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BIOLines Laboratory, University of Pennsylvania

A microengineered device designed by Dr. Donguen (Dan) Huh contains a lung-on-a-chip connected with a bone-marrow-on-a-chip. The device was launched to the International Space Station for a study of immunosuppression in microgravity.

Newer 3D lung models starting to remake research

BY CHRISTINE KILGORE
MDedge News

Pulmonologist-scientist Veena B. Antony, MD, professor of medicine at the University of Alabama in Birmingham, grows "pulmospheres" in her lab. The tiny spheres, about 1 mL in diameter, contain cells representing all of the cell types in a lung struck with pulmonary fibrosis.

They are a three-dimensional model of idiopathic pulmonary fibrosis (IPF) that can be used to study the behavior of invasive myofibroblasts and to predict in vivo responsiveness to antifibrotic drugs; they're among an array of 3D models of parts of the lung – from lung "organoids" to "lung-on-a-chip" models – that are moving pulmonary research forward and poised to affect toxicity testing, drug development, and other areas.

"The utility is extensive, including looking at the impact of early-life exposures on mid-life lung disease. We can ask all kinds of questions and answer them much faster, and with more accuracy, than with any 2D model," said Dr. Antony, also professor of environmental health sciences and director of UAB's program for environmental and translational medicine.

"The future of 3D modeling of the lung will happen step by step ... but we're right at the edge of a prime explosion of information coming

MODELS // *continued on page 6*

People of color bearing brunt of long COVID, doctors say

BY LISA RAPAPORT
MDedge News

From the earliest days of the COVID-19 pandemic, people of color have been hardest hit by the virus. Now, many doctors and researchers are seeing big disparities come about in who gets care for long COVID.

Long COVID can affect patients from all walks of life. But many of the same issues that have made the virus particularly devastating in communities of color are also shaping who gets diagnosed and treated for long COVID, said Alba Miranda Azola, MD, codirector of the post–acute COVID-19 team at Johns Hopkins University, Baltimore.

Non-White patients are more likely to lack access to primary care, face insurance barriers to see specialists, struggle with time off work or transportation for appointments, and have financial barriers to care as copayments for therapy pile up. "We are getting a very skewed population of Caucasian wealthy people who are coming to our clinic because they have the ability to access care, they have good insurance, and

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INSIDE HIGHLIGHT

NEWS FROM CHEST

Dr. Humayun Anjum provides 2022 billing and coding updates

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from these models, in all kinds of lung diseases," she said.

Two-dimensional model systems – mainly monolayer cell cultures where cells adhere to and grow on a plate – cannot approximate the variety of cell types and architecture found in tissue, nor can they recapitulate cell-cell communication, biochemical cues, and other factors that are key to lung development and the pathogenesis of disease.

Dr. Antony

Dr. Antony's pulmospheres resemble what have come to be known as organoids – 3D tissue cultures emanating from induced pluripotent stem cells (iPSC) or adult stem cells, in which multiple cell types self-organize, usually while suspended in natural or synthetic extracellular matrix (with or without a scaffold of some kind).

Lung-on-a-chip

In lung-on-a-chip (LOC) models, multiple cell types are seeded into miniature chambers, or "chips," that contain networks of microfabricated channels designed to deliver and remove fluids, chemical cues, oxygen, and biomechanical forces. LOCs and other organs-on-chips – also called tissues-on-chips – can be continuously perfused and are highly structured and precisely controlled.

It's the organs-on-chip model – or potential fusions of the organoid and organs-on-chip models – that will likely impact drug development. Almost 9 out of 10 investigational drugs fail in clinical trials – approximately 60% because of lack of efficacy and 30% because of toxicity. More reliable and predictive preclinical investigation is key, said Danilo A. Tagle, PhD, director of the Office of Special Initiatives in the National Center for Advancing Translational Sciences, of the National Institutes of Health.

"We have so many candidate drugs that go through preclinical safety testing, and that do relatively well in animal studies of efficacy, but then fail in clinical trials," Dr. Tagle said. "We need better preclinical models."

In its 10 years of life, the Tissue Chip for Drug Screening Program led by the NCATS – and funded by the NIH and Defense Advanced Research Projects Agency – has shown that organs-on-chips can be used to model disease and to predict both the safety and efficacy of clinical compounds, he said.

Lung organoids

Dr. Antony's pulmospheres emanate not from stem cells but from primary tissue obtained from diseased lung. "We reconstitute the lung cells in single-cell suspensions, and then we allow them to come back together to form lung tissue," she said. The pulmospheres take about 3 days to grow.

In a study published 5 years ago of pulmospheres of 20 patients with IPF and 9 control subjects, Dr. Antony and colleagues quantitated invasiveness and found "remarkable" differences in the invasiveness of IPF pulmospheres following exposure to the Food and Drug Administration–approved antifibrotic drugs nintedanib and pirfenidone. Some pulmospheres responded to one or the other drug, some to both, and two to neither – findings that Dr. Antony said offer hope for the goals of personalizing therapy and assessing new drugs (JCI Insight 2017;2[2]:e91377. doi: 10.1172/jci.insight.91377).

Moreover, clinical disease progression correlated with invasiveness of the pulmospheres, showing that the organoid-like structures "do give us a model that [reflects] what's happening in the clinical setting," she said. (Lung tissue for the study was obtained via video-assisted thoracic surgery biopsy of IPF patients and from failed donor lung explants, but bronchoscopic forceps biopsies have become a useful method for obtaining tissue.)

The pulmospheres are not yet in clinical use, Dr. Antony said, but her lab is testing other fibrosis modifiers and continuing to use the model as a research tool.

One state to the east, at Vanderbilt University, Nashville, Tenn., Amanda Linkous, PhD, grows "branching lung organoids" and brain organoids to study the biology of small cell lung cancer (SCLC).

"We want to understand how [SCLC] cells change in the primary organ site, compared with metastatic sites like the brain. ... Are different transcription factors expressed [for instance] depending on where the tumor is growing?" said Dr. Linkous, scientific center manager of the National Cancer Institute's Center for Systems Biology of SCLC at Vanderbilt. "Then we hope to start drug screening within the next year."

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MODELS *continued from previous page*

Her lung organoids take shape from either human embryonic stem cells or iPSCs. Within commercially available media, the cells mature through several stages of differentiation, forming definitive endoderm, anterior foregut endoderm, and then circular lung bud structures – the latter of which are then placed into droplets of Matrigel, an extracellular matrix gel.

"In the Matrigel droplets, the lung bud cells will develop proximal and distal-like branching structures that express things like EPCAM, MUC1, SOX2, SOX9, and NKX2.1 – key markers that you should see in a more mature lung microenvironment," she said. Tumor cells from established SCLC cell lines will then easily invade the branching lung organoid.

Dr. Linkous said she has found her organoid models highly reproducible and values their long-lasting nature – especially for future drug screening. "We can keep organoids going for months at a time," said Dr. Linkous, a research associate professor in Vanderbilt's department of biochemistry.

Dr. Linkous

Like Dr. Antony, she envisions personalizing treatment in the future. "SCLC is a very heterogeneous tumor with many different cell types, so what works for one patient may not work well at all for another patient," she said. As recently as 5 years ago, "many in the cancer field would have been resistant to moving away from mouse models," she noted. "But preclinical studies in mice often don't pan out in the clinic ... so we're moving toward a human microenvironment to study human disease."

The greatest challenge, Dr. Linkous and Dr. Antony said, lies in integrating vascular blood flow and air into these models. "We just don't have that combination as of yet," Dr. Antony said.

LOC models

One of the first LOC models – and a galvanizing event for organs-on-chips more broadly – was a 1- to 2-cm–long model of the alveolar-capillary interface developed at the Wyss Institute for Biologically Inspired Engineering at Harvard Medical School, Boston.

Microchannels ran alongside a porous membrane coated with extracellular matrix, with alveolar cells seeded on one side and lung endothelial cells on the other side. When a vacuum was applied rhythmically to the channels, the cell-lined membrane stretched and relaxed, mimicking breathing movements.

Lead investigator Dongeun (Dan) Huh, PhD, then a postdoctoral student working with Donald E. Ingber, MD, PhD, founding director of the institute, ran tests showing that the model could reproduce organ-level responses to bacteria and inflammatory cytokines, as well as to silica nanoparticles. The widely cited paper was published in 2010 (Science. 2010;328[5986]:1662-8), and was followed by another study published in 2012 (Sci Transl Med. 2012;4[159]:159ra147) that used the LOC to reproduce drug toxicty–induced pulmonary edema. "Here we were demonstrating for the first time that we could use the lung-on-chip to model human lung disease," said Dr. Huh, who started his own lab at the University of Pennsylvania, Philadelphia, in 2013.

Since then, "as a field we've come a long way in modeling the complexity of human lung tissues ... with more advanced devices that can be used to mimic different parts of the lung and different processes, like immune responses in asthma and viral infections," said Dr. Huh, "and with several studies using primary human cells" that were taken from patients with lung disease.

Among Dr. Huh's latest devices, built with NIH funding, is an asthma-on-a-chip device. Lung cells isolated from asthma patients are grown in a microfabricated device to create multilayered airway tissue, with airspace, that contains a fully differentiated epithelium and a vascularized stroma. "We can compress the entire engineered area of asthmatic human tissue in a lateral direction to mimic bronchoconstriction that happens during an asthma attack," he said.

A paper soon to be published will describe how "abnormal pathophysiologic compressive forces due to bronchoconstriction in asthmatic lungs can make the lungs fibrotic, and how those mechanical forces also can induce increased vascularity," said Dr. Huh, associate professor in the university's department of bioengineering. "The increased vascular density can also change the phenotype of blood vessels in asthmatic airways."

Dr. Huh also has an $8.3 million contract with the government's Biomedical Advanced Research and Development Authority to study how chlorine gas damages lung tissues and identify biomarkers of chlorine gas–induced lung injury, with the goal of developing therapeutics.

Dr. Ingber and associates have developed a device modeling cystic fibrosis (CF). The chip is lined with primary human CF bronchial epithelial cells grown under an air-liquid interface and interfaced with primary lung microvascular endothelium that are exposed to fluid flow.

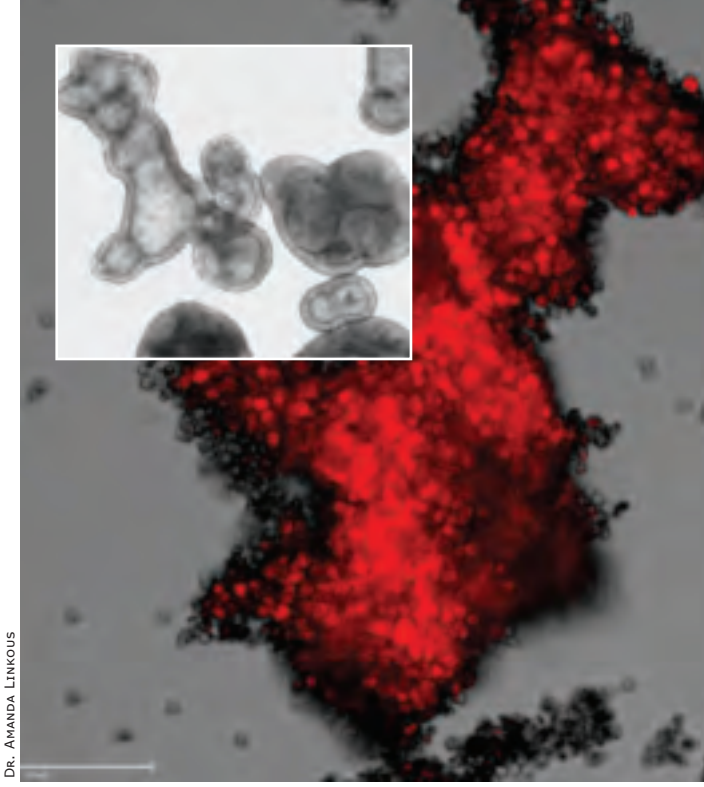
The chip reproduced, "with high fidelity, many of the structural, biochemical, and pathophysiological features of the human CF lung airway and its response to pathogens and circulating immune cells in vitro," Dr. Ingber and colleagues reported (J Cyst Fibros. 2022;21:605-15).

Government investment in tissue chips

Efforts to commercialize organs-on-chip platforms and translate them for nonengineers have also picked up in recent years. Several companies in the United States (including Emulate, a Wyss start-up) and in Europe now offer microengineered lung–tissue models that can be used for research and drug testing. And some large pharmaceutical companies, said Dr. Tagle, have begun integrating tissue–chip technology into their drug development programs.

The FDA, meanwhile, "has come to embrace the technology and see its promise," Dr. Tagle said. An FDA pilot program announced in 2021 – called ISTAND (Innovative Science and Technology Approaches for New Drugs) – allows for tissue chip data to be submitted, as standalone data, for some drug applications. The first 5 years of the government's Tissue Chip for Drug Screening Program focused on safety and toxicity, and it "was successful in that model organ systems were able to capture the human response that [had been missed in] animal models," he said.

For example, when a liver-tissue model was



Dr. Amanda Linkous

Inset (gray) image shows a normal branching lung organoid. Larger image shows red, flourescently-labeled SCLC cells invading a lung organoid.

used to test several compounds that had passed animal testing for toxicity/safety but then failed in human clinical trials – killing some of the participants – the model showed a 100% sensitivity and a 87% specificity in predicting the human response, said Dr. Tagle, who recently coauthored a review on the future of organs-on-chips (Nature Reviews I Drug Discovery. 2021;20:345-61).

The second 5 years of the program, currently winding down, have focused on efficacy – the ability of organs-on-chip models to recreate the pathophysiology of chronic obstructive pulmonary disease, influenza, and other diseases, so that potential drugs can be assessed. In 2020, with extra support from the Coronavirus Aid, Relief, and Economic Security Act, NCATS funded academic labs to use organs-on-chip technology to evaluate SARS-CoV-2 and potential therapeutics. Dr. Ingbar was one of the grantees. His team screened a number of FDA-approved drugs for potential repurposing using a bronchial-airway-on-a-chip and compared results with 2D model systems (Nat Biomed Eng. 2021;5:815-29). Amodiaquine inhibited infection in the 3D model and is now in phase 2 COVID trials. Several other drugs showed effectiveness in a 2D model but not in the chip.

Now, in a next phase of study at NCATS, coined Clinical Trials on a Chip, the center has awarded $35.5 million for investigators to test candidate therapies, often in parallel to ongoing clinical trials. The hope is that organs-on-chips can improve clinical trial design, from enrollment criteria and patient stratification to endpoints and the use of biomarkers. And in his lab, Dr. Huh is now engineering a shift to "organoids-on-a-chip" that combines the best features of each approach. "The idea," he said, "is to grow organoids, and maintain the organoids in the microengineered systems where we can control their environment better ... and apply cues to allow them to develop into even more realistic tissues."

Drs. Antony, Linkous, and Tagle reported no relevant disclosures. Dr. Huh is a co-founder of Vivodyne Inc, and owns shares in Vivodyne Inc. and Emulate Inc. ■

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The Importance of Guideline-Recommended Biomarker Testing and Multidisciplinary Treatment in Resectable Stage IB-IIIA Non–Small Cell Lung Cancer

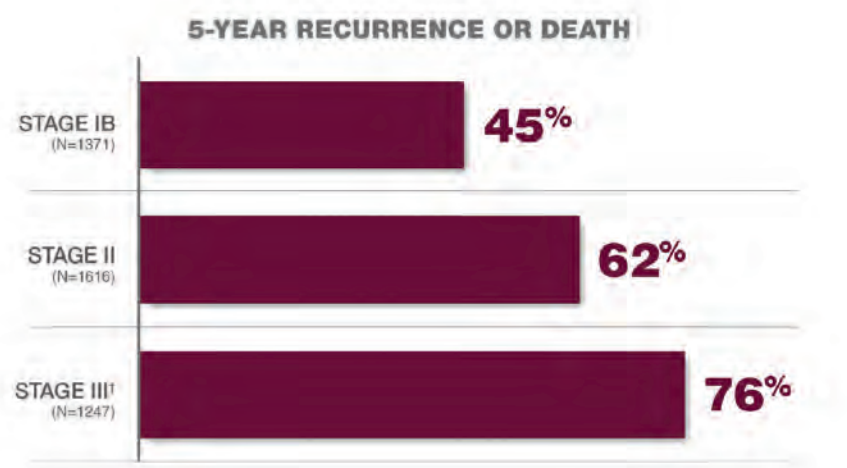
Disease recurrence rates remain high after surgery

Lung cancer accounts for 25% of all cancer deaths, making it by far the most lethal form of cancer.[1] Of the estimated 2.2 million new lung cancer cases diagnosed in 2020, approximately 80% to 85% were non–small cell lung cancer (NSCLC), which encompasses adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[2,3] Although early-stage NSCLC is considered potentially curable with surgical resection, disease recurrence rates remain unacceptably high.[4-6] Some patients with stage IB-III NSCLC—even with adjuvant treatment, including chemotherapy—can recur or die within 5 years after surgery.[6] **(Figure 1)**

Figure 1

Disease recurrence is a significant threat—some patients may experience disease recurrence or death within 5 years

Even when treated with adjuvant chemotherapy, some patients with stage IB-III NSCLC will have a recurrence or will have died within 5 years.[6*]



In a separate study, the 2016 IASLC database shows that 5-year survival rates in NSCLC are as follows: stage I, 68-92%; stage II, 53-60%; stage II, 13-36%; stage IV, 0-10%.[7‡]

*Pooled analysis of 5 randomized trials with 4584 patients; trials compared postoperative cisplatin-based chemotherapy vs no chemotherapy or cisplatin-based chemotherapy plus postoperative radiotherapy (administered sequentially) vs postoperative radiotherapy alone in patients with completely resected NSCLC.[6] †Resectable patients. ‡Based on the 8th edition of the AJCC tumor, node, and metastasis classification of lung cancer.[7]

NSCLC can recur as metastases throughout the body, with 68% of recurrences involving distant metastases.[8] The most common sites of recurrence include the brain, lung, bone, and liver.[8] This discussion focuses on the clinical rationale for guideline-recommended biomarker testing prior to selection of an adjuvant treatment plan.

Guideline recommendations for biomarker testing

One way to address high rates of disease recurrence is through the use of adjuvant treatment. To both identify potentially efficacious targeted therapies and avoid therapies unlikely to provide clinical benefit, the National Comprehensive Cancer Network® (NCCN®) recommends testing eligible patients with resectable NSCLC for targetable genomic alterations.[9] In recent years, NCCN updated the biomarker testing recommendations for resectable disease to include *EGFR* (resected stage IB-IIIA) and PD-L1 expression (resected stage II-IIIA).[9] Knowing the patient's complete molecular profile and PD-L1 status can help physicians make optimal treatment decisions for their patients.

EGFR mutations: an important driver of disease

EGFR mutations are a key biomarker in NSCLC, driving tumor growth across stages and impacting recurrence.[10-13] EGFR is a cell-signaling transmembrane protein that plays an important role in cell proliferation, leading to the unregulated growth and survival of tumor cells.[12]

Up to 1 in 5 patients with early-stage NSCLC may have an *EGFR* mutation, with 20% of stage I, 18% of stage II, and 18% of stage III patients having *EGFR* mutations, respectively.[10,11§] **(Figure 2)**

Patients with *EGFR*-mutated NSCLC face a greater risk of metastatic recurrence compared with patients without *EGFR*-mutated disease or with *EGFR* wild-type. One study found that when patients with *EGFR*-mutated disease had a recurrence, 97% had distant metastases, compared with 72% of those with wild-type *EGFR* (P=0.007).[14] Additionally, having an *EGFR* mutation doubles the risk that a patient will develop a metastasis to the central nervous system (odds ratio [OR]=1.99).[15] Notably, *EGFR* mutations commonly coexist with PD-L1 expression. Up to 57% of patients with stage IB-III resectable *EGFR*m NSCLC can also express at least 1% PD-L1.[16] **(Figure 3)**

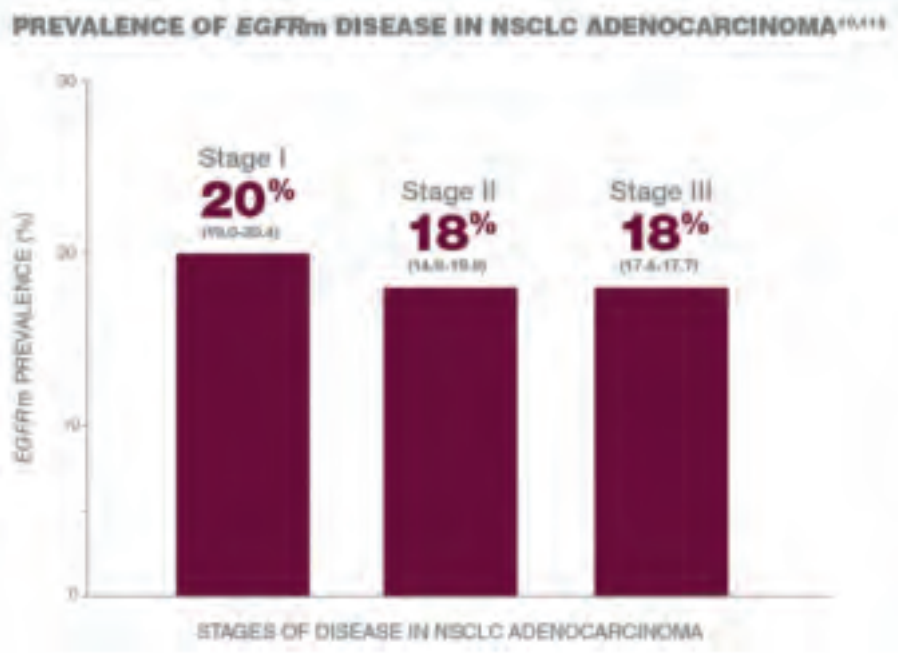
Given these data, a multidisciplinary treatment approach with guideline-recommended biomarker testing is critical for eligible patients with resectable NSCLC.[9]

A multidisciplinary treatment approach for guideline-recommended testing and treatment

It has been my experience that multidisciplinary care is paramount in treating NSCLC. Working with a multidisciplinary team can lead to lower rates of disease recurrence, shorter times to diagnosis, and more complete staging evaluations.[17-19||¶#] Patients presented at multidisciplinary tumor boards are more likely to receive guideline-recommended therapy compared with cases not reviewed at tumor boards.[19] At our institution, we engage a full multidisciplinary team, including a surgeon and a medical oncologist, for every patient with resectable NSCLC. We also have a shared decision-making visit as early as possible with patients regarding their options and eligibility for postsurgical treatment.

Guideline-recommended testing can help to determine optimal treatment options for patients, which can include chemotherapy, immunotherapy, radiation with or without chemotherapy,

Figure 2



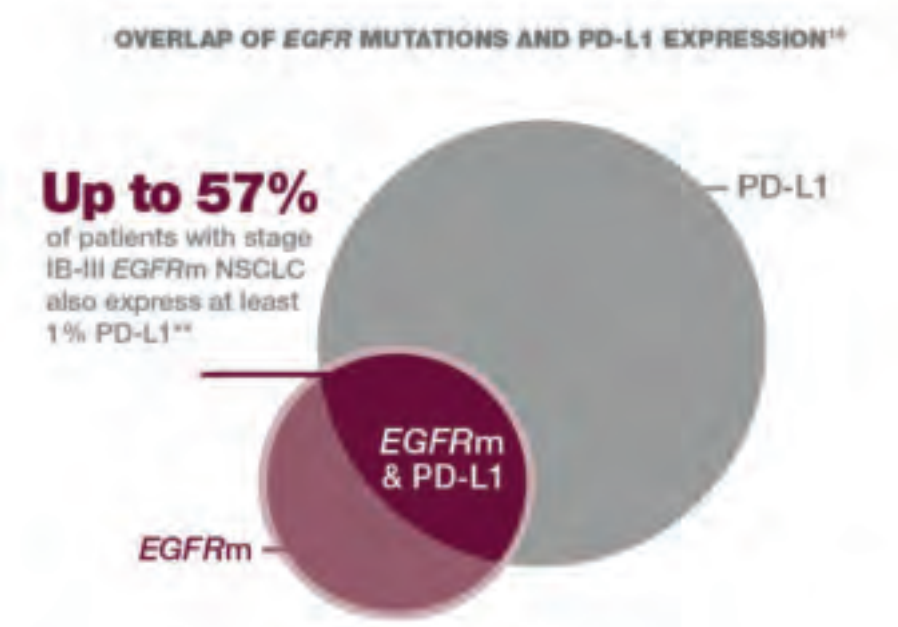
§Prevalence of *EGFR* mutations in NSCLC adenocarcinoma was based on data from 2 references: Sholl et al (2015) performed mutation analysis on 1007 specimens with confirmed diagnosis of lung adenocarcinoma with *EGFR* sensitizing mutations (exon 19 deletions, *EGFR* L858R mutations, *EGFR* G719X mutations, *EGFR* L861Q mutations) and other *EGFR* mutations (any 1 or more mutations in *EGFR* other than exon 19 deletions, L858R mutations, G719X mutations, or L861Q mutations); D'Angelo et al (2012) analyzed tumor specimens from a cohort of 1118 patients with stage I-III surgically resected lung adenocarcinomas with *EGFR* exon 19 deletions and L858R mutations only.[10,11,13,20]

or targeted therapy.[9] These approaches help ensure every eligible patient receives guideline-recommended *EGFR* and PD-L1 expression testing and is referred to a medical oncologist.

Conclusion

Rates of recurrence after complete resection remain high in resectable NSCLC.[6] NCCN recommends that eligible patients be tested for biomarkers to identify potentially effective treatments.[9] Knowing *EGFR* and PD-L1 expression status before deciding on a postsurgical treatment plan is critical and now guideline recommended.[9] Biomarker testing is an essential part of care—and referring patients to a medical oncologist helps ensure they get the testing and the care they need.[17,19] Pulmonologists should continue to follow up with patients even after referral to a medical oncologist to ensure continuity of treatment and assess for pulmonary-related toxicity associated with treatment and disease progression.[17] By working together with a multidisciplinary team, pulmonologists can help ensure every patient receives guideline-recommended biomarker testing and, ultimately, the optimal adjuvant treatment plan for their disease.[17,19]

Figure 3



***EGFR* mutation status and PD-L1 expression overlap were examined in a retrospective analysis of 319 patients with *EGFR*m NSCLC across all stages. *EGFR* mutations included exon 19 deletions (n=145), exon 21 L858R mutations (n=121), exon 19 nondeletions (n=26), exon 21 non-L858R mutations (n=3), exon 18 mutations (n=12), and exon 20 mutations (n=8). One patient had both exon 18 and exon 20 mutations and 3 patients had other mutations. PD-L1 expression ≥1% was observed in 86 out of 150 patients with stage IB-IIIA *EGFR*m NSCLC.[16]

Footnotes

‖Nemesure et al (2020) found that recurrence rates were significantly lower at 3 years in patients enrolled in a multidisciplinary team (MDT) program compared with those not enrolled in an MDT program (OR=0.51 [95% CI: 0.32, 0.79]) in a retrospective, longitudinal analysis of data from a lung cancer clinical registry. These data were only significant for patients with stage I lung cancer.[17]

¶In a single-center study using tumor registry data to identify all cases of stage III NSCLC seen at Lehigh Valley Health Network between March 2010 and 2013, Friedman et al (2016) compared the care received by patients seen in the thoracic multidisciplinary clinic (MDC) vs the care received by patients not seen in the thoracic MDC: 88.5% of patients (46 of 52 patients) seen in the MDC were treated according to the institutional clinical pathway for stage III NSCLC vs 35.1% of patients (20 of 57 patients) seen outside of the MDC (P<0.001). In addition, Friedman et al found that patients seen in the MDC started therapy within a mean of 19.85 ± 13.8 days as opposed to those not seen in the MDC, who started therapy within a mean of 29.09 ± 27.3 days (P=0.043); and that patients seen in the MDC were more likely to undergo pathologic staging of the mediastinum, with 57.7% of patients (30 of 52 patients) seen in the MDC receiving pathologic staging of the mediastinum vs 24.5% of patients (14 of 57 patients) not seen in the MDC (P<0.001).[19]

#Freeman et al (2015) found in a retrospective analysis of 12,354 propensity-matched patients with stage I, II, or III lung cancer followed from 2008 to 2013, 88% (5382 of 6627) of patients whose care was coordinated in an MDC received care that was within the standards of the NCCN Guidelines® vs 71% (4705 of 6627) of patients whose care was not coordinated in an MDC (P<0.0001); patients in the MDC cohort had a significantly shorter mean interval from the initial pathologic diagnosis to the initiation of treatment compared with patients in the non-MDC cohort (19 ± 8 days vs 32 ± 11 days; P<0.0001); and 91% of patients (6031 of 6627) in the MDC cohort received a complete staging evaluation vs 67% of patients (4572 of 6627) in the non-MDC cohort (P<0.0001).[18]

NCCN=National Comprehensive Cancer Network® (NCCN®)

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Inhaled, systemic steroids linked to changes in brain

BY PAULINE ANDERSON
MDedge News

New research links use of glucocorticoids with changes in white-matter microstructure – which may explain the development of anxiety, depression, and other neuropsychiatric side effects related to these drugs, investigators say. Results from a cross-sectional study showed use of both systemic and inhaled glucocorticoids was associated with widespread reductions in fractional anisotropy (FA) and increases in mean diffusivity.

Glucocorticoids have "a whole catalogue" of adverse events, and effects on brain structure "add to the list," co-investigator Onno C. Meijer, PhD, of Leiden University Medical Center, the Netherlands, told this news organization.

The findings should encourage clinicians to consider whether doses they are prescribing are too high, said Dr. Meijer. He added that the negative effect of glucocorticoids on the brain was also found in those using inhalers, such as patients with asthma. The findings were published online in the BMJ Open (2022. doi: 10.1136/bmjopen-2022-062446).

Glucocorticoids, a class of synthetic steroids with immunosuppressive properties, are prescribed for a wide range of conditions, including rheumatoid arthritis and asthma. However, they are also associated with potentially serious metabolic, cardiovascular, and musculoskeletal side effects as well as neuropsychiatric side effects such as depression, mania, and cognitive impairment. About 1 in 3 patients exposed to "quite a lot of these drugs" will experience neuropsychiatric symptoms, Dr. Meijer said.

Most previous studies that investigated effects from high levels of glucocorticoids on brain structure have been small and involved selected populations, such as those with Cushing disease.

The new study included participants from the UK Biobank, a large population-based cohort. Participants had undergone imaging and did not have a history of psychiatric disease – although they could have conditions associated with glucocorticoid use, including anxiety, depression, mania, or delirium.

The analysis included 222 patients using oral or parenteral glucocorticoids at the time of imaging (systemic group), 557 using inhaled glucocorticoids, and 24,106 not using glucocorticoids.

Inhaled steroids target the lungs, whereas a steroid in pill form "travels in the blood and reaches each and every organ and cell in the body and typically requires higher doses," Dr. Meijer noted.


Dr. Meijer

The groups were similar, however, the systemic glucocorticoid group was older (mean age, 66.1 years vs. 63.3 years for inhaled glucocorticoid users and 63.5 years for the control group). Researchers adjusted for age, sex, education level, head position in the scanner, head size, assessment center, and year of imaging.

Imaging analyses showed systemic glucocorticoid use was associated with reduced global FA (adjusted mean difference, -3.7e-3; 95% confidence interval, -6.4e-3 to 1.0e-3), and reductions in regional FA in the body and genu of the corpus callosum versus the control group.

Inhaled glucocorticoid use was associated with reduced global FA (AMD, -2.3e-3; 95% CI, -4.0e-3 to -5.7e-4), and lower FA in the splenium of the corpus callosum and the cingulum of the hippocampus. Global mean diffusivity was higher in systemic glucocorticoid users (AMD, 7.2e-6; 95% CI, 3.2e-6 to 1.1e-5) and inhaled glucocorticoid users (AMD, 2.7e-6; 95% CI, 1.7e-7 to 5.2e-6), compared with control.

The effects of glucocorticoids on white matter were "pervasive," and the "most important finding" of the study, Dr. Meijer said. He noted that it is likely that functional connectivity between brain regions is affected by use of glucocorticoids. "You could say communication between brain regions is probably somewhat impaired or challenged," he said.

Subgroup analyses suggested a potential dose-dependent or duration-dependent effect of glucocorticoids on white matter microstructure. Systemic glucocorticoid use was also associated with an increase in total and grey matter volume of the caudate nucleus.

In addition, there was a significant association between inhaled glucocorticoid use and decreased gray-matter volume of the amygdala, which Dr. Meijer said was surprising because studies have shown that glucocorticoids "can drive [changes in the] amygdala big time." Another surprise was that the results showed no hippocampal volume differences with steroid use, Dr. Meijer noted.

The modest association of glucocorticoid use and brain volumes could indicate that white matter integrity is more sensitive to glucocorticoids than is gray-matter volume, "at least at the structural level," he said. He added that longer use or higher doses may be necessary to also induce volumetric changes.

In addition, systemic glucocorticoid users had more depressive symptoms, disinterest, tenseness/restlessness, and tiredness/lethargy, compared with the control group. Inhaled glucocorticoid users only reported more tiredness/lethargy.

In terms of cognition, systemic glucocorticoid users performed significantly worse on the symbol digit substitution task, compared with participants in the control group. In light of these findings, pharmaceutical companies "should perhaps find out if glucocorticoids can be dosed by kilogram body weight rather than simply one dose fits all," Dr. Meijer said.

Commenting on the findings, E. Sherwood Brown, MD, PhD, of the University of Texas Southwestern Medical Center, Dallas, noted that previously, there had been only case reports of psychiatric symptoms with inhaled corticosteroids. That results are in the same direction but greater with systemic, compared with inhaled corticosteroids, is "particularly interesting" because this might suggest dose-dependent effects. He noted that cognitive differences were also only observed with systemic corticosteroids.

Some observations, such as smaller amygdala volume with inhaled but not systemic corticosteroids, "are harder to understand," said Dr. Brown. One study limitation is that results were unavailable for verbal and declarative memory test data, despite corticosteroids probably affecting the hippocampus and causing memory changes.

Dr. Meijer has received research grants and honoraria from Corcept Therapeutics. Dr. Brown is on an advisory board for Sage Pharmaceuticals.

PULMONARY PERSPECTIVES®

Advanced POCUS for us all?

BY CAPT STEPHEN GOERTZEN, DO, USAF, MC; MAJ KAYLA KNUF, MD, USAF, MC; AND CAPT NICHOLAS VILLALOBOS, MD, USAF, MC

Point-of-care ultrasound (POCUS) is a useful, practice-changing bedside tool that spans all medical and surgical specialties. While the definition of POCUS varies, most would agree it is an abbreviated exam that helps to answer a specific clinical question. With the expansion of POCUS training, the clinical questions being asked and answered have increased in scope and volume. The types of exams being utilized in "point of care ultrasound" have also increased and include transthoracic echocardiography; trans-esophageal echocardiography; and lung, gastric, abdominal, and ocular ultrasound. POCUS is used across multiple specialties, including critical care, anesthesiology, emergency medicine, and primary care.

Dr. Villalobos

Not only has POCUS become increasingly important clinically, but specialties now test these skills on their respective board examinations. Anesthesia is one of many such examples. The content outline for the American Board of Anesthesiology includes POCUS as a tested item on both the written and applied components of the exam. POCUS training must be directed toward both optimizing patient management and preparing learners for their board examination. A method for teaching this has yet to be defined (Naji A, et al. *Cureus*. 2021;13[5]:e15217).

One question – how should different specialties approach this educational challenge and should specialties train together? The answer is complicated. Many POCUS courses and certifications exist, and all vary in their content, didactics, and length. No true gold standard exists for POCUS certification for radiology or noncardiology providers. Additionally, there are no defined expectations or testing processes that certify a provider is "certified" to perform POCUS. While waiting for medical society guidelines to address these issues, many in graduate medical education (GME) are coming up with their own ways to incorporate POCUS into their respective training programs (Atkinson P, et al. *CJEM*. 2015 Mar;17[2]:161).

Who's training whom?

Over the past decade, several expert committees, including those in critical care, have developed recommendations and consensus statements urging training facilities to independently create POCUS curriculums. The threshold for many programs to enter this realm of expertise is high and oftentimes unobtainable. We've seen emergency medicine and anesthesia raise the bar for ultrasound education in their residencies, but it's unclear whether all fellowship-trained physicians can and should be tasked with obtaining official POCUS certification.

With the expansion of POCUS training, the clinical questions being asked and answered have increased in scope and volume.

While specific specialties may require tailored certifications, there's a considerable overlap in POCUS exam content across specialties. One approach to POCUS training could be developing and implementing a multidisciplinary curriculum. This would allow for pooling of resources (equipment, staff) and harnessing knowledge from providers familiar with different phases of patient care (ICU, perioperative, ED, outpatient clinics). By approaching POCUS from a multidisciplinary perspective, the quality of education may be enhanced (Mayo PH, et al. *Intensive Care Med*. 2014;40[5]:654). Is it then prudent for providers and trainees alike to share in didactics across all areas of the hospital and clinic? Would this close the knowledge gap between specialties who are facile with ultrasound and those not?

Determining the role of transesophageal echocardiography in a POCUS curriculum

This modality of imaging has been, until recently, reserved for cardiologists and anesthesiologists. More recently transesophageal echocardiography (TEE) has been utilized by emergency and critical care medicine physicians. TEE is part of recommended training for these specialties as a tool for diagnostic and rescue measures, including ventilator management, emergency procedures, and medication titration. Rescue TEE can also be utilized perioperatively where the transthoracic exam is limited by poor windows or the operative procedure precludes access to the chest. While transthoracic echocardiography (TTE) is often used in a point of care fashion, TEE is utilized less often. This may stem from the invasive nature of the procedure but likely also results from lack of equipment and training. Like POCUS overall, TEE POCUS will require incorporation into training programs to achieve widespread use and acceptance.

A deluge of research on TEE for the noncardiologist shows this modality is minimally invasive, safe, and effective. As it becomes more readily available and technology improves, there is no reason why an esophageal probe can't be used in a patient with a secured airway (Wray TC, et al. *J Intensive Care Med*. 2021;36[1]:123).

Ultrasound for hemodynamic monitoring

There are many methods employed for hemodynamic monitoring in the ICU. Although echocardiographic and vascular parameters have been validated in the cardiac and perioperative fields, their application in the ICU setting for resuscitation and volume management remain somewhat controversial. The use of TEE and more advanced understanding of spectral doppler and pulmonary ultrasonography using TEE has revolutionized the way providers are managing critically ill patients. (Garcia YA, et al. *Chest*. 2017;152[4]:736).

In our opinion, physiology and imaging training for residents and fellows should be required for critical care medicine trainees. Delving into the nuances of frank-starling curves, stroke work, and diastolic function will enrich their understanding and highlight the applicability of ultrasonography. Furthermore, all clinicians caring for patients with critical illness should be privy to the nuances of physiologic derangement, and to that end, advanced echocardiographic principles and image acquisition. The heart-lung interactions are demonstrated in real time using POCUS and can clearly delineate treatment goals (Vieillard-Baron A, et al. *Intensive Care Med*. 2019;45[6]:770).

If clinicians are making medical decisions based off imaging gathered at the bedside and interpreted in real-time, documentation should reflect that.

Documentation and billing

If clinicians are making medical decisions based off imaging gathered at the bedside and interpreted in real-time, documentation should reflect that. That documentation will invariably lead to billing and possibly audit or quality review by colleagues or other healthcare staff. Radiology and cardiology have perfected the billing process for image interpretation, but their form of documentation and interpretation may not easily be implemented in the perioperative or critical care settings. An abbreviated document with focused information should take the place of the formal study. With that, the credentialing and board certification process will allow providers to feel empowered to make clinical decisions based off these focused examinations. ■

Dr. Goertzen is Chief Fellow, Pulmonary/Critical Care; Dr. Knuf is Program Director, Department of Anesthesia; and Dr. Villalobos is Director of Medical ICU, Department of Internal Medicine, San Antonio Military Medical Center, San Antonio, Texas.

The possibilities are endless: A chat with the incoming CHEST Foundation President, Robert De Marco, MD, FCCP

As the presidency of the American College of Chest Physicians changes hands in January 2023, so will the role of President of the CHEST Foundation. To get to know the incoming President of the CHEST Foundation, we spoke with Robert (Bob) De Marco, MD, FCCP, about his philanthropy work and his goals for the philanthropic arm of CHEST.

Tell me about your history with philanthropy work.
My philanthropy work started long before the CHEST Foundation. While I've been a member of CHEST since my second year of fellowship, it wasn't until much later that I became involved with the philanthropic side of the organization. Earlier in my career, I was involved more so with the American Cancer Society. I had gotten involved with them by chance – participating in an event of theirs – and was encouraged to get more involved by one of their board members. Being involved with them made a lot of sense seeing as a strong percentage of my patients at the time were being treated for lung cancer. My most notable accomplishments with the American Cancer Society were in serving as the Chairmen of my local Relay for Life program for 10 years, as a board member, and then as a president of my local chapter.

When did you get involved with the CHEST Foundation?
I had served in a handful of positions within CHEST, including Chair of the (since reinvented) Practice Management Committee, so I was deeply involved in the association, and I thought to myself, "I have experience in fundraising through my work with the American Cancer Society, why don't I use it to help our association?" When I moved to Florida, I no longer had the local connection to the American Cancer Society, so it was an opportune time to transition over to the CHEST Foundation.

How has the Foundation changed in the time that you've been involved?
The Foundation has changed drastically since I first joined the Board of Trustees 9 years ago. When I first got involved, the primary goal of the Foundation was staying "out of the red." At that time, we were an organization that gave away more than we made.

After years of building a corpus to fund our own projects, we're in a really good place now with some phenomenal goals and some excellent initiatives to fundraise around, including a CHEST diversity initiative, First 5 Minutes™, and

I look forward to sharing the Foundation's impact with a new audience and reinvigorating the support of our existing donors.

Dr. De Marco

Bridging Specialties™: Timely Diagnosis for ILD Patients, which seeks to break down silos within medicine to improve patient care.

What will be a focus of your Foundation presidency?
You know, one thing I always appreciated about the American Cancer Society was that there were always notable accomplishments to point back to when supporting fundraising efforts. You could say, "Did you know that bone marrow transplantation was initially funded by the American Cancer Society?" and other examples that would truly inspire someone to want to get involved in supporting those efforts.

The CHEST Foundation may not have funded bone marrow transplantation, but in 25 years of awarding grants, there are equally good stories to share. The impact of the Foundation is tremendous, and we've only just begun to share examples of where grant recipients went with their research or community service projects.

A recent grant story that was shared with me was that of Panagis Galiatsatos, MD, MHS, who received a community service grant to start a program educating children in the Baltimore community about lung health. This program was so moving that it inspired one of the Baltimore teachers to pursue a career in medicine and that individual is now a practicing MD.

This is just one example of the Foundation's impact and it's through these stories that we share the "why" behind every dollar that is raised, and my first goal is to tell these stories.

Another key focus of not only my presidency, but Dr. Ian Nathanson's, as well, as we collaborated a lot on our roles, will be on member involvement and awareness. Even I wasn't involved in the CHEST Foundation until years into my CHEST membership, so I understand that there are competing demands. But I also know that there is a lot to be gained from the work with the Foundation. I want the CHEST members to be excited about the Foundation and to want to support its efforts.

These two goals go hand in hand, and I look forward to sharing the Foundation's impact with a new audience and reinvigorating the support of our existing donors.

Is there anything else you'd like to say to the reader?
We cannot accomplish anything without the support of our donors, and I want to sincerely thank everyone who has donated to the CHEST Foundation. I also encourage those who have never donated or have yet to donate this year to visit the Foundation's website (foundation.chestnet.org) and explore some of the inspiring initiatives you can support to strengthen the impact of the CHEST Foundation because the possibilities are truly endless. ■

PCCM diversity grant recipient looks to inhibit platelet endothelial interactions via NEDD9 to improve acute lung injury

In February, The American College of Chest Physicians (CHEST), the American Thoracic Society, and the American Lung Association announced a partnership with the prestigious Harold Amos Medical Faculty Development Program (AMFDP), a Robert Wood Johnson Foundation initiative, to sponsor a scholar in pulmonary and critical care medicine. The recipient of the grant was announced recently, and CHEST spoke with him about his background and the project that earned him the award.

George Alba, MD, is a pulmonary and critical care physician investigator at Massachusetts General Hospital. Dr. Alba studied English Literature and Biology as an undergraduate at Washington University in St. Louis, where he worked in a developmental biology laboratory; earned his MD at the Mount Sinai School of Medicine, where he graduated AOA with Distinction in Medical Education; and then completed both Internal Medicine and Pulmonary and Critical Care Medicine training at Massachusetts General Hospital.

During his fellowship, Dr. Alba specialized in pulmonary and critical care medicine because he appreciated the variety that comes with working in the intensive care unit.

"I love the medical complexity, the physiology, and the decision-making," said Dr. Alba. "I've always enjoyed all aspects of clinical medicine, so it was hard to choose a path, but the benefit of the ICU is that it allows me to take care of a spectrum of medical illness across all subspecialties."

He continued, "What I loved about pulmonary, specifically, was that I could see patients in the hospital and in the ICU, perform procedures, and still have a longitudinal relationship with patients in the clinic, which gave me a very flexible, wide grasp of medicine."

Growing up in a close-knit Cuban family and community, Dr. Alba was raised speaking Spanish at home and learned English primarily in school. Being bilingual helped him in medicine greatly: in clinic,

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in the hospital, and in the ICU, he is able to communicate directly with Spanish-speaking patients and their families. This became critically important during the COVID-19 pandemic when Chelsea, a primarily Hispanic community in Boston, was disproportionately impacted. The patients greatly benefited from Spanish-speaking clinicians to communicate with their family members who were unable to visit due to the infection control policies in place.

As an instructor of medicine at Harvard Medical School and pulmonary and critical care physician at Massachusetts General, Dr. Alba is actively engaged in clinical care, teaching, and research focusing primarily on mechanisms of pulmonary vascular dysfunction in lung disease.

Dr. Alba's AMFDP award project is titled "Pulmonary Endothelial NEDD9 and Acute Lung Injury," and through the proposed scientific aims, he looks to advance NEDD9 antagonism as a potential therapeutic target in acute respiratory distress syndrome (ARDS.) He is being co-mentored by Bradley Maron, MD, a pulmonary vascular disease researcher at Brigham and Women's Hospital, and Eric Schmidt, MD, an endothelial biologist and expert in animal models of acute lung injury at Massachusetts General Hospital.

This is especially relevant research during the COVID-19 pandemic, as patients with severe lung injury frequently develop clotting in the lung blood vessels. Dr. Alba's prior work demonstrated that NEDD9 is a pulmonary endothelial protein that is upregulated by hypoxia, that it binds to activated platelets to promote platelet adhesion and clotting, and that inhibition of NEDD9-platelet interactions with a custom antibody can decrease clotting in the lungs of animals. He recently showed that pulmonary endothelial NEDD9 is increased in patients with ARDS who demonstrate blood vessel clotting.

Now, Dr. Alba seeks to use a custom-made anti-NEDD9 antibody to block platelet adhesion in animal models of ARDS to decrease the extent of lung injury. While aspirin and anticoagulants have been unhelpful in treating ARDS in prior trials, Dr. Alba believes that circulating pulmonary endothelial protein NEDD9 can serve as a biomarker to identify subgroups of ARDS who may benefit from earlier targeted antithrombotic therapy.

Dr. Alba hopes that one day the anti-NEDD9 antibody may become one such therapeutic option for patients. The AMFDP will help support his ongoing work.

"This award comes at a critical time in my junior faculty career: It allows me to continue pursuing my research."

Dr. Alba

"Growing up, I saw through my father's example how education unlocks opportunities. Our community came together to help him on this path. Now a retired doctor of osteopathy in neonatology, he inspired me to pursue a career in medicine," said Dr. Alba. "This award comes at a critical time in my junior faculty career: It allows me to continue pursuing my research in a meaningful way while also gaining new skills that will be critical for my ongoing career development."

Dr. Alba continued, "Programs like the Robert Wood Johnson Foundation initiative that specifically try to increase the number of individuals traditionally underrepresented in academia are key and would not be possible without the support of groups like CHEST, the American Lung Association, and the American Thoracic Society.

These programs help folks who may have other external barriers to being in academia, including socioeconomic pressures, lack of resources – financial or otherwise – or simply not knowing what opportunities are available to them. Programs [like AMFDP] that can alleviate some of these additional pressures go a long way to improve the diversity of the medical workforce."

Dr. Alba is also committed to paying it forward: "I want to ensure that the type of invested mentorship I experienced to help get me this far is not a matter of serendipity for the fortunate few, but rather a standard for all students and trainees, especially those from underrepresented backgrounds." ■

CRITICAL CARE COMMENTARY

ICU telemedicine turns 40

BY JEFFREY D. GRAHAM II, MD, AND ITHAN D. PELTAN, MD, MSC

Intensive care telemedicine was first described in 1982 after implementation in a seven-bed, inner-city ICU using 19-inch television screens connected with intensivists at the University Hospitals of Cleveland (Grundy, et al. *Crit Care Med.* 1982;10[7]:471). After this proof-of-concept report, however, ICU telemedicine gained little traction for nearly 20 years, until Johns Hopkins Hospital established a continuously monitored ICU telemedicine service in a nonintensivist staffed surgical ICU. Their pre/post analysis suggested a 64% decrease in severity-adjusted ICU mortality and greater than 30% decrease in ICU length of stay, ICU complications, and costs (Rosenfeld, et al. *Crit Care Med*. 2000;28[12]:3925).

Dr. Graham

Dr. Peltan

Along with better and less costly telemedicine technology, rapid adoption of electronic medical records, and a nationwide intensivist shortage, this and other evidence for the service's clinical and cost effectiveness has spurred explosive growth in ICU telemedicine in the succeeding 2 decades, with at least 18% of hospitals and 28% of ICU beds supported by ICU telemedicine by 2018 (Ofoma, et al. *Crit Care Explor*. 2021;4[3]:e0468).

Importantly, what "ICU telemedicine" represents varies substantially across hospitals and even across ICUs within systems. Two-way audiovisual technology is the defining feature, and at a minimum, programs provide intensivists and/or nurses who respond to consultation requests. Commonly, telemedicine clinicians directly connect with patients; monitor labs, hemodynamics, and alarms; and proactively contact on-site clinicians with recommendations or place orders directly into the electronic health record depending on whether the clinician acts as the patients' primary, co-managing, or consultant provider. A centralized hub and spoke model with telemedicine personnel located at a single, remote center is the most common and best studied ICU telemedicine design. Additional staffing may include respiratory therapists, pharmacists, and advanced practice clinicians in coverage models that range from 24/7 to nocturnal and can also differ in whether patients are monitored continuously or on an as needed basis, triggered by alarms or clinician/nursing concerns.

On-demand services may extend to support for teams responding to medical emergencies inside and sometimes outside the ICU. Another equally important role that ICU telemedicine can provide is helping ensure facilities adhere to ICU quality metrics, such as ventilator bundles, DVT prophylaxis, and daily SAT/SBT.

Unsurprisingly, integrating ICU telemedicine into an existing system is very costly and complex, requiring substantial and thoughtful process redesign to maximize fiscal and clinical return on investment. One vendor of proprietary telemedicine technology, Philips eICU, estimates an implementation cost of $50,000 to $100,000 per bed with annual overhead, software maintenance, and IT staffing of ~20% of implementation costs in addition to clinician staffing of $1-2 million per 100 beds. However, some (but not all) evidence suggests that ICU telemedicine programs pay for themselves over time. An influential report from Sentara Healthcare, an early adopter of ICU telemedicine, described equipment costs of more than $1 million for a total of 103 critical care beds but attributed savings of $460,000 per month to decreased length of stay (Coustasse, et al. *The Permanente Journal*. 2014;18[4]:76).

Cost savings are great, of course, but ICU telemedicine's potential to improve clinical outcomes is the real priority. While Sentara's early report included a 27% decrease in ICU mortality after telemedicine adoption, a 2011 meta-analysis of 13 studies, including 35 ICUs and over 40,000 patients, suggested decreased ICU mortality and LOS with a statistically significant effect on overall hospital mortality and LOS (Young, et al. *Arch Intern Med.* 2011; 171[6]:498). This highlights the Achilles heel of ICU telemedicine evidence: the pretest/posttest studies that dominate this field and likely contribute substantially to the inconsistencies in the evidence base.

In the absence of risk adjustment and control groups, many studies observed postimplementation changes that may reflect trends in patient mix or the effects of unrelated practice changes rather than the causal influence of ICU telemedicine. In fact, in studies using more robust methods, ICU telemedicine's effect size has been smaller or nonexistent. For example, in 2016, Kahn and colleagues used CMS data to evaluate 132 ICU telemedicine programs using 389 matched controlled hospitals. There was a slight reduction in 90-day mortality (OR=0.96, CI 0.94-0.98) with only 12% showing a statistically significant reduction in mortality. Interestingly, hospitals in urban areas demonstrated greater benefit than rural facilities (Kahn, et al. *Medical Care*. 2016;54[3]:319).

The heterogeneity of the studied programs (eg, primary vs consultative role, on-demand vs proactive involvement) and recipient ICUs (eg, rural vs tertiary care facility, presence of bedside intensivists) further hinders a clear answer to the key question: Would ICU telemedicine benefit my hospital? Fortunately, some recent, well-designed studies have attempted to understand which attributes of ICU telemedicine programs provide results and which ICUs will see the most benefit. In a cohort of 118,990 patients across 56 ICUs, four interventions were associated with lower mortality and reduced LOS: (1) evaluation of patients within 1 hour of ICU admission, (2) frequent leadership review of performance data, (3) ICU best practice compliance, and (4) prompt response to alerts (Lilly, et al. *Chest*. 2014;145[3]:500). Kahn and colleagues have also investigated this issue, conducting an in-depth ethnographic evaluation of 10 hospitals identified in their 2016 study to have positive, neutral, or negative outcomes after ICU telemedicine implementation (Kahn, et al. *Am J Respir Crit Care Med*. 2019;199[8]:970). They found that successful programs:

(1) provided consistent services matched to recipient needs;

(2) provided services both proactively and reactively without being obtrusive;

(3) embedded routine engagements unobtrusively into usual routines;

(4) had engaged leadership who set clear expectations and mediated conflicts; and

(5) had bedside clinicians who valued and sought out telemedicine participation in care.

The authors concluded that, "the true value of ICU telemedicine lies not in whether the technology exists but in how it is applied." However, another recent analysis also suggested that, rather than telemedicine or recipient ICU design, targeting underperforming recipient ICU performance may be the key determinant of whether ICU telemedicine implementation improves outcomes (Fusaro, et al. *Crit Care Med*. 2019; 47[4]:501). While the finding may reflect regression to the mean, the idea that ICUs with above-expected mortality derive greater benefit from ICU telemedicine support than already well-performing ICUs is certainly logical.

As COVID-19 strained health care systems across the country, we and others found ways to use ICU telemedicine to preserve optimal care delivery for critically ill patients.

As COVID-19 strained health care systems across the country, we and others found ways to use ICU telemedicine to preserve optimal care delivery for critically ill patients. Our program at Intermountain Healthcare – already supporting 17 ICUs within our 24-hospital health system, as well as 10 external ICUs with experienced critical care physicians, nurses, respiratory therapists, and pharmacists – took on increased responsibility for ICU load balancing and interhospital transfers.

Leveraging telemedicine services also helped community ICUs care for sicker, more complex patients than usual and aided nonintensivist physicians called upon to manage critically ill patients in ad hoc ICUs at referral hospitals. While the

TELEMEDICINE *continued on page 16*

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Board of Regents meeting, August 16, 2022

BY MICHAEL NELSON, MD, FCCP
Regent at Large

The CHEST Board of Regents (BOR) convened a hybrid meeting in Atlanta prior to the pulmonary board review course. Hopefully, many of you had the opportunity to participate in that excellent learning experience. The function of the BOR is to provide direction and oversight for the organization's strategy and goals, including the development of the many programs that are so expertly crafted by our talented staff, with contributions from our volunteers. The BOR has adopted organizational goals and metrics around our four key pillars, including: education, people, products, and growth. Our EVP/CEO, Dr. Robert Musacchio, opened the meeting with a review of the organization's mid-year progress toward achieving these annual goals. Despite the current economic turmoil and need for flexibility in our COVID landscape, CHEST is on track to meet or exceed the majority of the stated goals. The team continues efforts to achieve our key metrics related to increasing learners, members, and growth in revenue – we anticipate the upcoming annual meeting will only bolster our progress.

Every BOR meeting includes a report from the Finance Committee, which is thoroughly reviewed by the BOR. CHEST investments have fared no better than the rest of the country, but our investment advisors assure us that things will improve.

Similar updates were given by the President of the CHEST Foundation, Dr. Ian Nathanson, who noted that the Foundation will be celebrating its 25th anniversary during CHEST 2022. I would like to personally encourage you to donate and make this year the best year of fundraising. We are eager to bolster our community and patients after the long journey through COVID. Every donation enables more investment in creating access to the profession and in piloting programs across our communities that improve access to care. Thank you to those who have already contributed.

The Board of Regents will meet a total of six times this year, either remotely or in person, to make certain that CHEST continues to fulfill its mission.

The morning session was completed with excellent presentations by the Chief Learning Officer/Education SVP, Richard Schuch and Publisher/Communications SVP, Nicki Augustyn. Rich provided an update on the education strategy and how it will change to keep up with the ever-changing needs of learners. He also made the observation that CHEST cannot do this alone, and partnering with companies to assist in new methods of content delivery will be important for the future of the organization. Nicki presented data regarding the current membership structure, as well as the effect of the pandemic on membership over the last 2 years.

In the afternoon session, the BOR and staff spent over 2 hours on the topic of advocacy. CHEST has become more active in the area of advocacy for both patients and the medical profession, specifically in the areas of pulmonary, critical care, and sleep medicine. The Health Policy and Advocacy Committee (HPAC) currently has workgroups working in five different areas, including: oxygen, pulmonary rehabilitation, coding and billing, noninvasive ventilation, and tobacco and vaping. However, CHEST is often asked to sign on to or support the advocacy efforts of other organizations, including other medical societies, patient groups, and industry groups. At times, the decision to support or not support is easy. While there is a process to make that decision, this session helped better define the process and started to create some norms around when CHEST itself should lead its own statement on a particular issue.

The BOR will meet a total of six times this year, either remotely or in person, to make certain that CHEST continues to fulfill its mission "to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research." ■

TELEMEDICINE *continued from page 14*

ad hoc ICUs at referral hospitals. While the pandemic certainly stressed ICU staff, we suspect that telemedicine's ability to balance caseloads and distribute clinical tasks helped mitigate these stresses. At age 40, ICU telemedicine is both mature and still growing, with continued expansion of bed coverage and the range of services available. Looking ahead, as we confront a national shortage of intensivists, ICU telemedicine likely represents a cost effective and efficient strategy to maintain critical care capacity with the potential to ensure low-cost, high-quality care for all, regardless of location. ■

Dr. Graham and Dr. Peltan are with the Division of Pulmonary & Critical Care Medicine, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah; and Dr. Peltan is also with the Division of Pulmonary & Critical Care Medicine, Department of Medicine, Intermountain Medical Center, Murray, Utah.

This month in the journal *CHEST*®

Editor's Picks

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

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By Orlando Garner, MD, et al.

Smartphone-Guided Self-Prone Positioning vs Usual Care in NonIntubated Hospital Ward Patients With COVID-19: A Pragmatic Randomized Clinical Trial.
By Garrett Rampon, MD, et al.

Military Service and COPD Risk.
By Laura Trupin, MPH, et al.

Comparison of Heart Rate After Phenylephrine Versus Norepinephrine Initiation in Patients With Septic Shock and Atrial Fibrillation.
By Anica C. Law, MD, et al.

High Flow Nasal Cannula Reduces Effort of Breathing but Not Consistently Via Positive End-Expiratory Pressure.
By Robert D. Guglielmo, MD, et al.

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By Travis Cruickshank, PhD, et al.

Structural and Functional Correlates of Higher Cortical Brain Regions in Chronic Refractory Cough.
By Eun Namgung, PhD, et al.

A Trial of Intranasal Corticosteroids to Treat the Childhood Obstructive Sleep Apnea Syndrome.
By Ignacio E. Tapia, MD, et al.

In Memoriam


fcafotodigital/Getty Images

CHEST has been informed of the following deaths of CHEST members.

We remember our colleagues and extend our sincere condolences.

Laurence C. Carmichael, MD, FCCP
Neil Goldberg, MD
Robin Kaplan, MD, MHA
John A. Nagle, MD
Nirav Patel, MD

NETWORKS

Bronchiectasis, obstetric critical care, and more ...

AIRWAYS DISORDERS NETWORK

Bronchiectasis Section

Antibiotics in non–cystic fibrosis bronchiectasis: new perspectives

The clearest benefit of antibiotics in managing non-cystic fibrosis bronchiectasis is for treatment of exacerbations and for chronic azithromycin use. There is a paucity of high-quality evidence for prophylactic antibiotics, though guidelines support this practice, particularly for adults with three or more exacerbations a year. A recent Cochrane database review (Spencer, et al. *Cochrane Database Syst Rev*. 2022;1[1]:CD013254) examined eight RCTs, with interventions ranging from 16 to 48 weeks, involving 2,180 adults and found little net benefit for prophylactic cycled antibiotics (fluoroquinolones, beta-lactams, and aminoglycosides) in terms of outcomes viz time-to-first-exacerbation and duration of exacerbations, but more than doubled the risk of emerging resistance.

Clinical equipoise exists regarding the duration of antibiotics during exacerbations. Guidelines favor 14 days. A recent RCT (Pallavi, et al. *Eur Respir J*. 2021;58:2004388) examined the feasibility of bacterial load-guided therapy in 47 participants with bronchiectasis requiring IV antibiotics.

Patients were randomized to either 14 days of antibiotics or treatment guided by bacterial load (BLGG). The 88% of participants in the BLGG group were able to stop antibiotics by day 8, and potentially 81% of participants in the 14-day group could have stopped antibiotics at day 8. Median time to next exacerbation was much longer – 60 days (18-110 days) in the in BLGG group vs 27.5 days (12.5-60 days) in the 14-day group vs (P = .0034). A larger multicenter RCT may clarify the benefits of this approach to shortening duration of antibiotic therapy in patients with bronchiectasis exacerbations.

O'Neil Green, MBBS, FCCP
Member-at-Large

PULMONARY VASCULAR DISEASE & CARDIOVASCULAR DISEASE NETWORK

Cardiovascular Medicine & Surgery Section

Emerging role of cardiopulmonary obstetric critical care

Despite being a developed country, maternal morbidity and mortality rates in some counties in the United States mirror that of third world countries, with 23.8 women dying per 100,000 live births (Hoyert DL, Miniño AM. Maternal mortality in the United States. *National Vital Statistics Reports*; vol 69 no 2. Hyattsville, MD: National Center for Health Statistics. 2020). The care of this vulnerable population testifies to the quality of care provided across the country. Some of these poor outcomes are directly attributed to in-hospital deaths due to pre-existing or newly discovered heart or lung diseases, such as valvular heart diseases, cardiomyopathies, pulmonary arterial hypertension, eclampsia, or other etiologies. With the development of advanced heart and lung programs across the nation capable of providing mechanical circulatory support and extracorporeal life support, we believe that incorporating a heart-lung-OB team approach to high-risk cases can identify knowledge gaps early and predict and prevent maternal complications.

We believe that incorporating a heart-lung-OB team approach to high-risk cases can identify knowledge gaps early and predict and prevent maternal complications.

In this proposed model, patients funnel to the hub facility to be cared for by a team of intensive care physicians, advanced heart failure physicians, cardiovascular and obstetric anesthesiologists, and maternal/fetal medicine physicians, with the potential addition of an adult ECMO team member.

A team huddle, using a virtual platform, would be organized by a designated OB coordinator at the patient's admission with follow-up huddles every 2 to 3 days, to ensure the team stays engaged through delivery into the postpartum period. Value could be added with subsequent cardiac or pulmonary rehabilitation. With an emphasis on shared decision making, we can make it a national priority to save every woman during the birthing process.

Bindu Akkanti, MD, FCCP,
Member-at-Large
Mark Warner, MD, FCCP,
Member-at-Large

DIFFUSE LUNG DISEASE & TRANSPLANT NETWORK

Lung Transplant Section

Strengthening lung transplant education

The number of lung transplants (LT) performed reached an all-time high in 2019 with a 52.3% increase over the previous decade. Transplants are being performed in older and sicker patients with 35% of recipients being over 65 years of age and 25% with lung allocation scores (LAS) over 60. (Valapour, et al. *Am J Transplant*. 2021;21[Suppl 2]:441). This growth has led to an increased demand for transplant pulmonologists.Lung transplant education has not kept pace with this growth, and, currently, there are limited avenues and variable models of training. There are about 15 dedicated LT fellowship programs located at 68 transplant centers with widely variable curricula. The vast majority of the 160 general pulmonary and critical care medicine (PCCM) fellowship programs do not have access to hands-on clinical transplant training and are guided by vague ACGME guidelines. A US national survey (Town JA, et al. *Ann Am Thorac Soc*. 2016;13[4]:568) of PCCM programs found that about 41% of centers did not have a transplant curriculum, and training was very variable. Another report found that a structured educational LT curriculum at a transplant center was associated with improved performance of PCCM fellows (Hayes, et al. *Teach Learn Med*. 2013;25[1]:59). The lack of a structured curriculum and wide variability coupled with lack of information about the training pathways impedes effective training.

Recognizing these issues, the lung transplant steering committee developed two webinars for the online CHEST learning portal (tinyurl.com/53pnne2k). These provide resources and information for fellows and junior faculty interested in a transplant pulmonology career as well as discuss needs and opportunities to develop a program for specialized training in LT. There is need for a multipronged approach addressing:

–Increase access to specialized transplant education for PCCM fellows.

–Develop a uniform structured curriculum for lung transplant education engaging the PCCM and transplant fellowship program directors as stakeholders.

–Increase collaboration between the transplant fellowship programs to address gaps in training.

Hakim Azhfar Ali, MBBS, FCCP
Member-at-Large

DIFFUSE LUNG DISEASE & TRANSPLANT NETWORK

Occupational & Environmental Health Section

Quaternary ammonium compounds: exposure and lung disease

Quaternary ammonium compounds (QACS) are a common ingredient in many major commercial disinfectant products. During the COVID pandemic, the use of QACS increased due to their efficacy in inactivating enveloped viruses such as SARS-COV-2 (Hora, et al. *Environ Sci & Technol Letters*. 2020;7[9]).

While these products reduce the risk of COVID-19 transmission, the increase in use has had unintended consequences. Increasing data suggest a link between QAC exposure and occupational lung disease (Migueres, et al. *J Allergy Clin Immunol Pract*. 2021;9[9]). Historically, exposure to QACs has been highest in health care workers. This is reflected in the increased risk of obstructive lung disease seen among nursing and operating room staff (Xie, et al. *JAMA Netw Open*. 2021;4[9]). In the setting of enhanced COVID-19 cleaning protocols, QACS are increasingly utilized outside of the health care setting. Custodians and janitorial staff may face increased and potentially underrecognized exposure to these compounds. In addition to the direct harms of COVID-19, we may see an increase in occupational obstructive lung disease as a result of cleaning product exposure. Early diagnosis and exposure removal is crucial to prevent a new epidemic of occupational asthma.

Maeve MacMurdo, MBChB
Member-at-Large
Abirami Subramanian, MD, MPH
Member-at-Large

CRITICAL CARE NETWORK

Palliative and End-of-Life Care Section

Time-limited trials of critical care

Many patients die in the ICU, often after long courses of aggressive interventions, with potentially nonbeneficial treatments. Surrogate

NETWORKS *continued on following page*

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decision makers are tasked with decisions to initiate or forgo treatments based on recommendations from clinicians in the face of prognostic uncertainty and emotional duress. A strategy that has been adopted by ICU clinicians to address this has been proposing a "time-limited trial" (TLT) of ICU-specific interventions. A TLT involves clinicians partnering with patients and their surrogate decision makers in a shared decision-making model, proposing initiation of treatments for a set time, evaluating for specific measures of what is considered beneficial, and deciding to continue treatment or stop if without benefit. Core elements of TLT include utilizing the multidisciplinary team caring for the patient, evaluating for any prior advanced care planning, using clear and concise communication, acknowledging uncertainty, and collaborating with palliative care teams (Vink EE, et al. *Intensive Care Med*. 2018;44:1369). Recent research about TLT in the ICU has found that when executed well, TLTs can improve quality of care and provide patients with the care they desire and can benefit from (Vink, et al). Additionally, the use of an education intervention for ICU clinicians regarding protocolled TLT interventions was associated with improved quality of family meetings, and, importantly, a reduced intensity and duration of ICU treatments (Chang DW, et al. *JAMA Intern Med*. 2021;181[6]:786).

Bradley Hayward, MD
Member-at-Large

A strategy that has been adopted by ICU clinicians has been proposing a "time-limited trial" (TLT) of ICU-specific interventions.

THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK

Pleural Disease Section

Aspirate or wait: changing the paradigm for PSP care

There is considerable heterogeneity in the management of primary spontaneous pneumothorax (PSP). Although observation for small asymptomatic PSP is supported by current guidelines, management recommendations for larger PSP remains unclear (MacDuff, et al. *Thorax*. 2010;65[Suppl 2]:ii18-ii31; Tschopp JM, et al. *Eur Respir J*. 2015;46[2]:321). Two recent RCTs explore conservative vs intervention-based management in those with larger or symptomatic PSP. In the PSP trial, Brown and colleagues prospectively randomized 316 patients with moderate to large PSP to either conservative management (≥ 4 hour observation) or small-bore chest tube without suction (Brown, et al. *N Engl J Med*. 2020;382[5]:405). Although non-inferiority criteria were met, the primary outcome of radiographic resolution of pneumothorax within 8 weeks of randomization was not statistically robust to conservative assumptions about missing data. They concluded that conservative management was noninferior to intervention, and it resulted in a

lower risk of serious adverse events or PSP recurrence than interventional management. The multicenter randomized Ambulatory Management of Primary Pneumothorax (RAMPP) trial compared ambulatory management of PSP using an 8F drainage device to a guideline-driven approach (drainage, aspiration, or both) amongst 236 patients with symptomatic PSP. Intervention shortened length of hospital stay (median 0 vs 4 days, *P*<.0001), but the intervention arm experienced more adverse events (including enlargement of pneumothorax, as well as device malfunction) (Hallifax RJ, et al. *Lancet*. 2020;396[10243]:39). These two trials challenge the current guidelines for management for patients with PSP, but both had limitations. Though more data are needed to establish a clear consensus, these studies suggest that a conservative pathway for PSP warrants further consideration.

Tejaswi R. Nadig, MBBS, Member-at-Large; Yaron Gesthalter, MD, Member-at-Large; Priya P. Nath, MD, Member-at-Large

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SLEEP MEDICINE NETWORK

Respiratory-Related Sleep Disorders Section

Sleep health and fatigue mitigation during medical training

Medical trainees may experience acute or chronic sleep deprivation due to extended work hours and shift-work sleep schedules. Extended work hours may lead to serious medical errors, percutaneous injuries, prolonged task completion, and car crashes or near misses while driving (Landrigan, et al. *N Engl J Med*. 2004;351:1838; Ayas, et al. *JAMA*. 2006;296[9]:1055; Taffinder, et al. *Lancet*. 1998;352[9135]:1191; Barger, et al. *N Engl J Med*. 2005 Jan 13;352[2]:125).

Chronic sleep restriction also results in neurobehavioral and cognitive dysfunction without a proportionate increase in self-perceived sleepiness [Belenky, et al. *J Sleep Res*. 2003;12[1]:1; Van Dongen, et al. *Sleep*. 2003;26[2]:117). In 1987, when sleep deprivation was cited as a major cause of 18-year-old Libby Zion's death, the ACGME restricted residents from working more than 80 hours per week. ACGME

mandates that training programs provide yearly fatigue mitigation education.

A "Sleep Alertness and Fatigue Education in Residency" module may be purchased through the American Academy of Sleep Medicine. While one-time education opportunities are available, there remains a need for access to longitudinal, individualized tools during varying rotations and circumstances, as education alone has not been shown to improve sleep quality (Mazar D, et al. *J Clin Sleep Med*. 2021;17[6]:1211). The American Thoracic Society Early Career Professional Working Group offers individualized lectures to training programs. Wake Up and Learn is a sleep education program for children and teens that is currently being expanded for medical trainees.

Further data are needed to see if longitudinal and individualized support can promote better sleep quality among trainees.

Aesha Jobanputra, MD
Section Member
Sreelatha Naik, MD
Member-at-Large

Access unmatched asthma education from anywhere

CHEST is proud to announce the launch of the newest addition to our e-learning options: the CHEST Asthma Curriculum Pathway.

This unique offering combines a variety of bite-sized educational resources from among CHEST's most popular and effective products, including case-based CHEST SEEK™ questions, podcasts and videos from asthma experts, the latest research from the journal *CHEST*®, and more.

The pathway comprises several different "paths," or tracks, that enable clinicians to target their education based on their knowledge gaps and career level. Users can opt to follow the curriculum from start to finish to gain a comprehensive

overview of asthma management. Or, they can select individual paths to focus their learning on topics including asthma pathophysiology, diagnosis and classification, exacerbations, phenotypes, and more.

According to early learners of the pathway: "The multiple ways of looking at different therapies in the management of asthma was helpful in remembering the information. It helped a lot with the knowledge check-in." Another commented: "It is very comprehensive on all aspects of asthma. I enjoyed the higher-level learning on the choice of biologics and asthma mimickers." The education modalities were highlighted, as well, with this feedback: "I really enjoyed the variety of media (lectures, discussions, papers, games)."

Exploring the education

The Asthma Curriculum Pathway offers targeted education options to fit the career level and clinical interest of clinicians, ranging from trainees and early career physicians to experienced asthma specialists and advanced practice providers.

ASTHMA *continued on following page*

ASTHMA *continued from previous page*

Paths include:
- Path 1: Pathophysiology
- Path 2: Diagnosis & Classification
- Path 3: Management
- Path 4: Mimickers
- Path 5: Comorbidities
- Path 6: Phenotypes
- Path 7: Exacerbations
- Path 8: Special Situations

Plus, each path offers claiming credit, including CME, for completion—all while driving clinicians to consistently advance best outcomes for their patients with asthma.

Visit (https://bit.ly/asthma-pathway) to access the best of CHEST's asthma education with the new Asthma Curriculum Pathway, accessible via web or mobile device. ■

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2022 billing and coding updates

Telehealth and Teaching Physician Services and ICD-10 codes updates

BY HUMAYUN ANJUM, MD, FCCP

In my previous article in June, 2022, we plowed through the billing and coding updates regarding critical care services, and, I hope that it helped our readers get more acquainted with the nuances of billing and coding in the ICU. In this piece, I would like to briefly elucidate three other areas of practice, which will be relevant to all physicians across various specialties.

Telehealth services

The Centers for Medicare & Medicaid Services (CMS) graciously added telehealth services temporarily to its list of services due to the COVID-19 public health emergency (PHE). Initially, the plan was to remove these from the list of covered services by the latter end of the COVID-19 PHE, which, created some uncertainty, or by December 31, 2021. Fortunately, CMS finalized that they will extend it through the end of the calendar year (CY) 2023. So, now all the telehealth services will remain on the CMS list until December 31, 2023. The general principle behind this ruling is to allow for more time for CMS and stakeholders to gather data and to submit support for requesting these services to be permanently added to the Medicare telehealth services list.

Not only has CMS extended the deadline for telehealth services but also they have gone far and beyond to extend some of the codes for cardiac and intensive cardiac rehabilitation until December 31, 2023, as well.

There has been a lot of debate regarding the geographic restrictions when it comes to telehealth visits for diagnosis, evaluation, or treatment of a mental health disorder. As per the latest Consolidated Appropriations Act of 2021 (Section 123), the home of the patient is a permissible site. But, the caveat is that there must be an in-person service with the practitioner/physician within 6 months

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prior to the initial telehealth visit. Additionally, there has to be a set frequency for subsequent in-person visits. And, usually the subsequent visits will need to be provided at least every 12 months. These requirements are not set in stone and can be changed on a case-by-case basis provided there is appropriate documentation in the chart.

Lastly, it is important to understand and use the appropriate telecommunication systems for the telehealth visits and the modifiers that are associated with them. By definition, it has to be audio and video equipment that allows two-way, real-time interactive communication between the patient and the provider when used for telehealth services for the diagnosis, evaluation, or treatment of mental health disorders. But, CMS is in the process of amending it to include audio-only communications technology. At this time, the use of audio-only interactive telecommunications system is limited to practitioners who have the capability to provide two-way audio/video communications but, where the patient is not capable, or does not consent to, the use of two-way audio/video technology. Modifier **FQ** should be attached to all the mental health services that were furnished using audio-only communications. And, mental health services can include services for treatment of substance use disorders (SUD). Please do not confuse modifier **FQ** with modifier **93** as **FQ** is only for behavioral health services. And, remember that the totality of the communication of information exchanged between the provider and the patient during the course of the synchronous telemedicine service (rendered via telephone or other real-time interactive audio only telecommunication system) must be of an amount and nature that is sufficient to meet the key components and/or requirements of the same service when rendered via a face-to-face interaction.

Dr. Anjum

Teaching physician services

As a general rule, a teaching physician can bill for the resident services only if they are present for the critical (key) portion of the service. But, there is one exception called the "primary care exception" under which in certain teaching hospital primary care centers, the teaching physician can bill for certain services as furnished independently by the resident without the teaching physician being physically present, but with the teaching physician's review.

The current model to bill for office/outpatient E/M visit level is either based on either total time spent (personally) or medical-decision-making (MDM). When time is used to select the visit level only the time spent by the teaching physician in qualifying activities can be included for the purposes of the visit level selection. And, this includes the time the teaching physician was present with the resident performing those qualifying activities. Also, under the primary care exception, time cannot be used to select the visit level. This is to guard against the possibility of inappropriate coding that reflects residents' inefficiencies rather than a measure of the total medically necessary time required to furnish the E/M services.

ICD-10 updates

Usually, the ICD-10 codes are updated annually and take effect every October 1. Some of the most relevant updates are as follows:

1. U09.9 Post COVID-19 condition, unspecified: This should be used to document sequelae of COVID-19 or "long COVID" conditions, after the acute illness has resolved. But, remember to code the conditions related to COVID-19 first and do not use this code with an active or current COVID-19 infection.

2. U07.0 Vaping-related disorder: This should be used for all vaping-related illnesses. However, additional codes for other diagnoses such as acute respiratory failure, acute respiratory distress syndrome, or pneumonitis can also be used with this code. Other respiratory signs and symptoms such as cough and shortness of breath should not be coded separately.

3. Cough is one of the most common reasons for referral to a pulmonologist. The CDC has expanded these codes so please remember to code the most specific diagnosis as deemed appropriate.

R05.1 Acute cough
R05.2 Subacute cough
R05.3 Chronic cough
R05.4 Cough, syncope
R05.8 Other specified cough
R05.9 Cough, unspecified

We will be back with some more exciting and intriguing billing and coding updates in our next article and hope to see everyone at CHEST 2022 in Nashville., TN. ■

Obstructive sleep apnea linked to unprovoked VTE

BY NEIL OSTERWEIL
MDedge News

Add unprovoked venous thromboembolic events (VTE) to the list of potential consequences of severe obstructive sleep apnea (OSA). That conclusion comes from a study showing that patients with OSA who had the longest nocturnal hypoxemia episodes had a twofold risk for venous thromboembolic events.

The association between nocturnal hypoxemia and VTE was strongest among patients who did not use continuous positive airway pressure (CPAP) systems, reported Wojciech Trzepizur, MD, of Angers University Hospital, France.

Previous studies have suggested links between OSA and both cancer and cognitive decline, but this is the first study to investigate the association between OSA and the incidence of unprovoked VTE, he reported in an oral abstract session at the annual congress of the European Respiratory Society.

"We found that those who spent more than 6% of their nighttime with levels of oxygen in their blood below 90% of normal had an almost twofold risk of developing VTEs compared to patients without oxygen deprivation," he said.

Dr. Trzepizur and colleagues conducted a retrospective study linking cohort data to an administrative health database. They identified unprovoked VTE in patients with a suspicion for OSA and no previous VTE. They created Cox proportional hazard models to assess the association of unprovoked VTE with apnea hypopnea index (AHI) measures and nocturnal hypoxemia markers, including the time patients spent below 90% oxygen saturation (T90), oxygen desaturation index (ODI), and hypoxic burden, defined as the total area under the respiratory event-related desaturation curve.

They found that, after a median follow-up of 6.3 years, 104 out of 7,355 patients had an unprovoked VTE. In an unadjusted hazard model, there were significant associations between VTE and T90, as well as with hypoxic burden, but not with either AHI or ODI.

However, in an analysis adjusted for age, gender, body mass index, alcohol intake, hypertension, depression, history of cardiovascular disease, statin use, type of

VTE *continued on following page*

COVID // *continued from page 1*

they are looking on the internet and find us," Dr. Azola said.

This mix of patients at Dr. Azola's clinic is out of step with the demographics of Baltimore, where the majority of residents are Black, half of them earn less than $52,000 a year, and one in five live in poverty. And this isn't unique to Hopkins. Many of the dozens of specialized long COVID clinics that have cropped up around the country are also seeing an unequal share of affluent White patients, experts say.

It's also a patient mix that probably doesn't reflect who is most likely to have long COVID.

During the pandemic, people who identified as Black, Hispanic, American Indian, or Alaska Native were more likely to be diagnosed with COVID than people who identified as White, according to the Centers for Disease Control and Prevention. These people of color were also at least twice as likely to be hospitalized with severe infections, and at least 70% more likely to die.

"Data repeatedly show the disproportionate impact of COVID-19 on racial and ethnic minority populations, as well as other population groups such as people living in rural or frontier areas, people experiencing homelessness, essential and frontline workers, people with disabilities, people with substance use disorders, people who are incarcerated, and non–U.S.-born persons," John Brooks, MD, chief medical officer for COVID-19 response at the CDC, said during testimony before the U.S. House Energy and Commerce Subcommittee on Health in April 2021.

"While we do not yet have clear data on the impact of post-COVID conditions on racial and ethnic minority populations and other disadvantaged communities, we do believe that they are likely to be disproportionately impacted ... and less likely to be able to access health care services," Dr. Brooks said at the time.

The picture that's emerging of long COVID suggests that the condition impacts about one in five adults. It's more common among Hispanic adults than among people who identify as Black, Asian, or White. It's also more common among those who identify as other races or multiple races, according survey data collected by the CDC.

It's hard to say how accurate this snapshot is because researchers need to do a better job of identifying and following people with long COVID, said Monica Verduzco-Gutierrez, MD, chair of rehabilitation medicine and director of the COVID-19 Recovery Clinic at the University of Texas Health Science Center at San Antonio. A major limitation of surveys like the ones done by the CDC to monitor long COVID is that only people who realize they have the condition can get counted.

"Some people from historically marginalized groups may have less health literacy to know about impacts of long COVID," she said.

Lack of awareness may keep people with persistent symptoms from seeking medical attention, leaving many long COVID cases undiagnosed.

When some patients do seek help, their complaints may not be acknowledged or understood. Often, cultural bias or structural racism can get in the way of diagnosis and treatment, Dr. Azola said.

"I hate to say this, but there is probably bias among providers," she said. "For example, I am Puerto Rican, and the way we describe symptoms as Latinos may sound exaggerated or may be brushed aside or lost in translation. I think we miss a lot of patients being diagnosed or referred to specialists because the primary care provider they see maybe leans into this cultural bias of thinking this is just a Latino being dramatic."

Dr. Azola

There's some evidence that treatment for long COVID may differ by race even when symptoms are similar. One study of more than 400,000 patients (PM R. 2022 Jul 5. doi: 10.1002/pmrj.12869), for example, found no racial differences in the proportion of people who have six common long COVID symptoms: shortness of breath, fatigue, weakness, pain, trouble with thinking skills, and a hard time getting around. Despite this, Black patients were significantly less likely to receive outpatient rehabilitation services to treat these symptoms.

Benjamin Abramoff, MD, who leads the long COVID collaborative for the American Academy of Physical Medicine and Rehabilitation, draws parallels between what happens with long COVID to another common health problem often undertreated among patients of color: pain. With both long COVID and chronic pain, one major barrier to care is "just getting taken seriously by providers," he said.

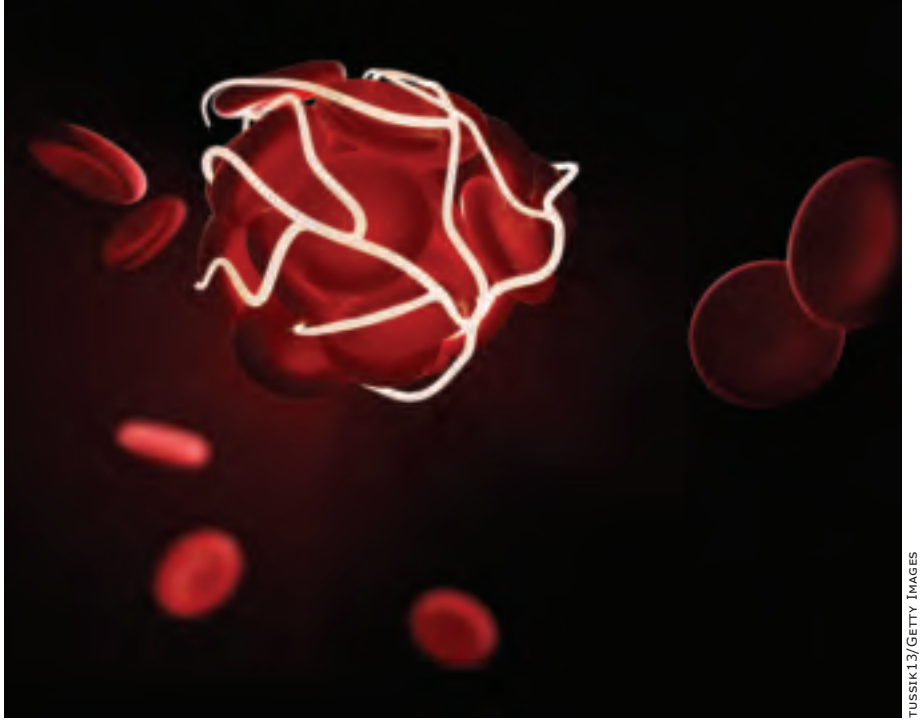
"There is significant evidence that racial bias has led to less prescription of pain medications to people of color," Dr. Abramoff said. "Just as pain can be difficult to get objective measures of, long COVID symptoms can also be difficult to objectively measure and requires trust between the provider and patient."

Geography can be another barrier to care, said Aaron Friedberg, MD, clinical colead of the post-COVID recovery program at Ohio State University Wexner Medical Center, Columbus. Many communities hardest hit by COVID – particularly in high-poverty urban neighborhoods – have long had limited access to care. The pandemic worsened staffing shortages at many hospitals and clinics in these communities, leaving patients even fewer options close to home.

"I often have patients driving several hours to come to our clinic, and that can create significant challenges both because of the financial burden and time required to coordinate that type of travel, but also because post-COVID symptoms can make it extremely challenging to tolerate that type of travel," Dr. Friedberg said.

Even though the complete picture of who has long COVID – and who's getting treated and getting good outcomes – is still emerging, it's very clear at this point in the pandemic that access isn't equal among everyone and that many low-income and non-White patients are missing out on needed treatments, Dr. Friedberg said.

"One thing that is clear is that there are many people suffering alone from these conditions," he said. ■



TUSSIK13/GETTY IMAGES

VTE *continued from previous page*

sleep study, study site, and CPAP adherence, the investigators found that only T90 remained a significant independent predictor of VTE, with a hazard ratio of 1.06, $P = .02$.

The association between T90 and VTE strengthened as the time spent below 90% saturation increased. Patients in the highest tercile, who spent more than 6% of the time undersaturated, had an HR for VTE of 1.95 ($P = .02$), compared with those patients who had a T90 less than 1%.

There were no significant differences in VTE risk between patients who used CPAP for more than 4 hours per night and those who either used the devices for less than 4 hours or refused CPAP.

"We see that T90 seems to be a strong parameter," said session comoderator Raphael Heinzer, MD, MPH, of Lausanne University Hospital, Switzerland.

Dr. Heinzer's comoderator, Silke Ryan, MD, of University College Dublin, pointed out that although T90 was the main predictor of responses, Dr. Trzepizur and colleagues did not control for other pulmonary diseases. "Obviously, there could be an influence of other hypoxic-related diseases," she said, and recommended controlling for this in future studies.

Winfried Randerath, MD, of the Bethanien Hospital at the University of Cologne, Germany, head of the ERS specialist group on sleep disordered breathing, said that this study and others presented at the meeting "show worrying associations between OSA and important diseases that affect survival and quality of life.

"While they cannot prove that OSA causes any of these health problems, people should be made aware of these links and should try to make lifestyle changes in order to reduce their risk of OSA, for instance, by maintaining a healthy weight. However, if OSA is suspected, definite diagnosis and treatment should be initiated. We look forward to further research that may help to clarify whether OSA may be causing some of the health problems seen in these studies," said Dr. Randerath, who was not involved with the study.

The study was supported by a grant from Institut de Recherche en Santé Respiratoire des Pays de la Loire (IRSR), Beaucouzé, France. Dr. Trzepizur, Dr. Heinzer, Dr. Ryan and Dr. Randerath reported no relevant financial relationships. ■

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