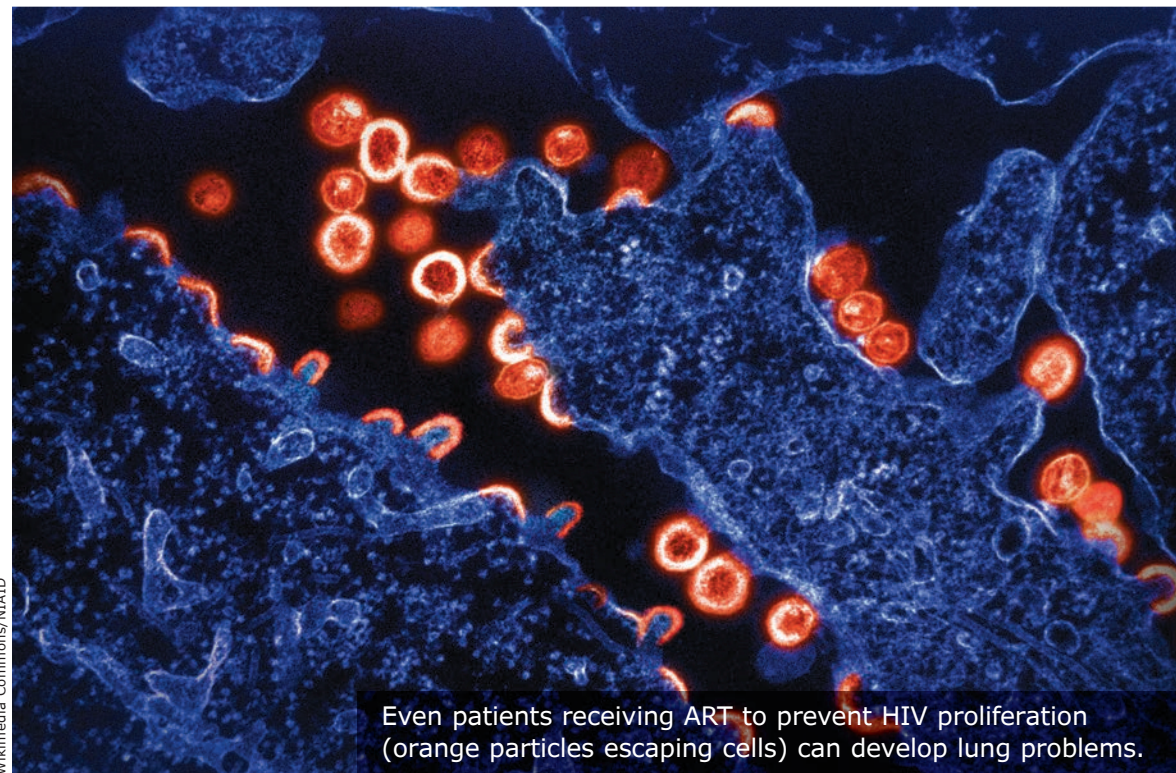


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Even patients receiving ART to prevent HIV proliferation (orange particles escaping cells) can develop lung problems.

The evolving pulmonary landscape in patients with HIV

BY CHRISTINE KILGORE
MDedge News

Chronic pulmonary disease continues to be a major cause of morbidity and mortality in individuals living with the human immunodeficiency virus, even with optimal HIV control. And this is independent, as seen in many studies, of age, smoking, and pulmonary infections.

Both chronic obstructive pulmonary disease (COPD) and lung cancer occur more frequently in people living with HIV than in the general population, and at earlier ages, and with worse outcomes. The risk for emphysema and interstitial lung abnormalities also appears to be higher, research has shown. And asthma has also

recently emerged as another important lung disease in people with HIV (PWH).

"There is evidence that the severity of immunocompromise associated with HIV infection is linked with chronic lung diseases. People who have a lower CD4 cell count or a higher viral load do have an increased risk of COPD and emphysema as well as potentially lung cancer. But [while] immunocompromise plays a role, it isn't the only story, given that even with well-controlled HIV there is increased risk," said Kristina Crothers, MD, professor in the division of pulmonary, critical care, and sleep medicine at the University of Washington, Seattle.

Research has evolved from a focus on the

HIV // continued on page 2

Which drug best reduces sleepiness in patients with OSA?

BY KATE JOHNSON

Solriamfetol, a norepinephrine-dopamine reuptake inhibitor, is probably more effective than other wakefulness-promoting medications in patients with obstructive sleep apnea (OSA) who have residual daytime sleepiness after conventional treatment, according to a systematic review and meta-analysis.

In a systematic review of 14 trials that included more than 3,000 patients, solriamfetol (Sunosi) was associated with improvements of 3.85 points on the Epworth Sleepiness Scale (ESS) score, compared with placebo.

"We found that solriamfetol is almost twice as effective as modafinil-armodafinil – the cheaper, older option – in improving the ESS score and much more effective at improving the Maintenance of Wakefulness Test (MWT)," study author Tyler Pitre, MD, an internal medicine physician at McMaster University, Hamilton, Ont., said in an interview.

The findings were published online in *Annals*

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epidemiology of HIV-related chronic lung diseases to a current emphasis on “trying to understand further the mechanisms [behind the heightened risk] through more benchwork and corollary translational studies, and then to the next level of trying to understand what this means for how we should manage people with HIV who have chronic lung diseases,” Dr. Crothers said. “Should management be tailored for people with HIV infection?”



Dr. Crothers

Impairments in immune pathways, local and systemic inflammation, oxidative stress, dysbiosis, and accelerated cellular senescence are among potential mechanisms, but until ongoing mechanistic research yields more answers, pulmonologists should simply – but importantly – be aware of the increased risk and have a low threshold for investigating respiratory symptoms, she and other experts said in interviews. Referral of eligible patients for lung cancer screening is also a priority, as is smoking cessation, they said.

Notably, while spirometry has been the most commonly studied lung function measure in PWH, another noninvasive measure, diffusing capacity for carbon monoxide (DLCO), has garnered attention in the past decade and thus far appears to be the more frequent lung function abnormality.

In an analysis published in 2020 (AIDS. Jul 1;34[8]:1227-35) from the longitudinal Multicenter AIDS Cohort Study (MACS) – a study of a subcohort of 591 men with HIV and 476 without HIV – those with HIV were found to have a 1.6-fold increased risk of mild DLCO impairment (< 80% of predicted normal) and a 3-fold higher risk of more severe DLCO impairment (< 60% of predicted normal). There was no significant difference in spirometry findings by HIV status.

Such findings on DLCO are worthy of consideration in clinical practice, even in the absence of HIV-specific screening guidelines for noncommunicable lung diseases, Dr. Crothers said. “In thinking about screening and diagnosing chronic lung diseases in these patients, I’d not only consider spirometry, but also diffusing capacity” when possible, she said. Impaired DLCO is seen with emphysema and pulmonary

vascular diseases like pulmonary hypertension and also interstitial lung diseases.

Key chronic lung diseases

Ken M. Kunisaki, MD, MS, associate professor of medicine at the University of Minnesota, Minneapolis, and the first author of the MACS analysis of lung function – one of the most recent and largest reports of DLCO impairment – points out that studies of chest computed



Dr. Kunisaki

tomography (CT) scanning have also documented higher rates of emphysema and interstitial lung abnormalities.

A chest CT scan analysis from a cohort in Denmark (the Copenhagen Comorbidity in HIV Infection [COCOMO] cohort) found interstitial lung abnormalities in 10.9% of more than 700 PWH which represented a 1.8-fold increased risk compared to HIV-negative controls. And a study from an Italian sample of never-smoking PWH and controls reported emphysema in 18% and 4%, respectively. These studies, which did not measure DLCO, are among those discussed in a 2021 review by Dr. Kunisaki (Curr Opin HIV AIDS. May 1;16[3]:156-62) of advances in HIV-associated chronic lung disease research.

COPD is the most commonly encountered chronic lung disease in PWH. “Particularly for COPD, what’s both interesting and unfortunate is that we haven’t really seen any changes in the epidemiology with ART [antiretroviral therapy] – we’re still seeing the same findings, like the association of HIV with



Dr. Morris

worse COPD at younger ages,” said Alison Morris, MD, MS, professor of medicine, immunology, and clinical and translational research at the University of Pittsburgh. “It doesn’t seem to have improved.”

Its prevalence has varied widely from cohort to cohort, from as low as 3% (similar to the general population) to over 40%, Dr. Kunisaki said, emphasizing that many studies,

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including studies showing higher rates, have controlled for current and past smoking. In evaluating patients with low or no smoking burden, “don’t discount respiratory symptoms as possibly reflecting underlying lung disease because COPD can develop with low to no smoking history in those with HIV,” he advised.

A better understanding of how a chronic viral infection like HIV leads to heightened COPD risk will not only help those with HIV, he notes, but also people without HIV who have COPD but have never smoked – a woefully underappreciated and understudied population. Ongoing research, he said, “should help us understand COPD pathogenesis generally.”

Research on asthma is relatively limited thus far, but it does appear that PWH may be more prone to developing severe asthma, just as with COPD, said Dr. Kunisaki, also a staff physician at the Minneapolis Veterans Administration Health Care System. Research has shown, for instance, that people with HIV more frequently needed aggressive respiratory support when hospitalized for asthma exacerbations.

It’s unclear how much of this potentially increased severity is attributable to the biology of HIV’s impact on the body and how much relates to social factors like disparities in income and access to care, Dr. Kunisaki said, noting that the same questions apply to the more frequent COPD exacerbations documented in PWH.

Dr. Crothers points out that, while most studies do not suggest a difference in the incidence of asthma in PWH, “there is some data from researchers looking at asthma profiles [suggesting] that the biomarkers associated with asthma may be different in people with and without HIV,” signaling potentially different molecular or biologic underpinnings of the disease.

Incidence rates of lung cancer in PWH, meanwhile, have declined over the last 2 decades, but lung cancer remains the leading cause of cancer-related mortality in PWH and occurs at a rate that is 2-2.5 times higher than that of individuals not infected with HIV, according to Janice Leung, MD, of the division of respiratory medicine at the University of British Columbia and the Centre for Heart Lung Innovation at St. Paul’s Hospital in Vancouver.

Patients with HIV have “worse outcomes overall and a higher risk of mortality, even when presenting at the same stage,” said Dr. Leung,

who reviewed trends in COPD and lung cancer in a recently published opinion piece (Curr Opin HIV AIDS. 2023 Mar 1;18[2]:93-101).

Potential drivers

A bird’s eye view of potential – and likely interrelated – mechanisms for chronic disease includes chronic immune activation impairing innate and adaptive immune pathways; chronic inflammation systemically and in the lung despite viral sup-



Dr. Leung

pression; persistence of the virus in latent reservoirs in the lung, particularly in alveolar macrophages and T cells; HIV-related proteins contributing to oxidative stress; accelerated cellular aging; dysbiosis; and ongoing injury from inhaled toxins.

All are described in the literature and are being further explored. “It’s likely that multiple pathways are playing a role,” said Dr. Crothers, “and it could be that the balance of one to another leads to different manifestations of disease.”

Biomarkers that have been elevated and associated with different features of chronic lung disease – such as airflow obstruction, low DLCO, and emphysema – include markers of inflammation (e.g., C-reactive protein, interleukin-6), monocyte activation (e.g., soluble CD14), and markers of endothelial dysfunction, she noted in a 2021 commentary marking 40 years since the first reported cases of acquired immunodeficiency syndrome (Am J Physiol Lung Cell Mol Physiol. Dec 1;321[6]:L1059-61).

In her laboratory, Dr. Leung and colleagues are using new epigenetic markers to look at the pathogenesis of accelerated aging in the lung. By profiling bronchial epithelial brushings for DNA methylation and gene expression, they have found that “people living with both HIV and COPD have the fastest epigenetic age acceleration in their airway epithelium,” she said. The findings “suggest that the HIV lung is aging faster.”

They reported their findings in 2022 (Am J Respir Crit Care Med. Jul 15;206:150-60), describing methylation disruptions along age-related pathways such as cellular senescence, longevity regulation, and insulin signaling.

Dr. Leung and her team have also studied the lung microbiome and found lower microbial diversity in

the airway epithelium in patients with HIV than those without, especially in those with HIV and COPD. The National Institutes of Health-sponsored Lung HIV Microbiome Project found that changes in the lung microbiome are most pronounced in patients who haven’t initiated ART, but research in her lab suggests ongoing suppression of microbial diversity even after ART.

Dr. Morris is particularly interested in the oral microbiome, having found through her research that changes in the oral microbiome in PWH were more related to impaired lung function than alterations in the lung and gut microbiome. “That may be in part because of the way we measure things,” she said. “But we also think that the oral microbiome probably seeds the lung [through micro-aspiration].” A study published in 2020 from the Pittsburgh site of the MACS described alterations in oral microbial communities in PWH with abnormal lung function (Am J Respir Crit Care Med. Feb 15;201[4]:445-57).

Preliminary research suggests that improved dental cleaning and periodontal work in PWH and COPD may influence the severity of COPD, she noted.

“Don’t discount respiratory symptoms as possibly reflecting underlying lung disease because COPD can develop with low to no smoking history in those with HIV.”

“We don’t see as much of a signal with the gut microbiome [and HIV status or lung function], though there could still be ways in which gut microbiome influences the lung,” through systemic inflammation, the release of metabolites into the bloodstream, or microbial translocation, for instance, she said.

The potential role of translocation of members of the microbiome, in fact, is an area of active research for Dr. Morris. Members of the microbiome – viruses and fungi in addition to bacteria – “can get into the bloodstream from the mouth, from the lung, from the gut, to stimulate inflammation and worsen lung disease,” she said.

Key research questions

Dr. Kunisaki looks forward to research providing a more longitudinal look at lung function decline – a move beyond a dominance of cross-sectional studies – as well as

research that is more comprehensive, with simultaneous collection of various functional measures (e.g., DLCO with chest imaging and fractional excretion of nitric oxide (FENO – a standardized breath measure of Th2 airway inflammation).

The several-year-old NIH-supported MACS/WIHS (Women’s Interagency HIV Study) Combined Cohort study, in which Dr. Kunisaki and Dr. Morris participate, aims in part to identify biomarkers of increased risk for chronic lung disease and other chronic disorders and to develop strategies for more effective interventions and treatments.

Researchers will also share biospecimens, “which will allow more mechanistic work,” Dr. Kunisaki noted. (The combined cohort study includes participants from the earlier, separate MACS and WIHS studies.)

Questions about treatment strategies include the risks vs. benefits of inhaled corticosteroids, which may increase an already elevated risk of respiratory infections in PWH, Dr. Kunisaki said. Also, inhaled corticosteroids can interact with ART regimens that contain CYP3A4 inhibitors (e.g., ritonavir and cobicistat) and lead to hypercortisolism. In patients needing both types of drugs, beclomethasone has the least interactions and is the preferred inhaled corticosteroid.

For Dr. Crothers, unanswered critical questions include – as she wrote in her 2021 commentary – the question of how guidelines for the management of COPD and asthma should be adapted for PWH. Is COPD in PWH more or less responsive to inhaled corticosteroids, for instance? And are antifibrotic treatments for interstitial lung disease and immunotherapies for asthma or lung cancer similarly effective, and are there any increased risks for harms in people with HIV?

There’s also the question of whether PWH should be screened for lung cancer earlier and with a lower smoking exposure than is advised under current guidelines for the general population, she said in the interview. “And should the approach to shared decision-making be modified for people with HIV?” she said. “We’re doing some work on these questions” right now.

None of the researchers interviewed reported any conflicts. Dr. Kunisaki reported that he has no conflicts, and that his comments are personal views and not official views of the U.S. Government, Department of Veterans Affairs, the Minneapolis VA, or the University of Minnesota. ■

of Internal Medicine (2023. doi: 10.7326/M22-3473).

High-certainty evidence

The analysis included 3,085 adults with excessive daytime sleepiness (EDS) who were receiving or were eligible for conventional OSA treatment such as positive airway pressure. Participants were randomly assigned to either placebo or any EDS pharmacotherapy (armodafinil, modafinil, solriamfetol, or pitolisant). The primary outcomes of the analysis were change in ESS and MWT. Secondary outcomes were drug-related adverse events.

The trials had a median follow-up time of 4 weeks. The meta-analysis showed that solriamfetol improves ESS to a greater extent than placebo (high certainty), armodafinil-modafinil and pitolisant (moderate certainty). Compared with placebo, the mean difference in ESS scores for solriamfetol, armodafinil-modafinil, and pitolisant was -3.85 , -2.25 , and -2.78 , respectively.

The analysis yielded high-certainty evidence that solriamfetol and armodafinil-modafinil improved MWT, compared with placebo. The former was “probably superior,” while pitolisant “may have little to no effect on MWT, compared with placebo,” write the authors. The standardized mean difference in MWT scores, compared with placebo, was 0.90 for solriamfetol and 0.41 for armodafinil-modafinil. “Solriamfetol is probably superior to armodafinil-modafinil in improving MWT (SMD, 0.49),” say the authors.

Compared with placebo, armodafinil-modafinil probably increases the risk for discontinuation due to adverse events (relative risk, 2.01), and solriamfetol may increase the risk for discontinuation (RR, 2.04), according to the authors. Pitolisant “may have little to no effect on drug discontinuations due to adverse events,” write the authors.

Although solriamfetol may have led to more discontinuations than armodafinil-modafinil, “we did not find convincing evidence of serious adverse events, albeit with very short-term follow-up,” they add.

The most common side effects for all interventions were headaches, insomnia, and anxiety. Headaches were most likely with armodafinil-modafinil (RR, 1.87), and insomnia was most likely with pitolisant (RR, 7.25).

“Although solriamfetol appears most effective, comorbid hypertension and costs may be barriers to its use,” say the researchers. “Furthermore, there are potentially effective candidate therapies such as methylphenidate, atomoxetine, or caffeine, which have not been examined in randomized clinical trials.”

Although EDS is reported in 40%-58% of patients with OSA and can persist in 6%-18% despite PAP therapy, most non-sleep specialists may not be aware of pharmacologic options, said Dr. Pitre. “I have not seen a study that looks at the prescribing habits of physicians for this condition, but I suspect that primary care physicians are not prescribing modafinil-armodafinil frequently for this and less so for solriamfetol,” he said. “I hope this paper builds awareness of

Saiprakash Venkateshiah, MD, FCCP, comments:

This is an interesting systematic review of 14 trials that included more than 3000 patients comparing the efficacy of wakefulness-promoting medications in patients with obstructive sleep apnea who have residual daytime sleepiness after treatment. Solriamfetol was superior to modafinil-armodafinil and pitolisant in improving the Epworth Sleepiness Scale. Solriamfetol was probably superior to modafinil-armodafinil in improving Maintenance of Wakefulness Test. However, solriamfetol increased the risk for discontinuation of therapy due to adverse events.

The prevalence of residual sleepiness after adequate treatment of OSA is 6% to 14% as described in the literature. It is good to have some comparison data available with both subjective and objective measures for the available wakefulness promoting medications used to treat excessive sleepiness in patients with OSA. Of note, pitolisant currently does not have an FDA indication to treat sleepiness in OSA.

It is important to consider that there are certain limitations to the study - the follow-up was limited to 4 weeks, and it is unknown if the effectiveness of this therapy is maintained long-term. Only 11 of the 14 trials required adherence to conventional OSA therapy (PAP, mandibular devices). It is unclear if this impacted the magnitude of the response observed.

A careful clinical evaluation is imperative before we consider initiating wakefulness-promoting medications in these patients



Clinicians have to ensure that patients with OSA are adherent to their treatment (positive airway pressure or mandibular advancement device) and demonstrate adequacy of therapy which occasionally may require a sleep study with the recommended therapy, and alternative causes of excessive sleepiness such as insufficient sleep, depression, side effects from their other medications and comorbid medical and psychiatric conditions are excluded. The adverse events associated with these medications such as headaches, insomnia, and

anxiety may lead to discontinuation of therapy. Moreover, higher dose of solriamfetol is associated with hypertension, which can be particularly problematic in obstructive sleep apnea patients who already may be suffering from hypertension and are at higher risk of cardiovascular sequelae.

Some OSA patients who have excessive sleepiness may start using less or completely stop their recommended CPAP or oral appliance therapy once they find relief of sleepiness with these medications, which can be problematic as these drugs do not treat OSA. These medications are expensive and that should be factored in the clinical decision-making. After assessing the risks and benefits, a shared decision making with the patient is necessary before starting these wakefulness-promoting medications for long-term use in OSA patients with residual sleepiness.

Dr. Venkateshiah is a member of the CHEST Physician Editorial Board.

this condition and also informs clinicians on the options available to patients, as well as common side effects to counsel them on before starting treatment.”

Dr. Pitre was surprised at the magnitude of solriamfetol’s superiority to modafinil-armodafinil but cautioned that solriamfetol has been shown to increase blood pressure in higher doses. It therefore must be prescribed carefully, “especially to a population of patients who often have comorbid hypertension,” he said.

Some limitations of the analysis were that all trials were conducted in high-income countries (most commonly the United States). Moreover, 77% of participants were White, and 71% were male.

Beneficial adjunctive therapy

Commenting on the findings, Sogol Javaheri, MD, MPH, who was not involved in the research, said that they confirm those of prior studies and are “consistent with what my colleagues and I experience in our clinical practices.”

Dr. Javaheri is associate program director of the sleep medicine fellowship at Brigham and Women’s Hospital and assistant professor of medicine at Harvard Medical School, both in Boston.

While sleep medicine specialists are more likely than others to prescribe these medications, “any clinician may use these medications, ideally if they have ruled out other potential reversible causes of EDS,” said Dr. Javaheri. “The medications do not treat the underlying cause, which is why it’s important to use them as an adjunct to conventional therapy that actually treats the underlying sleep disorder and to rule out additional potential causes of sleepiness that are treatable.”

These potential causes might include insufficient sleep (less than 7 hours per night), untreated anemia, and incompletely treated sleep disorders, she explained. In sleep medicine, modafinil is usually the treatment of choice because of its lower cost, but it may reduce the efficacy of hormonal contraception. Solriamfetol, however, does not. “Additionally, I look forward to validation of pitolisant for treatment of EDS in OSA patients, as it is not a controlled substance and may benefit patients with a history of substance abuse or who may be at higher risk of addiction,” said Dr. Javaheri.

The study was conducted without outside funding. Dr. Pitre and Dr. Javaheri report no relevant financial relationships. ■



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COMMENTARY

Should antibiotic treatment be used toward the end of life?

BY MIRKO RIOLFI

Around 50% of patients develop an infection in the final months, weeks, or days before their deaths. Diagnosing an infection is complex because of the presence of symptoms that are often nonspecific and that are common in patients in decline toward the end of life.

Use of antibiotic therapy in this patient population is still controversial, because the clinical benefits are not clear and the risk of pointless overmedicalization is very high.

Etiology

For patients who are receiving palliative care, the following factors predispose to an infection:

- Increasing fragility.
- Bedbound status and anorexia/cachexia syndrome.
- Weakened immune defenses owing to disease or treatments.
- Changes to skin integrity, related to venous access sites and/or bladder catheterization.

Four-week cutoff

For patients who are expected to live for fewer than 4 weeks, evidence from the literature shows that antimicrobial therapy does not resolve a potential infection or improve the prognosis. Antibiotics should therefore be used only for improving symptom management.

In practice, the most common infections in patients receiving end-of-life care are in the urinary and respiratory tracts.

Antibiotics are beneficial in the short term in managing symptoms associated with urinary tract infections (effective in 60%-92% of cases), so they should be considered if the patient is not in the agonal or pre-agonal phase of death.

Antibiotics are also beneficial in managing symptoms associated with respiratory tract infections (effective in up to 53% of cases), so they should be considered if the patient is not in the agonal or pre-agonal phase of death.

However, the risk of futility is high. As an alternative, opioids and antitussives could provide greater benefit for patients with dyspnea and cough.

No benefit to patients has been observed with the use of antibiotics to treat symptoms associated with sepsis, abscesses, and deep and complicated infections. Antibiotics are therefore deemed futile in these cases.

In any unclear cases, the “2-day rule” has proved useful. This rule involves waiting for 2 days, and if the patient remains clinically stable, then prescribing antibiotics is appropriate. If the patient’s condition deteriorates rapidly and progressively, the use of antibiotics should not be prescribed.

Alternatively, one can prescribe antibiotics immediately. If no clinical improvement is observed after 2 days, the antibiotics should be stopped, especially if deterioration of the patient’s condition is rapid and progressive.

Increased body temperature is somewhat common in the last days and hours of life and is not generally associated with symptoms. Fever in these cases is not considered an indication for the use of antimicrobial therapy.

The most common laboratory markers of infection (C-reactive protein level, erythrocyte sedimentation rate, leukocyte level) are not particularly useful in this patient population, because they are affected by the baseline condition as well as by any treatments given and the state of systemic inflammation, which is associated with the decline in overall health in the last few weeks of life.

The choice should be individualized and shared with patients and family members so that the clinical appropriateness of the therapeutic strategy is evident and that decisions regarding antibiotic treatment are not regarded as a failure to treat the patient.

The longer term

In deciding to start antibiotic therapy, consideration must be given to the patient’s overall health, the treatment objectives, the possibility that the antibiotic will resolve the infection or improve the patient’s symptoms, and the estimated prognosis, which must be sufficiently long to allow the antibiotic time to take effect. ■

Antibiotics for acute exacerbation of COPD: It's still controversial

BY AARON B. HOLLEY, MD, FCCP

In late 2021, the Rome Proposal for diagnosing acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and grading their severity was published. The 2023 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (GOLD) Report has adopted the Rome Proposal criteria. Given that an endorsement by GOLD is tantamount to acceptance by clinicians, researchers, and policymakers alike, I guess we're all using them now.

Anyone who's ever cared for patients with COPD knows that treatment and reduction of exacerbations is how we improve outcomes. AECOPD are associated with considerable morbidity, greater health care utilization and costs, and a long-term decline in lung function. While we hope our pharmacotherapies improve symptoms, we know they reduce AECOPD. If our pharmacotherapies have any impact on mortality, it's probably via AECOPD prevention.

Methods for reducing AECOPD are not controversial, but the approach to AECOPD treatment is, particularly decisions about who gets an antibiotic and who doesn't. Since antibiotic indications are tied to severity, using the Rome Proposal criteria may affect management in unpredictable ways. As such, it's worth reviewing the data on antibiotics for AECOPD.

What do the data reveal?

To start, it's important to note that GOLD doesn't equate having an AECOPD with needing an antibiotic. I myself have conflated the diagnosis with the indication and thereby overprescribed. The bar for diagnosis is quite low. In previous

GOLD summaries, any "change in respiratory symptoms" would warrant the AECOPD label. Although the Rome Proposal definition is more specific, it leaves room for liberal interpretation. It's likely to have a greater effect on research than on clinical practice. My guess is that AECOPD prevalence doesn't change.

The antibiotic hurdle is slightly higher than that for diagnosis but is equally open to interpretation. In part, that's related to the inherent subjectivity of judging symptoms, sputum production, and changes in color, but it's also because the data are so poor. The meta-analyses that have been used to establish the indications include fewer than 1,000 patients spread across 10 to 11 trials. Thus, the individual trials are small, and the sample size remains nominal even after adding them together. The addition of antibiotics – and it doesn't seem to matter which class, type, or duration – will decrease mortality and hospital length of stay. One study says these effects are limited to inpatients while the other does not. After reading GOLD 2013, GOLD 2023, and both the meta-analyses used to support the recommendations, I'm still not sure who benefits. Do you have to be hospitalized? Is some sort of ventilatory support required? Does C-reactive protein help or not?

In accordance with the classic Anthonisen criteria, GOLD relies on sputum volume and color as evidence of a bacterial infection. Soon after GOLD 2023 was published, a meta-analysis found that sputum color isn't particularly accurate for detecting bacterial infection. Because it doesn't seem to matter which antibiotic class is used, I always thought we were using antibiotics for their magical, pleiotropic anti-inflammatory effects anyway. I didn't think the presence of an actual



Dr. Holley is a professor of medicine at Uniformed Services University in Bethesda, Md., and a pulmonary/sleep and critical care medicine physician at MedStar Washington Hospital Center in Washington. He reported conflicts of interest involving Metapharm, CHEST, and WebMD.

bacterial infection was important. If I saw an infiltrate on chest x-ray, I'd change my diagnosis from AECOPD to community-acquired pneumonia (CAP) and switch to CAP coverage. I've been doing this so long that I swear it's in a guideline somewhere, though admittedly I couldn't find said guideline while reading for this piece.

Key takeaways

In summary, I believe that the guidance reflects the data, which is muddy. The Rome Proposal should be seen as just that – a framework for moving forward with AECOPD classification and antibiotic indications that will need to be refined over time as better data become available. In fact, they allow for a more objective, point-of-care assessment of severity that can be validated and tied to antibiotic benefits. The Rome criteria aren't evidence-based; they're a necessary first step toward creating the evidence.

In the meantime, if your AECOPD patients are hospitalized, they probably warrant an antibiotic. If they're not, sputum changes may be a reasonable surrogate for a bacterial infection. Considerable uncertainty remains. ■

Endobronchial valves: Sustained emphysema improvement

BY HEIDI SPLETE

WASHINGTON – Patients with emphysema treated with one-way endobronchial valves showed consistent improvement in lung function after 5 years compared with controls, based on data from 174 individuals.

One-way endobronchial valves demonstrated benefits for patients with severe emphysema over a 12-month period in the EMPROVE trial, according to Gerard J. Criner, MD, of Temple University, Philadelphia, and colleagues. Five-year results from the EMPROVE study were presented in a poster session at the American Thoracic Society's international conference.

The initial EMPROVE trial demonstrated safety and efficacy of

the Spiration Valve System (SVS) over 12 months. However, data on the long-term benefits of one-way endobronchial valves are limited, the researchers wrote.

The valve was designed for use in selected areas of the bronchial airways and features a flexible umbrella that allows air and mucus to clear from treated airways while blocking inspired air flow to areas of the lungs affected by disease, the researchers explained in the poster.

Dr. Criner and colleagues assessed 172 patients randomly assigned to treatment with a one-way valve system (113 patients) or a control group (59 patients). Participants were evaluated at 1, 3, 6, and 12 months, then annually for 5 years.

The primary efficacy outcome was lung function, measured by

forced expiratory volume per second (FEV₁). At five years, the FEV₁ values improved by 0.1098 liters in the treatment group ($P < .001$). Treated patients and controls experienced decreased FEV₁ at a rate of 0.0440 liters per year from baseline, a significant difference ($P < .001$). Assuming a steady rate of disease progression, "the treatment group gained approximately 2.5 years of FEV₁ improvement immediately following SVS treatment, which was maintained, compared to controls," the researchers noted in their abstract.

Overall, 210 SAEs occurred in the treatment group and 35 occurred in controls, for rates of 0.60 and 0.48, respectively ($P = .201$). The most common SAEs in the treatment and control groups were COPD exacerbations, pneumothorax, and death.

The results suggest that the FEV₁ improvements seen in patients with severe emphysema after one-way endobronchial valve placement compared with usual care are enduring after 5 years, with no significant changes in safety, the researchers concluded.

The original EMPROVE study was supported by Olympus Respiratory America, the developer of the Spiration Valve System. The study was published in the American Journal of Respiratory and Critical Care Medicine (2019;200:1354-62). Dr. Criner is associate editor of the American Journal of Respiratory and Critical Care Medicine. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works. ■

NETWORKS

Transitioning from pediatric to adult care; Challenges in treating IPF; RAPID updates in pleural infection, and more ...

AIRWAYS DISORDERS NETWORK Pediatric Chest Medicine Section

Transitioning from pediatric to adult care

For young adults with chronic health conditions, the process of transitioning to adult health care is complicated, resulting in frustration for patients and families, and clinicians, as well as increased morbidity and mortality (Varty et al. *J Pediatr Nurs.* 2020;55:201). As such, there have been efforts to determine practices that can minimize risk and improve satisfaction with the transition process.

The National Alliance to Advance Adolescent Health developed the “Got Transition” program with input from pediatric and adult clinicians, as well as patient advocates (White, et al. *Six Core Elements of Health Care Transition™ 3.0.* Washington, DC: Got Transition, The National Alliance to Advance Adolescent Health, July 2020.) CF R.I.S.E is a similar program aimed specifically at improving the transition to adult care among patients with cystic fibrosis (www.cfrise.com). Got Transition provides the following recommendations pertinent to both pediatric and adult providers.

Pediatric clinics should start to assess transition readiness in early adolescence, and provide training pertinent to any skill gaps identified. This may include knowledge about condition-specific self-care skills, as well as navigation of the health care system. An individualized plan can then be developed, including timing of transition and identification of an appropriate adult provider.

The transfer should include communication between the pediatric and adult care providers prior to and, if needed, after the patient’s first appointment with the adult provider. Adult clinics can enhance the transition process by establishing a method to welcome

transitioning young adult patients and orient them to the practice, addressing patient concerns regarding the transition, and assessing the patients’ self-management skills with resources provided, as needed.

Both pediatric and adult providers have a role in helping patients transition safely and smoothly from pediatric to adult care.

Sarah Cohen, MD
Section Fellow-in-Training

DIFFUSE LUNG DISEASE & LUNG TRANSPLANT NETWORK Interstitial Lung Disease Section

Challenges in developing effective treatments for idiopathic pulmonary fibrosis: Lessons from the ISABELA trials

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease that affects an estimated 100,000 people in the United States alone. Despite the availability of two approved antifibrotic drugs, nintedanib and pirfenidone, there is still a need for effective treatments to improve patient outcomes.

The ISABELA 1 and 2 trials were two Phase III clinical trials designed to evaluate ziritaxestat, a novel autotaxin inhibitor, in patients with IPF. Unfortunately, both trials were terminated early after an interim analysis revealed a lack of efficacy and safety concerns. Specifically, neither dose of ziritaxestat showed any benefit on the rate of decline for FVC over 52 weeks. Moreover, the treatment with ziritaxestat showed no benefit on the reported secondary outcomes. Patients in the ziritaxestat groups experienced worse outcomes in terms of time to first respiratory-related hospitalization, respiratory-related mortality, and first acute IPF exacerbation. Pooled data for both trials showed higher all-cause mortality for the ziritaxestat groups in relation to placebo (Maher T, et al. *JAMA.* 2023;329[18]:1567).

These disappointing results highlight the challenges of developing effective treatments for IPF. The complexity of IPF as a disease, with multiple pathways contributing to its pathogenesis, makes it difficult to

identify effective therapeutic targets. In addition, clinical trials for new treatments must also account for the availability of approved antifibrotic therapies, which creates an added challenge for clinical trial design.

Matthew Huang, MD
Section Fellow-in-Training
Brad Bemiss, MD
Section Member-at-Large

SLEEP MEDICINE NETWORK Home-Based Mechanical Ventilation & Neuromuscular Disease Section

Noninvasive mechanical ventilation in unilateral diaphragm paralysis

The diaphragm plays a key role in respiratory mechanics, particularly during the inspiratory cycle. Unilateral diaphragm paralysis (UDP) from traumatic, compressive, inflammatory, neuropathic, or iatrogenic phrenic nerve injury presents with exertional dyspnea or orthopnea, though more severe cases may present with hypoventilation, hypercapnia, and daytime fatigue. Diagnostic workup requires evaluation beyond radiography to determine if diaphragm elevation indicates paralysis with or without paradox. Severity of symptoms and degree of impairment do not consistently correlate with fluoroscopic/ultrasound findings during sniff maneuver, degree of restriction by spirometry, or supine forces. Compensatory accessory muscle use during daytime breathing can mask symptoms, and there can be severe nocturnal hypoventilation related to UDP.

For symptomatic patients,

treatment recommendations require understanding of the etiology and the likelihood of resolution vs progression, or association with progressive systemic conditions. Nighttime noninvasive ventilation (NIV) is considered useful since diaphragmatic weakness worsens in supine position, and hypoventilation during REM sleep without accessory muscle support is exacerbated (Steier J, et al. *Eur Respir J.* 2008;32[6]:1479). However, evidence for NIV in UDP remains low quality. NIV has been proposed for ventilatory support particularly when hypercapnia is present (Wiebel M, et al. *Med Klin.* 1995;90[1 Suppl 1]:20). For patients with progressive neuromuscular conditions, NIV with a backup rate is strongly recommended (Steindor M, et al. *Respir Care.* 2021;66[3]:410; Benditt JO. *Respir Care.* 2019;64[6]:679), but access to respiratory assist devices is limited for isolated UDP under current reimbursement algorithms without demonstrable hypercapnia or significant restrictive spirometry. The recent ONMAP recommendations calling for use of symptom severity to support initiating NIV if FVC>80% have not yet been adopted (Morgenthaler TI, et al. *Chest.* 2021;160[5]:e419). Without marked spirometric restriction or hypercapnia, most patients must fail conservative PAP therapy prior to escalation to NIV, and initiation of a backup rate remains debated. Nevertheless, the only large case series evaluating the predominant features of polysomnography in UDP suggests high incidence of central apneas, suggesting a backup rate may indeed be required independent of the need to support neuromuscular function (Singh M, et al. 2021;68[7]:1064). Further assessment of the features, needs, and understanding of the natural trajectory is essential to guide approach to sleep-related hypoventilation in UDP.

Landy V. Luna Diaz
Section Fellow-in-Training
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Dr. Cohen



Dr. Luna Diaz



Dr. Lussier

SLEEP STRATEGIES

CPAP for OSA: What is the verdict?

BY LAUREN TOBIAS, MD, FCCP, AND
VESNA BUNTAK, MD

Obststructive sleep apnea (OSA) affects roughly 1 billion people worldwide, according to a report by the American Academy of Sleep Medicine. Severe OSA has been associated with an elevated risk of all-cause and cardiovascular-specific mortality. Studies support an association between OSA and a host of comorbidities, including hypertension, stroke, atrial fibrillation, mood disorders, and neurocognitive outcomes. Undiagnosed and untreated OSA also has major economic and societal costs, reducing workplace productivity and increasing one's risk of accidents both on the job and while driving.

Positive airway pressure (PAP) is widely considered the most effective treatment for OSA. The majority of patients tolerate CPAP: real-world estimates using international big data show good adherence in over 70% of patients. Robust evidence shows that PAP reduces snoring, decreases daytime sleepiness, and improves quality of life in a dose-dependent manner. Economic analyses have also found CPAP to be cost-effective (Streatfeild, et al. *Sleep*. 2019;42[12]:zsz181).

But what do we know about the impact of PAP on health outcomes? Perhaps the best studied outcome is cardiovascular disease. Results of observational trials have suggested that CPAP adherence was associated with survival (Pepin JL et al. *Chest*. 2022;161[6]:1657). However, it has been speculated that these findings may have been driven, at least in part, by the “healthy user effect.” This phenomenon refers to the tendency for people who engage in one health-promoting behavior (eg, CPAP adherence) to engage in another as well (eg, eating well, exercising, taking prescribed medications). When we observe that patients who use CPAP live longer, we must ask ourselves whether perhaps their better outcomes resulted from healthy habits in general, as opposed to their CPAP usage per se.

Randomization eliminates the potential for

the healthy user effect, by assigning patients to a certain intervention as opposed to simply observing whether they choose to use it. And herein lies one of the great disappointments for our field over the past decade: multiple large-scale randomized controlled trials have failed to demonstrate that CPAP reduces cardiovascular mortality, even in patients with pre-existing CAD. The first two of these were the SAVE (Sleep Apnea Cardiovascular Endpoints) (McEvoy R, et al. *N Engl J Med*. 2016;375[10]:919) and RIC-CADSA (Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA) (Peker Y, et al. *Am J Respir Crit Care Med*. 2016;194[5]:613) trials evaluating the effects of PAP on a composite endpoint that included cardiovascular death and nonfatal cardiovascular events. Both trials found no difference between PAP and control groups, leading to a conclusion that PAP did not prevent cardiovascular events in patients with moderate-to-severe OSA and established cardiovascular disease. The ISAAC study (Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome) also failed to show a benefit of CPAP for secondary prevention of cardiovascular events in patients with moderate to severe OSA.

These negative findings were echoed in a recent report by the Agency for Healthcare Research and Quality evaluating a variety of long-term health outcomes in obstructive sleep apnea. The authors stated that “RCTs do not provide evidence that CPAP prescription affects long-term, clinically important outcomes. Specifically, with low strength of evidence, RCTs do not demonstrate that CPAP affects all-cause mortality, various CV outcomes, clinically important changes in psychosocial measures, or other clinical events” (AHRQ, Project ID: SLPT0919, 12/1/2022).

What plausible explanations have been offered for these negative results? Perhaps trials were underpowered. Perhaps patients did not use PAP for a sufficient duration to achieve benefit (usage was under 3 hours in most studies). Perhaps the patients selected for these trials were



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at such low-risk of adverse outcomes in the first place that treating their OSA didn't have much impact. Many trials have excluded sleepy patients due to ethical concerns about withholding treatment from this population. But this may have effectively excluded the patients most likely to benefit; in other studies, sleepy patients seem to experience the greatest cardiovascular risk reduction with CPAP. For example, a meta-analysis showed that CPAP is most strongly associated with blood pressure reduction in patients who are sleepy, compared with those with minimally symptomatic OSA (Bratton D, et al. *Thorax*. 2014;69[12]:1128). And, recent work suggests that even among non-sleepy patients, it might be possible to identify a subset who could benefit from CPAP. A recent analysis suggested that non-sleepy patients who exhibit a higher change in heart rate following a respiratory event may derive greater cardiovascular benefit from CPAP therapy (Azarbarzin, et al. *Am J Respir Crit Care Med*. 2022;206[6]:767).

Another, distinct reason for these negative results is that the AHI – our main metric for

CPAP continued on following page

NETWORKS continued from previous page

THORACIC ONCOLOGY & CHEST IMAGING NETWORK Interventional Procedures Section RAPID updates in pleural infection

The MIST-2 trial (Rahman, et al. *N Engl J Med*. 2011;365:518), the first randomized trial to show the benefit of intrapleural enzyme therapy (IET) with tissue plasminogen activator and deoxyribonuclease for the treatment of complicated pleural infection (cPI) is the foundational study for the use of IET. It was from this cohort that the first prospectively validated mortality prediction

score for cPI was developed – the RAPID score (Rahman, et al. *Chest*. 2014;145[4]:848).

The RAPID score, comprised of Renal, Age, Purulence, Infection source, and Dietary factors (albumin) divides patients with cPI into three 3-month mortality groups: low (1.5%), medium (17.8%), and high (47.8%). The score was externally validated in the PILOT trial (Corcoran, et al. *Eur Respir J*. 2020;56[5]:2000130). Mortality outcomes were separately assessed in 1-, 3-, and 5-year follow-up by White, et al (*Ann Am Thorac Soc*. 2015;12[9]:1310) and found to bear out with an increased OR

for mortality of 14.3 and 53.3 in the medium and high risk groups, respectively. Of note, there was a surgical referral rate of only 4% to 16% in the study cohort, and the original study did not distinguish between IET use or surgery.

To look at RAPID in a purely surgical cohort, Stüben, et al (*Sci Rep*. 2023;13[1]:3206) applied the RAPID score to a cohort of patients with empyema all treated with initial surgical drainage. They found the RAPID score to be an accurate predictor of 90-day mortality and improved with the addition of diabetes and renal replacement therapy. Liou, et al (*J Thorac*

Dis. 2023;15[3]:985) showed that patients with a low RAPID score who were taken to surgery early had improved length of stay and organ failure and mortality rates compared with those taken later.

Can the RAPID score differentiate between those who need IET alone, early surgery, or late surgery? Not yet, but several prospective studies are underway to help improve outcomes in this ancient disease. Until then, the RAPID score remains a useful risk-stratification tool for an increasingly broad population of patients with pleural infection.

Max Diddams, MD
Section Fellow-in-Training

CPAP continued from previous page

quantifying OSA severity for several decades – fails to capture the disorder’s heterogeneity. Identifying different phenotypes of OSA may enable more personalized approaches to prognostication as well as treatment. For example, one study identified four symptom clusters of OSA – patients with disturbed sleep, minimally symptomatic, excessively sleepy, and moderately sleepy – who may exhibit different responses to CPAP treatment. Further work is needed to discern whether these clusters reliably predict outcomes in a manner that can be useful clinically (Zinchuk A, et al. *Sleep Med Rev.* 2017;35:113).

So, what is the verdict for CPAP? Sleepy patients with even mild OSA warrant treatment, as is common practice, and these patients are more likely to adhere to therapy. Patients with other symptoms potentially related to untreated OSA should be offered treatment as well. But in asymptomatic patients, it is difficult to make a compelling case to start CPAP on the basis of the AHI alone. It is our hope that novel ways of classifying OSA severity and phenotype will allow better prediction of which patients will experience a protective effect from CPAP. For example, certain subsets of patients may realize greater benefits from CPAP, including those with a high hypoxic burden (Trzepizur W, et al. *Am J Respir Crit Care Med.* 2022;205[1]:108).

For now though, we can allow the evidence that has accumulated in recent years to guide our collaborative decision-making with patients about whether to try CPAP. Depending on how

exuberantly we sang CPAP’s praises, we may need to temper our song – at least with regards to cardiovascular risk reduction. In the sleep world, patients are educated not only by sleep providers but also by respiratory therapists who help patients with initial CPAP setups. Consistent, evidence-based messaging by the entire health care team is key. We cannot say that “using CPAP prevents heart attacks” but rather “we’re still not quite sure.”

Sleepy patients with even mild OSA warrant treatment, as is common practice, and these patients are more likely to adhere to therapy. Patients with other symptoms potentially related to untreated OSA should be offered treatment as well.

As in other areas of medicine, sleep medicine may see a shift in focus toward symptoms and patient-oriented outcomes as opposed to the presence of comorbidities. In fact, the recently revised International Classification of Sleep Disorders (ICSD-3-TR) released this year eliminated comorbidity criteria from the definition of Obstructive Sleep Apnea in adults. If adopted by Centers for Medicare & Medicaid Services and other insurers, patients with mild OSA by sleep testing (AHI \geq 5 but <15) who lack symptoms will no longer qualify for CPAP on the basis of having hypertension, a mood disorder, cognitive

dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus. How will this major revision impact the sleep medicine world? Practically speaking, it is likely that fewer patients who present without symptoms and are found to have only mild OSA will end up on PAP.

There will undoubtedly be frustration related to these greater restrictions on who qualifies for PAP. On the other hand, perhaps our energy is better focused on procuring PAP not for asymptomatic patients but rather promoting access and adherence in those who are symptomatic. Differential access to CPAP remains a major problem that very likely contributes to health disparities. In fact, a recent international committee acknowledged that the current CMS criteria for PAP coverage create disproportionate difficulties for non-white patients and those of low socioeconomic background to meet adherence criteria. Their specific recommendations to reduce this disparity in PAP access included eradication of requirements for repeat polysomnography and eliminating the 4-hour rule.

We are moving toward a more personalized approach to characterizing OSA, which eventually may allow for more nuanced, individualized counseling rather than a “one-size-called-CPAP-fits-all” approach. Until we are there, a patient-centered approach that elicits the presence of sleep-related symptoms and daytime impairment, as opposed to isolated comorbidities, provides the most compelling justification for CPAP. ■

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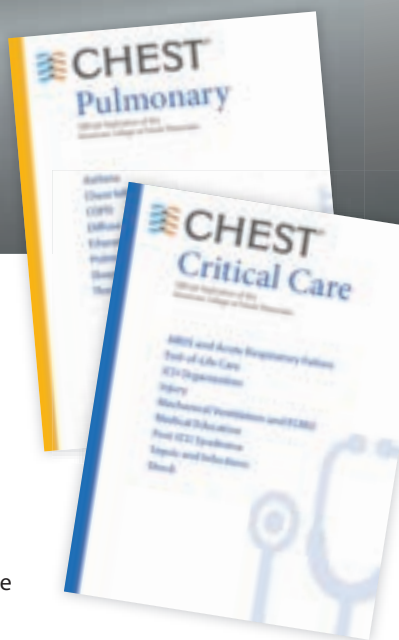
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FROM THE PRESIDENT

Take this chance to be a mentor at CHEST 2023

When we celebrated Women's History Month in March, Drs. Carolyn D'Ambrosio, Aneesa Das, and I discussed our experiences as women in chest medicine and why connecting is so important. We touched on the critical role of mentors. This conversation prompted me to dedicate this President's column to the value of mentorship. The conversation is available on the CHEST YouTube for viewing.

Pursuing a career in medicine is not something you do on your own, and I have been fortunate to have had a strong support system. I think many of us who have been successful and fulfilled in our careers can say we were blessed by having great mentors along the way.

I have been blessed in having mentors who were both within my institution and outside, but one

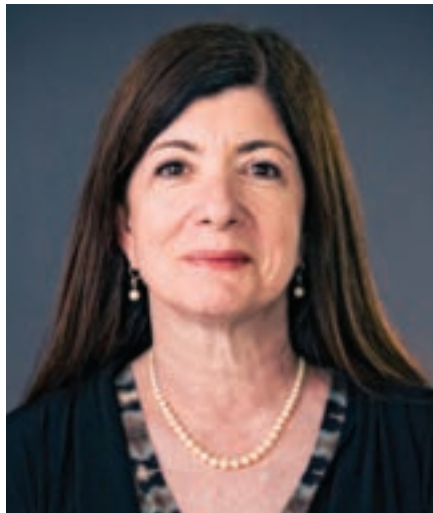
Before the upcoming annual meeting, consider who among your newer colleagues could benefit from having a mentor. Take the time to tell them you are there to support their development.

of the most important places that I found mentors was through my involvement with CHEST. It is critically important to find a mentor or mentors who can guide you through the initial phases of your career. It is also very important to allow yourself time to be a mentor to those who need you.

To the junior faculty or trainees who have yet to connect with someone to provide guidance, I cannot stress enough the importance of getting involved in an organization like CHEST.

The best way to begin is to attend the annual meeting. Know that you are invited to approach any member of CHEST leadership, introduce yourself, and tell us that you want to get involved. (Conveniently, registration for CHEST 2023 in Hawaii just opened.)

I genuinely believe our community would say yes to anyone



Dr. Addrizzo-Harris

looking for guidance.

To my colleagues who are established in their careers, I am issuing a personal request (and a bit of a challenge). Before the upcoming annual meeting, consider who among your newer colleagues could benefit from having a mentor.

Take the time to tell them that you are there to support their development. Making that connection could mean re-establishing a relationship that got off track and that you want to re-engage.

Show how the commitment to mentorship matters by sharing a post (with a picture, if possible) on social media. Tag your post using the hashtags #CHESTMentee and #CHEST2023 to introduce them to your network. This type of exposure and support can have a lasting impact.

While attending CHEST 2023 – ideally with your mentee – be sure to add the mentoring ribbons to your badge. We will be heavily socializing these ribbons, sharing that anyone wearing the “I’m a mentor” ribbon is either open to accepting new mentees or will help facilitate a conversation that may lead to mentorship.

Beyond its incredible education opportunities, the CHEST Annual Meeting is well-known for being a welcoming environment. It's up to us to take the extra steps to help earlier-career clinicians succeed by providing the best possible education and guidance for years to come.

Until next time,

Doreen J. Addrizzo-Harris, MD, FCCP



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CHEST journal CME program designed to reinforce key points in research

If you're a regular reader of the journal *CHEST*, you may have noticed an exciting new initiative for clinicians looking to enhance their understanding of the latest advances in research, improve their clinical knowledge, and earn credits toward certification: the opportunity to earn continuing medical education (CME) credits from monthly journal issues. Launched in late 2022, this new initiative was inspired by the desire to complement the excellent clinical work already being done by readers of the journal.



Dr. Morris

"Essentially, the idea was that *CHEST* journal readers are doing the work to keep themselves current and stay excellent doctors, and they should get credit for that work," said Amy Morris, MD, FCCP, Chair of the *CHEST* Journal CME Editorial Board. "We all have to do CME, so why not get some credit for the reading that we do on a regular basis to stay current, and add some additional value for journal readers?"

But the initiative isn't just an opportunity to offer free credits. The

goal of the CME Editorial Board is to create greater awareness of important research and offer readers regular opportunities to improve their knowledge in a wide variety of specialties and clinical areas.

"We try to rotate topics month to month, but more than that, we look

"We couldn't do this without a dedicated team and a lot of volunteer time from individuals who really care about education and clinical practice, and making the literature relevant to clinical practice."

for articles that either have a broad impact on current clinical practice for a lot of providers, or convey some particular new interest – a way for our readers to learn about something new and interesting," she said. "We avoid trivia, essentially "gotcha" questions that simply ensure you read the article, but rather focus on questions that reinforce key points in the article."

To ensure the content covers a wide breadth of topics, the CME Editorial Board – comprising leaders from pulmonary, critical care, and sleep medicine to ensure the process meets a high clinical

standard – reviews articles that are slated for publication monthly and selects one or more manuscripts with impactful findings. Once the articles are selected, they are sent to a cohort of experienced question writers sourced from the Network specialty areas within *CHEST* to draft clinically relevant questions. The final questions and answers then are returned to the Board for a careful review of their accuracy, quality, and relevancy.

Readers can visit chestnet.org/journalcme every month to see a new selection of CME-eligible articles and access questions from past issues – an offering that will only grow more robust as the initiative progresses.

"We have a regularly accumulating collection of questions such that folks who read the journal every month will always have questions to answer, and those who prefer to do some reading and CME acquisition in bulk can find a rich database of useful, interesting articles that maybe they didn't have a chance to read when they first came out," said Dr. Morris.

As the initiative evolves, so too will the content selected and the questions offered – a process readers will have an integral role in guiding. After answering the questions, readers will have the opportunity to provide feedback on whether the activity

CHEST JOURNAL CME EDITORIAL BOARD

Angel Coz Yataco, MD, FCCP
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achieved its learning objectives, future topics to cover, and more.

Although the initiative will evolve with this feedback, said Dr. Morris, one thing remains constant: the commitment of the team developing these resources to their fellow clinicians. "We couldn't do this without a dedicated team and a lot of volunteer time from individuals who really care about education and clinical practice, and making the literature relevant to clinical practice. It takes a lot of time and effort, and I so appreciate the work those individuals are doing."

To access the latest CME-eligible research, and review past questions, visit chestnet.org/journalcme or scan the QR code. ■



This month in the journal *CHEST*®

Editor's picks

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

Did you know that you can claim CME credit for reading articles in each issue of the journal *CHEST*? Eligible articles are indicated below with an asterisk. Just read the article, then scan the QR code here to test your learning and earn your credits.

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Contamination of Blood Cultures From Arterial Catheters and Peripheral Venipuncture in Critically Ill Patients: A Prospective Multi-center Diagnostic Study
By Izumi Nakayama, MD, PhD, et al.

Critical Care Staffing in Pandemics and Disasters: A Consensus Report From a Subcommittee of the Task Force for Mass Critical Care-Systems Strategies to Sustain the Health Care Workforce
By Charles L. Sprung, MD, FCCP, et al.

Disability Rights and Life-Sustaining Treatment: Building Bridges Between Clinicians and Advocates
By Ari Ne'eman and Erin DeMartino, MD

Evaluation of Frailty Measures and Short-term Outcomes After Lung Transplantation
By Aparna C. Swaminathan, MD, MHS, et al.

***Guideline-Concordant Antibiotic Therapy for the Hospital Treatment of Community-Acquired Pneumonia and 1-Year All-Cause and Cardiovascular Mortality in Elderly Patients Surviving to Discharge**



By Vicente F. Corrales-Medina, MD, and Carl van Walraven, MD

Health Disparities: Interventions for Pulmonary Disease – A Narrative Review
By Logan J. Harper, MD, et al.

Health Expectations and Quality of Life After Acute Respiratory Failure: A Multicenter Prospective Cohort Study
By Alison E. Turnbull, DVM, MPH, PhD, et al.

By Alison E. Turnbull, DVM, MPH, PhD, et al.

Is Left Ventricular Systolic Dysfunction Associated With Increased Mortality Among Patients With Sepsis and Septic Shock?
By Siddharth Dugar, MD, et al.

Single-Night Diagnosis of Sleep Apnea Contributes to Inconsistent Cardiovascular Outcome Findings
By Bastien Lechat, PhD, et al.

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CHEST 2023 Master Classes offer advanced learning from big names in chest medicine

BY KATLYN CAMPBELL
CHEST Communications Coordinator

Maximize your learning experiences at CHEST 2023 (October 8-11 in Hawai'i) by attending a Master Class. Taking place before and after the annual meeting, these advanced-level courses on October 7, 12, and 13 will give you a deep dive into specific clinical areas with the guidance of distinguished faculty. Replacing the "postgraduate courses" offered in previous years, the new Master Classes are open to both CHEST 2023 registrants and non-registrants. Faculty will explore complex topics,

These classes will have some didactic elements, but a lot of time will be spent reviewing challenging cases that aren't easily addressed by guidelines or a quick read of the literature and will go beyond what's easily found online.

"Master Classes will focus on deeper-dive learning, in-depth pathophysiology and research, and conversational, interactive discussions," Dr. Morris said.

She encourages everyone to seize the opportunity to attend these classes taught by "true masters of clinical medicine" in Hawai'i after years of strictly virtual learning that didn't allow for as much interactivity.

"That's why we're in medicine – to learn from each other. This is an opportunity not just to learn facts or new ways of doing things, but a chance to interact on a personal level with providers from around the globe and master clinicians who are not always available to us in person," she said. "In an increasingly digital world, an opportunity like this is harder to come by these days."

Make the most of your trip to Hawai'i with advanced learning taught by highly regarded speakers. Take a look at the Master Classes available to you this year, and add a course to your meeting registration. For more information on CHEST 2023 educational offerings, browse the preliminary program at chestmeeting.chestnet.org.

October 7 (held in Honolulu on O'ahu)

How I Do It – Challenging Cases in Sleep Medicine

Faculty: Babak Mokhlesi, MD, FCCP; Timothy Morgenthaler, MD, FCCP; Lauren A. Tobias, MD, FCCP; and Lisa F. Wolfe, MD.

Interstitial Lung Disease

Faculty: Ayodeji Adegunsoye, MD, FCCP; Jonathan H. Chung, MD; Tejaswini Kulkarni, MD, MBBS, FCCP; Ganesh Raghu, MD; and Mary Beth Scholand, MD, FCCP.

Advances in Lung Cancer – Rocketing Forward With the Cancer Moonshot

Faculty: A. Christine Argento, MD, FCCP; Frank C. Detterbeck, MD, FCCP; Gerard A. Silvestri, MD, Master FCCP; and Lynn T. Tanoue, MD, FCCP.

Pulmonary Hypertension – Expert Didactics and Discussion

Faculty: Jean M. Elwing, MD, FCCP; Peter Leary, MD, PhD; and Namita Sood, MBChB, FCCP.



October 12-13 (held in Wailea on Maui)

2023 Pulmonary Literature Review and Complex Case Presentations – An Interactive Course With the Masters in Pulmonology

Faculty: Doreen Addrizzo-Harris, MD, FCCP; Kevin M. Chan, MD, FCCP; Stephanie M. Levine, MD, FCCP; Diego J. Maselli, MD, FCCP; Marcos I. Restrepo, MD, PhD, FCCP; Linda Rogers, MD, FCCP; Gerard A. Silvestri, MD, Master FCCP; and David J. Steiger, MBChB, FCCP.

Avoiding Catastrophic Crisis in the ICU and Mastering Critical Care

Faculty: Kristin Burkart, MD, MS, FCCP; David Janz, MD; Patricia A. Kritek, MD; Matthew E. Prekker, MD; Nida Qadir, MD; Todd W. Rice, MD, FCCP; and Jonathan Sevransky, MD, FCCP. ■

CHEST 2023 hands-on and interactive learning opportunities

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Meet the Professor sessions

Connect with leading chest medicine experts during these limited-capacity discussions capped at 24 registrants per session.

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and you will have the opportunity to participate in intensive case-based discussions with master clinicians.

"At CHEST, we're always looking for ways to tailor the learning experience for the folks who come to the annual meeting. These Master Classes will be particularly useful for seasoned providers who are looking for a challenging education experience," said Education Committee Chair, Amy E. Morris, MD, FCCP.

In memoriam

CHEST has been informed of the following deaths of CHEST members. We remember our colleagues and extend our sincere condolences.

- Michael Cutaia, MD
- Dennis H. Nicholson, MD, FCCP
- D. Keith Payne, MD, FCCP



Fibrotic ILD outcomes linked to nocturnal hypoxemia

BY WALTER ALEXANDER

MDedge News

FROM THE JOURNAL CHEST® ■ In patients with fibrotic interstitial lung disease (F-ILD), nocturnal hypoxemia (NH) is associated with poor clinical outcomes, according to results of a prospective observational cohort study. Obstructive sleep apnea (OSA) in the absence of NH was not independently associated with poor clinical outcomes.

While both OSA and NH are known to be common in patients with F-ILD, how they affect disease outcomes has remained unclear, Katherine J. Myall, MBChB, and colleagues reported in their published study (*Chest*. 2023 May 13. doi: 10.1016/j.chest.2023.05.013). They noted that deposition of extracellular matrix within the lung parenchyma found in F-ILD is associated with restrictive lung disease and impaired gas exchange leading to progressive breathlessness and exercise intolerance and ultimately respiratory failure.

Prior research has suggested that sleep architecture is disrupted in F-ILD, with nocturnal desaturations from relative hypoventilation during rapid-eye movement sleep and higher incidence of OSA. While disrupted sleep architecture has been associated with poorer outcomes including worse survival, the relationship between sleep and F-ILD is not well understood, especially whether either total time spent in sleep with hypoxemia or repeated desaturations and arousals seen in OSA might promote disease progression, the researchers wrote.

They conducted a prospective observational cohort study among 102 idiopathic pulmonary

fibrosis patients without daytime hypoxemia (74.5% male; age 73.0 years), among whom 91.1% and 31.4% had NH and OSA, respectively. There were no significant differences between those with and without NH or OSA at baseline. The study's primary outcome measure was change in King's Brief Interstitial Lung Disease questionnaire (KBILD) at 12 months from baseline. The

“These data provide support for screening for nocturnal hypoxemia, as well as obstructive sleep apnea in patients with F-ILD.”

secondary outcome measures were annualized change in forced vital capacity (FVC), transfer factor for carbon monoxide (TLCO), and mortality at 12 months.

Mortality association?

The analysis showed NH was associated with a more rapid decline in both quality of life (KBILD change -11.3 in the NH group vs. -6.7 in those without NH, $P = .005$) and higher all-cause mortality at 1 year (hazard ratio [HR], 8.21; 95% confidence interval [CI], 2.40-28.1; $P < .001$). There was no increased risk of death in patients with OSA compared with those without (HR, 2.78; 95% CI 0.85-9.12; $= .19$), and OSA in the absence of NH was not associated with worsening of KBILD scores ($P = .30$). Analysis of findings did not reveal any relationship between disease severity and sleep characteristics.

“This suggests that the excess mortality

demonstrated in earlier studies of patients with OSA may be related to prolonged hypoxemia rather than sleep disruption or the other deleterious physiological effects of OSA, such as sympathetic excitation,” according to Dr. Myall and colleagues.

Underscoring that the current study is the first to elucidate the contribution of prolonged NH to disease progression and death in this population, they added that since the central process in the development of idiopathic pulmonary fibrosis is thought to be one of repeated or sustained lung injury, one hypothesis is that prolonged hypoxia of the alveolar epithelium due to prolonged nocturnal hypoxemia may be the source of this insult.

“These data provide support for screening for nocturnal hypoxemia, as well as obstructive sleep apnea in patients with F-ILD to allow early identification of these potentially modifiable conditions.

Trials of CPAP and nocturnal oxygen therapy would offer a potential intervention to correct prolonged nocturnal hypoxemia, offering the potential to improve quality of life and survival for patients who otherwise have limited treatment options,” the researchers concluded.

A possible limitations of the study was the fact that patients were offered referral for CPAP therapy, and were used in the analysis only if they elected not to commence therapy. This may have introduced a bias, although there was no statistically significant difference between patients who opted to be referred and those who did not, according to the authors.

Dr. Myall reported having no conflicts of interest to declare. ■

ILD risk elevated in patients with arthritis after starting biologic and targeted synthetic DMARDs

BY BECKY MCCALL

MDedge News

MILAN – Patients with psoriatic arthritis (PsA) who are using biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) have fivefold higher risk for interstitial lung disease (ILD) than does the general population, according to the first study to explore risk of ILD in this particular patient group.

The study also found 10-fold higher risk of ILD in those patients with RA who were starting a b/tsDMARD, compared with the general population, while the addition of methotrexate did not appear to be associated with increased risk for ILD in either RA nor PsA.

Sella Aarrestad Provan, MD, of the Diakonhjemmet Hospital, Oslo, presented the results at

the annual European Congress of Rheumatology.

Hospital and death registries across five Nordic countries (Denmark, Norway, Finland, Iceland, and Sweden) were analyzed and compared with general population controls. They calculated risk ratios for people who developed ILD within 5 years of starting a b/tsDMARD (with or without methotrexate).

A total of 37,010 patients with RA, 12,341 with PsA, and 569,451 members of the general population were included in the analysis, with respective disease durations of 10 and 8.9 years. Methotrexate was used along with b/tsDMARDs in 49% of patients with RA and 41% with PsA, and most patients were already on methotrexate when b/tsDMARDs were started. The tumor necrosis factor inhibitor etanercept (Enbrel) was the most

commonly used b/tsDMARD in both RA and PsA, followed by infliximab (Remicade and biosimilars) and adalimumab (Humira and biosimilars).

The incidence of ILD within 5 years of starting a b/tsDMARD was 0.8% in patients with RA, 0.2% with PsA, and 0.1% in the general population, and these findings generated hazard ratios of 10.1 (95% confidence interval, 8.6-11.9) for RA and 5.0 (95% CI, 3.4-7.4) for PsA, compared with the general population.

When the risk for ILD was explored according to methotrexate use in RA patients, “there was no signal of increased risk across patients using methotrexate,” Dr. Aarrestad Provan reported. When risk of ILD was explored according to b/tsDMARD use in RA patients, a signal of increased risk was observed with rituximab, she noted,

“but upon adjusting for age, sex, and comorbidities, this association was no longer significant, but was still numerically increased.”

Iain McInnes, MD, PhD, of the University of Glasgow, said that “epidemiologic studies suggest that PsA often coexists with the presence of cardiometabolic syndrome and obesity, which has a higher prevalence in PsA than in RA. Obesity is also related to ILD. As such, it begs the question of whether cardiometabolic, diabetes, or obesity-related features may give us a clue as to what is going on in these PsA patients.”

The research was supported by NordForsk and FOREUM. Dr. Aarrestad Provan reported consulting for Boehringer Ingelheim and Novartis and receiving support from Boehringer Ingelheim. Dr. McInnes declared no relevant disclosures. ■

Trial shows some relief for long-COVID fatigue

BY JAY CROFT

In a phase 2 clinical trial of a potential treatment for fatigue associated with long COVID-19, people who received the medicine reported positive results over those receiving a placebo.

The study was conducted by researchers at the University of Oxford, England, and published in *eClinical Medicine* (2023 Apr 14. doi: 10.1016/j.eclinm.2023.101946).

It was one of the first randomized double-blind placebo-controlled trial for a possible treatment for long COVID, according to a press release from the university.

“People living with long COVID in the trial who received AXA1125 had a significant improvement in fatigue compared to those who received a placebo,” the university reported.

Forty-one people participated. They had fatigue for 18 months beforehand. All completed the study, and none reported serious side effects.

AXA1125 was developed by U.S. pharmaceutical company Axcella Therapeutics.

“Potential causes [of long-COVID fatigue] include reduced mitochondrial function and cellular bioenergetics,” the researchers reported.

“AXA1125 was tested in long COVID fatigue as previous data from Axcella showed effects on cellular energetics and inflammation. Emerging data on long COVID suggests that the virus targets the mitochondrial, which are essential to normal energy generation and control of inflammation,” the university noted in its press release. “AXA1125 may improve energy generation and reduce the amount of inflammation in the body.”

The study’s authors wrote that AXA1125 was tied to a “significant reduction in 28-day Chalder Fatigue Questionnaire score relative to placebo.” They said participants who reported less fatigue also had better mitochondrial health and walked farther in a 6-minute test. ■

Review supports health care-visit mask-wearing

BY JAY CROFT

A new study urges people to continue wearing protective masks in medical settings, even though the U.S. public health emergency declaration around COVID-19 has expired.

Masks continue to lower the risk of catching the virus during medical visits, according to the study, published in *Annals of Internal Medicine* (2023 May 16. doi: 10.7326/M23-0570). And there was not much difference between wearing surgical masks and N95 respirators in health care settings.

The researchers reviewed 3 randomized trials and 21 observational studies to compare the effectiveness of those and cloth masks in reducing COVID-19 transmission.

“Masking in interactions between patients and health care personnel should continue to receive serious consideration as a patient safety measure,” Tara N. Palmore, MD, of George Washington University, Washington, and David K.

Henderson, MD, of the National Institutes of Health, Bethesda, Md., wrote in an opinion accompanying the study (*Ann Intern Med.* 2023 May 16. doi: 10.7326/M23-1190).

“In our enthusiasm to return to the appearance and feeling of normalcy, and as institutions decide which mitigation strategies to discontinue, we strongly advocate not discarding this important lesson learned for the sake of our patients’ safety,” Drs. Palmore and Henderson wrote. While masks are not 100% effective, they substantially lower the amount of virus put into the air.

One reason people should wear masks to medical settings is because “health care personnel are notorious for coming to work while ill.” Transmission from patient to staff and staff to patient is still possible, but rare, with dual masking.

The authors reported no conflicts. Dr. Palmore received grants from Rigel, Gilead, and AbbVie, and Dr. Henderson had no relevant disclosures. ■



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Five ways docs may qualify for discounts on medical malpractice premiums

BY CHRISTINE LEHMANN, MA

As the cost of malpractice insurance continues to increase in many states, physicians in private practice may want to take advantage of discounts insurers offer to reduce premiums.

Getting a better deal might simply mean taking advantage of incentives and discounts your insurer may already offer. These include claims-free, new-to-practice, and part-time work discounts.

However, if you decide to shop around, keep in mind that discounts are just one factor that can affect your premium price – insurers look at your specialty, location, and claims history.

One of the most common ways physicians can earn discounts is by participating in risk management programs. With this type of program, physicians evaluate elements of their practice and documentation practices and identify areas that might leave them at risk for a lawsuit. While they save money, physician risk management programs also are designed to reduce malpractice claims, which ultimately minimizes the potential for bigger financial losses, insurance experts say.

“It’s a win-win situation when liability insurers and physicians work together to minimize risk, and it’s a win for patients,” said Gary Price, MD, president of The Physicians Foundation.

Doctors in private practice or employed by small hospitals that are not self-insured can qualify for these discounts, said David Zetter, president of Zetter HealthCare Management Consultants.

“I do a lot of work with medical malpractice companies trying to find clients policies. All the carriers are transparent about what physicians have to do to lower their premiums. Physicians can receive the discounts if they follow through and meet the insurer’s requirements,” said Mr. Zetter.

State insurance departments regulate medical malpractice insurance, including the premium credits insurers offer. Most states cap discounts at 25%, but some go as high as 70%, according to The Doctors Company, a national physician-owned medical malpractice insurer.

Insurers typically offer doctors several ways to earn discounts. The size of the discount also can depend on whether a doctor is new to a practice, remains claims free, or takes risk management courses.

In addition to the premium discount, some online risk management classes and webinars are eligible for CME credits.

“The credits can add up and they can be used for recertification or relicensure,” said Susan Boisvert, senior patient safety risk manager at The Doctors Company.

Here are five ways you may qualify for discounts with your insurer.

1. Make use of discounts available to new doctors

Doctors can earn hefty discounts on their premiums when they are no longer interns or residents and start practicing medicine. The Doctors Company usually gives a 50% discount on member premiums the first year they’re in practice and a 25% discount credit in their second year. The discounts end after that.

Other insurance carriers offer similar discounts to doctors starting to practice medicine. The deepest one is offered in the first year (at least 50%) and a smaller one (20%-25%) the second year, according to medical malpractice brokers.

“The new-to-practice discount is based solely on when the physician left their formal training to begin their practice for the first time; it is not based on claim-free history,” explained Mr. Zetter.

This is a very common discount used by different insurer carriers, said Dr. Price. “New physicians don’t have the same amount of risk of a lawsuit when they’re starting out. It’s unlikely they will have a claim and most liability actions have a 2-year time limit from the date of injury to be filed.”

2. Take advantage of being claims free

If you’ve been claims free for at least a few years, you may be eligible for a large discount.

“Doctors without claims are a better risk. Once a doctor has one claim, they’re likely to have a second, which the research shows [JAMA Health Forum. 2023;4(2):e225436],” said Mr. Zetter.

The most common credit The Doctors Company offers is 3 years of being claim free – this earns doctors up to 25%, he said. Mr. Zetter explained that the criteria and size of The Doctors Company credit may depend on the state where physicians practice.

“We allowed insurance carriers that we acquired to continue with their own claim-free discount program such as Florida’s First Professionals Insurance Company we acquired in 2011,” he said.

Doctors with other medical malpractice insurers may also be eligible for a credit up to 25%. In some instances, they may have to be claims free for 5 or 10 years, say insurance experts.

It pays to shop around before purchasing insurance.

3. If you work part time, make sure your premium reflects it

Physicians who see patients part time can receive up to a 75% discount on their medical liability insurance premiums.

The discounts are based on the hours the physician works per week. The fewer hours worked, the larger the discount. This type of discount does not vary by specialty.

According to The Doctors Company, working 10 hours or less per week may entitle doctors to a 75% discount; working 11-20 hours per week may entitle them to a 50% discount, and working 21-30 hours per week may entitle them to a 25% discount. If you are in this situation, it pays to ask your insurer if there is a discount available to you.

4. Look into your professional medical society insurance company

“I would look at your state medical association [or] state specialty society and talk to your colleagues to learn what premiums they’re paying and about any discounts they’re getting,” advised Mr. Zetter.

Some state medical societies have formed their own liability companies and offer lower premiums to their members because “they’re organized and managed by doctors, which makes their premiums more competitive,” Dr. Price said.

Other state medical societies

endorse specific insurance carriers and offer their members a 5% discount for enrolling with them.

5. Enroll in a risk management program

Most insurers offer online educational activities designed to improve patient safety and reduce the risk of a lawsuit. Physicians may be eligible for both premium discounts and CME credits.

Medical Liability Mutual Insurance Company, owned by Berkshire Hathaway, operates in New York and offers physicians a premium discount of up to 5%, CME credit, and maintenance of certification credit for successfully completing its risk management program every other year.

ProAssurance members nationwide can earn 5% in premium discounts if they complete a 2-hour video series called “Back to Basics: Loss Prevention and Navigating Everyday Risks: Using Data to Drive Change.”

They can earn 1 credit for completing each webinar on topics such as “Medication Management: Minimizing Errors and Improving Safety” and “Opioid Prescribing: Keeping Patients Safe.”

MagMutual offers its insured physicians 1 CME credit for completing their specialty’s risk assessment and courses, which may be applied toward their premium discounts.

The Doctors Company offers its members a 5% premium discount if they complete 4 CME credits. One of its most popular courses is “How To Get Rid of a Difficult Patient.”

“Busy residents like the shorter case studies worth 1/4 credit that they can complete in 15 minutes,” said Ms. Boisvert.

“This is a good bargain from the physician’s standpoint and the fact that risk management education is offered online makes it a lot easier than going to a seminar in person,” said Dr. Price. ■

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