procedures should be combined (bronchoscopy and endobronchial ultrasound with needle aspiration of lymph nodes) to improve time to diagnosis and clinical staging.[30] Invasive mediastinal staging is recommended before surgical resection.[30] The organization of lung cancer care requires development of a multidisciplinary program committed but not limited to the expeditious coordination of the patient's care among various disciplines to avoid unnecessary tests and procedures, delay in care, costly care, and patient frustration and anxiety.[31] Multidisciplinary care has been shown to decrease time to diagnosis and improve referral for appropriate treatment.[32] In particular, patients with Stage III NSCLC are more

TABLE 1. Summary of NSCLC Staging & Prognosis[3,21,22]

Stage	TNM Classification[21] (Tumor, Node, Metastases)	Nodal Zones & Stations[3,22]		Treatment/Goal[22]	5-Year Survival[21]
IA_1	T1a or T1a(mi), N0, M0			Surgery or radiation	92%
IA_2	T1b, N0, M0			Surgery ± radiation, OR Radiation	83%
IA_3	T1c, N0, M0				77%
IB	T2a, N0, M0			Surgery ± Chemotherapy± Radiation	68%
IIA	T2b, N0, M0				60%
IIB	T1a-c, N1, M0 <or> T2a-b, N1, M0 <or> T3, N0, M0	N1 generally resectable N2 heterogenous resectability	N1 = Hilar Zone if ipsilateral • Station 10 (Hilar nodes) Peripheral Zone if ipsilateral • Station 11 (Interlobar nodes) • Station 12 (Lobar Nodes) • Station 13 (Segmental Nodes) • Station 14 (Subsegmental Nodes		53%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or> T3-4, N1, M0 <or> T4, N1, M0			Surgery ± Chemotherapy ± Radiation	36%
IIIB	T3, N2, M0 <or> T4, N2, M0		N2 = Lower Zone if ipsilateral • Station 8 (Paraesophageal nodes) • Station 9 (Pulmonary ligament nodes) Subcarinal Zone if ipsilateral • Station 7 (Subcarinal nodes) Aortopulmonary Zone • Station 5 (subaortic & aortopulmonary nodes) • Station 6 (para-aortic nodes) Superior Mediastinal Zone • Station 2 (Upper paratracheal nodes) • Station 3 (Prevascular & retrotracheal nodes) • Station 4 (Lower paratracheal nodes)		26%
IIIA	T1a-c, N2, M0 <or> T2a-b, N2, M0 <or>	N2 = heterogenous resectability N3 generally non-resectable		Radiation ± Chemotherapy ± Immunotherapy	36-41%†
IIIB	T1a-c, N3, M0 <or> T2a-b, N3, M0 <or> T3, N2, M0 <or> T4, N2, M0		N3 = Supraclavicular Zone • Station 1 (Low cervical, supraclavicular, sternal notch nodes • contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, superclavicular nodes	Radiation ± Chemotherapy ± Immunotherapy	24-26%†
IIIC	T3-4, N3, M0				12-13%†
IVA	Any T, Any N, M1a-b			Palliative Care with Systemic Therapy	0%
IVB	Any T, Any N, M1c				0%

Abbreviations: M1a, separate tumor contralateral lobe or primary tumor with pleural/pericardial nodules or malignant effusions; M1b, single extrathoracic mass; M1c, multiple extrathoracic masses; mi, minimally invasive adenocarcinoma.
T1a ≤ 1cm; T1b >1cm, ≤ 2cm; T1c >2cm, ≤ 3cm; T2a >3cm, ≤ 3cm; T2b >4cm, ≤ 5cm; T3 >5cm, ≤ 7cm; T4 >7cm.
†Reflects changes in 5-year survival of all stage III NSCLC when staging included pathology information.

likely to receive appropriate treatment when referred to oncology specialists.[7] Still, data suggest that up to 20% of patients diagnosed with Stage III NSCLC are never evaluated by an oncologist.[33]

The tumor, node, metastasis (TNM) system for staging has been used since 1944.[8] Now governed by the International Association for the Study of Lung Cancer (IASLC), the eighth edition took effect in 2017.[21] Several changes from the seventh edition, including new TNM definitions and addition of categories, have caused shifts in staging, with a greater emphasis on tumor size and invasion of surrounding tissues.[3] As a result, Stage III now includes subtype C (T3-T4, N3, M0), which is still treated in a curative intent setting.[21] Additionally, nodal zones were further broken down into more specific stations that clearly define anatomic landmarks within each zone, as this too proved to be associated with prognosis.[3] Differentiating Stage IIIC from Stage IVA has provided more patients the opportunity to be treated in a curative intent setting, as further data collection and new research are expanding within each subtype and allowing for individualized treatment approaches.[3,21]

Clinically, the distinction between resectable and unresectable Stage III disease is of significance because unresectable Stage III does not afford a treatment path as well-established as resectable disease (surgery).[34] Unresectable generally includes Stage IIIA tumors (T1-T2 tumors with multiple positive ipsilateral mediastinal notes), often described as bulky or extensive; Stage IIIB (T1-T2 tumors with positive contralateral mediastinal or supraclavicular nodes or T3-T4 tumors with positive ipsilateral mediastinal nodes); and Stage IIIC (T3-T4 tumors with positive contralateral mediastinal or supraclavicular nodes).[11]

Treatment of Stage III NSCLC

Patients clinically determined to have resectable Stage III NSCLC are candidates for a variety of treatment options, none of which have proven to be superior.[11] The 2019 NCCN Guidelines® suggest the following course for resectable Stage III NSCLC: (1) Preoperative chemotherapy (CT) and radiation (CTR), or preoperative CT followed by postoperative RT (split-panel decision); and (2) surgery, using minimally invasive techniques where possible.[30] The panel acknowledges that controversy remains regarding the sequencing of surgery, chemotherapy, and radiation techniques.

The majority of patients with Stage III NSCLC have unresectable disease.[35] Platinum-based CT has been preferred over other chemotherapeutic modalities for over 3 decades.[36] Evidence supports its use as part of definitive CRT along with a minimum of 60 Gy in escalated doses; concurrent treatment is currently preferred over sequential in all histological findings.[30] Accelerated RT alone imparts some benefit to those who refuse CT.[11]

Severe immune-mediated adverse reactions are associated with all immune checkpoint inhibitors, including pneumonitis, causing discontinuation.[37] A recent retrospective single-center study suggests that patients who are on corticosteroids for cancer-unrelated indications have similar outcomes on immunotherapy as patients who are receiving 0 to < 10 mg of prednisone.[37] However, additional mechanistic studies as well as prospective clinical trials are needed to identify whether the use of corticosteroids affects specific aspects of the immune system necessary for immunotherapy activity. Optimal treatment duration for immune checkpoint inhibitors requires further study, and their use in patients with autoimmune disorders and a past organ transplantation should be avoided.[38]

Conclusion

Locally advanced and metastatic NSCLC patients have benefitted from intensive research into immunologic approaches to treatment. Accurate diagnosis and staging are critical, particularly in the differentiation between Stage III, which is treated with curative intent, and Stage IV, which is metastatic. CRT is the current standard of care for unresectable Stage III disease and has shown improvement in overall survival, while the introduction of immunotherapy following CRT treatment can be discussed as a treatment option. To reap the benefits of these advances in treatment, patients with suspected or confirmed lung cancer should be managed by an MDT that includes a pulmonologist, thoracic surgeon, and medical and radiation oncologists, and referral for appropriate treatment of Stage III and IV NSCLC is crucial to improving patient outcomes.

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Dupilumab shrinks nasal polyps in severe chronic rhinosinusitus

BY TED BOSWORTH
MDedge News

MADRID – In adults with severe chronic rhinosinusitus with nasal polyps (CRSwNP), the monoclonal antibody dupilumab is effective for shrinking the polyps, improving symptoms, and reducing the need for systemic corticosteroids and surgery, according to results of two phase 3 studies reported together at the annual congress of the European Respiratory Society.

"Dupilumab improved all of the disease components, and the improvement was observed in most of them at the first assessment," reported Jorge F. Máspero, MD, research director, Fundacion Cidea, Buenos Aires.

The data were drawn from multicenter phase 3 trials called LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52. Both included stratifications for asthma and for NSAID-exacerbated respiratory disease (ERD), which are common comorbidities. Findings of the two studies were published together just prior to Dr. Máspero's presentation at the ERS (Lancet. 2019 Sep 26. doi: 10.1016/S0140-6736[19]31881-1).

For the coprimary end point of endoscopic nasal polyp score (NSP), the reductions were 2.06 and 1.8 at 24 weeks from baseline (both *P* less than .0001) in SINUS-24 and SINUS-52, respectively. For the nasal congestion or obstruction score, another primary end point, the reductions were 0.89 and 0.87, respectively (both *P* less than .0001).

There were also major improvements at week 24 on secondary end points, including the Lund-McKay CT score for staging of CRSwNP (*P* less than .0001), total symptom score (*P* less than .0001), the UPSIT test for smell (*P* less than .0001), and SNOT-22 (*P* less than .0001), a quality of life instrument specific for nasal and sinus diseases.

When these outcomes were graphed, curves for the dupilumab and placebo arms had already separated by 4 weeks, "and then we see the dupilumab patients keep getting better over the course of follow-up, and the effect was seen regardless of comorbidities," said Dr. Máspero, referring to concomitant asthma or ERD.

The SINUS-24 trial randomly assigned 276 CRSwNP patients to 300 mg dupilumab or placebo, each given subcutaneously every 2 weeks. The SINUS-52 trial, which randomized 448 patients, included the same two arms plus a third arm in which patients also received 300 mg dupilumab every 2 weeks for 24 weeks and then 300 mg every month for an additional 26 weeks.


Ted Bosworth/MDedge News

Dr. Jorge F. Máspero

In a pooled analysis of these trials, patients randomized to dupilumab had a 78% reduction in likelihood of receiving systemic corticosteroids and a 79% reduction in being referred for surgery relative to placebo, Dr. Máspero reported.

Dupilumab, a monoclonal antibody that inhibits the activity of interleukin-4, IL-5, and IL-13, was well tolerated. Among the most common adverse events, there were lower rates of headache (9% vs. 7%), epistaxis (7% vs. 6%), and injection-site erythema (8% vs. 6%) in the dupilumab and placebo arms, respectively, but the rate of serious adverse events (6% vs. 3%) and adverse events leading to treatment discontinuation (5% vs. 3%) were only slightly higher in the active-treatment group.

Both trials, which required a bilateral baseline NPS score of 5.0 for entry, recruited a population with relatively severe CRSwNP, according to Dr. Máspero. Of the 724 patients, 204 had ERD.

A restored sense of smell was one of the contributors to an improvement in quality of life.

"The sense of smell improves very quickly after starting dupilumab. Patients reported results within 2 weeks, and there was an almost complete lack of improvement in the placebo group," Dr. Máspero reported.

Dupilumab is already indicated for the treatment of CRSwNP, but this study confirms a major effect on polyp size, sinus congestion, and symptoms irrespective of the presence of common comorbidities affecting the airways, Dr. Máspero said.

Dr. Maspero reports no potential conflicts of interest.

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SOURCE: Bachert C et al. Lancet. 2019 Sep 26. doi: 10.1016/S0140-6736(19)31881-1.

In-hospital flu shot curbed readmissions in patients with CAP

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – In-hospital flu shots were rare, yet linked to a lower readmission rate for patients hospitalized with community-acquired pneumonia in a recent retrospective study, suggesting a "missed opportunity" to improve outcomes for these patients, an investigator said.

Less than 2% of patients admitted for community-acquired pneumonia (CAP) received in-hospital influenza vaccination, yet receiving it was linked to a 20% reduction in readmissions, according to investigator Kam Sing Ho, MD, a resident at Mount Sinai St. Luke's, New York.

Those patients who were readmitted had a significantly higher death rate vs. index admissions, Dr. Ho said in a poster discussion session at the annual meeting of the American College of Chest Physicians.

"I know (vaccines) are pretty much pushed out to the outpatient setting, but given what we showed here in this abstract, I think there's a role for influenza vaccines to be a discussion in the hospital," Dr. Ho said in his presentation.

The retrospective analysis was based on 825,906 adult hospital admissions with a primary diagnosis of CAP in data from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP). Of that large cohort, just 14,047 (1.91%) received in-hospital influenza vaccination, according to Dr. Ho.

In-hospital influenza vaccination independently predicted a lower risk of readmission (hazard ratio, 0.821; 95% confidence interval, 0.69-0.98; *P* less than .02) in a propensity score – matching analysis that included 9,777 CAP patients who received the vaccination and 9,777 with similar demographic and clinical characteristics.

Private insurance and high-income status also predicted lower risk of readmission in the analysis, while by contrast, factors associated with higher risk of readmission included advanced age, Medicare insurance, and respiratory failure, among other factors, Dr. Ho reported.

The overall 30-day rate of readmission in the study was 11.9%, and of those readmissions, the great majority (about 80%) were due to pneumonia, he said.

The rate of death in the hospital was 2.96% for CAP patients who were readmitted, versus 1.11% for the index admissions (*P* less than .001), Dr. Ho reported. Moreover, readmissions were associated with nearly half a million hospital days, $1 billion in costs, and $3.67 billion in charges.

Based on these findings, Dr. Ho and colleagues hope to incorporate routine influenza vaccination for all adults hospitalized with CAP.

"We're always under pressure to do so much for patients that we can't comprehensively do everything. But the 20% reduction in the risk of coming back, I think that's significant," Dr. Ho said in an interview.

The authors reported having no disclosures related to this research.

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SOURCE: Ho KS et al. CHEST 2019. Abstract doi: 10.1016/j.chest.2019.08.450.

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Recent COPD exacerbation did not affect aclidinium's efficacy in high-risk patients

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – A history of recent exacerbations did not significantly affect the safety or efficacy of aclidinium bromide (Tudorza) in patients with moderate to severe chronic obstructive pulmonary disease and high cardiovascular risk, analysis of a postmarketing surveillance trial suggests.

Regardless of exacerbation history, the long-acting muscarinic antagonist reduced the rate of moderate or severe COPD exacerbations versus placebo in this subgroup analysis of the phase IV ASCENT-COPD trial, presented here at the annual meeting of the American College of Chest Physicians.

At the same time, there were no significant increases in the risk of mortality or major adverse cardiac events (MACE) for those patients who had an exacerbation in the past year versus those who did not, according to investigator Robert A. Wise, MD.

ANDREW D. BOWSER/MDEDGE NEWS

Dr. Robert A. Wise

Those findings may be reassuring, given that COPD patients commonly have comorbidities and cardiovascular risk factors, according to Dr. Wise, professor of medicine at the Johns Hopkins University, Baltimore.

"There's a concern and some evidence that patients who have a propensity to COPD exacerbations may also have an increased risk for cardiovascular events," Dr. Wise said in a podium presentation.

Accordingly, he and coinvestigators sought to tease out the impact of COPD exacerbations on safety as well as efficacy in the randomized, placebo-controlled ASCENT-COPD trial, which included 3,630 patients with moderate to severe COPD plus a cardiovascular disease history or multiple atherothrombotic risk factors.

Of the patients who were analyzed in the study, 1,433 patients had at least one treated COPD exacerbation in the year before screening for the study, while 2,156 had no exacerbations in the prior year, Dr. Wise said.

Top-line results of that study, published several months ago, showed that aclidinium did not increase MACE risk over 3 years, and reduced the rate of moderate to severe COPD exacerbations over the first year (JAMA. 2019 7 May 7;321[17]:1693-701).

In this latest analysis, presented at the meeting, risk of MACE with aclidinium treatment was not increased versus placebo, irrespective of whether they had exacerbations in the prior year (interaction $P = .233$); likewise, the risk of all-cause mortality was similar between groups ($P = .154$).

In terms of reduction in moderate or severe COPD exacerbations in the first year, aclidinium was superior to placebo both for the patients who had at least one exacerbation in the prior year (rate ratio, 0.80) and those who had no exacerbations in the prior year (RR, 0.69).

"This translates into a number needed to treat to prevent one exacerbation of about 11 patients for those without an exacerbation, compared to about 6 patients for those with a prior exacerbation," Dr. Wise said in his presentation.

The ASCENT-COPD study was funded initially by Forest Laboratories and later by AstraZeneca and Circassia. Dr. Wise provided disclosures related to AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Sunovion, Mylan/Theravance, Contrafect, Pearl, Merck, Verona, Novartis, AbbVie, Syneos, Regeneron, and Kiniksa.

SOURCE: Wise RA et al. CHEST 2019 Abstract doi: 10.1016/j.chest.2019.08.231.

Race mismatch may affect survival in lung transplant setting

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – Race compatibility is a factor that can affect survival and needs to be considered when matching lung transplant candidates to potential donors, results from a large retrospective analysis suggest.

Specifically, whites had significantly worse survival when receiving lungs from African American donors in this registry analysis, according to study investigator Alexis Kofi Okoh, MD.

By contrast, donor-to-recipient race compatibility (DRRC) did not affect posttransplant survival among African American or Hispanic patients, said Dr. Okoh, who is with the lung transplant division at the Rutgers Robert Wood Johnson Medical School, New Brunswick, N.J.

While race mismatch has been shown to affect outcomes in kidney, heart, and liver transplant settings, the data for DRRC in lung transplant prior to this analysis generally have been limited to small, single-center studies, according to Dr. Okoh.

"If you do have the option, [race compatibility] should highly be considered, because it clearly has an impact on outcomes," Dr. Okoh said in an interview here at the annual meeting of the American College of Chest Physicians.

Considering the race of both donor and recipient is especially important now that the lung transplant population is becoming more ethnically diverse, he added.

The study was based on an analysis of 19,504 lung transplant recipients in the prospectively maintained United Network for Organ Sharing (UNOS) database during 2006-2018. In that cohort, 16,485 recipients were white, 1,787 were African American, and 1,232 were Hispanic.

ANDREW BOWSER/MDEDGE NEWS

Dr. Alexis Kofi Okoh

Race-matched donor organs were used in two-thirds (66.2%) of white recipients, about one-quarter (26.8%) of African American recipients, and one-third (33.0%) of Hispanic recipients.

Overall, survival post–lung transplant was significantly poorer among recipients who did not receive a race-matched organ in Kaplan-Meier survival estimates. Dr. Okoh said that this effect was diminished after they adjusted for patient baseline characteristics ($P = 0.2809$).

For African American recipients, the unadjusted and adjusted survival estimates were no different regardless of donor race, and likewise, there were no apparent survival differences between Hispanic recipients who received race matched or mismatched organs.

Survival among white recipients, however, was significantly affected by race of the recipient, with decreased survival estimates noted even after adjustment for patient characteristics, according to Dr. Okoh's presentation.

Results of regression analysis showed that white recipient/African American donor was the only race mismatch to significantly affect survival, Dr. Okoh said in the interview.

The posttransplant survival hazard ratios (and 95% confidence intervals) reported by Dr. Okoh with a no race mismatch serving as reference were 1.15 (1.08-1.23) for whites with African American donors, and 1.09 (1.01-1.18) for Whites with Hispanic donors.

Dr. Okoh and coinvestigators reported no relevant conflicts in relation to their study.

SOURCE: Okoh AK et al. CHEST 2019 Abstract doi: 10.1016/j.chest.2019.08.220.

FDA approves elexacaftor/ivacaftor/tezacaftor for CF

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved elexacaftor/ivacaftor/tezacaftor (Trikafta) for the treatment of the most common type of cystic fibrosis in patients aged 12 years or older, the first triple-combination therapy approved for that indication.

Approval for Trikafta was based on results from two clinical trials in patients with cystic fibrosis with an F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In the first trial, a 24-week, randomized, double-blind, placebo-controlled study of 403 patients, the mean percent predicted forced expiratory volume in 1 second increased by 14% from baseline, compared with placebo. In the second trial, a 4-week, randomized, double-blind, active-controlled study of 107 patients, mean percent predicted forced expiratory volume in 1 second was increased 10% from baseline, compared with tezacaftor/ivacaftor, according to the FDA press release.

Approval for the combination was based on results from two clinical trials in patients with cystic fibrosis with an F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

In the first trial, patients who received Trikafta also saw improvement in sweat chloride, reduction in the number of pulmonary exacerbations, and reduction of body mass index, compared with placebo.

The most common adverse events associated with Trikafta during the trials were headaches, upper respiratory tract infections, abdominal pains, diarrhea, rashes, and rhinorrhea, among others. The label includes a warning related to elevated liver function tests, use at the same time with products that induce or inhibit a liver enzyme called cytochrome P450 3A4, and cataract risk.

"At the FDA, we're consistently looking for ways to help speed the development of new therapies for complex diseases, while maintaining our high standards of review. Today's landmark approval is a testament to these efforts, making a novel treatment available to most cystic fibrosis patients, including adolescents, who previously had no options and giving others in the cystic fibrosis community access to an additional effective therapy," said acting FDA Commissioner Ned Sharpless, MD.

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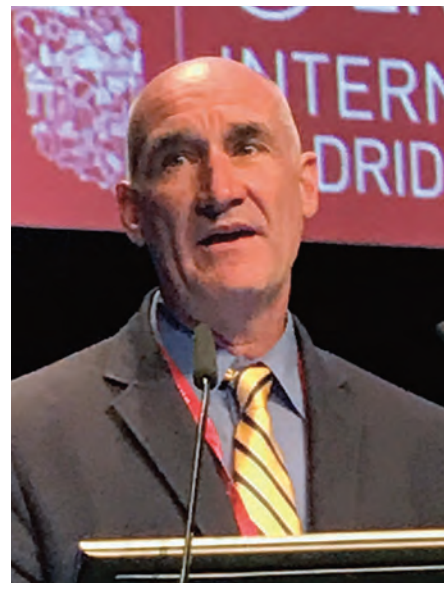
TKI preserved lung function in patients with fibrosing pulmonary disease

BY TED BOSWORTH
MDedge News

MADRID – In patients with fibrosing lung diseases other than idiopathic pulmonary fibrosis (IPF), nintedanib, a tyrosine kinase inhibitor (TKI), substantially reduced the rate of decline in lung function, according to findings from a phase 3, placebo -controlled trial presented at the annual congress of the European Respiratory Society.

The trial, called INBUILD, enrolled patients who had a progressive lung disease with a fibrosing phenotype, such as interstitial pneumonia with autoimmune features or noninterstitial pneumonia, on the premise that these conditions might share a pathology responsive to a common therapy, explained Kevin R. Flaherty, MD, of National Jewish Health, Denver. The INBUILD trial was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 153 sites in 15 countries. A total of 663 patients underwent randomization and received at least one dose of nintedanib (332) or placebo (331).



Ted Bosworth/MDedge News

Dr. Kevin R Flaherty

Patients with fibrosing lung disease affecting more than 10% of lung volume were randomized to 150 mg twice daily of nintedanib, which inhibits intracellular growth factors implicated in fibrosis and is already indicated for IPF, or matching placebo.

On the primary endpoint of change in forced vital capacity (FVC) at 52 weeks, those in the nintedanib arm lost lung function at a rate that was less than half that of those randomized to placebo (–80.8 vs. –187.8 mL/year; *P* less than .001).

In a preplanned stratification, the protection from nintedanib against a decline in lung function was found to be at least as good in those with a usual interstitial pneumonia (UIP-like) pattern of fibrosis on baseline imaging (–82.9 vs. –211.1 mL/year), compared with those with other fibrotic patterns (–79.0 vs. –154.2 mL/year). The UIP-like subgroup represented about 60% of those enrolled.

"The relative protection from decline in lung function supports the hypothesis that progressive fibrosing interstitial lung diseases have a similar pathobiologic mechanism," said Dr. Flaherty. Results from the INBUILD were published simultaneously with his ERS presentation (N Engl J Med. 2019 Sep 29. doi: 10.1056/NEJMoa1908681).

The curves documenting change of lung function in favor of nintedanib relative to placebo separated within 12 weeks of treatment initiation, according to Dr. Flaherty. The ERS-invited discussant, Martin Kolb, MD, PhD, professor of respirology, McMaster University, Hamilton, Ont., called the reductions in loss of lung function "profound" and "very impactful."

However, despite these reductions, there was no significant difference in quality of life as measured with the King's Brief Interstitial Lung Disease (KBILD) questionnaire, which was a secondary outcome. The problem was that there was little change in KBILD in either group at 52 weeks, limiting the ability to show differences.

"The relative protection from decline in lung function supports the hypothesis that progressive fibrosing interstitial lung diseases have a similar pathobiologic mechanism."

The rates of death were numerically lower at 52 weeks in the nintedanib arm for the study overall (4.8% vs. 5.1%) and for the UIP-like subgroup (5.3% vs. 7.8%), but the differences did not reach statistical significance.

A suggestion of benefit was derived from a design feature of INBUILD that called for patients to remain on blinded therapy until all enrolled patients completed the trial. When the effect of nintedanib was evaluated in this extended analysis, the event curves for the combined endpoint of interstitial lung disease or death separated and approached significance.

In this extended analysis, which

Continued on following page

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: One of the most noticeable continuing voids in pulmonary medicine is the lack of effective therapy for some patients with non-IPF interstitial lung disease. The morbidity and mortality associated with these conditions often mirror those of IPF, and anything that potentially could improve patients' lives and outlook would be highly welcomed. This study of nintedanib provides exciting data suggesting its effectiveness in reducing the rate of lung function decline in these conditions – with reductions similar to those demonstrated in IPF patients. Similar to the initial IPF studies, this study failed to show a statistically significant decline in mortality versus placebo – although they report a trend that with extended use this may show significance, and further study is needed in this regard. Finally, it is notable that approximately 20% of patients discontinued the drug due to side effects (mostly GI) – which may limit its use somewhat but also may suggest an even larger-than-mean effect in patients able to tolerate it long term.

New guideline conditionally recommends long-term home NIV for patients with COPD

BY STEVE CIMINO
MDedge News

Long-term home noninvasive ventilation (LTH-NIV) has conditional value for patients with chronic hypercapnic chronic obstructive pulmonary disease (COPD), according to a new guideline from a European Respiratory Society task force.

"Our recommendations, based on the best available evidence, can guide the management of chronic hypercapnic respiratory failure in COPD patients aimed at improving patient outcomes," wrote Begum Ergan, MD, of Dokuz Eylul University, Izmir, Turkey, and coauthors. The guideline was published in the European Respiratory Journal.

To provide insight into the clinical application of LTH-NIV, the European Respiratory Society convened a task force of 20 clinicians, methodologists, and experts. Their four recommendations were developed based on the GRADE (Grading, Recommendation, Assessment, Development and Evaluation) methodology.

The first recommendation was to use LTH-NIV for patients with chronic stable hypercapnic COPD. Though an analysis of randomized, controlled trials showed little effect on mortality or hospitalizations, pooled analyses showed that NIV may decrease dyspnea scores (standardized mean difference, –0.51; 95% confidence interval, –0.06 to –0.95) and increase health-related quality of life (SMD, 0.49; 95% CI, –0.01 to 0.98).

The second was to use LTH-NIV in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists. Though it was not associated with a reduction in mortality (risk ratio, 0.92; 95% CI, 0.67-1.25), it was found to potentially reduce exacerbations (SMD, 0.19; 95% CI, –0.40 to 0.01) and hospitalizations (RR, 0.61; 95% CI, 0.30-1.24).

The third was to titrate LTH-NIV to normalize or reduce $PaCO_2$ levels in patients with COPD. While this recommendation was issued with a very low certainty of evidence, it was driven by the "minimal potential harms of targeted $PaCO_2$ reduction."

The fourth was to use fixed pressure support mode as first-choice ventilator mode in patients with COPD using LTH-NIV. The six trials on this subject did not provide insight into long-term outcomes, nor were there significant improvements seen in health-related quality of life, sleep quality, or exercise tolerance. As such, it was also issued with a very low certainty of evidence.

The authors acknowledged all four recommendations as weak and conditional, "due to limitations in the certainty of the available evidence." As such, they noted that their recommendations "require consideration of individual preferences, resource considerations, technical expertise, and clinical circumstances prior to implementation in clinical practice."

The authors reported numerous disclosures, including receiving grants and personal fees from various medical supply companies.

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Continued from previous page

suggests that clinical benefit is likely to accrue after longer periods of treatment, "we saw similar trends when we looked at mortality as an independent outcome," Dr. Flaherty reported.

More patients in the nintedanib group discontinued therapy because of adverse events (19.6% vs. 10.3%), but Dr. Flaherty characterized the rate of serious adverse events as "similar." He made this statement even though several adverse events, particularly those involving the gastrointestinal tract, such as diarrhea (66.9% vs. 23.9%), nausea (28.9% vs. 9.4%), vomiting (18.4% vs. 5.1%), and abdominal pain (10.2% vs. 2.4%), were higher in the nintedanib arm.

The INBUILD trial demonstrates that nintedanib preserves lung function in fibrosing lung diseases other than IPF. In his review of this paper, Dr. Kolb pointed out that non-IPF etiologies represent about 75% of interstitial lung diseases. For these patients "we have no drugs, so there is a big medical need."

Dr. Flaherty reports no potential conflicts of interest. The study was funded by Boehringer-Ingelheim, which produces nintedanib.

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SOURCE: Flaherty KR et al. N Engl J Med. 2019 Sep 29. doi: 10.1056/NEJMoa1908681.

Histologic analysis of vaping-associated lung injury suggests chemical pneumonitis

BY LUCAS FRANKI
MDedge News

VLADEE/GETTY IMAGES

Vaping-associated lung injury is likely a form of airway-centered chemical pneumonitis, not exogenous lipoid pneumonia, according to Yasmeen M. Butt, MD, of the University of Texas Southwestern Medical Center, Dallas, and associates.

Dr. Butt and associates performed a review of lung biopsies from 17 patients (13 men; median age, 35 years) with a history of vaping and either suspected or confirmed vaping-associated lung injury. All cases showed patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia, the authors noted in a letter to the editor published in the New England Journal of Medicine.

While no histologic findings were specific, foamy macrophages and pneumocyte vacuolization were seen in all cases, the authors added. Pigmented macrophages were occasionally present but not dominant, neutrophils were often prominent, eosinophils were rare, and granulomas were not seen. Two patients eventually died, despite treatment with glucocorticoids and maximum supportive care.

"None of our cases showed histologic evidence of exogenous lipoid pneumonia and no radiologic evidence thereof has been found; this calls into question the diagnostic utility of identifying lipid-laden macrophages or performing oil red O staining on bronchioloalveolar lavage fluid as a marker of vaping-associated lung injury, as has been proposed," Dr. Butt and associates wrote.

No conflicts of interest were reported.

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SOURCE: Butt YM et al. N Engl J Med. 2019 Oct 2. doi: 10.1056/NEJMc1913069.

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Sleep problems can presage postnatal depression

BY BRUCE JANCIN
MDedge News

COPENHAGEN – Sleep problems during pregnancy are a risk factor for subsequent clinically significant postnatal depressive symptoms, Tiina Paunio, MD, PhD, reported at the annual congress of the European College of Neuropsychopharmacology.

"I think it is very important to understand that we need to screen pregnant women for sleep problems, even those without a history of depression, so we can have early treatment of insomnia – and also depression – because postnatal maternal depression is very much a risk for the child during a vulnerable period for development," said Dr. Paunio, professor of psychiatry at the University of Helsinki.

She was a coinvestigator in a prospective study of the Finnish CHILD-SLEEP longitudinal birth cohort in which 1,398 women completed the Basic Nordic Sleep Questionnaire and the 10-item version of the Center for Epidemiological Studies Depression Scale (CES-D) at about gestational week 32 and again around 3 months following delivery. Postnatal depressiveness as defined by a CES-D score of at least 10 points was present in 10.3% of the mothers. After adjusting for prenatal depressiveness and other potential confounders, the investigators found that tiredness during the day, poor general sleep quality, getting less than 6 hours of sleep, taking longer than 20 minutes to fall asleep, and sleep loss of 2 hours or more per night during pregnancy were each associated with clinically significant postnatal depressive symptoms, with odds ratios of 1.87-2.19.

BRUCE JANCIN/MDEDGE NEWS

Dr. Tiina Paunio

The full details of the study have been published (Arch Womens Ment Health. 2019 Jun;22[3]:327-37).

The impetus for this study of sleep problems in pregnancy as a predictor of postnatal depressive symptoms was a body of evidence linking insomnia to depression in both men and women. But it turns out that insomnia is a significant predictor of later onset of a wide variety of psychiatric disorders, not only depression, as highlighted in a recent systematic review and meta-analysis conducted by an international team of investigators, Dr. Paunio observed.

Baseline insomnia symptoms were associated with a 183% increased risk of later onset of depression, a 223% increased risk of anxiety, a 35% greater risk of alcohol abuse, and a 28% increased risk of psychosis. However, the insomnia/psychosis link must be viewed as tentative, as it was examined in only a single published study. The investigators rated the overall risk of bias in the studies included in their meta-analysis as moderate (Sleep Med Rev. 2019 Feb;43:96-105).

For Dr. Paunio, these findings suggest that interventional studies of early and effective treatment of insomnia as a potential means of preventing psychiatric disorders are in order.

She reported receiving research funding from the Academy of Finland, the Gyllenberg Foundation, and Finska Lakaresallskapet.

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Screen teens with insomnia for mental health disorders

BY JENNIE SMITH
MDedge News

Adolescents diagnosed with insomnia have a high prevalence of concurrent mental health disorders and should be screened for them, according to new research.

For a study published in the Journal of Clinical Sleep Medicine, Tori R. Van Dyk, PhD, of Loma Linda (Calif.) University, and colleagues, enrolled 376 adolescents aged 11-18 years (mean age 14.5, 55% female) diagnosed with primary insomnia and referred to a sleep clinic. Subjects were evaluated using two validated questionnaires used to measure sleep disorders in adolescents, while caregivers reported and mental health diagnoses and symptoms using a standard behavioral checklist for adolescents.

Dr. Van Dyk and colleagues found that 75% of subjects had at least one or more parent-reported mental health diagnosis, most commonly anxiety, mood disorders, and ADHD. Some 64% had a clinical elevation of mental health symptoms on evaluation, most commonly affective disorders, with 40% of the cohort having two or more elevations. Specific mental health symptoms were seen linked with particular sleep symptoms. A greater burden of ADHD symptoms, for example, was significantly associated with more difficulties falling asleep, maintaining sleep, and reinitiating sleep after waking at night.

A total of 15% of subjects were reported by caregivers to engage in deliberate self-harming behaviors or talking about or attempting suicide – a higher rate than in the general adolescent population. "Because youth presenting for insomnia treatment may be even more likely to engage in self-harm behavior or to be suicidal, particular attention should be paid to directly assessing for these high-risk behaviors within the context of behavioral sleep medicine evaluations," Dr. Van Dyk and colleagues wrote in their analysis.

Although mental health symptoms have been linked to sleep problems in other studies of children and adults, "associations identified in younger youths and/or adults should not be assumed to hold true among adolescents," the researchers wrote, adding that adolescence "is a distinctive developmental period characterized by increases in both psychopathology and sleep problems, changing biology, increasing independence, and unique social and societal demands." The investigators noted that because pediatric sleep specialists are relatively rare, the management of adolescent sleep problems and related mental health symptoms is likely to fall on primary care and other providers who "would benefit in recognizing the relationship between sleep problems and mental health symptoms in this population."

DEMAERRE/ISTOCK/GETTY IMAGES

Dr. Van Dyk and colleagues noted among the weaknesses of their study its cross-sectional design, use of parent-reported mental health symptoms only, lack of information on medication use or mental health treatment, and the potential for selection bias toward more severe cases.

The authors disclosed no outside funding or conflicts of interest related to their study.

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SOURCE: Van Dyk TR et al. J Clin Sleep Med. 2019 Sep 6. doi: 10.5664/jcsm.7970.

Dysregulated sleep is common in children with EoE

BY MICHELE G. SULLIVAN
MDedge News

Children with eosinophilic esophagitis (EoE) often experience respiratory and motor disturbances during sleep, which appear related to dysregulated sleep architecture, Rasintra Siriwat, MD, and colleagues have ascertained.

Children with EoE also were found to have a high prevalence of atopic diseases, including allergic rhinitis and eczema – findings that could be driving the breathing problems, said Dr. Siriwat, a neurology fellow at the Cleveland Clinic, and coauthors.

The retrospective study comprised 81 children with a diagnosis of EoE who were referred to sleep clinics. In this group, 46 of the children had active EoE (having gastrointestinal symptoms, including feeding difficulties, dysphagia, reflux, nausea/vomiting, or epigastric pain at presentation). The other 35 had an EoE diagnosis but no symptoms on presentation and were categorized as having inactive EoE. Most were male (71.6%) and white (92.5%). The mean age in the cohort was 10 years and the mean body mass index for all subjects was 22 kg/m^2. A control group of 192 children without an EoE diagnosis who had overnight polysomnography were included in the analysis.

Allergic-type comorbidities were common among those with active EoE, including allergic rhinitis (55.5%), food allergy (39.5%), and eczema (26%). In addition, a quarter had attention-deficit/hyperactivity disorder, 22% an autism spectrum disorder, 21% a neurological disease, and 29% a psychiatric disorder.

ALEX VASILEV/FOTOLIA

Several sleep complaints were common in the entire EoE cohort, including snoring (76.5 %), restless sleep (66.6%), legs jerking or leg discomfort (43.2%), and daytime sleepiness (58%).

All children underwent an overnight polysomnography. Compared with controls, the children with EoE had significantly higher non-REM2 sleep, significantly lower non-REM3 sleep, lower REM, increased periodic leg movement disorder, and increased arousal index.

"Of note, we found a much higher percentage of [periodic leg movement disorder] in active EoE compared to inactive EoE," the authors said.

The most common sleep diagnosis for the children with EoE was sleepd disordered breathing. Of 62 children with EoE and sleep disordered breathing, 37% had obstructive sleep apnea (OSA). Two patients had central sleep apnea and five had nocturnal hypoventilation. Children with EoE also reported parasomnia symptoms such as sleep talking (35.8%), sleepwalking (16%), bruxism (23.4%), night terrors (28.4%), and nocturnal enuresis (21.2%).

Of the 59 children with leg movement, 20 had periodic limb movement disorder and 5 were diagnosed with restless leg syndrome. Two were diagnosed with narcolepsy and three with hypersomnia. Four children had a circadian rhythm disorder.

"Notably, the majority of children with EoE had symptoms of sleep-disordered breathing, and more than one-third of total subjects were diagnosed with OSA," the authors noted. "However, most of them were mild-moderate OSA. It should be noted that the prevalence of OSA in the pediatric population is 1%-5% mostly between the ages of 2-8 years, while the mean age of our subjects was 10 years old. The high prevalence of mild-moderate OSA in the EoE population might be explained by the relationship between EoE and atopic disease."

Dr. Siriwat had no financial disclosures. The study was supported by Cincinnati Children's Hospital Research Fund.

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SOURCE: Siriwat R et al. Sleep Med. 2019 Sep 11. doi: 10.1016/j.sleep.2019.08.018.

Benzodiazepines, opioids carry greater risk of COPD-related hospitalization

BY JEFF CRAVEN
MDedge News

Patients with chronic obstructive pulmonary disease who received opioids or benzodiazepines had a greater risk of hospitalization for respiratory-related adverse events, according to recent research from Annals of the American Thoracic Society.

In addition, the risk of hospitalization because of respiratory events for patients with chronic obstructive pulmonary disease (COPD) was greater when opioid and benzodiazepine medications were combined, compared with patients who did not take either medication, Jacques G. Baillargeon, PhD, of the department of preventive medicine and community health at the University of Texas, Galveston, and colleagues wrote.

"Patients with COPD and their physicians should judiciously assess the risks and benefits of opioids and benzodiazepines, alone and in combination, and preferentially recommend nonopioid and nonbenzodiazepine approaches for pain, sleep, and anxiety management in patients with COPD," the investigators wrote.

The researchers performed a case-control study of 3,232 Medicare beneficiary cases of COPD patients who were aged at least 66 years. Patients were included if they experienced a hospitalization related to a COPD-related adverse event with a respiratory diagnosis in 2014 and then matched to one or two control patients (total, 6,247 patients) based on age at hospitalization, gender, COPD medication, COPD complexity, obstructive sleep apnea, and socioeconomic status. COPD complexity was assigned to three levels (low, moderate, high) and calculated using the patient's comorbid respiratory conditions and associated medical procedures in the 12 months prior to their hospitalization.

They found that, in the 30 days before COPD-related hospitalization, use of opioids was associated with greater likelihood of hospitalization (adjusted odds ratio, 1.73; 95% confidence interval, 1.52-1.97), as was use of benzodiazepines (aOR, 1.42; 95% CI, 1.21-1.66). When patients used both opioids and benzodiazepines, they had a significantly higher risk of hospitalization, compared with patients who did not use opioids or benzodiazepines (aOR, 2.32; 95% CI, 1.94-2.77).

In the 60 days prior to hospitalization, there was also a greater likelihood of hospitalization among COPD patients who used opioids (aOR, 1.66; 95% CI, 1.47-1.88), benzodiazepines (aOR, 1.44; 95% CI, 1.24-1.67), and both opioids and benzodiazepines (aOR, 2.27; 95% CI, 1.93-2.67); at 90 days, this higher risk of hospitalization persisted among COPD patients taking opioids (aOR, 1.58; 95% CI, 1.40-1.78), benzodiazepines (aOR, 1.40; 95% CI, 1.20-1.63), and both opioids and benzodiazepines (aOR, 2.21; 95% CI, 1.88-2.59).

The researchers acknowledged that one potential limitation in the study was how COPD diagnoses were obtained through coding performed by clinicians instead of from laboratory testing. Confounding by COPD indication and severity; use of over-the-counter medication or opioids and benzodiazepines received illegally; and lack of analyses of potential confounders such as diet, alcohol use, smoking status and herbal supplement use were other limitations.

This study was supported by an award from the National Center for Advancing Translational Sciences and National Institutes of Health. Dr. Baillargeon had no disclosures.

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SOURCE: Baillargeon JG et al. Ann Am Thorac Soc. 2019 Oct 1. doi: 10.1513/AnnalsATS.201901-024OC.

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TAVR, SAVR share same infective endocarditis risk

BY BRUCE JANCIN
MDedge News

PARIS – The risk of infective endocarditis following transcatheter aortic valve replacement (TAVR) for the treatment of severe aortic stenosis proved to be the same as after surgical replacement in a French national propensity score–matched study.

This finding from what is believed to be the largest-ever study of infective endocarditis following TAVR will come as a surprise to many physicians. It's easy to mistakenly assume the risk of this feared complication is lower – and perhaps even negligible – in TAVR patients since the procedure doesn't involve a significant surgical wound, it's briefer, the hospital length of stay is shorter, and recovery time is markedly less than with surgical aortic valve replacement (SAVR).

Not so, Laurent Fauchier, MD, PhD, said in presenting the study findings at the annual congress of the European Society of Cardiology.

"Do not think there is a lower risk of infective endocarditis. Be aware, be careful, and provide appropriate antibiotic prophylaxis, just as surgeons do in SAVR. Don't think, as I did, that with TAVR with no pacemaker implantation there is no risk of infective endocarditis. The TAVR valve is a device, it's a prosthesis, and the risk is very similar to that of surgery," advised Dr. Fauchier, a cardiologist at Francois Rabelais University in Tours, France.

He presented a study of all of the nearly 108,000 patients who underwent isolated TAVR or SAVR in France during 2010-2018. The data source was the French national administrative hospital discharge record system. Since the TAVR patients were overall markedly older and sicker than the SAVR patients, especially during the first years of the study, he and his coinvestigators performed propensity score matching using 30 variables, which enabled them to narrow the field of inquiry down to a carefully selected

Continued on following page

Bruce Jancin/MDedge News

Dr. Laurent Fauchier

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: Prosthetic valve endocarditis is a dreaded complication associated with a high mortality rate. This large study confirms that prosthetic valves are at risk for infection regardless of the technique used for the implantation. Anemia and atrial fibrillation as predictors of mortality in the TAVR group are hallmarks of higher comorbidity index. The study spans over 8 years and it is not clear whether the incidence rate of infection was different between the first half of the study vs the latter half. The message, however, is clear: meticulous surgical antisepsis and appropriate antibiotic prophylaxis should be used for TAVR patients similar to SAVR patients.

FOUNDATION FOCUS

With nearly 100 projects submitted for funding consideration, the CHEST Foundation is excited to announce our 2019 research and community service grant winners! **Thank you to everyone who submitted projects, and congratulations to this year's winners!**

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Beta-blockers safe for HFrEF with renal dysfunction

BY MITCHEL L. ZOLER
MDedge News

PARIS – Beta-blocking drugs were as effective for improving survival in patients with moderately severe renal dysfunction as they were in patients with normal renal function in a meta-analysis of more than 13,000 patients, a finding that seemed to solidify the role for this drug class for essentially all similar heart failure patients, regardless of their renal function.

This evidence could reshape usual care because "renal impairment is often considered a barrier in clinical practice" for starting a beta-blocker drug in patients with heart failure with reduced ejection fraction (HFrEF), Dipak Kotecha, MBChB, said at the annual congress of the European Society of Cardiology.

"We have shown with sufficient sample size that beta-blockers are effective in reducing mortality in patients with HFrEF and in sinus rhythm, even in those with an eGFR [estimated glomerular filtration rate] of 30-44 mL/min per 1.73 m^2," said Dr. Kotecha, a cardiologist at the University of Birmingham (England). "The results suggest that renal impairment should not obstruct the prescription and maintenance of beta-blockers in patients with HFrEF."

"This important study was a novel attempt to look at [HFrEF] patients with renal insufficiency to see whether they received the same benefit from beta-blockers as other patients, and they did. So renal insufficiency is not a reason to withhold beta-blockers" from these patients, commented Mariell Jessup, MD, a heart failure physician and chief science and medical officer for the American Heart Association in Dallas. "The onus is on clinicians to find a reason not to give a beta-blocker to a patient with HFrEF because they are generally well tolerated and they can have enormous benefit, as we saw in this study," she said in a video interview.


Dr. Kotecha

The analysis run by Dr. Kotecha and associates used data collected in 11 of the pivotal randomized, controlled trials run for beta-blockers during the 1990s and early 2000s, with each study comparing bucindolol, bisoprolol, carvedilol, metoprolol XL, or nebivolol against placebo. The studies collectively enrolled 18,637 patients, which the investigators whittled down in their analysis to 17,433 after excluding patients with a left ventricular ejection fraction below 50% or who were undocumented. The subgroup with HFrEF included 13,861 patients in sinus rhythm at entry, 2,879 with atrial fibrillation, and 693 with an unknown atrial status. The main analysis ran in the 13,861 patients with HFrEF and in sinus rhythm; 14% of this cohort had an eGFR of 30-44 mL/min per 1.73 m^2 and 27% had an eGFR of 45-59 mL/min per 1.73 m^2. The median age of all patients in the main analysis was 65 years, 23% were women, and their median left ventricular ejection fraction was 27%.

During follow-up of about 3 years, the impact of beta-blocker treatment on survival, compared with placebo, was "substantial" for all strata of patients by renal function, except for those with eGFRs below 30 mL/min per 1.73 m^2. (Survival was similar regardless of beta-blocker treatment in the small number of patients with severe renal dysfunction.) The number needed to treat to prevent one death in patients with an eGFR of 30-44 mL/min per 1.73 m^2 was 21, the same as among patients with an eGFR of 90 mL/min per 1.73 m^2 or more, Dr. Kotecha said.

Among the subgroup of patients with atrial fibrillation, beta-blockers appeared to exert no survival benefit, compared with placebo. The investigators did not assess the survival benefits exerted by any individual beta-blocker, compared with the others, and Dr. Kotecha stressed that "my belief is that this is a class effect" and is roughly similar across all the beta-blockers used in the studies.

The analysis also showed good safety and tolerability of the beta-blockers in patients with renal dysfunction. The incidence of adverse events leading to treatment termination was very similar in the beta-blocker and placebo arms, and more than three-quarters of patients in each of the two subgroups with renal dysfunction were maintained on more than 50% of their target beta-blocker dosage.

Dr. Kotecha has been an adviser to Bayer, has been a speaker on behalf of Atricure, and has received research funding from GlaxoSmithKline and Menarini. Dr. Jessup had no disclosures.

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Continued from previous page

study population of 16,291 TAVR patients and an equal number of closely similar SAVR patients.

A total of 1,070 cases of infective endocarditis occurred during a mean follow-up of just over 2 years. The rate of hospital admission for this complication was 1.89% per year in the TAVR group and similar at 1.71% per year in the SAVR cohort.

Of note, all-cause mortality in TAVR patients who developed infective endocarditis was 1.32-fold greater than it was in SAVR patients with infective endocarditis, a statistically significant difference. The explanation for the increased mortality risk in the TAVR group probably has to do at least in part with an inability on the part of the investigators to fully capture and control for the TAVR group's greater frailty, according to the cardiologist.

Risk factors for infective endocarditis shared in common by TAVR and SAVR patients included male gender, a higher Charlson Comorbidity Index score, and a greater frailty index. The main predictors unique to the TAVR patients were atrial fibrillation, anemia, and tricuspid regurgitation. And although pacemaker and defibrillator implantation were risk factors for infective endocarditis in the SAVR patients, it wasn't predictive of increased risk in the TAVR population. Dr. Fauchier called this finding "quite reassuring" given that roughly 20% of the TAVR group received a pacemaker.

The causative microorganisms for infective endocarditis were essentially the same in the TAVR and SAVR groups, simplifying antimicrobial prophylaxis decision making.

Dr. Fauchier reported having no financial conflicts regarding the study, conducted free of commercial support. He serves as a consultant to and/or on speakers' bureaus for Bayer, BMS Pfizer, Boehringer Ingelheim, Medtronic, and Novartis.

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European guidelines push LDL targets below 55 mg/dL

BY MITCHEL L. ZOLER
MDedge News

PARIS – The 2019 dyslipidemia management guidelines from the European Society of Cardiology set an LDL cholesterol target for very-high-risk people of less than 55 mg/dL (as well as at least a 50% cut from baseline), a class I recommendation. This marks the first time a cardiology society has either recommended a target goal for this measure below 70 mg/dL or endorsed treating patients to still-lower cholesterol once their level was already under 70 mg/dL.

The guidelines went further by suggesting consideration of an even lower treatment target for LDL cholesterol in very-high-risk, secondary-prevention patients who have already had at least two atherosclerotic cardiovascular disease events during the past 2 years, a setting that could justify an LDL cholesterol goal of less than 40 mg/dL (along with a cut from baseline of at least 50%), a class IIb recommendation that denotes a "may be considered" endorsement.

"In all the trials, lower was better. There was no lower level of LDL cholesterol that's been studied that was not better" for patient outcomes, Colin Baigent, BMBCH, said while presenting the new guideline at the annual congress of the European Society of Cardiology. "It's very clear" that the full treatment benefit from lowering LDL cholesterol extends to getting very-high-risk patients below these levels, said Dr. Baigent, professor of cardiology at Oxford (England) University and one of three chairs of the ESC's dyslipidemia guideline-writing panel.

While this change was seen as a notably aggressive goal and too fixed on a specific number by at least one author of the 2018 American Heart Association/American College of Cardiology cholesterol management guideline (J Am Coll Cardiol. 2019 Jun;73[24]:e285-350), it was embraced by another U.S. expert not involved in writing the most recent U.S. recommendations.

"A goal for LDL cholesterol of less than 55 mg/dL is reasonable; it's well documented" by trial evidence "and I support it," said Robert H. Eckel, MD, an endocrinologist and professor of medicine at the University of Colorado in Aurora. Dr. Eckel added that he "also supports" an LDL cholesterol of less than 40 mg/dL in very-high-risk patients with a history of multiple events or with multiple residual risk factors, and he said he has applied this lower LDL cholesterol goal in his practice for selected patients. But Dr. Eckel acknowledged in an interview that the evidence for it was less clear-cut than was the evidence behind a goal of less than 55 mg/dL. He also supported the concept of including a treatment goal in U.S. lipid recommendations, which in recent versions has been missing. "I fall back on a cholesterol goal for practical purposes" of making the success of cholesterol-lowering treatment easier to track.


Dr. Baigent


Dr. Stone


Dr. Sabatine

The new ESC goal was characterized as "arbitrary" by Neil J. Stone, MD, vice-chair of the panel that wrote the 2018 AHA/ACC guideline, which relied on treating secondary-prevention patients at high risk to an LDL cholesterol at least 50% less than before treatment, and recommended continued intensification for patients whose LDL cholesterol level remained at or above 70 mg/dL.

"If the patient is at 58 mg/dL, I'm not sure anyone can tell me what the difference is," compared with reaching less than 55 mg/dL, Dr. Stone said in an interview. "I worry about focusing on a number and not on the concept that people at the very highest risk deserve the most intensive treatment; the Europeans agree, but they have a different way of looking at it. Despite this difference in approach, the new ESC guidelines and the 2018 U.S. guideline "are more similar than different," stressed Dr. Stone, professor of medicine and preventive medicine at Northwestern University, Chicago.

However, other experts see an important difference in the risk faced by patients who reach the ESC's recommended treatment goals and those who fall just short.

"It's hard to lower an LDL cholesterol that is already relatively low. People who are close to their cholesterol target need the most intensified treatment" to reach their goal, said Rory Collins, FMedSci, professor of epidemiology at Oxford University. He was not on the ESC guidelines panel.

"It's a mind shift that clinicians need to be most aggressive in treating patients with the highest risk" even when their LDL cholesterol is low but not yet at the target level, Dr. Collins said during a discussion session at the congress.

The new ESC guidelines is about "both getting the LDL cholesterol down to a certain level and also about achieving a big [at least 50%] change" from baseline. "I think the ESC guidelines make that crystal clear," said Marc S. Sabatine, MD, professor of medicine at Harvard Medical School, Boston, and the sole American to participate in the ESC guidelines-writing panel.

The ESC also broke new ground by advocating an aggressive path toward achieving these LDL cholesterol goals by elevating the newest and most potent class of approved LDL cholesterol–lowering drugs, the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, to a top-tier, class I recommendation ("is recommended") for secondary prevention in very-high-risk patients not reaching their goal LDL cholesterol level on a maximally tolerated statin plus ezetimibe. This recommendation to unequivocally add a PCSK9 inhibitor for this patient population contrasts with the 2018 AHA/ACC guideline that deemed adding a PCSK9 inhibitor a IIa recommendation ("is reasonable").

A similar uptick in treatment aggressiveness appeared in the ESC's recommendations for managing very-high-risk patients in a primary prevention setting, including those without familial hypercholesterolemia. For these people, the ESC panel, which worked in concert with the European Atherosclerosis Society, pegged adding a PCSK9 inhibitor as a IIb ("may be considered") recommendation when these very-high-risk people fail to reach their LDL cholesterol target on a maximally tolerated statin and ezetimibe. Once again, this opening to use a PCSK9 inhibitor contrasted with the 2018 U.S. guideline, which never mentioned an option of adding a PCSK9 inhibitor for primary prevention except when someone also has familial hypercholesterolemia and starts treatment with an LDL level of at least 190 mg/dL (a IIb recommendation). The new European guidelines proposed using a PCSK9 inhibitor as a second-line option to consider when needed for people whose very high risk derives primarily from older age and other factors such as smoking or hypertension that give them at least a 10% 10-year risk for cardiovascular death as estimated with the European-oriented SCORE risk calculator tables.

Updated SCORE risk designations appear in the new ESC dyslipidemia guidelines, and they show, for example, that in lower-risk European countries (mostly Western European nations) virtually all men who are at least 70 years old would fall into the very-high-risk category that makes them potential candidates for treatment with a PCSK9 inhibitor regardless of any other risk they may or may not have. In higher-risk (mostly Eastern European) countries this designation kicks in for most men once they reach the age of 65.

Several Congress attendees who came to a discussion session on the guidelines voiced concerns that the new revision will lead to substantially increased use of the these drugs and hence will significantly boost medical costs, because these drugs today are priced at about $6,000 annually to treat one patient. In response, members of the guideline-writing panel defended their decision as unavoidable given what's been reported on the clinical impact of PCSK9 inhibitors when lowering LDL cholesterol and cutting atherosclerotic cardiovascular disease events.

Dr. Baigent has received research funding from Boehringer Ingelheim, Novartis, and Pfizer. Dr. Eckel has been an expert witness on behalf of Sanofi/Regeneron. Dr. Sabatine and Dr. Ference have received honoraria and research funding from several companies including those that market lipid-lowering drugs. Dr. Stone and Dr. Collins had no disclosures.

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Next-generation genomic test plus bronchoscopy may improve lung nodule management

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – The use of a next-generation genomic test may enable improved management of patients with pulmonary nodules when results of bronchoscopy are inconclusive, results of a recent clinical validation study suggest.

The Percepta Genomic Sequencing Classifier (GSC) was able to up- and down-classify probability of malignancy for a considerable proportion of nondiagnostic bronchoscopies in the study, Peter J. Mazzone MD, FCCP, reported at the annual meeting of the American College of Chest Physicians.

The test is seen as complementary to bronchoscopy, improving the sensitivity of bronchoscopy overall and showing a combined sensitivity of greater than 95% in low- and intermediate-risk groups, according to Dr. Mazzone.

While the clinical utility of this genomic test needs to be further tested, the eventual goal is to improve clinician decision making when bronchoscopy results don't clearly classify nodules as malignant or benign, Dr. Mazzone said in an interview.

"In that situation, you're often left wondering, 'what should I do next? Can I just watch this, and see if it grows and changes, or do I have to be even more aggressive – do another biopsy, or have a surgery to take it out?'" he explained. "So the test hopes to help make a more informed decision by further stratifying those patients as being quite low risk and maybe safe to follow, or quite high risk and maybe you should be considering more aggressive management."

The GSC improves on the performance of an earlier molecular test, the Percepta Bronchial Genomic Classifier, which uses a brushing of bronchial epithelium to enhance nodule management in smokers, according to the researcher.

The next-generation GSC uses 1,232 gene transcripts from whole-transcriptome RNA sequencing, along with clinical factors, to help with nodule diagnosis, he said.

To establish the diagnostic accuracy of the GSC, Dr. Mazzone and colleagues evaluated data on 412 patients from three independent cohorts, all of whom had bronchoscopies for lung nodule evaluation that were nondiagnostic. Of those patients, 5% had nodules that physicians had deemed as low probability of malignancy prior to bronchoscopy, 28% deemed intermediate risk, and 74% high risk.

They found that the Percepta GSC down-classified the low–pretest risk patients with 100% negative predictive value (NPV) and down-classified intermediate–pretest risk patients with a 91.0% NPV, Dr. Mazzone reported, while patients with intermediate pretest risk were up-classified with a 65.4% positive predictive value (PPV) and patients with high pretest risk were upclassified with a 91.5% PPV.

The proportion of patients reclassified was about 55% for the low-risk group, 42% for the intermediate-risk group, and 27% for the high-risk group, according to the report at the meeting.

These results suggest the Percepta GSC could help in the "sticky situation" where a bronchoscopy result is inconclusive, Dr. Mazzone told attendees.

"When a bronchoscopy is recommended, despite fantastic advances in navigation systems to get to those nodules, we often come back without a solid answer, and that leaves the clinician in a bit of a predicament," he said in a late-breaking clinical trial presentation.

Dr. Mazzone provided disclosures related to Veracyte, Exact Sciences, SEER, Tencent, and PCORI (research support to institution).

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SOURCE: Mazzone PJ et al. CHEST 2019, Abstract. doi: 10.1016/j.chest.2019.08.307.

Survey finds barriers to molecular testing for lung cancer

BY SHARON WORCESTER
MDedge News

BARCELONA – Molecular testing to guide treatment in patients with lung cancer remains underused, and awareness of related evidence-based guidelines is suboptimal, results of an international survey suggest.

Overall, 61% of the 2,537 respondents from 102 countries and across multiple relevant medical specialties reported that molecular testing rates in their country were less than 50%, with the lowest rates reported in Latin America. And 33% of those requesting molecular testing said they were unaware of the most updated guidelines supporting the use of such testing in lung cancer, Matthew Smeltzer, PhD, of the University of Memphis reported during a press conference at the World Conference on Lung Cancer.

The findings from the International Association for the Study of Lung Cancer Global Survey on Molecular Testing in Lung Cancer also showed that 41% of respondents who perform or interpret molecular testing assays report being dissatisfied with the conditions of molecular testing in their country, 17% said they feel that patients are not satisfied, and 35% said they aren't sure about the state of testing in their country.

Specific concerns reported by respondents included trouble understanding results, the time it takes to receive the results, and the reliability of samples.


Sharon Worcester/MDedge News

Dr. Matthew Smeltzer

The top five barriers to molecular testing included cost, quality, access, awareness, and time, Dr. Smeltzer said at the meeting which is sponsored by the IASLC.

"These five were the same five top barriers in each region of the world," he said, noting that the ordering of the barriers differed somewhat among regions.

The survey included a 7-question introduction, with 32 additional questions for respondents who request tests and treat patients, 45 questions on performing and interpreting assays, and 24 questions on tissue acquisition. Additionally, all respondents were asked to list barriers that impede their country's ability to offer molecular testing.

"I'd say we got a pretty good geographic distribution of responses; 56% of these responses were from developing countries, 44% from developed countries," he said, noting that medical oncologists constituted the highest percentage of respondents, followed by pulmonologists, thoracic surgeons, pathologists, and other scientists.

When asked specifically what would prompt molecular testing, respondents most often listed adenocarcinoma, never-smoker status, female gender, and young age, Dr. Smeltzer said.

"Overall, we're still finding that many in the lung cancer community are not satisfied with the current state of molecular testing. We've got suboptimal awareness of the evidence-based guidelines. We have barriers that remain to molecular testing, which we've identified, and [we're] recommending continuous education around molecular testing, and that should be intensified on a national and international level to ensure that patients receive optimal therapy," he concluded.

The IASLC survey was funded by AstraZeneca. Dr. Smeltzer reported receiving research support from the Bristol Myers Squibb Foundation.

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LDCT plus miRNA bolsters prevention efforts

BY SHARON WORCESTER
MDedge News

BARCELONA – Adding a blood microRNA (miRNA) assay to low-dose computed tomography (LDCT)–based lung cancer screening in heavy smokers bolsters lung cancer prevention efforts, according to findings from the prospective bioMILD trial.

Specifically, the addition of the miRNA assay appears to reduce unnecessary repeat LDCT scans based on individual risk profiles without adversely affecting lung cancer detection or mortality, Ugo Pastorino, MD, director of thoracic surgery at the Istituto Nazionale dei Tumori Foundation, Milan, reported at the World Conference on Lung Cancer.

Of 4,119 volunteers with a median age of 60 years and a median of 42 pack-years who were enrolled between January 2013 and March 2016, 2,384 (58%) were assigned a 3-year LDCT repeat according to their double-negative baseline LDCT and miRNA profile, whereas 1,526 (37%) with a single-positive screen (either a positive miRNA or indeterminate/positive LDCT) and 209 (5%) with double positive (both a positive miRNA and indeterminate/positive LDCT) were assigned to annual or shorter LDCT repeat.

After four screening runs, a total of 115 lung cancers were diagnosed. The cumulative lung cancer rates "were enormously different" in the 3 groups, despite similar group composition with respect to age, gender, and tobacco consumption (0.6% for double-negative screening, 3.8% for single-positive screening, and 20.1% for double -positive screening), and lung cancer mortality was 0.1%, 0.6%, and 3.8% in the groups, respectively, Dr. Pastorino said at the conference, which is sponsored by the International Association for the Study of Lung Cancer.

However, no significant differences were seen in the proportion of stage I lung cancers, resection rates, or interval cancer incidence in subjects sent to 3-year LDCT repeat, he noted.

Sharon Worcester/MDedge News

Dr. Ugo Pastorino

The bioMILD trial was designed in the wake of the National Lung Screening Trial (NLST), which showed that three annual LDCT rounds for lung cancer screening reduced lung cancer mortality, and the Multicentric Italian Lung Detection (MILD) trial, which provided additional evidence that intervention beyond 5 years with annual or biennial rounds enhanced the benefit of screening.

Dr. Pastorino, the lead author on the MILD trial, previously reported that miRNA expression profiles in tumors and in normal lung tissue indicate aggressive lung cancer development and that specific miRNA signatures can be identified in plasma samples up to 2 years before spiral-CT detection of the disease.

The bioMILD trial tested the additional value of an miRNA assay at the time of LDCT.

Subjects were current (79%) or former heavy smokers, and 39% were women.

The findings suggest that adding the miRNA assay to LDCT for lung cancer screening is a "valuable and safe tool to assess individual risk profile and reduce unnecessary LDCT repeats in lung cancer screening," Dr. Pastorino said.

"But what is more important for us [is that] the knowledge of individual biologic risk can improve the efficacy of screening, but can [also] guide prevention strategies because the problem in a heavy smoker is not to just detect lung cancer, it's to reduce mortality," he said at a press conference highlighting the findings. "And so, personalized prevention is a real option now, and that means diagnosis, but also preventive measures [such as] smoking cessation and chemoprevention."

Invited discussant Harry J. de Koning, MD, PhD, professor of public health and screening evaluation at Erasmus Medical Center, Rotterdam, the Netherlands, noted that no other studies have evaluated screening intervals longer than 2 years, but he agreed that "reducing regular follow-up scans based on additional risk information is a way forward."

However, the approach would increase costs, he said, adding that large, prospective, randomized, controlled trials are needed to confirm the safety of such approaches in nationwide programs.

Dr. Pastorino and Dr. de Koning each reported having no disclosures.

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SOURCE: Pastorino U et al. WCLC 2019, Abstract PL02.04

Cardiotoxicity after checkpoint inhibitor treatment seen early, linked to elevated biomarkers

BY ANDREW D. BOWSER
MDedge News

PHILADELPHIA – While immune checkpoint inhibitors were not significantly more cardiotoxic than other lung cancer treatments, major adverse cardiac events (MACE) did occur earlier, and occurred more frequently in patients with elevated biomarkers, in a retrospective cohort study reported at the annual scientific meeting of the Heart Failure Society of America.

The findings support monitoring of cardiac biomarkers in the initial phase of checkpoint inhibitor treatment to identify patients at high cardiac risk, according to Kalyan R. Chitturi, DO, a resident physician with the DeBakey Heart and Vascular Center, Houston Methodist Hospital, who presented the results.

"It's the early period that warrants the closest monitoring, as within the first 30-40 days, there's higher risk," Dr. Chitturi said in an interview. "When there was a biomarker elevation, it markedly increased the risk of MACE, warranting a closer vigilance during that time period."

The retrospective study conducted by Dr. Chitturi and colleagues included a total of 252 patients with lung cancer who had been treated at one of seven different sites in Houston Methodist Cancer Center between Aug. 1, 2015, and Aug. 1, 2018.

Immune checkpoint inhibitors did not significantly increase the risk of MACE, compared with other lung cancer therapies, with incidences of 13.3% and 10.3%, respectively (P = .632), the investigators found.

However, MACE did occur earlier in the checkpoint inhibitor group, at a median time to event of 40 days, compared with 118 days in the patients not treated with checkpoint inhibitors, they found.

Risk of MACE with checkpoint inhibitor treatment was increased in patients with elevated troponin (hazard ratio, 2.48; 95% confidence interval, 1.18-5.21; P = .017) or elevated brain natriuretic peptide (HR, 5.77; 95% CI, 2.70-12.35; P less than .001), according to multivariate logistic regression analysis results.

These results suggest biomarkers such as cardiac troponin and brain natriuretic peptide are warranted to monitor patients in the early phase of checkpoint inhibitor treatment, according to Dr. Chitturi. "In the cost-benefit ratio of often-lethal MACE, it's well worth it to collect these," he said in the interview.

The results corroborate findings from some other recent studies, he noted. These include a recent study that linked elevated serum troponin to myocarditis in patients treated with immune checkpoint inhibitors (J Am Coll Cardiol. 2018 Apr 24;71[16]:1755-64).

Dr. Chitturi and coauthors reported no disclosures related to their presentation at the HFSA meeting.

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SOURCE: Chitturi KR et al. HFSA 2019, Abstract 127.

Vitamin C–based regimens in sepsis plausible, need more data, expert says

BY ANDREW D. BOWSER
MDedge News

EXPERT ANALYSIS FROM CHEST 2019 ▪ While further data are awaited on the role of vitamin C, thiamine, and steroids in sepsis, there is at least biologic plausibility for using the combination, and clinical equipoise that supports continued enrollment of patients in the ongoing randomized, controlled VICTAS trial, according to that study's principal investigator.

"There is tremendous biologic plausibility for giving vitamin C in sepsis," said Jon Sevransky, MD, professor of medicine at Emory University in Atlanta. But until more data are available on vitamin C–based regimens, those who choose to use vitamin C with thiamine and steroids in this setting need to ensure that glucose is being measured appropriately, he warned.

Andrew Bowser/MDedge News

Dr. Jon Sevransky

"If you decide that vitamin C is right for your patient, prior to having enough data – so if you're doing a Hail Mary, or a 'this patient is sick, and it's probably not going to hurt them' – please make sure that you measure your glucose with something that uses whole blood, which is either a blood gas or sending it down to the core lab, because otherwise, you might get an inaccurate result," Dr. Sevransky said at the annual meeting of the American College of Chest Physicians.

Results from the randomized, placebo-controlled Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS) trial may be available within the next few months, according to Dr. Sevransky, who noted that the trial was funded for 500 patients, which provides an 80% probability of showing an absolute risk reduction of 10% in mortality.

The primary endpoint of the phase 3 trial is vasopressor- and ventilator-free days at 30 days after randomization, while 30-day mortality has been described as "the key secondary outcome" by Dr. Sevransky and colleagues in a recent report on the trial design.

Clinicians have been "captivated" by the potential benefit of vitamin C, thiamine, and hydrocortisone in patients with severe sepsis and septic shock, as published in CHEST in June 2017, Dr. Sevransky said. In that study, reported by Paul E. Marik, MD, and colleagues, hospital mortality was 8.5% for the treatment group, versus 40.4% in the control group, a significant difference.

That retrospective, single-center study had a number of limitations, however, including its before-and-after design and the use of steroids in the comparator arm. In addition, little information was available on antibiotics or fluids given at the time of the intervention, according to Dr. Sevransky.

In results of the CITRIS-ALI randomized clinical trial, just published in JAMA, intravenous administration of high-dose vitamin C in patients with sepsis and acute respiratory distress syndrome (ARDS) failed to significantly reduce organ failure scores or biomarkers of inflammation and vascular injury.

In an exploratory analysis of CITRIS-ALI, mortality at day 28 was 29.8% for the treatment group and 46.3% for placebo, with a statistically significant difference between Kaplan-Meier survival curves for the two arms, according to the investigators.

Dr. Sevransky disclosed current grant support from the Biomedical Advanced Research and Development Authority (BARDA) and the Marcus Foundation, as well as a stipend from Critical Care Medicine related to work as an associate editor. He is also a medical adviser to Project Hope and ARDS Foundation and a member of the Surviving Sepsis guideline committees.

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SOURCE: Sevransky J et al. Chest 2019.

ICU automated ventilation outperformed usual care

BY TED BOSWORTH
MDedge News

MADRID – In patients managed on mechanical ventilation in an intensive care unit following cardiac surgery, a fully automated system provides more reliable ventilatory support than highly experienced ICU nurses, suggest results of a randomized trial.

The study's control group received usual care, which means that nurses adjusted mechanical ventilation manually in response to respiratory rate, tidal volume, positive end-respiratory pressure (PEEP), and other factors to maintain ventilation within parameters associated with safe respiration. The experimental group was managed with a fully automated closed-loop system to make these adjustments without any nurse intervention.

Ted Bosworth/MDedge News

Dr. Marcus J. Schultz

For those in the experimental group "the proportion of time in the optimal zone was increased and the proportion of time in the unsafe zone was decreased" relative to those randomized to conventional nursing care, Marcus J. Schultz, MD, reported at the annual congress of the European Respiratory Society.

Conducted at a hospital with an experienced ICU staff, the study had a control arm that was managed by "dedicated nurses who, I can tell you, are very eager to provide the best level of care possible," said Dr. Schultz, professor of experimental intensive care, University of Amsterdam, the Netherlands.

The investigator-initiated POSITiVE trial randomized 220 cardiac surgery patients scheduled to receive postoperative mechanical ventilation in the ICU. Exclusions included those with class III COPD, a requirement for extracorporeal membrane oxygenation (ECMO), or a history of lung surgery.

The primary endpoint was the proportion of time spent in an optimal zone, an acceptable zone, or a dangerous zone of ventilation based on predefined values for tidal volume, maximum airway pressure, end-tidal CO_2, and oxygen saturation (SpO_2).

The greatest between-group difference was seen in the proportion of time spent in the optimal zone. This climbed from approximately 35% in the control arm to slightly more than 70% in the experimental arm, a significant difference. The proportion of time in the dangerous zone was reduced from approximately 6% in the control arm to 3% in the automated arm. On average nurse-managed patients spent nearly 60% of the time in the acceptable zone versus less than 30% for those in the automated experimental arm.

A heat map using green, yellow, and red to represent optimal, acceptable, and dangerous zones, respectively, for individual participants in the trial provided a more stark global impression. For the control group, the heat map was primarily yellow with scattered dashes of green and red. For the experimental group, the map was primarily green with dashes of yellow and a much smaller number of red dashes relative to the control group.

In addition, the time to spontaneous breathing was 38% shorter for those randomized to automated ventilation than to conventional care, a significant difference.

There are now many devices marketed for automated ventilation, according to Dr. Schultz. The device used in this study was the proprietary INTELLiVENT-ASV system, marketed by Hamilton Medical, which was selected based on prior satisfactory experience. Although not unique, this system has sophisticated software to adjust ventilation to reach targets set by the clinician on the basis of information it is receiving from physiologic sensors for such variables as respiratory rate, tidal volume, and inspiratory pressure.

"It is frequently adjusting the PEEP levels to reach the lowest driving pressure," said Dr. Schultz. Among its many other features, it also "gives spontaneous breathing trials automatically."

Uncomplicated patients were selected purposefully to test this system, but Dr. Schultz said that a second trial, called POSITiVE 2, is now being planned that will enroll more complex patients. Keeping complex patients within the optimal zone as defined by tidal volume and other critical variables has the potential to reduce lung damage that is known to occur when these are not optimized.

"Applying safe ventilatory support in clinical practice remains a serious challenge and is extremely time consuming," Dr. Schultz said. He reported that fully automated ventilation appears to be reliable, and "it takes out the human factor" in regard to diligence in monitoring and potential for error.

Overall, these results support the potential for a fully automated system to improve optimal ventilatory support, reduce risk of lung injury, and reduce staffing required for monitoring of mechanical ventilation, according to Dr. Schultz.

Dr. Schultz reports no potential conflicts of interest.

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Lefamulin found noninferior to moxifloxacin for pneumonia

BY HEIDI SPLETE
MDedge News

Oral lefamulin, the first pleuromutilin antibiotic approved for intravenous and oral administration, was noninferior to oral moxifloxacin for inducing an early clinical response in patients with bacterial pneumonia, acording to data from a global multicenter study of 738 individuals.

Persistent high rates of bacterial resistance to current treatments have created the need for more options, especially for the treatment of community-acquired bacterial pneumonia (CABP), which remains a leading cause of hospitalization and death in the United States, wrote Elizabeth Alexander, MD, of Nabriva Therapeutics in King of Prussia, Penn., and colleagues. Lefamulin, "the first pleuromutilin antibiotic approved for intravenous and oral use in humans," has demonstrated activity against many CABP-causing pathogens, including some not susceptible to other classes of antimicrobials, they noted.

Findings of Lefamulin Evaluation Against Pneumonia 2 (LEAP2) were published in JAMA. In this study, the researchers randomized 370 patients to 600 mg of oral lefamulin every 12 hours for 5 days and 368 patients to 400 mg of oral moxifloxacin every 24 hours for 7 days.

Early clinical response rates at 96 hours were 90.8% for both medications (difference of 0.1%). In addition, the rates of clinical response success were similar between the groups in both the modified intent-to-treat population (87.5% with lefamulin and 89.1% with moxifloxacin) and the clinically evaluable population (89.7% with lefamulin and 93.6% with moxifloxacin).

Gastrointestinal issues of diarrhea and nausea were the two most frequently reported treatment-emergent adverse events in both groups. Both conditions occurred more often in the lefamulin group, compared with the moxifloxacin group, but the differences were not significant (12.2% vs. 1.1% and 5.2% vs. 1.9%, respectively).

The study findings were limited by several factors including strict exclusion criteria that may limit the generalizability of the results, as well as a lack of testing for viral copathogens, low recovery of resistant pathogens, and possible misclassification of patient ethnicity, the researchers noted.

However, the results were strengthened by the randomized design, inclusion of patients with more severe CABP, and low rate of discontinuation, they said. The data support previous studies of lefamulin. Its lack of cross-resistance to other drug classes, coverage of typical and atypical CABP pathogens, and options for both oral and intravenous use suggest that it "may provide an alternative approach for the treatment of vulnerable patients," the researchers said.

The study was supported by Nabriva Therapeutics. Dr. Alexander and several coauthors are employees of Nabriva Therapeutics and own stock in the company.

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SOURCE: Alexander E et al. JAMA. 2019 Sep 27. doi:10.1001/jama.2019.15468.

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Checklist may improve quality measures in the surgical ICU

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – A standardized checklist may help reduce errors and improve common quality measures in critically ill patients, results of a recent retrospective analysis of 200 consecutive patients suggest.

Use of the checklist was linked to significantly shorter hospital length of stay and ICU length of stay as well as fewer days on a ventilator in the analysis, which was presented at the annual meeting of the American College of Chest Physicians. The 10-item standardized checklist covered a variety topics ranging from comfort, prophylaxis, and sedation to infection control and prevention, nutrition, and medication management review.

Although health economics weren't evaluated in this analysis, changes in those quality measures might also impact the bottom line, according to study coauthor Priscilla Chow, DO, a resident at Suburban Community Hospital in East Norriton, Pa.

"Obviously, if the patient is spending less time in the hospital and fewer days on the ventilator and in the ICU, then we can potentially also be more cost effective in our care," Dr. Chow said in a podium presentation at the meeting.

The use of checklists to standardize processes and reduce errors is a "relatively simple approach" that was adopted from the airline industry and now has been evaluated in a variety of medical care settings, according to Dr. Chow.

Previous studies have demonstrated that checklist-driven care may reduce the incidence of postoperative complications, central line–associated bloodstream infection, ventilator-associated pneumonia, and catheter-associated urinary tract infection.

The present retrospective data analysis by Dr. Chow and colleagues included 200 consecutive patients admitted to the surgical ICU at an urban level 1 trauma center, including 100 patients managed according to the checklist and 100 managed according to standard processes.

Though survival to discharge was comparable between the groups, use of the checklist was associated with a significantly shorter hospital length of stay versus standard care (23.9 vs. 9.5 days). Likewise, the ICU length of stay was shorter in the checklist group (13.0 vs. 6.5 days), and the checklist group had fewer ventilator days (7.7 to 2.8).

Injury Severity Score did not differ between groups; though overall, use of the checklist resulted in more of the underlying topics being addressed in clinical documentation (5.0 vs. 8.7 items).

Dr. Chow and colleagues disclosed that they had no relationships relevant to their study.

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SOURCE: Akella K et al. CHEST 2019. Abstract, doi: 10.1016/j.chest.2019.08.201.

Early palliative care consult decreases in-hospital mortality

BY ANDREW D. BOWSER
MDedge News

FROM CHEST 2019 ▪ NEW ORLEANS – When initiated early, a palliative care consultation may increase the number of discharges to hospice critical care patients meeting certain end-of-life criteria, results of a recent randomized clinical trial suggest.

The rate of in-hospital mortality was lower for critical care patients receiving an early consultation, compared with those who received palliative care initiated according to usual standards in the randomized, controlled trial, described at the annual meeting of the American College of Chest Physicians.

"There are a lot of things that can get in the way of adequate conversations, and that's when the palliative care team can come in."

More health care surrogates were chosen in the hospital when palliative care medicine was involved earlier, according to investigator Scott Helgeson, MD, fellow in pulmonary critical care at the Mayo Clinic in Jacksonville, Fla.

Taken together, Dr. Helgeson said, those findings suggest the importance of getting palliative care involved "very early, while the patient can still make decisions. ... There are a lot of things that can get in the way of adequate conversations, and that's when the palliative care team can come in," Dr. Helgeson said in an interview.

This study is the first reported to date to look at the impact on patient care outcomes specifically within 24 hours of medical ICU admission, according to Dr. Helgeson and coinvestigators

In their randomized study, patients were eligible if they met at least one of several criteria, including advanced age (80 years or older), late-stage dementia, post–cardiac arrest, metastatic cancer, end-stage organ failure, recurrent ICU admissions, an APACHE II score of 14 or higher, a SOFA score of 9 or higher, preexisting functional dependency, or consideration for a tracheostomy or permanent feeding tube.

Of 29 patients randomized, 14 received early palliative care, and 15 received standard palliative care, which was defined as starting "whenever the treating team deems (it) is appropriate," according to the published abstract.

Hospital mortality occurred in none of the patients in the early palliative care group, versus six in the usual care group ($P = .01$), Dr. Helgeson and colleagues found. Moreover, seven health care surrogates were chosen in hospital in the early palliative care group, versus none in the usual care group (P less than .01).

About one-fifth of deaths in the United States take place in or around ICU admissions, according to the investigators, who noted that those admissions can result in changing goals from cure to comfort – though sometimes too late.

Dr. Helgeson and coauthors disclosed that they had no relationships relevant to this research presentation.

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SOURCE: Helgeson S et al. CHEST 2019 Abstract doi: 10.1016/j.chest.2019.08.803.

FDA approves lefamulin for bacterial CAP in adults

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has announced its approval of lefamulin (Xenleta) for the treatment of community-acquired bacterial pneumonia in adults.

Approval was based on results of two clinical trials assessing a total of 1,289 people with community-acquired bacterial pneumonia. In these trials, lefamulin was compared with moxifloxacin with and without linezolid. Patients who received lefamulin had similar rates of treatment success as those taking moxifloxacin alone or moxifloxacin plus linezolid.

The most common adverse reactions associated with lefamulin include diarrhea, nausea, reactions at the injection site, elevated liver enzymes, and vomiting. Patients with prolonged QT interval, patients with arrhythmias, patients receiving treatment with antiarrhythmic agents, and patients receiving other drugs that prolong the QT interval are contraindicated. In addition, because of evidence of fetal harm in animal studies, pregnant women should be advised of potential risks before receiving lefamulin.

"This new drug provides another option for the treatment of patients with community-acquired bacterial pneumonia, a serious disease. For managing this serious disease, it is important for physicians and patients to have treatment options," Ed Cox, MD, director of the FDA's Office of Antimicrobial Products, said in the press release.

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Newly described lung disorder strikes children with systemic juvenile idiopathic arthritis

BY MICHELE G. SULLIVAN
MDedge News

An uncommon but potentially deadly inflammatory lung disease is emerging among children with systemic juvenile idiopathic arthritis, and its history appears to coincide with the rise of powerful biologics as first-line therapy for children with the disease.

Most confirmed cases of systemic juvenile idiopathic arthritis with lung disease (sJIA-LD) are in the United States. But it's popping up in other places that have adopted early biologic treatment for sJIA – including Canada, South America, Europe, and the Middle East.

The respiratory symptoms are relatively subtle, so by the time of lung disease detection, the amount of affected lung can be extensive, said Elizabeth Mellins, MD, a Stanford (Calif.) University researcher who, along with first author Vivian Saper, MD, recently published the largest case series comprising reports from 37 institutions (Ann Rheum Dis. 2019 Sep 27. doi: 10.1136/annrheumdis-2019-216040). By the end of follow-up, 22 of the 61 children in her cohort had died, including all 12 patients who demonstrated excessively high neutrophil levels in bronchoalveolar lavage samples.

Another recent report, authored by Grant Schulert, MD, PhD, and colleagues of the Cincinnati Children's Hospital Medical Center, described 18 patients, 9 of whom were also included in the Stanford cohort (Arthritis Rheumatol. 2019 Aug 5. doi: 10.1002/art.41073).

Both investigators have now identified new patients.

"We are aware of 60 additional cases beyond what were included in our series," Dr. Mellins said in an interview, bringing her entire cohort to 121. Dr. Schulert also continues to expand his group, detailing nine new cases at a recent private meeting.

"We are up to 27 now," he said. "The features of these new patients are all very similar: The children are very young, all have had macrophage activation syndrome in the past and very-difficult-to-control JIA. Reactions to tocilizumab [Actemra] were also not uncommon in this group."

Dr. Mellins also saw this association with allergic-type tocilizumab reactions, severe delayed hypersensitivity reactions to anakinra (Kineret) or canakinumab (Ilaris). Although serious lung disease in sJIA patients is not unheard of, this phenotype was virtually unknown until about a decade ago. Both investigators said that it's been rising steadily since 2010 – just about the time that powerful cytokine-inhibiting biologics were changing these patients' world for the better. After decades of relying almost solely on steroids and methotrexate, with rather poor results and significant long-term side effects, children were not only improving, but thriving. Gone was the life-changing glucocorticoid-related growth inhibition. Biologics could halt fevers, rash, and joint destruction in their tracks.

Courtesy Dr. Elizabeth Mellins

Dr. Vivian Saper (left) and Dr. Elizabeth Mellins

But the emergence of this particular type of lung disease could throw a pall over that success story, he said. If sJIA-LD is temporally associated with increasing reliance on long-term interleukin-1/IL-6 inhibition in children with early-onset disease, could these drugs actually be the causative agent?

Some of the 18 in his initial series have improved, while 36% of those in the Stanford series died. Most who do recover stay on their IL-1 or IL-6–blocking therapy with good disease control without further lung problems. Both investigators found compelling genetic hints, but nothing conclusive. Children with trisomy 21 appear especially vulnerable. Most patients are very young – around 2 years old – but others are school aged. Some had a history of macrophage activation syndrome. Some had hard-to-control disease and some were clinically well controlled when the lung disease presented.

With so many potential links, all unproven, clinicians may question the wisdom of embarking on long-term biologic therapy for their children with sJIA. Peter Nigrovic, MD, of Boston Children's Hospital, addressed this in an accompanying editorial (Arthritis Rheumatol. 2019 Aug 7. doi: 10.1002/art.41071).

"My take on this is that it's a very worrisome trend," he said in an interview. "We've been going full bore toward early biologic therapy in sJIA and at the same time we are seeing more of this lung disease. Is it guilt by association? Or is there something more? The challenge for us is not to jump too soon to that conclusion."

Although the association is there, he said, association does not equal causation. And there's no doubt that biologics have vastly improved the lives of sJIA patients. "The drugs might be causal, and I worry about that and think we need to study it. But we absolutely need stronger evidence before we change practice."

"This is a new manifestation of the disease, and it's coming at the same time we are changing the treatment paradigm," Dr. Nigrovic continued. "It could be because of interleukin-1 or interleukin-6 blockade. There is biological plausibility for such a link. It could also be related to the fact that we are using less steroids and methotrexate, which might have been preventing this. The appearance of sJIA lung disease could also be that a distinct secular trend unrelated to treatment, just as we saw amyloid come and go in this population in Europe. These other therapies were actually preventing this. We just don't know."

Clinical characteristics

Children presented with similar symptoms. Respiratory symptoms are usually subtle and mild. These can include tachypnea, hypoxia (43% in the Stanford series), and pulmonary hypertension (30% in the Stanford series).

Digital clubbing, often with erythema, was a common finding. Some children showed pruritic, nonevanescent rashes. Eosinophilia occurred in 37% of the Stanford series and severe abdominal pain in 16%, although Dr. Mellins noted that belly pain may be underestimated, as it was only volunteered, not queried, information.

"There are some red flags that should raise suspicion even without obvious respiratory symptoms," Dr. Mellins said. These include lymphopenia, unexplained abdominal pain, eosinophilia, an unusual rash, and finger clubbing with or without erythema.

Findings on imaging were consistent in both series. Several key clinic features emerged: pleural thickening, septal thickening, bronchial wall or peribronchovascular thickening, "tree-in-bud" opacities, "ground-glass" opacities, peripheral consolidation, and lymphadenopathy.

The research groups were supported by grants from the sJIA Foundation, the Lucile Packard Foundation for Children's Health, Stanford graduate fellowships, the Life Sciences Research Foundation, the Bill & Melinda Gates Foundation, Cincinnati Children's Research Foundation, the Childhood Arthritis and Rheumatology Research Alliance, the Arthritis Foundation, and the National Institutes of Health. Many authors on both papers reported financial ties to Genentech, which markets tocilizumab, and other pharmaceutical companies. Dr. Nigrovic reported receiving consulting fees and research support from Novartis and other companies.

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SOURCES: Saper V et al. Ann Rheum Dis. 2019 Sep 27. doi: 10.1136/annrheumdis-2019-216040; Schulert G et al. Arthritis Rheumatol. 2019 Aug 5. doi: 10.1002/art.41073; Nigrovic P Arthritis Rheumatol. 2019 Aug 7. doi: 10.1002/art.41071.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: More information is needed for this new and rare but important interstitial lung disease. The Children's Interstitial and Diffuse Lung Disease Research Network and the chILD Foundation are important groups that help support pediatric interstitial lung disease research and patients. Pulmonary alveolar proteinosis (PAP), specifically, is an interstitial lung disease that can occur in children and adults. Acquired PAP can occur, for example, in firefighters, amyloidosis. This research points to a new cause of lung disease that appears to be very similar to PAP.

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NAM offers recommendations to fight clinician burnout

BY KERRY DOOLEY YOUNG
MDedge News

WASHINGTON – The practice of medicine needs a major reset to address the stresses that lead to clinician burnout, a condition now estimated to affect one-third to one-half of clinicians in the United States, according to a report from an influential federal panel.

On Oct. 23, the National Academy of Medicine (NAM) released a report, "Taking Action Against Clinician Burnout: A Systems Approach to Professional Well-Being." The report calls for a broad and unified approach to tackling the root causes of burnout.

There must be a concerted effort by leaders of many fields of health care to create less stressful workplaces for clinicians, Pascale Carayon, PhD, cochair of the NAM committee that produced the report, said during the NAM press event.

"This is not an easy process," said Dr. Carayon, a researcher into patient safety issues at the University of Wisconsin–Madison. "There is no single solution."

The NAM report assigns specific tasks to many different participants in health care through a six-goal approach, as described below.

• Create positive workplaces. Leaders of health care systems should consider how their business and management decisions will affect clinicians' jobs, taking into account the potential to add to their levels of burnout. Executives need to continuously monitor and evaluate the extent of burnout in their organizations, and report on this at least annually.

• Address burnout in training and in clinicians' early years. Medical, nursing, and pharmacy schools should consider steps such as monitoring workload, implementing pass-fail grading, improving access to scholarships and affordable loans, and creating new loan repayment systems.

• Reduce administrative burden. Federal and state bodies and organizations such as the National Quality Forum should reconsider how their regulations and recommendations contribute to burnout. Organizations should seek to eliminate tasks that do not improve the care of patients.

• Improve usability and relevance of health information technology (IT). Medical organizations should develop and buy systems that are as user-friendly and easy to operate as possible. They also should look to use IT to reduce documentation demands and automate nonessential tasks.

Dr. Vindell Washington

• Reduce stigma and improve burnout recovery services. State officials and legislative bodies should make it easier for clinicians to use employee assistance programs, peer support programs, and mental health providers without the information being admissible in malpractice litigation. The report notes the recommendations from the Federation of State Medical Boards, American Medical Association, and the American Psychiatric Association on limiting inquiries in licensing applications about a clinician's mental health. Questions should focus on current impairment rather than reach well into a clinician's past.

• Create a national research agenda on clinician well-being. By the end of 2020, federal agencies – including the Agency for Healthcare Research and Quality, the National Institute for Occupational Safety and Health, the Health Resources and Services Administration, and the U.S. Department of Veterans Affairs – should develop a coordinated research agenda on clinician burnout, the report said.

In casting a wide net and assigning specific tasks, the NAM report seeks to establish efforts to address clinician burnout as a broad and shared responsibility. It would be too easy for different medical organizations to depict addressing burnout as being outside of their responsibilities, Christine K. Cassel, MD, the cochair of the NAM committee that produced the report, said during the press event.

"Nothing could be farther from the truth. Everyone is necessary to solve this problem," said Dr. Cassel, who is a former chief executive officer of the National Quality Forum.

Darrell G. Kirch, MD, chief executive of the Association of American Medical Colleges, described the report as a "call to action" at the press event.

Previously published research has found between 35% and 54% of nurses and physicians in the United States have substantial symptoms of burnout, with the prevalence of burnout ranging between 45% and 60% for medical students and residents, the NAM report said.

Leaders of health organizations must consider how the policies they set will add stress for clinicians and make them less effective in caring for patients, said Vindell Washington, MD, chief medical officer of Blue Cross Blue Shield of Louisiana and a member of the NAM committee that wrote the report.

"Those linkages should be incentives and motivations for boards and leaders more broadly to act on the problem," Dr. Washington said at the NAM event.

Dr. Kirch said he experienced burnout as a first-year medical student. He said a "brilliant aspect" of the NAM report is its emphasis on burnout as a response to the conditions under which medicine is practiced. In the past, burnout has been viewed as being the fault of the physician or nurse experiencing it, with the response then being to try to "fix" this individual, Dr. Kirch said at the event.

The NAM report instead defines burnout as a "work-related phenomenon studied since at least the 1970s," in which an individual may experience exhaustion and detachment. Depression and other mental health issues such as anxiety disorders and addiction can follow burnout, he said. "That involves a real human toll."

Joe Rotella, MD, MBA, chief medical officer at American Academy of Hospice and Palliative Medicine, said in an interview that this NAM paper has the potential to spark the kind of transformation that its earlier research did for the quality of care. Then called the Institute of Medicine, NAM in 1999 issued a report, "To Err Is Human," which is broadly seen as a key catalyst in efforts in the ensuing decades to improve the quality of care. IOM then followed up with a 2001 report, "Crossing the Quality Chasm."

"Those papers over a period of time really did change the way we do health care," said Dr. Rotella, who was not involved with the NAM report.

In Dr. Rotella's view, the NAM report provides a solid framework for what remains a daunting task, addressing the many factors involved in burnout.

"The most exciting thing about this is that they don't have 500 recommendations. They had six and that's something people can organize around," he said. "They are not small goals. I'm not saying they are simple."

The NAM report delves into the factors that contribute to burnout. These include a maze of government and commercial insurance plans that create "a confusing and onerous environment for clinicians," with many of them juggling "multiple payment systems with complex rules, processes, metrics, and incentives that may frequently change."

Clinicians face a growing field of measurements intended to judge the quality of their performance. While some of these are useful, others are duplicative and some are not relevant to patient care, the NAM report said.

The report also noted that many clinicians describe electronic health records as taking a toll on their work and private lives. Previously published research has found that, for every hour spent with a patient, physicians spend an additional 1-2 hours on the EHR at work, with additional time needed to complete this data entry at home after work hours, the report said.

In an interview, Cynda Rushton, RN, PhD, a Johns Hopkins University researcher and a member of the NAM committee that produced the report, said this new publication will support efforts to overhaul many aspects of current medical practice. She said she hopes it will be a "catalyst for bold and fundamental reform.

"It's taking a deep dive into the evidence to see how we can begin to dismantle the system's contributions to burnout," she said. "No longer can we put Band-Aids on a gaping wound."

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Judge rules for insurer in doctor's allocation lawsuit

BY ALICIA GALLEGOS
MDedge News

A judge has sided with a medical malpractice insurer in a legal challenge that accused the company of misallocating blame among physicians after a liability settlement.

In a Sept. 27 decision, Judge Debra Squires-Lee of the Commonwealth of Massachusetts Superior Court ruled that Medical Professional Mutual Insurance Company (ProMutual) acted reasonably when it settled a medical liability claim for $500,000 against several health providers and allocated responsibility for 30% of the settlement ($150,000) to internist Nataly Minkina, MD. ProMutual was well within its rights and obligations when it settled the underlying claim and did not act in bad faith when assigning responsibility in the case, Judge Squires-Lee wrote in her 49-page ruling.

"At its heart, this case is about a multiple defendant malpractice lawsuit with finger pointing by Dr. Minkina against her codefendants and others, and a disagreement about ProMutual's ultimate determination about how to allocate a global settlement with the plaintiffs amongst ProMutual's insureds," Judge Squires-Lee wrote in the decision. "Dr. Minkina strongly believes that she did not fail [the patient], that she acted reasonably, and that her treatment of [the patient] satisfied the standard of care. She also questions why ProMutual failed to allocate liability in the [patient's] suit to other physicians. However ... the question for this court is whether ProMutual committed unfair or deceptive acts or practices in its settlement and allocation of its settlement. I conclude that ProMutual did not."

The case stems from a patient's lawsuit against Dr. Minkina and several others at Blue Hills Medical Associates in Braintree, Mass.

The patient alleged that the health care professionals were responsible for a missed breast cancer diagnosis. Dr. Minkina saw the patient just once in 2002 while covering for another doctor. During the visit, she confirmed some nodularity in the 55-year-old women's breast and referred her for a mammogram and an ultrasound. A radiologist twice reported no abnormalities, which Dr. Minkina said she relayed to the patient. Dr. Minkina left the practice shortly after.

The patient visited the practice several more times and was referred for another mammogram in 2006, the results of which revealed some signs of malignancy, according to court documents. However, a nurse at the practice misread, misunderstood, or overlooked the signs and recorded that "the benign breast condition had no changes," according to court transcripts. Later that year, the patient visited the practice complaining of headaches and a droopy eye at which time her primary care physician diagnosed sinusitis and prescribed antibiotics. In 2007, the patient underwent MRIs of the brain and the breast, which revealed widespread metastatic carcinoma. She and her family sued Dr. Minkina and several others in June 2007. The patient died in 2008.

ProMutual settled the case against the defendants for $500,000 in 2008, allocating 30% of the liability to Dr. Minkina, 10% of the nurse practitioner, 60% to the medical practice, and no liability to the other doctors named. ProMutual contended Dr. Minkina bore more responsibility than the other health care professionals named for the delayed diagnosis because of causation factors and standard of care violations, namely that Dr. Minkina should have pursued a biopsy for the patient.

Dr. Minkina sued the insurer in 2012, claiming chiefly that the insurer allocated an unjustifiably high percentage of liability to her because she was no longer insured and because the company had an economic incentive to allocate a disproportionate percentage of responsibility and damages.

A lower court initially dismissed Dr. Minkina's suit, but the Commonwealth of Massachusetts Appeals Court in 2015 overturned that decision, ruling the case could move forward. In 2018, the superior court agreed Dr. Minkina had a valid bad faith claim, stating that she had provided information about ProMutual's conduct from which "a reasonable juror could infer the defendant's bad faith in connection with its settling the underlying malpractice suit, including the allocation of liability.

But Judge Squires-Lee ruled that trial evidence showed that ProMutual did not act for its own benefit or favor other insureds over Dr. Minkina. The judge wrote that the insurer satisfied its contractual and legal obligations when defending the underlying legal claim.

Dr. Minkina said she was disappointed with the ruling, but that she is considering her legal avenues.

ProMutual declined to comment about the decision.

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President to nominate oncologist to lead FDA

BY ALICIA GALLEGOS
MDedge News

Stephen M. Hahn, MD, a radiation oncologist and researcher, may soon take the reins of the Food and Drug Administration.

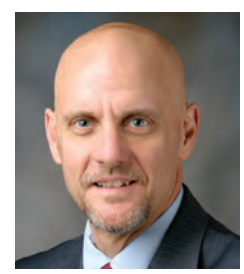
President Trump indicated his intent to nominate Dr. Hahn as FDA Commissioner in a brief Nov.1 statement that outlined Dr. Hahn's background. Dr. Hahn currently serves as chief medical executive at MD Anderson Cancer Center, Houston, where he heads the radiology oncology division.

Dr. Hahn specializes in treating lung cancer and sarcoma and has authored 220 peer-reviewed original research articles. He was previously chair of the department of radiology oncology at the University of Pennsylvania, Philadelphia, and also served as a senior investigator at the National Cancer Institute.

Dr. Hahn completed his residency in radiation oncology at NCI and his residency in internal medicine at the University of California, San Francisco.

Margaret Foti, PhD, chief executive officer for the American Association for Cancer Research called Dr. Hahn a renowned expert in radiation oncology and research, an experienced and highly effective administrator, and an innovative leader.

"I have seen firsthand Dr. Hahn's extraordinary dedication and commitment to cancer patients, and the AACR is extremely confident that he will be an outstanding leader for the FDA," Dr. Foti said in a statement. "Dr. Hahn, who is board certified in both radiation and medical oncology, is esteemed for the breadth and depth of his scientific knowledge and expertise, and he has consistently advocated for a drug review process at the FDA that is both science directed and patient focused."



Dr. Hahn

The American Society of Clinical Oncology also congratulated Dr. Hahn on the upcoming nomination, noting that he has a strong grasp of the drug development process and understands the realities of working in a complex clinical care environment.

"The role of FDA commissioner requires a strong commitment to advancing the agency's mission to protect public health across the United States, and an understanding of how to help speed innovations to get new treatments to patients, while also ensuring the safety and efficacy of the medical products that millions of Americans rely on to manage, treat, and cure their cancer," the society stated. "ASCO has a long and productive history of collaborating with FDA, including with current Acting Commissioner, Ned Sharpless, MD, in support of the agency's important role in reducing cancer incidence, advancing treatment options, and improving the lives of individuals with cancer. We look forward to continuing our close collaboration to make it possible for every American with cancer to have access to medical products that are safe and effective."

Dr. Sharpless will return to his position as NCI director; he served as interim FDA commissioner from the April departure of then-FDA commissioner, Scott Gottlieb, MD.

"As one of the nation's leading oncologists who has devoted his entire professional career to helping patients in the fight against cancer, Ned is returning home to NCI to continue this work and we look forward to working closely with him once again," Francis S. Collins, MD, director of the National Institutes of Health, said in a statement. "

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Demeaning patient behavior takes emotional toll on physicians

BY STEVE CIMINO
MDedge News

Despite an increasingly diverse workforce, a new study has found that many patients remain biased toward certain physicians, which can produce substantial negative – and occasionally positive – effects.

"Addressing demeaning behavior from patients will require a concerted effort from medical schools and hospital leadership to create an environment that respects the diversity of patients and physicians alike," wrote Margaret Wheeler, MD, of the University of California, San Francisco and her coauthors. The study was published in JAMA Internal Medicine.

To determine the perspectives of physicians and trainees in regard to patient bias, along with potential barriers to responding effectively, the researchers led 13 focus groups attended by 11 internal medicine hospitalist physicians, 26 internal medicine residents, and 13 medical students affiliated with the UCSF School of Medicine.

In describing biased and demeaning patient behavior, the participants recalled remarks that ranged from refusal of care and questioning the clinician's role to ethnic jokes, questions as to their ethnic backgrounds, and inappropriate flirtations or compliments. The effects of these behaviors on the participants included negative responses like carrying an emotional burden and withdrawing from work, along with positive responses like an increased desire for self-growth and to pursue leadership opportunities.

Barriers to addressing these behaviors included a lack of support, uncertainty as to the appropriate response, and a fear of being perceived as unprofessional. Deciding how to respond – or to respond at all – was often dictated by the level of support from colleagues, a professional responsibility to peers, and the presence of a positive role model who would've done the same.

The study was supported by the Greenwall Foundation. The authors reported no conflicts of interest.

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SOURCE: Wheeler M et al. JAMA Intern Med. 2019 Oct 28. doi: 10.1001/jamainternmed.2019.4122.

VIEW ON THE NEWS

The results of the patient bias study from Wheeler et al. are troubling, but not surprising. As the physician workforce becomes more diverse in regard to race, ethnicity, sex, gender identity, and sexual orientation, considering and addressing the negative impacts of demeaning patient interactions becomes increasingly important. And though a recent analysis stated a decline in biases between 2007 and 2016, discriminatory and disrespectful treatment remains the norm for members of many minority groups.

Strategies to address these behaviors include codes of professional ethics offering guidance on responding to disrespectful behavior, antidiscrimination training for all health professionals, and health care leaders themselves practicing and preaching respectfulness and civility within their institutions. Patients can be expected to behave respectfully towards physicians only if the culture of health care is also respectful. When anyone, including a patient, exhibits biased and disrespectful behavior, silence is not golden. It is tacit approval. We all have the responsibility to speak and act.

Lisa A. Cooper, MD, and Mary Catherine Beach, MD, of Johns Hopkins University in Baltimore; and David R. Williams, PhD, of Harvard University, Boston, made these comments in an accompanying editorial (JAMA Intern Med. 2019 Oct 28. doi: 10.1001/jamainternmed.2019.4100). They reported no conflicts of interest.

Judge dismisses doctors' lawsuit against ABIM

BY ALICIA GALLEGOS
MDedge News

A district court has dismissed a lawsuit levied by a group of physicians against the American Board of Internal Medicine (ABIM) over its maintenance of certification (MOC) program, calling the legal challenge "flawed."

In a Sept. 26 decision, U.S. District Court Judge for the Eastern District of Pennsylvania Robert F. Kelly Sr. said the plaintiffs failed to demonstrate sufficient evidence for their antitrust and unjust enrichment claims against ABIM. The doctors also did not establish any showing of anticompetitive conduct by ABIM to support a monopolization claim, the judge ruled.

"We disagree with plaintiffs and find that ABIM's initial certification and MOC products are part of a single product and do not occupy distinct markets," Judge Kelly wrote in his decision. "Not only are we unconvinced by plaintiffs' arguments, we find that plaintiffs' entire framing of the ABIM certification to be flawed. In essence, plaintiffs are arguing that, in order to purchase ABIM's initial certification, internists are forced to purchase MOC products as well. However, this is not the case. ... Nowhere in the amended complaint do plaintiffs allege that they were forced to buy MOC products in order to purchase the initial certification."

The judge dismissed the suit, but allowed the plaintiffs 14 days to submit an amended complaint reoutlining their claims of illegal monopolization and racketeering against the board. If the amended complaint passes legal muster, the judge could revive those claims.

ABIM President Richard J. Baron, MD, expressed satisfaction that the court granted the board's motion to dismiss the case for failure to state a valid claim.

"ABIM is pleased that the United States District Court for the Eastern District of Pennsylvania dismissed in its entirety a lawsuit that alleged physicians were harmed by the requirements for maintaining ABIM board certification," Dr. Baron said in a statement.

C. Philip Curley, a Chicago-based attorney for the physician plaintiffs, said the case is far from over.

"The four internists who brought the lawsuit were invited to file amended claims, which is certainly being considered," Mr. Curley said in an interview.

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NEWS FROM CHEST

This month in the journal *CHEST*®

Editor's Picks

BY PETER J. MAZZONE, MD, MPH, FCCP

Editorials

Preventing Patient and Physician Harm.
By Dr. J. D.Zibrak

Intensivist Burnout: Running on Empty?
By Dr. Curtis N. Sessler

Original Research

Medical Malpractice Involving Pulmonary/Critical Care Physicians.
By Dr. L. C. Myers, et al.

Impaired Sleep Quality in COPD Is Associated With Exacerbations: The CanCOLD Cohort Study.
By Dr. M. Shorofsky et al.

Environmental scan: Drivers of social, political, and environmental change

BY THERESE BORDEN
MDedge News

We are living through an era of rapidly accelerated social, political, and environmental change. Spiraling costs of medical care, consumer activism around health care delivery, an aging population, and growing evidence of climate change are just some of the big currents of change. These trends are national and global in scope, and as such, far beyond any one profession or sector to shape or control. It remains for the medical profession to understand the currents of the time and adapt in order to thrive in the future.

David A. Schulman, MD, FCCP, Professor of Medicine at Emory University School of Medicine, Atlanta, has reflected on these trends of the times and their impact on chest physicians. He commented, "In 1957, the American Medical Association adopted the Principles of Medical Ethics, which noted that 'the responsibilities of the physician extend not only to the individual, but also to society where these responsibilities deserve his [her] interest and participation in activities which have the purpose of improving both the health and the well-being of the individual and the community.'[1] While this terminology has evolved in more recent iterations of the Code of Medical Ethics, it is more important than ever for physicians to be cognizant of the effects of social, political, and environmental factors on personal and public health. These external pressures seem to be growing in a climate where the country is more polarized than ever, and conversations on some of these topics can introduce unnecessary tension on interpersonal relationships, but there are still many things in this domain on which we can all agree."

CHEST® INSPIRATION: Pacing the Future

Two trends of particular interest to chest physicians are the potential impact of climate change on patients, and the "greying" of the patient population. Both are likely to have a significant impact on medical practice in the decades to come.

Patients will feel climate change

Environmental factors affecting the air we breathe are of primary concern for patients with a broad range of cardiorespiratory conditions.[2] Healthy but vulnerable infants, children, pregnant women, and the elderly may also feel the effects.[3] Air pollution, increased levels of pollen and ground-level ozone, and wildfire smoke are all tied to climate change and all can have a direct impact on the patients seen by chest physicians. Individuals exposed to these environmental conditions may experience diminished lung function, resulting in increased hospital admissions. Keeping up with the latest research on probable health impacts of these environmental trends will be on the agenda of most chest physicians.[4] Professional societies will need to provide for the educational needs of members, as the field will respond with new diagnostic tools and treatments.

Dr. Schulman said, "Stresses on our physical environment are affecting our patients. Environmental warming may increase the spread of mosquito-borne illnesses.[5] The lack of available clean water in many areas of the world will increase the risk of water-borne infections. Higher levels of pollution will lead to poorer air quality and an increased risk of respiratory infections, exacerbations of respiratory disease, loss of lung function, and the eventual development of lung cancer. While any one of us may not be able to make a change on a global level, we do bear a responsibility to ensure that our patients are cognizant of the effects of environmental exposures on their health, and how these effects can be mitigated (which may include minimizing time outside on days with poor air quality and implementing methods to improve indoor air quality)."


Dr. Schulman

Mind the generation gap

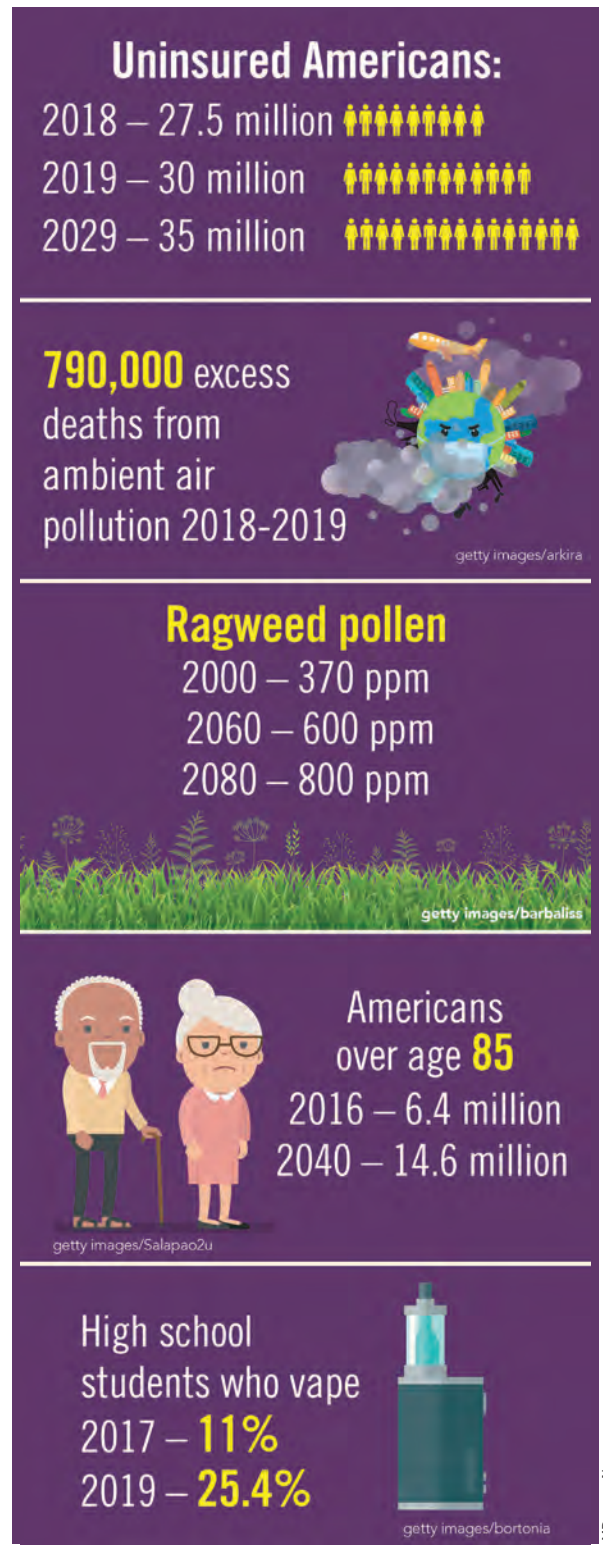
The population in the United States is primarily under age 65 (84%), but the number of older citizens is on the rise. In 2016, there were 49.2 million people age 65 or older, and this number is projected to almost double to 98 million in 2060. The 85 and over population is projected to more than double from 6.4 million in 2016 to 14.6 million in 2040 (a 129% increase).[6]

The medical needs of the aging population are already part of most medical institutions' planning, but the current uncertainty in the health insurance market and the potential changes in Medicare coverage, not to mention the well-documented upcoming physician shortage,[7] are complicating the planning process. Almost all acknowledge the "greying" of the population, but current approaches may not be sufficient given the projected scale of the problems. This includes major increases in patients with chronic illnesses and the need for upscaling long-term geriatric care.

Dr. Schulman notes that there will likely be "a workforce shortage, unless we make deliberate efforts to increase the workforce. More aggressive recruitment of individuals into the health-care industry, including those traditionally under-represented in medicine, will be an important component of this endeavor. Mitigating burnout, which impacts both provider efficiency and leads to early exit from the practice of medicine, will be another critical step in this process."

In addition to the problem of planning for treating a growing elderly population, several concerning trends are appearing among younger groups. E-cigarette use among middle- and high-school students may create millions of future patients with lung damage and nicotine addictions.[8] Government intervention in this smoking epidemic is lagging behind the rapid spread of this unhealthy habit among young people.[9] Dr. Schulman is concerned about new sources of tobacco delivery to young people. "Independent of the recent spate of vaping-associated pulmonary injury, the increasing use of nicotine-delivery systems by our youth is highly troubling. In much the same way that we have long advised our tobacco-abusing patients to minimize or discontinue smoking, health-care providers need to aggressively screen for (and advocate against) the use of alternative methods of nicotine delivery, at least until such time that one of them is proven to be safe in long-term studies."

Continued on page 61



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How to carve out a career as an educator during fellowship

BY JUSTIN K. LUI, MD

Editor's Note - As CHEST has just awarded the designation of Distinguished CHEST Educator (DCE) to 173 honorees at CHEST 2019 in New Orleans, this blog reminds fellows to start early to pursue a clinician educator role throughout their career.

While fellowship training is a time to continue building the foundation of expert clinical knowledge, it also offers an opportunity to start assembling a portfolio as a clinician educator. It takes time to compile educational scholarship and to establish a reputation within the communities of both teachers and learners, so it pays to get a head start. Moreover, it also takes time to master techniques for effective teaching to become that outstanding educator that you once looked up to as a medical student or resident. Below are some things that I found helpful in jump-starting that path during fellowship training.

Find a capable mentor

As with any sort of career planning, mentorship is key. Mentorship can open doors to expand your network and introduce opportunities for scholarship activities. Find a mentor who shares similar views and values with something that you feel passionate about. If you are planning on starting a scholarly project, make sure that your mentor has the background suited to help you maximize the experience and offer you the tools needed to achieve that end.

Determine what you are passionate about

Medical education is a vast field. Try to find something in medical education that is meaningful to you, whether it be in undergraduate medical education or graduate medical education or something else altogether. You want to be able to set yourself up for success, so the work has to be worthwhile.

If you are planning on starting a scholarly project, make sure that your mentor has the background suited to help you maximize the experience and offer you the tools needed to achieve that end.

Seek out opportunities to teach

There are always opportunities to teach whether it entails precepting medical students on patient interviews or going over pulmonary/critical care topics at resident noon conferences. What I have found is that active participation in teaching opportunities tends to open a cascade of doors to more teaching opportunities.

Look for opportunities to be involved in educational committees

Medical education, much like medicine, is a highly changing field. Leadership in medical education is always looking for resident/fellow representatives to bring new life and perspective to educational initiatives. Most of these opportunities do not require too much of a time commitment, and most committees often meet on a once-monthly basis. However, it connects you with faculty who are part of the leadership who can guide and help set you up for future success in medical education. During residency, I was able to take part in the intern curriculum committee to advise the direction of intern report. Now as a fellow, I've been able to meet many faculty and fellows with similar interests as mine in the *CHEST* Trainee Work Group.

Engage in scholarly activities

It is one thing to have a portfolio detailing teaching experiences, but it is another thing to have demonstrated published works in the space of medical education. It shows long-term promise as a clinician educator, and it shows leadership potential in advancing the field. It doesn't take much to produce publications in medical education—there are always journals who look for trainees to contribute to the field whether it be an editorial or systematic review or innovative ideas.

About the author

Justin K. Lui, MD, is a graduate of Boston University School of Medicine. He completed an internal medicine residency and chief residency at the University of Massachusetts Medical School. He is currently a second-year pulmonary and critical care medicine fellow at Boston University School of Medicine.

Reprinted from CHEST's Thought Leader's Blog, July 2019. This post is part of Our Life as a Fellow blog post series and includes "fellow life lessons" from current trainees in leadership with CHEST.

Continued from page 57

In 2019, health coverage for adults has started to decline again after a decade of gains,[10] so the possibility of this becoming a long-term trend has to be considered in planning for the treatment of the young population as they enter adulthood.[11]

Final thoughts

Some issues, including the increase in tobacco usage and aging patients with more complex problems, are likely to be addressed through both continuing education and guidelines/standards. On the other hand, with a growing population of individuals under 30, we can expect increasing unrest with the status quo, a demand for change in public policy, and a higher adoption of new models for the diagnosis, treatment, and ongoing care of health-related issues.

In order to have a real impact, organizations will need to explore new partnerships for addressing issues related to climate change and the increase in tobacco use by minors. Members need to stay up-to-date using information curated and shared by trusted organizations and sources.

Note: Background research performed by Avenue M Group.

CHEST Inspiration is a collection of programmatic initiatives developed by the American College of Chest Physicians leadership and aimed at stimulating and encouraging innovation within the association. One of the components of CHEST Inspiration is the Environmental Scan, a series of articles focusing on the internal and external environmental factors that bear on success currently and in the future. See "Envisioning the Future: The CHEST Environmental Scan," CHEST Physician, June 2019, p. 44, for an introduction to the series.

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SLEEP STRATEGIES

CPAP vs noninvasive ventilation for obesity hypoventilation syndrome

BY NARESH A. DEWAN MD, FCCP

The conventional approach to treat hypoventilation has been to use noninvasive ventilation (NIV), while continuous positive airway pressure (CPAP) that does not augment alveolar ventilation improves gas exchange by maintaining upper airway patency and increasing functional residual capacity. Why, then, are we debating the use of CPAP vs NIV in the treatment of obesity hypoventilation syndrome (OHS)? To understand this rationale, it is important to first review the pathophysiology of OHS. The hallmark of OHS is resting daytime awake arterial $PaCO_2$ of 45 mm Hg or greater in an obese patient (BMI > 30 kg/m^2) in absence of any other identifiable cause. To recognize why only some but not all obese subjects develop OHS, it is important to understand the different components of pathophysiology that contribute to hypoventilation: (1) obesity-related reduction in functional residual capacity and lung compliance with resultant increase in work of breathing; (2) central hypoventilation related to leptin resistance and reduction in respiratory drive with REM hypoventilation; and (3) upper airway obstruction caused by upper airway fat deposition along with low FRC contributing to pharyngeal airway narrowing and increased airway collapsibility (Masa JF, et al. *Eur Respir Rev.* 2019; 28:180097).

Dr. Dewan

CPAP vs NIV for OHS

Let us examine some of the studies that have compared the short-term efficacy of CPAP vs NIV in patients with OHS. In a small randomized controlled trial (RCT), the effectiveness of CPAP and NIV was compared in 36 patients with OHS (Piper AJ, et al. *Thorax.* 2008;63:395). Reduction in $PaCO_2$ at 3 months was similar between the two groups. However, patients with persistent nocturnal desaturation despite optimal CPAP were excluded from the study. In another RCT of 60 patients with OHS who were either in stable condition or after an episode of acute on chronic hypercapnic respiratory failure, the use of CPAP or NIV showed similar improvements at 3 months in daytime $PaCO_2$, quality of life, and sleep parameters (Howard ME, et al. *Thorax.* 2017;72:437).

In one of the largest randomized control trials, the Spanish Pickwick study randomized 221 patients with OHS and AHI >30/h to NIV, CPAP, and lifestyle modification (Masa JF, et al. *Am J Respir Crit Care Med.* 2015:192:86). PAP therapy included NIV that consisted of in-lab titration with bilevel PAP therapy targeted to tidal volume 5-6 mL/kg of actual body weight or CPAP. Lifestyle modification served as the control group. Primary outcome was the change in $PaCO_2$ at 2 months. Secondary outcomes were symptoms, HRQOL, polysomnographic parameters, spirometry, and 6-min walk distance (6 MWD). Mean AHI was 69/h, and mean PAP settings for NIV and CPAP were 20/7.7 cm and 11 cm H_2O, respectively. NIV provided the greatest improvement in $PaCO_2$ and serum HCO_3 as compared with control group but not relative to CPAP group. CPAP improved $PaCO_2$ as compared with control group only after adjustment of PAP use. Spirometry and 6 MWD and some HRQOL measures improved slightly more with NIV as compared with CPAP. Improvement in symptoms and polysomnographic parameters was similar between the two groups.

In another related study by the same group (Masa JF, et al. *Thorax.* 2016;71:899), 86 patients with OHS and mild OSA (AHI <30/h), were randomized to NIV and lifestyle modification. Mean AHI was 14/h and mean baseline $PaCO_2$ was 49 +/-4 mm Hg. The NIV group with mean PAP adherence at 6 hours showed greater improvement in $PaCO_2$ as compared with lifestyle modification (6 mm vs 2.8 mm Hg). They concluded that NIV was better than lifestyle modification in patients with OHS and mild OSA.

To determine the long-term clinical effectiveness of CPAP vs NIV, patients in the Pickwick study, who were initially assigned to either CPAP or NIV treatment group, were continued on their respective treatments, while subjects in the control group were again randomized at 2 months to either CPAP or NIV (Masa JF, et al. *Lancet.* 2019;393:1721). All subjects (CPAP n=107; NIV n=97) were followed for a minimum of 3 years. CPAP and NIV settings (pressure-targeted to desired tidal volume) were determined by in-lab titration without transcutaneous CO_2 monitor, and daytime adjustment of PAP to improve oxygen saturation. Primary outcome was the number of hospitalization days per year. Mean CPAP was 10.7 cm H_2O pressure and NIV 19.7/8.18 cm H_2O pressure with an average respiratory rate of 14/min. Median PAP use and adherence > 4 h, respectively, were similar between the two groups (CPAP 6.0 h, adherence > 4 h 67% vs NIV 6.0/h, adherence >4 h 61%). Median duration of follow-up was 5.44 years (IOR 4.45-6.37 years) for both groups. Mean hospitalization days per patient-year were similar be-

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tween the two groups (CPAP 1.63 vs NIV 1.44 days; adj RR 0.78, 95% CI 0.34-1.77; *P*=0.561). Overall mortality, adverse cardiovascular events, and arterial blood gas parameters were similar between the two groups, suggesting equal efficacy of CPAP and NIV in this group of stable patients with OHS with an AHI >30/h. Given the low complexity and cost of CPAP vs NIV, the authors concluded that CPAP may be the preferred PAP treatment modality until more studies are available.

An accompanying editorial (Murphy PB, et al. *Lancet.* 2019; 393:1674), discussed that since this study was powered for superiority as opposed to noninferiority of NIV (20% reduction in hospitalization with NIV when compared with CPAP), superiority could not be shown, due to the low event rate for hospitalization (NIV 1.44 days vs CPAP 1.63 days). It is also possible optimum NIV titration may not have been determined since TCO_2 was not used. Furthermore, since this study was done only in patients with OHS and AHI >30/h, these results may not be applicable to patients with OHS and low AHI < 30/h who are more likely to have central hypoventilation and comorbidities, and this group may benefit from NIV as compared with CPAP.

Novel modes of bi-level PAP therapy

There are limited data on the use of the new bi-level PAP modalities, such as volume-targeted pressure support ventilation (PS) with fixed or auto-EPAP. The use of intelligent volume-assured pressure support ventilation (iVAPS) vs standard fixed pressure support ventilation in select OHS patients (n=18) showed equivalent control of chronic respiratory failure with no worsening of sleep quality and better PAP adherence (Kelly JL, et al. *Respirology.* 2014;19:596). In another small randomized, double-blind, crossover study, done on two consecutive nights in 11 patients with OHS, the use of auto-adjusting EPAP was noninferior to fixed EPAP (10.8 cm vs 11.8 cm H_2O pressure), with no differences in sleep quality and patient preference (McArdle N. *Sleep*. 2017;40:1). Although the data are limited, these small studies suggest the use of new PAP modalities, such as variable PS to deliver target volumes and auto EPAP could offer the potential to initiate bi-level PAP therapy in outpatients without the in-lab titration. More studies are needed before bi-level PAP therapy can be safely initiated in outpatients with OHS.

Summary

How can we utilize the most effective PAP therapy for patients with OHS? Can we use a phenotype-dependent approach to PAP treatment options? The answer is probably yes. Recently published ATS Clinical Practice Guideline (*Am J Respir Crit Care Med.* 2019;200:e6-e24) suggests the use of PAP therapy for stable ambulatory patients with OHS as compared with no PAP therapy, and patients with OHS with AHI >30/h (approximately 70% of the OHS patients) can be initially started on CPAP instead of NIV. Patients who have persistent nocturnal desaturation despite optimum CPAP can be switched to NIV. On the other hand, data are limited on the use of CPAP in patients with OHS with AHI <30/h, and these patients can be started on NIV. PAP adherence >5-6 h, and weight loss using a multidisciplinary approach should be encouraged for all patients with OHS.

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