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 to "lung-on-a-chip" models – that are moving pulmonary research forward and poised to affect toxicity testing, drug development, and other areas.

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...
NUCALA is for the:

- add-on maintenance treatment of patients 6+ with SEA. Not for acute bronchospasm or status asthmaticus.
- add-on maintenance treatment of CRSwNP in patients 18+ with inadequate response to nasal corticosteroids.
- treatment of adult patients with EGPA.
- treatment of patients aged 12+ with HES for ≥6 months without an identifiable non-hematologic secondary cause.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.
IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred
with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie,
days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistische Infections: Herpes Zoster
Herpes zoster infections have occurred in patients receiving NUCALA. Consider vaccination if medically appropriate.

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

Parasitic (Helminth) Infection
Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become
infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until
infection resolves.

ADVERSE REACTIONS

Most common adverse reactions (≥5%) in patients receiving NUCALA:

• Severe asthma trials: headache, injection site reaction, back pain, fatigue
• CRSwNP trial: oropharyngeal pain, arthralgia
• EGPA and HES trials (300 mg of NUCALA): no additional adverse reactions were identified to those reported in
severe asthma clinical trials

Systemic reactions, including hypersensitivity, occurred in clinical trials in patients receiving NUCALA. Manifestations
included rash, pruritus, headache, myalgia, flushing, urticaria, erythema, fatigue, hypertension, warm sensation in
trunk and neck, cold extremities, dyspnea, stridor, angioedema, and multifocal skin reaction. A majority of systemic
reactions were experienced the day of dosing.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women with asthma exposed to NUCALA during
pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/asthma.

The data on pregnancy exposures are insufficient to inform on drug-associated risk. Monoclonal antibodies, such
as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore,
potential effects on a fetus are likely to be greater during the second and third trimesters.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.
MUCALA (mepolizumab) for injection, for subcutaneous use

MUCALA (mepolizumab) is indicated for:

- For the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma and an eosinophilic phenotype [see Use in Specific Populations (8.4) and Clinical Studies (14.1) of full prescribing information].
- For the reduction of corticosteroid dosage in adult and adolescent patients aged 12 years and older with severe asthma and an eosinophilic phenotype [see Use in Specific Populations (8.4) and Clinical Studies (14.1) of full prescribing information].

BRIEF SUMMARY

52-Week Trial: Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthma, bronchitis, cystitis, dizziness, dyspnea, ear infection, gas troesophageal reflux disease, nasopharyngitis, nasopharyngitis, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in patients receiving mepolizumab 75 mg IV compared with 2 patients in the placebo group.

Systemic Reactions, including hypersensitivity reactions: In Trials 1, 2, and 3 described above, the incidence of patients who experienced systemic allergic or non-allergic reactions was 3% in the group receiving MUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving MUCALA 100 mg and 2% of patients in the placebo group. The most commonly reported manifestations of systemic allergic reactions reported in the group receiving MUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving MUCALA 100 mg and 3% of patients in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving MUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in patients receiving MUCALA 100 mg (5%) were experienced on the day of dosing.

Injection Site Reactions: injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 5% in patients receiving MUCALA 100 mg compared with 3% in patients receiving placebo. Local injection reactions were experienced by a hundred ninety-eight patients receiving MUCALA 100 mg in ongoing open-label extension trials during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

Pediatric Patients: Aged 6 to 11 Years

The safety data for MUCALA is based upon a 1 open-label clinical trial that enrolled 36 patients with severe asthma aged 6 to 11 years. Patients received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of MUCALA administered subcutaneously once every 4 weeks. Patients received MUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 patients received MUCALA for a further 52 weeks (long phase). The adverse reaction profile for patients aged 6 to 11 years was similar to that observed in patients aged 12 years and older.

6.2 Clinical Trials Experience in Chronic Rhinosinusitis with Nasal Polyps

A total of 457 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial who received MUCALA 100 mg or placebo subcutaneously every 4 weeks. Patients had recurrent CRSwNP with a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS. Of those, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS. Of those 1,192 patients, 18% were White, and ages ranged from 12 to 82 years. Approximately 2% of patients receiving MUCALA 100 mg withdrew from study treatment due to adverse events compared with 2% of patients receiving placebo. Table 2 summarizes adverse reactions that occurred in ≥3% of MUCALA-treated patients and more frequently than in patients treated with placebo in the CRSwNP trial.

6.3 Clinical Trials Experience in Chronic Rhinosinusitis with Polyangiitits

A total of 136 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received MUCALA subcutaneously once every 4 weeks. Patients received MUCALA subcutaneously once every 4 weeks. Of those 136 patients, 53% were White, 40% were Asian, and 7% were Black or African American. Of the patients enrolled, 62% were female. Ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously every 4 weeks; 263 patients received MUCALA (mepolizumab 100 mg subcutaneously) for at least 24 weeks. Serious adverse events occurred in 15 patients and in a greater percentage of patients receiving MUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 patients vs. 0 patients, respectively). Approximately 2% of patients receiving MUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of patients receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with MUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with MUCALA with ≥3% Incidence and More Common Than Placebo in Patients with Severe Asthma (Trials 2 and 3)
6 ADVERSE REACTIONS (cont'd)
Injection Site Reactions
Injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of NUCALA compared with 4% in patients receiving placebo.

6.5 Immunogenicity
In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab.

There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 mg or 100 mg, 25/36 (70%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.

In patients with CSRwNP, 263 patients received NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with EGPA.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sampling timing, timing of sample collection, concomitant medications, and underlying disease.

6.6 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to NUCALA or a combination of these factors.

In the postmarketing experience, a single, open-label, single-blind European Registry trial evaluated the safety and effectiveness of NUCALA in patients aged 6 to 11 years with severe asthma or asthma with CRSwNP. 2,435 patients with asthma and 111 with asthma and CRSwNP were enrolled in this 52-week extension trial [see Clinical Studies (14.5) of full prescribing information].

56 patients developed antibodies against mepolizumab. Of these, 55% of patients receiving 100 mg NUCALA and 2% of patients receiving placebo developed anti-mepolizumab antibodies. No patient developed a neutralizing antibody.

Injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving 300 mg NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA were: respiratory symptoms (7%), skin manifestations (5%), and injection site reactions (2%). No serious allergic/hypersensitivity reactions were reported. There were no reports of development of anaphylaxis.

Anaphylaxis: Anaphylaxis has been reported with mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 mg or 100 mg, 25/36 (70%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.

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7 DRUG INTERACTIONS
Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary
The data on pregnancy exposure are insufficient to inform on drug-associated risk. Maternal antibodies, such as mepolizumab, are transferred across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg subcutaneous (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preterm labor in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as needed to maintain optimal control.

Data
Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an AUC basis with maternal IV dosages up to 100 mg/kg over every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.

A study that investigated the potential for mepolizumab to cause fetal effects found mepolizumab to be completely cleared before birth. In a study that evaluated the potential for mepolizumab to cause fetal effects, the potential for mepolizumab to cause fetal effects, the observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sampling timing, timing of sample collection, concomitant medications, and underlying disease.

8.2 Lactation
Risk Summary
There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy (see Use In Specific Populations (8.1)). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.3 Pediatric Use
Severe Asthma
The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 to 11 years.

Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT01691521) and had a mean age of 14.8 years. Patients had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS and additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/μL at screening or ≥300 cells/μL within 12 months prior to enrolment. [See Clinical Studies (14.1) of full prescribing information] Patients had a reduction in the rate of exacerbations that trended in favor of NUCALA. Of the 10 adolescents who received NUCALA 100 mg and the mean age approximately 16 years, 3 patients developed antibodies against mepolizumab. Of these, 55% of patients receiving 100 mg NUCALA and 2% of patients receiving placebo developed anti-mepolizumab antibodies. No patient developed a neutralizing antibody.

Use of NUCALA in pediatric patients aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial (NCT02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneous every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg SC [see Clinical Pharmacology (12.3) of full prescribing information].
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’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 – approximatley 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 emulate 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 (ICI 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 tissue 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.”

Models // continued from page 1

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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.

“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 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 toxicity–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 a lung-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 vascularility,” said Dr. Huh, associate professor in the university’s department of bioengineering. “The increased vascular density can also change the pharmacokinetics of drugs 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 pathophysiologic 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 new 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 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 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. Ingber 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.
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)

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-IIIIA).10 Knowing the patient’s complete molecular profile and PD-L1 status can help physicians make optimal treatment decisions for their patients.7

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 III, 13-36%; stage IV, 0-10%.11

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-IIIIA).10 Knowing the patient’s complete molecular profile and PD-L1 status can help physicians make optimal treatment decisions for their patients.7

EGFR mutations: an important driver of disease
EGFR mutations are a key biomarker in NSCLC, driving tumor growth across stages and impacting recurrence.12-13 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-IIIB resectable EGFRm 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.

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.
or targeted therapy.\(^9\) These approaches help ensure every eligible patient receives guideline-recommended \(\text{EGFR}\) and \(\text{PD-L1}\) 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 \(\text{EGFR}\) and \(\text{PD-L1}\) 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.\(^12-19\) 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.\(^7,14\)

**Footnotes**

1. 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 (HR=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.\(^13\)

2. In a single-center study using tumor registry data to identify all cases of stage II 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 II NSCLC vs 35.1% of patients (20 of 57 patients) seen outside of the MDC (P<0.001). In addition, Friedman et al identified 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).\(^13\)

3. 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 6267) of patients whose care was coordinated in an MDC received care that was within the standards of the NCCN Guidelines\(^6\) 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).\(^16\)

4. NCCN-National Comprehensive Cancer Network\(^9\) (NCCN)\(^\)®

**References**


9. References with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2022. ©National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed September 2, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.


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 drugs 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 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.

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).

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 spleum 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) than 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 glucocorticoids 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 Concept 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

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oint-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.

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 anesthesiology 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 transthoracic echocardiography in a POCUS curriculum

This modality of imaging has been, until recently, reserved for cardiologists and anesthesiologists. More recently transthoracic 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 (TEE) 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.
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 Chairman 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 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 Galatsatos, 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 with 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 is a raised speaking Spanish at home and learned English primarily in school. Being bilingual helped him in medicine greatly: in clinic, he could communicate with patients in their native language.

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

Dr. De Marco

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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 truly endless.

Grant continued on following page
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 under-represented 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.”

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ICU telemedicine turns 40

BY JEFFREY D. GRAHAM II, MD, AND ITATHAN 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).

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. However, 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 (Cousstasse, 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 (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 consultation 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...
Discover updated results from the ADAURA Trial

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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. Pelton 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. Pelton 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

Management of Life-Threatening Asthma: Severe Asthma Series.
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 Phrenylephrine 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.

Reproducibility of Maximum Respiratory Pressure Assessment: A Systematic Review and Metaanalysis.
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.

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

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 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.
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 6, 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 (Hoyer DL, Minño 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.

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/53pmnc2k). 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 Ashfar 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.

Maeva 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

NEWS FROM CHEST

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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

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<0.001), 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

See how the clinical trial data adds up at OFEVhcp.com/experience

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)
Elevated Liver Enzymes and Drug-Induced Liver Injury (cont’d)
• Patients with low body weight (less than 65 kg), patients who are Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may result in increased liver enzymes.
• Conduct liver function tests prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Gastrointestinal Disorders
Diarrhea
• Events were primarily mild to moderate in intensity and occurred within the first 3 months.
• In IPF studies, diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and less than 1% in placebo patients, respectively.

Please see additional Important Safety Information on the following pages and accompanying Brief Summary of Prescribing Information.
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[915]: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

**NEWS FROM CHEST**

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (Cont’d)**

**Gastrointestinal Disorders (cont’d)**

**Diarrhea (cont’d)**

- In the chronic fibrosing ILDs with a progressive phenotype study, diarrhea was reported in 67% versus 24% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 16% and discontinuation in 6% of OFEV patients, compared to less than 1% of placebo-treated patients, respectively.

- In the SSc-ILD study, diarrhea was the most frequent gastrointestinal event reported in 76% versus 32% of patients treated with OFEV and placebo, respectively. Diarrhea led to permanent dose reduction in 22% and discontinuation in 7% of OFEV patients versus 1% and 0.3% in placebo patients, respectively.

- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and anti-diarrheal medication (e.g., loperamide), and consider dose reduction or treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

**Nausea and Vomiting**

- In IPF studies, nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.

- In the chronic fibrosing ILDs with a progressive phenotype study, nausea was reported in 29% versus 9% and vomiting was reported in 18% versus 5% of patients treated with OFEV and placebo, respectively. Nausea led to discontinuation of OFEV in less than 1% of patients, and vomiting led to discontinuation of OFEV in 1% of the patients.

- In the SSc-ILD study, nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.

- In most patients, events were primarily of mild to moderate intensity. If nausea or vomiting persists despite appropriate supportive care including antiemetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

**Embryo-Fetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use highly effective contraception at initiation of treatment, during treatment, and at least 3 months after the last dose of OFEV. Mirtedanih does not change the exposure to oral contraceptives containing ethinylestradiol and levonorgestrel in patients with SSC-ILD. However, the efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhea or other conditions where drug absorption may be reduced. Advise women taking oral hormonal contraceptives experiencing these conditions to use alternative highly effective contraception. Verify pregnancy status prior to starting OFEV and during treatment as appropriate.

**Arterial Thromboembolic Events**

- In IPF studies, arterial thromboembolic events were reported in 2.5% of OFEV and less than 1% of placebo patients, respectively. Myocardial infarction (MI) was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and in less than 1% of placebo patients.

- In the chronic fibrosing ILDs with a progressive phenotype study, arterial thromboembolic events and MI were reported in less than 1% of patients in both treatment arms.

- In the SSc-ILD study, arterial thromboembolic events were reported in 0.7% of patients in both the OFEV-treated and placebo-treated patients. There were 0 cases of MI in OFEV-treated patients compared to 0.7% of placebo-treated patients.

- Use caution when treating patients at higher cardiovascular risk, including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

**Risk of Bleeding**

- OFEV may increase the risk of bleeding.

- In IPF studies, bleeding events were reported in 10% of OFEV versus 7% of placebo patients.

- In the chronic fibrosing ILDs with a progressive phenotype study, bleeding events were reported in 11% of OFEV versus 13% of placebo patients.

- In the SSc-ILD study, bleeding events were reported in 11% of OFEV versus 8% of placebo patients.

- In clinical trials, epistaxis was the most frequent bleeding event. There have been post-marketing reports of non-serious and serious bleeding events, some of which were fatal. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

**Gastrointestinal Perforation**

- OFEV may increase the risk of gastrointestinal perforation.

- In IPF studies, gastrointestinal perforation was reported in less than 1% of OFEV versus 0% of placebo patients.

- In the chronic fibrosing ILDs with a progressive phenotype study, gastrointestinal perforation was not reported in any treatment arm.

- In the SSc-ILD study, no cases of gastrointestinal perforation were reported in either OFEV or placebo-treated patients.
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.

Asha Jobanputra, MD
Section Member
Sreevaltha Naik, MD
Member-at-Large

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**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONT'D)**

**Gastrointestinal Perforation (cont’d)**
- In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, have a previous history of diverticular disease, or who are receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

**Nephrotic Range Proteinuria:** Cases of proteinuria within the nephrotic range have been reported in the postmarketing period. Histological findings, when available, were consistent with glomerular microangiopathy with or without renal thrombi. Improvement in proteinuria has been observed after OFEV was discontinued; however, in some cases, residual proteinuria persisted. Consider treatment interruption in patients who develop new or worsening proteinuria.

**ADVERSE REACTIONS**

Adverse Reactions observed in clinical trials were as follows:

**Idiopathic Pulmonary Fibrosis**
- The most common adverse reactions reported (greater than or equal to 5%) were diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.
- The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and MI (1.5% vs. 0.4%). The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

**Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype**
- The most common adverse reactions were consistent with those observed in IPF and also included nasopharyngitis, upper respiratory infection, urinary tract infection, fatigue and back pain.
- The most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of OFEV patients and in 5% of placebo patients. No pattern was identified in the adverse events leading to death.

**Systemic Sclerosis-Associated Interstitial Lung Disease**
- The most common adverse reactions reported (greater than or equal to 5%) were diarrhea, nausea, vomiting, skin ulcer, abdominal pain, liver enzyme elevation, weight decreased, fatigue, decreased appetite, headache, pyrexia, back pain, dizziness, and hypertension.

**DRUG INTERACTIONS**

- P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

- Anticoagulants: Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

**USE IN SPECIFIC POPULATIONS**

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.
- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

**INDICATIONS**

OFEV is indicated in adults for:
- Treatment of idiopathic pulmonary fibrosis (IPF).
- Treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
- Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

CL-OF-100055 01.18.2022

Please see accompanying Brief Summary of Prescribing Information on the following pages.

**References:**
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 asthmas 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 understanding of the latest asthma research and management strategies.

**OFEV** (nintedanib) capsules, for oral use

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Please see package insert for full Prescribing Information, including Patient Information

1 INDICATIONS AND USAGE: 1.1 Idiopathic Pulmonary Fibrosis: OFEV is indicated for the treatment of adults with idiopathic pulmonary fibrosis (IPF) 1.2 Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype: OFEV is indicated for the treatment of adults with chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. 1.3 Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV is indicated for the treatment of adults with systemic sclerosis (SSc)-ILD and the majority of patients with SSc-ILD had elevations less than 2 times ULN. In the SSc-ILD study (Study 4), a maximum ALAT and ALT greater than or equal to 3 times ULN was observed for 0.4% of patients in the OFEV group and for 0.3% of patients in the placebo group, and all such events were within the first 3 months of treatment. In the Clinical Trials Experience: 5.3 Gastrointestinal Disorders: Diarrhea led to permanent dose reduction in 1% of patients treated with OFEV compared to 0.2% of placebo-treated patients. Diarrhea led to permanent dose interruption in 1% of patients treated with OFEV compared to 0.2% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 6% of the patients compared to 6% of placebo-treated patients. In the SSc-ILD study (Study 4), diarrhea was reported in 76% versus 74% of patients treated with OFEV and placebo, respectively. Diarrhea was not associated with increased serum creatinine, proteinuria or hypertension.

**Liver Function Tests**

**Clinical Trials Experience:**

- **Liver Function Tests:**
  - Gastrointestinal Disorders:
    - Diarrhea led to permanent dose reduction in 1% of patients treated with OFEV compared to 0.8% of placebo-treated patients. Diarrhea led to permanent dose interruption in 1% of patients treated with OFEV compared to 0.8% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 6% of the patients compared to 6% of placebo-treated patients. In the SSc-ILD study (Study 4), diarrhea was reported in 76% versus 74% of patients treated with OFEV and placebo, respectively. Diarrhea was not associated with increased serum creatinine, proteinuria or hypertension.

**Arterial Thromboembolic Events:**

- **Arterial Thromboembolic Events:** Drug-induced liver injury (DILI) has been reported rarely in clinical trials and postmarketing experience. Drug-induced liver injury (DILI) has been reported rarely in clinical trials and postmarketing experience. Drug-induced liver injury (DILI) has been reported rarely in clinical trials and postmarketing experience. Drug-induced liver injury (DILI) has been reported rarely in clinical trials and postmarketing experience. Drug-induced liver injury (DILI) has been reported rarely in clinical trials and postmarketing experience.
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

Pathways 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.

2022 billing and coding updates

Telehealth and Teaching Physician Services and ICD-10 codes updates

By Humayun Anjam, MD, FCP

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, 2023. 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 practitician/physician within 6 months.
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 telecommunication 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.

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.
SLEEP MEDICINE

Obstructive sleep apnea linked to unprovoked VTE

BY NEIL OSTERWEIL
MDedge News

A large 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 VTE 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 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 may lean into this cultural bias of thinking this is just a Latino being dramatic." 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 many long COVID 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. ■
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 used for less than 4 hours or refused CPAP.

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

Dr. Heinzler's comoderator, Silke Randerath, MD, of Bethanien Hospital at the University of Cologne, Germany, head of the ERS specialist group on sleep disordered breathing, said that this meeting “show worrying associations between OSA and important hypoxic-related diseases,” she said, and recommended controlling for 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), Beaucozé, France. Dr. Trzepizur, Dr. Heinzler, Dr. Ryan and Dr. Randerath reported no relevant financial relationships.

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