Go to **MDedge.com/CHESTPhysician** for the latest news on coronavirus and long COVID.

CORONAVIRUS
Long COVID's grip will tighten as the pandemic continues. // **8**

LUNG CANCER
The majority of younger adults were diagnosed at later stages. // **10**

SLEEP STRATEGIES
What are we missing in the OSA/atrial fibrillation connection? // **11**

VOL. 17 • NO. 9 • SEPTEMBER 2022

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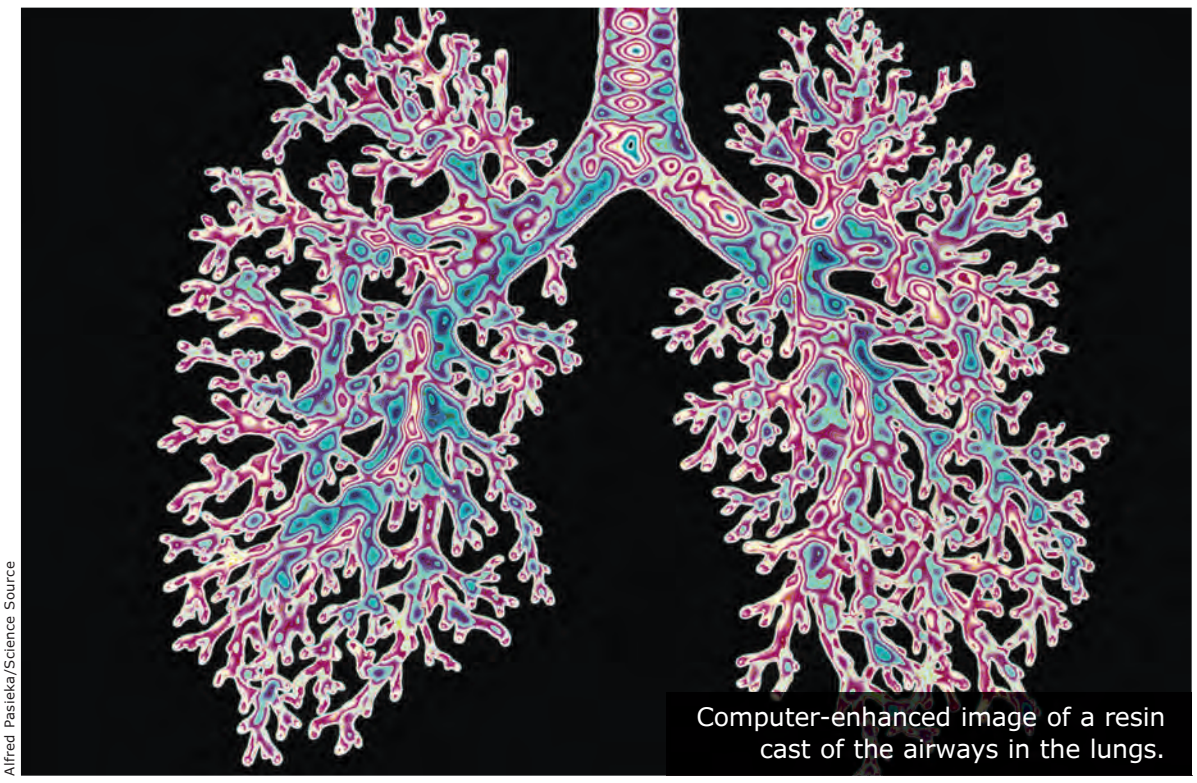

Alfred Pasieka/Science Source

Computer-enhanced image of a resin cast of the airways in the lungs.

Airway structure in women leads to worse COPD outcomes

BY WALTER ALEXANDER
MDedge News

Researchers examined whether anatomical structure could be behind some of the differences seen in the prevalence and clinical outcomes of chronic obstructive pulmonary disease (COPD) found between women and men. Their study showed that structural differences existed between the sexes in airways, specifically airway lumen sizes as quantified through chest CT. Overall, airways were found to be smaller in women than in men.

The findings, published in Radiology (2022 Aug 2. doi: 10.1148/radiol.212985), took into account height and lung size. The lower baseline airway lumen sizes in women conferred lower reserves against respiratory morbidity and mortality for equivalent changes, compared with results seen in men, according to the researchers.

Among the key findings seen in a secondary analysis of consecutive participants (9,363 ever-smokers and 420 never-smokers) enrolled in the Genetic Epidemiology of COPD (COPDGene) study, airway lumen dimensions were lower in never-smoker women than in men (segmental lumen diameter, 8.1 mm vs. 9.1 mm; $P < .001$).

In addition, ever-smoker women were also found to have narrower segmental lumen

AIRWAY // *continued on page 6*

High plasma IgE predicts COPD exacerbation, mortality

BY WILL PASS
MDedge News

Patients with chronic obstructive pulmonary disease (COPD) with high plasma immunoglobulin E are more likely to have exacerbations and die from any cause, based on a Danish population-cohort study.

The predictive power of IgE was independent from blood eosinophil level, hinting at different subsets of patients with COPD, first author Yunus Çolak MD, PhD, of Copenhagen University Hospital, and colleagues reported.

"Additional biomarkers are necessary as blood eosinophils alone seem insufficient for risk stratification in COPD," the investigators wrote in Annals of Allergy, Asthma & Immunology (2022 Jul 11. doi: 10.1016/j.anai.2022.06.028).

"Since asthma and COPD share some pathophysiological mechanisms, a logical approach would be to investigate well-known biomarkers for asthma in COPD and vice versa," the researchers added.

Dr. Çolak and colleagues cited previous studies supporting this perspective. Specifically,

PLASMA IgE // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Get to know President-Elect Doreen Addrizzo-Harris, MD, FCCP

Page 19

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Nucala
(mepolizumab)
Injection 100 mg/mL

The targeted therapy for 4 eosinophil-driven diseases

Severe eosinophilic asthma (SEA)

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Eosinophilic granulomatosis with polyangiitis (EGPA)

Hypereosinophilic syndrome (HES)

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.

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

Visit Nucala4EOS.com to learn more →

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.

Opportunistic 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.

NUCALA (mepolizumab) for injection, for subcutaneous use
NUCALA (mepolizumab) injection, for subcutaneous use
The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

NUCALA is indicated for the add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype *[see Use in Specific Populations (8.4) and Clinical Studies (14.1) of full prescribing information]*.

Limitations of Use

NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

1.2 Maintenance Treatment of Chronic Rhinosinusitis with Nasal Polyps

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

1.3 Eosinophilic Granulomatosis with Polyangiitis

NUCALA is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

1.4 Hypereosinophilic Syndrome

NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

4 CONTRAINDICATIONS

NUCALA is contraindicated in patients with a history of hypersensitivity to mepolizumab or excipients in the formulation *[see Warnings and Precautions (5.1) and Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster

Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions (6.1)]*. Consider vaccination if medically appropriate.

5.4 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dosage, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dosage may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:
- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Severe Asthma

Adult and Adolescent Patients Aged 12 Years and Older

A total of 1,327 patients with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT01000506; Trial 2, NCT01691521; and Trial 3, NCT01691508). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 patients required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All patients had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1) of full prescribing information]*. Of the patients enrolled, 59% were female, 85% were White, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 patients received NUCALA (mepolizumab 100 mg subcutaneous) for at least 24 weeks. Serious adverse events that occurred in more than 1 patient and in a greater percentage of patients receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 patients vs. 0 patients, respectively). Approximately 2% of patients receiving NUCALA 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 NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with Severe Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

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, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, 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 percentage of patients who experienced systemic (allergic and non-allergic) reactions was 3% in the group receiving NUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving NUCALA 100 mg and 2% of patients in the placebo group. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving NUCALA 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 NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in patients receiving NUCALA 100 mg (5/7) 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 8% in patients receiving NUCALA 100 mg compared with 3% in patients receiving placebo.

Long-term Safety: Nine hundred ninety-eight patients received NUCALA 100 mg in ongoing open-label extension studies, 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 NUCALA is based upon 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 NUCALA administered subcutaneously once every 4 weeks. Patients received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 patients received NUCALA 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 407 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received NUCALA 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent CRSwNP with a history of prior surgery and were on nasal corticosteroids for at least 8 weeks prior to screening *[see Clinical Studies (14.2) of full prescribing information]*. Of the patients enrolled, 35% were female, 93% were White, and ages ranged from 18 to 82 years. Approximately 2% of patients receiving NUCALA 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 NUCALA-treated patients and more frequently than in patients treated with placebo in the CRSwNP trial.

Table 2. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with CRSwNP

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 206) %	Placebo (n = 201) %
Oropharyngeal pain	8	5
Arthralgia	6	2
Abdominal Pain Upper	3	2
Diarrhea	3	2
Pyrexia	3	2
Nasal dryness	3	<1
Rash	3	<1

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic [type I hypersensitivity] and other) reactions was <1% in the group receiving NUCALA 100 mg and <1% in the placebo group. Systemic allergic (type I hypersensitivity) reactions were reported by <1% of patients in the group receiving NUCALA 100 mg and no patients in the placebo group. The manifestations of systemic allergic (type I hypersensitivity) reactions included urticaria, erythema, and rash and 1 of the 3 reactions occurred on the day of dosing. Other systemic reactions were reported by no patients in the group receiving NUCALA 100 mg and <1% of patients in the placebo group.

Injection Site Reactions

Injection site reactions (e.g., erythema, pruritus) occurred at a rate of 2% in patients receiving NUCALA 100 mg compared with <1% in patients receiving placebo.

6.3 Clinical Trials Experience in Eosinophilic Granulomatosis with Polyangiitis

A total of 136 patients with EGPA were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment *[see Clinical Studies (14.3) of full prescribing information]*. Of the patients enrolled, 59% were female, 92% were White, and ages ranged from 20 to 71 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of NUCALA and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of NUCALA and 1% of patients in the placebo group. The manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving 300 mg of NUCALA included rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor. Systemic non-allergic reactions were reported by 1 (1%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of systemic non-allergic reactions reported in the group receiving 300 mg of NUCALA was angioedema. Half of the systemic reactions in patients receiving 300 mg of NUCALA (2/4) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving 300 mg of NUCALA compared with 13% in patients receiving placebo.

6.4 Clinical Trials Experience in Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES were evaluated in a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients with non-hematologic secondary HES or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients must have been on a stable dose of background HES therapy for the 4 weeks prior to randomization [*see Clinical Studies (14.4) of full prescribing information*]. Of the patients enrolled, 53% were female, 93% were White, and ages ranged from 12 to 82 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the trial, no systemic allergic (type I hypersensitivity) reactions were reported. Other systemic reactions were reported by 1 (2%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of other systemic reaction was multifocal skin reaction experienced on the day of dosing.

(continued on next page)

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 or 100 mg, 2/35 (6%) 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 CRSwNP receiving NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with CRSwNP.
In patients with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with EGPA.
In adult and adolescent patients with HES receiving 300 mg of NUCALA, 1/53 (2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with HES.
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, sample handling, 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.
Immune System Disorders
Hypersensitivity reactions, including anaphylaxis.

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. Monoclonal antibodies, such as mepolizumab, are transported 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 preeclampsia 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 necessary 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 doses up to 100 mg/kg once 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.
In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

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 G (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.

8.4 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 years and older.
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 plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[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 19 adolescents who received NUCALA, 9 received 100 mg and the mean apparent clearance in these patients was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.
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]*.
The effectiveness of NUCALA in pediatric patients aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents *[see Clinical Pharmacology (12.3) of full prescribing information]*. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2) of full prescribing information]*. The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.
Chronic Rhinosinusitis with Nasal Polyps
The safety and effectiveness in patients aged younger than 18 years with CRSwNP have not been established.
Eosinophilic Granulomatosis with Polyangiitis
The safety and effectiveness in patients aged younger than 18 years with EGPA have not been established.
Hypereosinophilic Syndrome
The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older. The safety and effectiveness in pediatric patients aged younger than 12 years with HES have not been established. Use of NUCALA for this indication is supported by evidence from an adequate and well-controlled study (NCT02836496) in adults and adolescents and an open-label extension study (NCT03306043). One adolescent received NUCALA during the controlled study and this patient and an additional 3 adolescents received NUCALA during the open-label extension study *[see Clinical Studies (14.4) of full prescribing information]*. The 1 adolescent treated with NUCALA in the 32-week trial did not have a HES flare or an adverse event reported. All adolescents received 300 mg of NUCALA for 20 weeks in the open-label extension.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of patients aged 65 years and older that received NUCALA (n = 79) to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.
Not for Acute Symptoms or Deteriorating Disease
Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.
Opportunistic Infections: Herpes Zoster
Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.
Reduction of Corticosteroid Dosage
Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.
Pregnancy Exposure Registry
Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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diameters than men (7.8 mm ± 0.05 vs. 8.7 mm ± 0.04; $P < .001$).

Of particular interest, the investigators found that a unit change in the wall thickness or lumen area resulted in more severe airflow obstruction, more dyspnea, worse respiratory quality of life, lower 6-minute walk distance, and worse survival in women, compared with men.

Epidemiologically, while COPD is diagnosed more often in men than women, continuing changes in smoking behavior and increasing urbanization have led to the prevalence of COPD in women fast approaching the rate found in men, according to the researchers.

"[These] findings highlight how the 'one size fits all' approach to COPD management of using exacerbation history alone to guide preventive therapies is incorrect."

In addition, although the age-adjusted rates for COPD-related deaths have continued to decline in men, in women they have not. Indeed, the category of never-smoking women accounted for two-thirds of COPD as seen in a population-based study (Chest. 2011;139[4]:752-63).

COPDGene, a prospective, multicenter, observational cohort study, enrolled current and former smokers, as well as never-smokers, aged 45-80 years at 21 clinical centers across the United States from January 2008 to June 2011 with longitudinal follow-up until November 2020.

The investigators quantified airway disease through CT imaging using the following metrics: airway wall thickness of segmental airways, wall area percent of segmental airways, the square root of the wall area of a hypothetical airway with 10-mm internal perimeter, total airway count, lumen diameter of segmental airways, airway volume, and airway fractal dimension.

"Not all sex differences in prevalence of COPD have been explained, and structural differences may explain some of these differences. Our findings may have implications for patient selection for clinical trials," corresponding author Surya P. Bhatt, MD, associate professor of medicine and director of the University of Alabama Imaging Core at Birmingham, said in an interview.

The investigators wrote: "Our findings have implications for airflow limitation and the consequent clinical outcomes. ... We confirmed that men have more emphysema than women with equivalent smoking burden, and our results suggest that the lower reserve conferred by smaller airways predisposes women to develop airflow limitation predominantly through the airway phenotype.

All airway remodeling changes were associated with more dyspnea, worse respiratory quality of life, and lower functional capacity in women than in men. The smaller airways in women can result in higher airway resistance and more turbulent airflow, and thus place a higher ventilatory constraint during exertion.

Alteration in each airway measure was also associated with worse survival in women than in men, partially explaining the comparable mortality between the sexes for COPD despite the differing degrees of emphysema."

"I think these findings highlight underappreciated sex differences in the natural history of COPD," Mohsen Sadatsafavi, MD, PhD, associate professor, faculty of pharmaceutical sciences, at the University of British Columbia, Vancouver, said in an interview.

"To me, first and foremost, the Bhatt et al. findings highlight how the 'one size fits all' approach to COPD management of using exacerbation history alone to guide preventive therapies is incorrect.

"These findings have the potential to change the management paradigm of COPD in the long term, but before getting there, I think we need to relate these findings to clinically relevant and patient-reported outcomes."

Noting study limitations, the authors stated that a higher proportion of men were active smokers, compared with women, and despite adjustments for smoking status, some of the airway wall differences may be from the impact of active cigarette smoking on airway wall thickness.

Five study authors reported receiving support from various government and industry sources and disclosed conflicts of interest based on relationships with industry. The rest reported no conflicts of interest. ■

NEWS FROM CHEST // 11

NETWORKS // 20

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Angel Coz, MD, FCCP, is Editor in Chief of *CHEST Physician*.

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PLASMA IgE // *continued from page 1*

IgE-targeting monoclonal antibodies have shown promise in those patients with severe asthma as well as those in whom asthma-COPD overlap, whereas COPD with high IgE has been associated with a history of lung function decline and previous exacerbations.

The present study drew from a database of 46,598 adults enrolled in the Copenhagen General Population study. All participants underwent physical examination, completed a questionnaire, and provided blood for analysis. In this overall population, 1,559 individuals had COPD, among whom 446 had high plasma IgE (at least 76 IU/mL).

Over a median follow-up of 6.9 years in the COPD group, 224 severe exacerbations and 434 deaths of any cause occurred. Compared with COPD patients who had normal plasma IgE, those with high IgE were 43% more likely to have severe exacerbation (hazard ratio, 1.43; 95% confidence interval, 1.07-1.89) and 30% more likely to die of any cause (HR, 1.30; 95% CI, 1.06-1.62). These risks were similar when excluding patients with IgE of 700 IU/mL or higher.

Dr. Afzal

"These findings suggest that plasma IgE concentration may be a potential prognostic biomarker and treatment target for a subset of COPD patient," wrote Dr. Çolak and colleagues.

The above risks increased moderately when the high-IgE group was trimmed to include only those with low eosinophils (less than 300 cells/mcL); in this subgroup, risk of exacerbation was increased 62% (HR, 1.62; 95% CI, 1.17-2.24), while risk of all-cause mortality was increased 47% (HR, 1.47; 95% CI, 1.14-1.88).

"We were not able to show that individuals with higher blood eosinophils further stratified by IgE had higher risk of severe exacerbation or all-cause mortality," the investigators wrote, although they noted "the relatively low statistical power in stratified analysis," considering the wide confidence intervals observed.

"Thus, we should be careful with interpreting the results in relation to blood eosinophils and IgE combined," they suggested. "However, we believe that the mechanisms driving exacerbations through plasma IgE are different from those driving blood eosinophils, and we believe that plasma IgE may be a marker for a subset of COPD patients similar to blood eosinophils, which is compatible with the heterogeneity of patients with COPD."

According to principal author Shoaib Afzal, MD, PhD, of Copenhagen University Hospital, the findings are "probably no surprise for practitioners that often observe overlap between asthma and COPD pathology."

As smoking prevalence goes down in many countries, relatively more never-smokers are being diagnosed with COPD, Dr. Afzal said in a written comment, "which means that asthma as a risk factor for COPD is gaining importance."

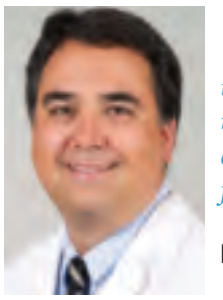
While patients with asthma can be treated with IgE-targeting omalizumab, a trial evaluating the same biologic for COPD patients with high IgE was withdrawn because of a lack of recruitment; however, Dr. Afzal suggested that this should not be the end of the story, since these new data imply that more patients could benefit than previously recognized.

"Our observational study has generated a hypothesis that needs to be tested by pulmonologists in randomized interventions trials designed with updated inclusion criteria," he said.

Such trials are needed, Dr. Afzal went on, because they could help unlock the "huge" potential benefit that may come from characterizing COPD patients beyond "exposures, symptoms, and spirometry."

"Sadly, the progress in establishing biomarkers in COPD for improving risk stratification and treatment allocation have been rather disappointing in the last decades, with the exception of small successes with eosinophils and perhaps FeNO," Dr. Afzal said.

Nathaniel Marchetti, DO, medical director of the respiratory ICU at Temple University Hospital in Philadelphia, said the study by Dr. Afzal and colleagues is noteworthy because "biomarkers for COPD are desperately needed to help risk stratify patients for exacerbation risk and risk of disease progression and even mortality."



"Biomarkers will be important in driving personalized medicine in COPD. We already know the disease seems to vary greatly from patient to patient."

Dr. Marchetti

In a written comment, Dr. Marchetti agreed with Dr. Afzal that the findings "open the possibility for interventional trials targeting IgE," which could one day reshape the way patients with COPD are treated.

"I think that biomarkers will become vital in caring for patients with COPD in the future," Dr. Marchetti said. "There will be medications that will be used to target different pathways of inflammation that drive disease progression and exacerbations. Biomarkers will be important in driving personalized medicine in COPD. We already know the disease seems to vary greatly from patient to patient."

The study was supported by the Capital Region of Copenhagen, the Danish Lung Foundation, the Velux Foundation, and others.

The investigators disclosed relationships with Boehringer Ingelheim, AstraZeneca, Sanofi Genzyme, and others. Dr. Marchetti disclosed no conflicts of interest. ■

Air pollution mediates temperature's impact on COPD

BY HEIDI SPLETE
MDedge News

Air pollution levels mediated the impact of temperature on oxygen saturation in adults with chronic obstructive pulmonary disease (COPD) based on data from 117 individuals.

COPD is attributed to environmental factors including air pollution, and air pollution has been linked to increased risk of hospitalization and mortality because of acute COPD exacerbation, wrote Huan Minh Tran, PhD, of Taipei (Taiwan) Medical University and colleagues. However, the effects of air pollution on climate-associated health outcomes in COPD have not been explored, they said.

In a study published in Science of The Total Environment (2022 Jun 25. doi:10.1016/j.scitotenv.2022.156969) the researchers identified 117 adult COPD patients at a single center in Taiwan. They measured lung function, 6-minute walking distance, oxygen desaturation, white blood cell count, and percent emphysema (defined as low attenuation area [LAA]) and linked them to 0- to 1-year, 0- to 3-year, and 0- to 5-year lags in exposures to relative humidity (RH), temperature, and air pollution. The mean age of the participants was 72.9 years; 93% were men.

Pollution was defined in terms of fine particulate matter (PM2.5). Overall, an increase in RH by 1% was associated with increases in forced expiratory volume in 1 second (FEV_1), eosinophils, and lymphocytes. A 1% increase in RH also was associated with a decrease in the total-lobe LAA.

As for temperature, an increase of 1°C was associated with decreased oxygen desaturation and with decreases in right-, left-, and upper-lobe LAA values.

The researchers found that a 1-mcg/m^3 increase in PM2.5 was associated with a decrease in the FEV_1 as well as with an increase in oxygen desaturation. A 1-mcg/m^3 increase in PM10 and PM2.5 was associated with increases in the total-, right-, left, and upper-lobe LAA; increases in lower-lobe LAA were associated with an increase in PM2.5 only.

"This is reasonable because PM2.5 can travel and deposit in distal parts of the lung, while PM10 is preferably deposited in the larger airways of the upper lung regions," the researchers wrote in their discussion.

A one part per billion increase in nitrogen dioxide (NO_2) was associated with decreased FEV_1 and increased upper-lobe LAA.

"We observed that NO_2 fully mediated the association between RH and FEV_1, while PM2.5 fully mediated associations of temperature with oxygen saturation and emphysema severity in COPD patients," the researchers added.

The study findings were limited by several factors including the relatively small and homogeneous male, Taiwanese population, which may limit generalizability, the researchers noted.

However, the results suggest that air pollution could have an effect on the established associations between climate and adverse health outcomes in COPD, and more research is needed," they concluded.

The researchers had no financial conflicts to disclose. ■

CORONAVIRUS

Long COVID's grip will likely tighten as infections continue

BY ELIZA PARTIKA

COVID-19 is far from done in the United States, with more than 111,000 new cases being recorded a day in the second week of August, according to Johns Hopkins University, and 625 deaths being reported every day (https://coronavirus.jhu.edu/region/united-states).

And as that toll grows, experts are worried about a second wave of illnesses from long COVID, a condition that already has affected between 7.7 million and 23 million Americans, according to U.S. government estimates.

"It is evident that long COVID is real, that it already impacts a substantial number of people, and that this number may continue to grow as new infections occur," the U.S. Department of Health and Human Services (HHS) said in a research action plan released Aug. 4 (www.covid.gov/assets/files/National-Research-Action-Plan-on-Long-COVID-08012022.pdf).

"We are heading towards a big problem on our hands," says Ziyad Al-Aly, MD, chief of research and development at the Veterans Affairs Hospital in St. Louis. "It's a real problem. We needed to bring attention to this yesterday," he said.

Bryan Lau, PhD, professor of epidemiology at Johns Hopkins Bloomberg School of Public Health, Baltimore, and co-lead of a long COVID study there, says whether it's 5% of the 92 million officially recorded U.S. COVID-19 cases, or 30% – on the higher end of estimates – that means anywhere between 4.5 million and 27 million Americans will have the effects of long COVID.

"If we conservatively assume 100 million working-age adults have been infected, that implies 10 to 33 million may have long COVID," Alice Burns, PhD, associate director for the Kaiser Family Foundation's Program on Medicaid and the Uninsured, wrote in an analysis (https://www.kff.org/policy-watch/what-are-the-implications-of-long-covid-for-employment-and-health-coverage/).

And even the Centers for Disease Control and Prevention says only a fraction of cases have been recorded (www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html).

That, in turn, means tens of millions of people who struggle to work, to get to school, and to take care of their families – and who will be making demands on an already stressed U.S. health care system.

Surveys showed more than half of adults with long COVID who worked before becoming infected are either out of work or working fewer hours.

The HHS said in its Aug. 4 report that long COVID could keep 1 million people a day out of work, with a loss of $50 billion in annual pay.

Dr. Lau said health workers and policymakers are woefully unprepared.

"If you have a family unit, and the mom or dad can't work, or has trouble taking their child to activities, where does the question of support come into play? Where is there potential for food issues, or housing issues?" he asked. "I see the potential for the burden to be extremely large in that capacity."

Dr. Lau said he has yet to see any strong estimates of how many cases of long COVID might develop. Because a person has to get COVID-19 to ultimately get long COVID, the two are linked. In other words, as COVID-19 cases rise, so will cases of long COVID, and vice versa.

Evidence from the Kaiser Family Foundation analysis suggests a significant impact on employment: Surveys showed more than half of adults with long COVID who worked before becoming infected are either out of work or working fewer hours. Conditions associated with long COVID – such as fatigue, malaise, or problems concentrating – limit people's ability to work, even if they have jobs that allow for accommodations.

Two surveys of people with long COVID who had worked before becoming infected showed that between 22% and 27% of them were out of work after getting long COVID. In comparison, among all working-age adults in 2019, only 7% were out of work.

Given the sheer number of working-age adults who have long COVID, the effects on employment may be profound and are likely to involve more people over time. One study estimates that long COVID already accounts for 15% of unfilled jobs (https://www.brookings.edu/research/is-long-covid-worsening-the-labor-shortage/).

The most severe symptoms of long COVID include brain fog and heart complications, known to persist for weeks for months after a COVID-19 infection.

A study from the University of Norway published in the July 2022 edition of Open Forum Infectious Diseases found 53% of people tested had at least one symptom of thinking problems 13 months after infection with COVID-19. According to the HHS' latest report on long COVID, people with thinking problems, heart conditions, mobility issues, and other symptoms are going to need a considerable amount of care (www.covid.gov/assets/files/Services-and-Supports-for-Longer-Term-Impacts-of-COVID-19-08012022.pdf). Many will need lengthy periods of rehabilitation.

Dr. Al-Aly worries that long COVID has already severely affected the labor force and the job market, all while burdening the country's health care system.

"While there are variations in how individuals respond and cope with long COVID, the unifying thread is that with the level of disability it causes, more people will be struggling to keep up with the demands of the workforce and more people will be out on disability than ever before," he said.

Studies from Johns Hopkins and the University of Washington estimate that 5%-30% of people could get long COVID in the future. Projections beyond that are hazy.

"So far, all the studies we have done on long COVID have been reactionary. Much of the activism around long COVID has been patient led. We are seeing more and more people with lasting symptoms. We need our research to catch up," Dr. Lau said.

Theo Vos, MD, PhD, professor of health sciences at University of Washington, Seattle, said the main reasons for the huge range of predictions are the variety of methods used, as well as different sample sizes. Much long-COVID data are self-reported, which makes tracking difficult. "With self-reported data, you can't plug people into a machine and say this is what they have or this is what they don't have. At the population level, the only thing you can do is ask questions. There is no systematic way to define long COVID," he said.

Dr. Vos's most recent study (www.medrxiv.org/content/10.1101/2022.05.26.22275532v1), which is being peer-reviewed and revised, found that most people with long COVID have symptoms similar to those seen in other autoimmune diseases.

But sometimes the immune system can overreact, causing more severe symptoms, such as brain fog and heart problems. "There's a wide diversity in severity. Someone can have long COVID and be fully functional, while others are not functional at all. We still have a long way to go before we figure out why," Dr. Lau said. ■

Majority of younger adults diagnosed at later stages

BY JIM KLING
MDedge News

Advances have been made in earlier diagnosis and better overall survival among older patients with lung cancer, but younger adults have not experienced the same benefit, according to a new study.

The improvements in patients aged 55-80 are likely associated with the introduction in 2013 of low-dose computed tomography screening.

"It was unknown whether young adults diagnosed with lung cancer, who are ineligible for screening, have experienced a similar shift to earlier stages of lung cancer. While previous studies have shown that young adults diagnosed with lung cancer have distinct tumor characteristics and survival compared to older adults diagnosed with lung cancer, no study has examined whether recent improvements in early diagnosis and survival among older adults with lung cancer extend to younger adults diagnosed with lung cancer," study coauthor Alexandra Potter told this news organization.

The study was presented by Chi-Fu Jeffrey Yang, MD, at a press conference held at the World Conference on Lung Cancer. Dr. Yang is a thoracic surgeon at Massachusetts General Hospital, Boston.

The difference might be explained by difference in tumor biology, as younger adults are often diagnosed with more aggressive cancers. Other factors include delayed diagnosis and a lack of early-detection strategies for this population. Older patients likely benefited from the onset of lung cancer screening, as well as an increase in non-screening chest CT use in hospital settings, which may lead to more incidental diagnoses, according to Ms. Potter, a research assistant at Massachusetts General Hospital and president of the American Lung Cancer Screening Initiative.

Investigators found that about three in four lung cancer diagnoses among adults aged 20-29 were stage IV disease, and only 8% in that group were stage I. "I was surprised" by the high frequency of stage IV cancer, said Ms. Potter. "I would also highlight that there has been no improvement in early diagnosis among patients aged 20-49 during the study period," she added.

And although it is often assumed that patients diagnosed at a younger age have better survival, the study painted a grim picture: Five-year survival was 10%-15% among patients diagnosed at age 20-49 with stage IV cancer. "More research is needed to better understand the risk factors, diagnosis, treatment, and survival of lung cancer in young adults," Ms. Potter said.

There are strategies in development, including biomarkers, machine learning analysis of CT scans, and risk prediction models, but none have yet borne fruit. "Once we are able to [identify high-risk young adults], this will allow us to offer lung cancer screening to these young adults who are at high risk for developing lung cancer," she said.

The researchers analyzed data from the United States Cancer Statistics (USCS) database and the National Cancer Database (NCDB). They included patients aged 20-79 diagnosed with non–small cell lung cancer (NSCLC) between 2010 and 2018. The study included 1,328 individuals aged 20-29, 5,682 men and women aged 30-39, 39,323 individuals aged 40-49, 202,709 aged 50-59, 410,482 aged 60-69, and 447,366 aged 70-79.

Stage IV diagnoses were most common in the youngest group (76% versus 8% stage I), and steadily declined with age 30-39 (70% versus 10%), age 40-49 (60% versus 14%), 50-59 (52% versus 19%), 60-69 (45% versus 25%), and 70-79 (40% versus 25%; $P < .001$). The trend reversed among patients aged 80-89, with 45% of patients diagnosed with stage IV cancer, though the rising trend of stage I diagnoses continued at 29%. Between 2010 and 2018, there was a statistically significant increase in stage IV diagnoses among those aged 40-49, and a decrease among those aged 50-59, 60-69, and 70-79.

Five-year overall survival was lowest among patients aged 20-29 at 20%. It was 27%-28% among each 10-year age group up to age 69, then dropped to 24% among those aged 70-79 ($P < .001$).

The study was limited by a lack of data on disease- or recurrence-free survival, as well as use of biomarkers or targeted therapy.

Ms. Potter had no conflicts. ■

SLEEP STRATEGIES

What are we missing when it comes to obstructive sleep apnea and atrial fibrillation?

BY HARSHA V. MUDRAKOLA, MD, MS; AND BERNARDO SELIM, MD, FCCP

Obstructive sleep apnea is a prevalent and underdiagnosed sleep-related breathing disorder. The estimated prevalence of OSA in the general population of North America ranges from 9% to 38%. This prevalence is higher in men, with a roughly 2:1 male to female ratio, and it also increases with age (Senaratna CV, et al. *Sleep Med Rev*. 2017;34:70-81). In large epidemiologic studies, the association between OSA and atrial fibrillation (AF) has been well established. The prevalence of OSA in patients with AF is high, with estimates ranging from 21% to 74%. In the OSA population, the Sleep Heart Health Study (Mehra R, et al. *Am J Respir Crit Care Med*. 2006;173[8]:910-16) and the Multi Ethnic Study of Atherosclerosis (Lin GM, et al. *Am J Epidemiol*. 2015;182[1]:49-57) found that patients with OSA had a twofold to fourfold increased risk of AF compared with those who did not have OSA. Therefore, the most current American Heart Association guidelines recommend assessing OSA symptoms in all patients with AF and screening for OSA in recurrent patients with AF.

The pathophysiology of OSA involves multiple physiologic stressors that may contribute to an increased propensity for atrial arrhythmias in this population. Among these factors are large changes in intrathoracic pressures that may cause atrial and ventricular wall stretching, recurrent oxidative stress, and a sympathetic surge associated with shortening atrial refractory periods and atrial extrasystoles. By occurring nightly over many years, these physiologic stressors may lead to permanent atrial dilation and structural remodeling, eventually affecting the conduction system and producing a substrate conducive to reentrant circuits. Other common comorbidities in patients with OSA–such as hypertension, obesity, and metabolic syndrome–may also contribute to arrhythmogenicity (Linz D, et al. *JAMA Cardiol*. 2018;3[6]:532).

Does treating OSA with CPAP prevent the development of AF?

Previous case-control and retrospective observational studies suggested that having OSA makes treating AF more difficult. Patients with OSA had lower response rates to antiarrhythmic drugs, with the lowest in those with more severe OSA. Rhythm control with cardioversion and catheter-based pulmonary vein isolation was also less successful in patients with OSA due to higher rates of AF recurrence. According to one meta-analysis, patients with OSA had a 31% higher rate of AF recurrence after pulmonary vein isolation (Li L, et al. *Europace*. 2014;16[9]:1309-14).

The most current American Heart Association guidelines recommend assessing OSA symptoms in all patients with AF and screening for OSA in recurrent patients with AF.

Prospective studies using CPAP to treat OSA have not demonstrated a reduced risk of adverse cardiovascular outcomes. The SAVE trial is the most well-known of these studies. The primary endpoint was death from cardiovascular causes (myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack). There was no difference in this outcome between the CPAP and usual care groups. A secondary outcome in this study was new-onset AF detected by electrocardiography, and there was no difference between the CPAP and the usual care group. The low amount of CPAP usage in the treatment group was a commonly cited shortcoming of the SAVE trial–mean usage was 4.4 hours per night during the first month of treatment and subsequently decreased to 3.3 hours per night by the 12-month time point (McEvoy RD, et al. *N Engl J Med*. 2016;375[10]:919-31).

Caples and colleagues screened patients undergoing direct current cardioversion or catheter ablation. They chose those who were also positive for OSA by polysomnography (apnea-hypopnea index – AHI greater than five events per hour). Twenty-five patients were included in the study and were randomly assigned to either CPAP treatment or usual care. Body mass index, blood pressure, ejection fraction, AHI, and nocturnal desaturation levels were comparable between the two groups. The rate of recurrence of AF and the time point following randomization at which the AF recurred did not differ between the two groups (Caples SM, et al. *Int J Cardiol*. 2019;278:133-6).

A Norwegian trial by Traaen and colleagues included a larger sample of 108 patients with moderate to severe sleep apnea and paroxysmal AF who underwent catheter ablation. Patients were followed for 5 months before and 12 months after ablation. They were randomly assigned to either CPAP therapy plus usual care or usual care alone. The primary goal was to assess AF burden using implanted loop recorders. There was no significant difference in AF burden between the two groups from baseline to the final 3 months of the study (Traaen GM, et al. *Am J Respir Crit Care Med*. 2021;204[5]:573-82). These two prospective trials, which had AF recurrence or burden as primary outcomes, found no interaction between AF burden and CPAP use, at least within the first year of therapy. Both trials found that their participants used CPAP for more extended periods of time than the SAVE trial, with over 6 hours in the Caples and coworkers' trial and nearly 5 hours in the Traaen and coworkers' study.

Is the lack of efficacy due to starting CPAP too late in the course of OSA?

It has been proposed that there may be a critical early period after the onset of OSA when intervention with CPAP (or alternative therapies) will be most effective in preventing adverse cardiovascular outcomes. An answer will almost certainly necessitate a long-term prospective study enrolling people before they develop OSA. Additionally, the AHI is used in most trials to determine the presence and severity of OSA. However, the AHI has been shown to have a poor correlation with sleep-related symptoms, and it may fail to capture key OSA pathophysiologic stressors (e.g., hyperadrenergic drive, cyclical hypoxemia, etc), which may increase the risk of AF. Other disease characteristics and polysomnographic features may better capture disease severity and the cardiovascular risk factors associated with it. The respiratory arousal threshold, arousal index, degree of loop gain, hypoxic burden, heart rate variability, and cardiopulmonary coupling are some examples of such features.

Dr. Mudrakola

Another possible explanation is that AF is not causally related, and the demonstrated association between the two is because both conditions share risk factors such as age and BMI, among others. Or, if they are causally linked, OSA may be a minor contributor, and the magnitude of that contribution is insufficient to reduce the risk of AF significantly by treating OSA. More research is needed to define the salient intervenable aspects of OSA better and design the optimal timing and duration of intervention. ■

Dr. Mudrakola is with the Department of Pulmonary & Critical Care Medicine, Summa Health, Akron, Ohio. Dr. Selim is with the Department of Pulmonary & Critical Care Medicine, Mayo Clinic, Rochester, Minnesota.

The LIVE CHEST Challenge Championship is back!

BY MAURICIO DANCKERS, MD, FCCP
Chair, CHEST Training and Transitions Committee

Absence does make the heart grow fonder. Three years have passed since our last in person CHEST Challenge Championship.

It was CHEST 2019 New Orleans when we last saw the enthusiasm and camaraderie of talented fellow teams cheered on by that irreplaceable, engaged audience, creating moments and memories through that magical combination of education and entertainment ("edutainment"). We were blissfully ignorant then to the terrible challenges that would soon come with the pandemic.

COURTESY CHEST

Since its inception, now 21 years ago, the live CHEST Challenge Championship has become a highly anticipated capstone event at the annual scientific meeting. Fellows from across the country first compete in a challenging, secure online knowledge quiz from which top-performing programs are selected as finalists.

All along the way, the participants engage in social media challenges that build excitement and collegiality (see tweeted image above). A recent commentary in the *CHEST*® journal highlighted the competition's important milestones,[1] and organizers continue to innovate year after year.

Dr. William Kelly, creator of CHEST Challenge, noted, "Our 20th anniversary broadcast during CHEST 2021 was our most innovative, had the most generous prizes, and the largest, most interactive audience to date. Our team of amazing committee members, CHEST staff, and contributors are somehow going even bigger this year! When combining never-before-seen challenges, surprises, giveaways, and a special 'opening act' with the joy and energy of all of us being back together again in person – I just can't wait.

"That necessary pivot to online-only events in 2020 and 2021 brought new challenges to the game but also provided lessons to be learned, inspired reflection, and gave us opportunities to interact, play, and learn together in new ways.

"As chair of the Training and Transitions Committee, I recall the innovations: CHEST Challenge has always been about innovation in medical education.

"Two decades of history allowed pushing the boundaries into the online arena, allowing competitors to play from their own institutions, audience to join from home, and the camaraderie and support characteristics of the CHEST community to transcend virtual barriers.

The audience became part of the competition, including winning substantial prizes for themselves.

"Using advanced, remote video recordings with virtual proctoring by judges, we were able to offer more extensive skills challenges. Highly engaged online audiences had contagious and hilarious chat room banter. And, virtual watch

CHALLENGE *continued on following page*

CHALLENGE *continued from previous page*

parties allowed for greatly increased viewership. Leveraging social media, the audience became part of the competition, including winning substantial prizes for themselves.

"It takes an extraordinary number of dedicated individuals to deliver the experience."

Dr. Matthew Miles, past chair of T&T Committee, comments: "One of the joys of working on CHEST Challenge is just being part of the production team. We have brilliant faculty who specialize in cutting-edge education, visionaries who concoct new and imaginative ways for fellows to compete, and incredible CHEST staff who somehow pull off an amazing event every year.

"I'm so thankful for the way that our CHEST community celebrates learning and prioritizes our fellows-in-training," he added.

"Years after each in-person championship, the attendees still comment on the electrifying atmosphere they thoroughly enjoyed.

"It is literally a nail-biter – you can see people in the audience sitting at the edge of their

seats, holding their breath while teams play to win big in surprise hands-on simulation-based challenges during the Championship," says Dr. Subani Chandra, who helped implement surprise simulation challenges into the live CHEST Challenge Championship in 2017 that are now an integral part of the experience.

On October 18, at CHEST 2022, championship fellow teams from New York Presbyterian Brooklyn Methodist, Mayo Clinic, and Brooke Army Medical Center, cheered on live by all of us, will compete in order to hoist the Rosen Cup and be declared the CHEST Challenge Champions!

Come experience for yourself the rapid-fire pulmonary, critical care, and sleep medicine knowledge review, the thrill of competition, and see the energy of some of our best and brightest fellows.

Being together in person again to support and learn with each other will be a big win for all of us. ■

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Enhance your critical care expertise with CHEST SEEK

Two new resources from SEEK, the self-education and knowledge assessment learning tool for chest medicine clinicians, are now available. *CHEST SEEK™ Critical Care Medicine: 32nd Edition*, the print book developed directly from the critical care medicine board subspecialty examination content blueprints, now includes QR codes that enable you to connect to video imaging with the scan of your phone. Updates also include a new table format for conventional and SI unit lab values, making the content easier to review and reference.

For those who prefer to learn in a digital format, the CHEST SEEK™ Library now offers 150 questions from the 32nd book edition, which

includes case-based questions on acid-base disorders, cerebrovascular disease, and mechanical ventilation. The library now allows you to select your confidence level in your answers when responding and offers a highlighter function to easily identify content for future reference.

According to Editor in Chief and Chair of *CHEST SEEK™ Critical Care Medicine: 32nd Edition*, Steve M. Hollenberg, MD, FCCP, the updates to the print and electronic formats were designed to reflect the changing needs and expectations of learners.

"This year's critical care SEEK edition continues our adaptation to the needs of today's learners. Even the formulation of the edition itself required adaptation, as COVID necessitated a hybrid in-person/virtual meeting for question review and discussion," he said.

"The latest edition has also begun to tailor SEEK to the electronic world while keeping the print format as well," he added. "We are incorporating more videos, with QR codes embedded in the book with links to those videos. New SEEK digital flashcards are available in SEEK Library Plus

SEEK *continued on following page*

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.
5.8 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.

6 ADVERSE REACTIONS: The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: Elevated Liver Enzymes and Drug-Induced Liver Injury [*see Warnings and Precautions*]; Gastrointestinal Disorders *[see Warnings and Precautions]*; Embryo-Fetal Toxicity [*see Warnings and Precautions*]; Arterial Thromboembolic Events [*see Warnings and Precautions*]; Risk of Bleeding *[see Warnings and Precautions]*; Gastrointestinal Perforation [*see Warnings and Precautions*]; Nephrotic Range Proteinuria *[see Warnings and Precautions]*.
6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients, 332 patients with chronic fibrosing ILDs with a progressive phenotype, and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. Idiopathic Pulmonary Fibrosis: OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than 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-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients with Idiopathic Pulmonary Fibrosis and More Commonly Than Placebo in Study 1, Study 2, and Study 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).
Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [*see Warnings and Precautions*]. Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype: OFEV was studied in a phase 3, double-blind, placebo-controlled trial (Study 5) in which 663 patients with chronic fibrosing ILDs with a progressive phenotype were randomized to receive OFEV 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. At 52 weeks, the median duration of exposure was 12 months for patients in both treatment arms. Subjects ranged in age from 27 to 87 years (median age of 67 years). The majority of patients were Caucasian (74%) or Asian (25%). Most patients were male (54%). 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 patients treated with OFEV and in 5% of patients treated with placebo. No pattern was identified in the adverse events leading to death. Adverse reactions leading to permanent dose reductions were reported in 33% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (16%). Adverse reactions leading to discontinuation were reported in 20% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reaction that led to discontinuation in OFEV-treated patients was diarrhea (6%). The safety profile in patients with chronic fibrosing ILDs with a progressive phenotype treated with OFEV was consistent with that observed in IPF patients. In addition, the following adverse events were reported in OFEV more than placebo in chronic progressive fibrosing ILD: nasopharyngitis (13% vs. 12%), upper respiratory tract infection (7% vs 6%), urinary tract infection (6% vs. 4%), fatigue (10% vs. 6%), and back pain (6% vs. 5%). Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients with Systemic Sclerosis-Associated Interstitial Lung Disease and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.
[b] Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.
[c] Includes hypertension, blood pressure increased, and hypertensive crisis

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. 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. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions]*, non-serious and serious bleeding events, some of which were fatal

SEEK *continued from previous page*

(which also gives access to previous editions), with questions on the front and answers on the back." One thing that stays the same is the scientific rigor of the content development process. "Those interested can see examples of the peer review process we follow on CHEST SEEK Library Plus; the hope is that viewers will get a sense of its rigor, as well as the willingness of the editorial board to question everything in the interest of making SEEK as clear as possible but also relevant to clinical practice," Dr. Hollenberg said.

For more information about the CHEST SEEK Library, visit http://tiny.cc/8l6yuz. To purchase *CHEST SEEK™ Critical Care Medicine: 32nd Edition*, visit http://tiny.cc/al6yuz or find it at the Experience CHEST area in the exhibit hall at CHEST 2022. ■

This month in the journal *CHEST*®

Editor's picks

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

Asthma Control, Airway Mucus, and 129Xe MRI Ventilation After a Single Benralizumab Dose. *By Marrissa J. McIntosh, BSc, et al.*

Influenza Testing and Treatment Among Patients Hospitalized With Community-Acquired Pneumonia. *By Abhishek Deshpande, MD, PhD, et al.*

Impact of Airline Secondhand Tobacco Smoke Exposure on Respiratory Health and Lung Function Decades After Exposure Cessation. *By Fernando Diaz del Valle, MD, et al.*

Factors Associated With Spontaneous Awakening Trial and Spontaneous Breathing Trial Performance in Critically Ill Adults: Analysis of a Multicenter, Nationwide, Cohort Study. *By Michele C. Balas, PhD, RN, CCRN-K, et al.*

Cough-Specific Quality of Life Predicts Disease Progression Among Patients With Interstitial Lung Disease: Data From the Pulmonary Fibrosis Foundation Patient Registry. *By Janet Lee, MD, et al.*

Sex and Gender in Lung Disease and Sleep Disorders: A State-of-the-Art Review. *By Amik Sodhi, MBBS, MPH, et al.*

Withdrawing Life Sustaining Therapies and the Conundrum of "Brain Death": A Clinical Case at the Intersection of Spiritual and Clinical Care for Muslims. *By Aasim I. Padela, MD, MSc, FACEP, et al.*

Endobronchial Ultrasound Transbronchial Needle Aspiration With a 19-Gauge Needle vs 21- and 22-Gauge Needles for Mediastinal Lymphadenopathy. *By Nicholas P.J. Romatowski, MD, et al.*

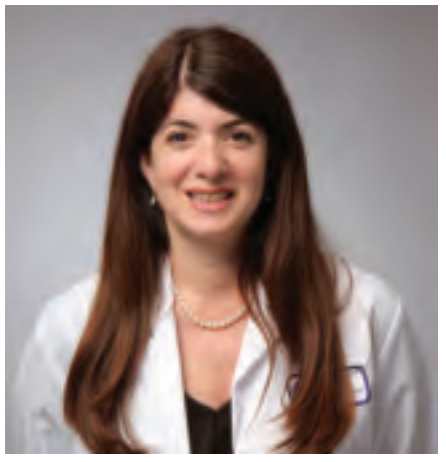
Impact of Esophageal Pressure Measurement on Pulmonary Hypertension Diagnosis in Patients With Obesity. *By Ghaleb Khirfan, MD, et al.*

How I Do It: Treating Severe Refractory and Augmented RLS. *By John W. Winkelman, MD, PhD* ■

Getting to know the incoming CHEST President

Q and A with Doreen J. Addrizzo-Harris, MD, FCCP

Starting January 1, 2023, current President-Elect Doreen J. Addrizzo-Harris, MD, FCCP, will become the new President of the American College of Chest Physicians. Dr. Addrizzo-Harris is a pulmonary/critical care physician with an extensive background in bronchiectasis and nontuberculous mycobacterial infection and medical education working as a Professor of Medicine at the NYU Grossman School of Medicine.



Dr. Doreen J. Addrizzo-Harris

Before she steps into the role of President, we spoke with Dr. Addrizzo-Harris for a glimpse into what she looks to bring to the CHEST organization.

What would you like to accomplish as President of CHEST?

For my presidency, I want to continue the great trajectory CHEST is on by focusing on increasing membership, expanding our educational offerings and advancing our communication strategies, and continuing the initiatives that strive to make diversity seamless and a part of everything we do.

As many know, I have a very strong passion for the work of the CHEST Foundation, and, throughout my presidency, I will focus on how CHEST can support and integrate with the Foundation's goal of improving patient care – whether it's through supporting clinical research grants, expanding patient education and advocacy events, or through funding programs like the First 5 Minutes™, which touches on strengthening the rapport and trust between clinician and patient and enhances cultural competency by building an understanding of barriers to care. I can also see increasing patient involvement in CHEST to lend a unique perspective to upcoming initiatives.

Another key focus will be to strengthen and expand our membership through many venues.

We will focus on increasing physician membership of both new members and lapsed members but will also focus on increasing membership of those other providers who help us care for our patients, including advanced practice providers, respiratory therapists and more. CHEST is already an inclusive organization to a variety of health care providers, but we can do more.

"My presidency will also focus on increasing collaborations with our sister societies to find new ways to reach fellows-in-training, as well as residents and medical students who are interested in pulmonary, critical care, or sleep medicine."

My presidency will also focus on increasing collaborations with our sister societies to find new ways to reach fellows-in-training, as well as residents and medical students who are interested in pulmonary, critical care, or sleep medicine.

Along those lines, I'm also planning a dedicated focus on providing more opportunities to fellows and early career members. The goal is to enhance communications between trainees and key thought-leaders in a way that is simple, seamless, and welcoming. CHEST already does this better than anyone else, but an expanded offering, particularly in the area of career development, can help reach even more individuals – both on a national and on an international level. One such event was our successful Young Professionals Event at the Belmont event in New York City this past June.

INCOMING PRESIDENT *continued following page*

NETWORKS

Diagnosic tools, biomarker testing, and more ...

CHEST INFECTIONS & DISASTER RESPONSE NETWORK

Chest Infections Section

An evolving diagnostic tool: Microbial cell-free DNA

The diagnosis of the microbial etiology of pneumonia remains a significant challenge with <50% yield of blood and sputum cultures in most studies. More reliable samples, like bronchoalveolar lavage, require invasive procedures. Undifferentiated pneumonia hampers antimicrobial stewardship and increases the risk of suboptimal treatment.


Dr. Wigger

New diagnostic tools that detect degraded microbial DNA in plasma, known as microbial cell-free DNA (cfDNA), may offer improved diagnostic yield. Through metagenomic next-generation approaches, these tools sequence DNA fragments to identify viral, bacterial, and fungal sequences.

Earlier studies of cfDNA in pneumonia have been mixed, correctly identifying the pathogen in 55% to 86% of cases – though notably cfDNA was superior to PCR and cultures and provided early detection of VAP in some cases (Farnaes L, et al. *Diagn Microbiol Infect Dis*. 2019;94:188; Langelier C, et al. *Am J Respir Crit Care Med*. 2020;201:491). However, a recent study of cfDNA in severe complicated pediatric pneumonia had promising results with significant clinical impact. cfDNA provided an accurate microbial diagnosis in 89% of cases, with it being the only positive study in 70% of cases. Further, cfDNA narrowed the antimicrobial regimen in 81% of cases (Dworsky ZD, et al. *Hosp Pediatr*. 2022;12:377).

The use of cfDNA is still in its infancy. Limitations, such as a lack of validated thresholds to differentiate colonization vs infection are noted given its detection sensitivity. Its utility, including ideal timing and patient population, needs further investigation. However, diagnostic cfDNA may soon provide earlier and less invasive microbial diagnostics in patients with chest infections and beyond.

Gregory Wigger, MD
Section Fellow-in-Training

THORACIC ONCOLOGY & CHEST IMAGING NETWORK

Lung Cancer Section

What is comprehensive biomarker testing and who should order it?

For non–small cell lung cancer, comprehensive biomarker testing is generally defined as testing eligible patients for all biomarkers that direct the use of FDA-approved therapies (Mileham KF, et al. *Cancer Med*. 2022;11[2]:530. What comprises comprehensive testing has changed over time and will likely continue to change as advances in biomarkers, therapies, and indications for their use continue to evolve. There are also some potential benefits to testing biomarkers without FDA-approved therapies, such as assessing eligibility for treatment as part of a clinical trial or for identifying treatment options that gain FDA-approval in the future. As for who should be responsible for biomarker test ordering, this remains unclear and variable between institutions and practices (Fox AH, et al. *Chest*. 2021;160[6]:2293). All subspecialties involved, including pulmonology, pathology, interventional radiology, surgery, and oncology, have the potential for knowledge gaps surrounding biomarker testing (Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8[3]:286; Smeltzer MP, et al. *J Thorac Oncol*. 2020;15[9]:1434). Those obtaining diagnostic tissue, including pulmonologists, surgeons, and interventional radiologists may not appreciate the downstream use of each biomarker but are in the place to order testing as soon as the time of biopsy. Pathologists may be unaware of clinical aspects to the patient's case, such as the suspected clinical stage of disease. Oncologists arguably have the best chance of having the expertise to order testing but, ideally, biomarker results would be available by the time a patient meets with an oncologist to discuss treatment options. There is no perfect solution to this question at present, but if you are involved with the diagnosis of lung cancer, you should collaborate with your multidisciplinary team to streamline testing and strategize how to best serve patients.

Adam Fox, MD
Section Fellow-in-Training

SLEEP MEDICINE NETWORK

Nonrespiratory Sleep Section

Sleep in cancer patients

Sleep disturbance is among the most common symptoms in patients with cancer with an estimated prevalence of up to two out of three patients experiencing sleep disruption during their cancer journey.[1,2] Sleep disruption arises from a variety of preexisting clinical factors and is compounded by adjustment to cancer diagnosis and therapy.[3,4]

Common sleep disorders in cancer patients:

Insomnia: Cancer patients have at least a two-fold higher incidence of insomnia compared with the general population.[5,6] Predisposing factors may include age, the presence of hyper-arousability,a prior history of insomnia, or a preexisting psychiatric disorder. Cancer-related factors include surgery, hospitalization, chemotherapy, hormonal therapy, radiation therapy, and use of steroids.[7] If sedative-hypnotics are considered, they should be used in conjunction with cognitive and behavioral therapy for insomnia (CBT-I). Recent meta-analyses provide data to support a strong recommendation to utilize CBT-I to treat insomnia in cancer patients.[6,8,9]


Dr. Balachandran

Hypersomnolence: Hypersomnolence or excessive daytime sleepiness is a common symptom noted among cancer patients.[10] Hypersomnia related to cancer can be often classified as either hypersomnia due to a medical condition or hypersomnia due to a drug or substance, especially for those patients taking opioid or other sedative medications.

Movement Disorders: Sleep movement disorders occur in patients with cancer and may be primary or attributable to chemotherapy-related neuropathy from therapy regimens, including platinum compounds, taxanes, vinca alkaloids, proteasome inhibitors, or thalidomide-based agents.[11,12]

NETWORKS *continued on following page*

INCOMING PRESIDENT *continued from previous page*

What do you consider to be the greatest strength of CHEST, and how will you build upon this during your presidency?

CHEST has many strengths, but I think our greatest is the strength of our team – our members, our faculty, our volunteer leaders, and our staff.

To build on this, my presidency will include a strong communications strategy to reach, educate, and share the variety of opportunities with our members. I want to build on some of the excellent initiatives Dr. David Schulman started this year to continue engaging and showing our newer members, or soon-to-be members how to get involved with CHEST.

What are some challenges facing CHEST, and how will you address these challenges?

A challenge for all associations, CHEST included, will be redefining what associations look like in the wake of a global pandemic now that virtual and hybrid learning has become a part of what we do on a day-to-day basis. What will the CHEST Annual Meeting look like 3 years from now? What will keep learners coming to a physical meeting when so much is accessible on the internet? What will keep members engaged in settings where we no longer get together in-person – like the board review that is now virtual?

This all will take a lot of strategy, which is already being worked on. It will include ideas like enhancing the networking opportunities to extend beyond the annual meeting, strengthening our international strategy, and continuing to innovate in the area of medical education.

And finally, what do you ask of the members and Fellows of CHEST to support you during your presidency?

I ask that everyone get involved. Please reach out if you have questions. I am (and all our leaders are) very accessible and we can connect you with the right people to get you engaged. Also, please spread the word. Tell your colleagues, trainees, etc., how great CHEST is and get them involved with CHEST too. We have so much to offer. ■

Everything but the education

Things to do at CHEST 2022 between education sessions

CHEST 2022 may offer unparalleled access to the newest research in pulmonary, critical care, and sleep medicine, but that's not all you'll have to see and do while onsite in Nashville this October. Check out just a few of the many other options for education, networking, and entertainment you can expect to experience at this year's event.

Have fun – and support important patient initiatives – with the Foundation

The CHEST Foundation is offering a host of opportunities for attendees at CHEST 2022 to reconnect with peers, support initiatives designed to improve the lives of patients with pulmonary diseases, and to have a lot of fun.

Women in the fields of pulmonary, critical care, and sleep medicine can connect with colleagues at the Women & Pulmonary luncheon on Monday, October 17, from 12:00 to 130 PM. Attend this afternoon event to learn more about advancing your career as a woman in pulmonary medicine and the unique manifestations of pulmonary diseases in women and girls. Then, plan to join the W&P group for a Continuing the Conversation breakfast on Tuesday, October 18, or Wednesday, October 19, at 8:00 AM to learn even more.

Plus, donate $250 to the CHEST Foundation any time before December 31, 2022, to enter a giveaway for your chance to receive two first-class airline tickets, accommodations, and registration to CHEST 2023 in Hawaii. Don't miss this opportunity to support a great cause and save your seat for next year's event.

Starting off on the right step

Kick off your CHEST 2022 meeting experience with a with a step kick, a swivel, and a stomp at the Opening Reception on Sunday, October 16, 6:00 to 8:30 PM at Nashville's famous Wildhorse Saloon. Attendees can learn line dancing steps on the largest dance floor in the downtown area while enjoying Nashville favorites, like Nashville hot chicken and a selection of entrees and desserts featuring a "Jack Daniels" single barrel whiskey glaze in honor of the host location's history of whiskey distilling.

Are you a member of a CHEST Network or want to learn more about the groups? Attend the Network Mixer on the second floor of the Wildhorse, also from 6:00 to 8:30 PM to meet CHEST leaders, and learn more about each Section's unique contributions on important topics in pulmonary, critical care, and sleep medicine.

Challenge accepted

One of the most popular and exciting events at every annual meeting, the CHEST Challenge Championship, is back in person, Tuesday, October 18, at 7:30 PM. At this Jeopardy-style challenge, watch the three finalist teams of fellows battle it out in a difficult test of their clinical knowledge that rivals even board review examinations. The first-place team will walk away with $5,000 for their fellowship program. Come and cheer your team on to victory!

Experience CHEST

Get a look at so much CHEST has to offer at Experience CHEST, located at booth 2026 in the Exhibit Hall.

Learn more about CHEST guidelines – including what they are, what they are not, and how you can get involved in the development of future publications – at the Guidelines Pod. Access even more education with bite-sized presentations from Network members on topics including racial bias, sepsis, lung transplantation, and much more. And, take the next step in your professional journey with the Career Connection team, who will walk you through using our online platform for posting and identifying open positions. Plus, learn more about CHEST products and publications – including updates to the CHEST SEEK™ Education line and news about our two new open access journals, *CHEST Pulmonary* and *CHEST Critical Care*. Help us test new features on the CHEST website, and get your free CHEST 2022 souvenir T-shirt.

Don't miss your chance to connect with giants in pulmonary, critical care, and sleep medicine – access the latest research in the field. Register for CHEST 2022 today at https://www.chestnet.org/Learning-and-Events/Events/CHEST-Annual-Meeting. ■

NETWORKS *continued from previous page*

Obstructive sleep apnea (OSA): OSA occurs in patients with cancer and may be increased in patients with specific cancers such as head and neck tumors.[13] Patients with sleep apnea have a five-fold increased risk of cancer-related mortality, and several studies show an increased incidence of cancer in those with sleep apnea.[14-16] There is an increasing realization that not only sleep apnea, but sleep disturbance, in general, may be oncogenic based on increased autonomic tone, chronic stress, variation in the pituitary-hypothalamic axis, as well as circadian mechanisms.[17]

Early recognition/treatment of sleep issues is essential to improve quality of life in cancer patients.

Diwakar Balachandran, MD, FCCP
Member-at-Large

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INDEX OF ADVERTISERS

From the President

With just about a month to go until CHEST 2022, the Annual Meeting Innovations Group has been hard at work putting some finishing touches on the Nashville experience that we are very excited to unveil. And, while I will not go into great depth (to let others share their creations or, even better, for attendees to enjoy the novel experiences in real-time), I hope to use my space this month to at least whet your appetite for the kinds of things you can expect to see in October. There have long been numerous sessions at the annual meeting covering the newest scientific advancements and cutting-edge research. Contemporary meetings feature more novel session types, including interactive case-based sessions, pro-con debates (such as the popular Pardon the Interruption!), and in-depth reviews of clinical topics that help our members provide the best possible management for patients under their care. Having a variety of ways to learn not only improves content retention but also goes a long way to making the meeting a more enjoyable experience for everyone.

Over the last several years, CHEST meeting content has moved into some atypical spaces and formats, including presentations from our partners in the device and pharmaceutical industries and interactive, educational games you can play against your peers in our CHEST Games booth in the exhibit hall. Undoubtedly, these games represent the most fun you can have while at the meeting; in addition to some classics (like ASPIRATED! and Peer Pressure), we are rolling out two new live gameshows where you can test your knowledge, play with (and against) other attendees, and win fabulous prizes! There will also be two new escape rooms, which will grow on the successful adventures that many of you embarked upon over the past 3 years.

For all of the wonderful experiences that we have planned, the best reason to join us in October is to catch up with colleagues. Opportunities to see our long-time friends from whom we have been separated over the last 30 months have been

Dr. David Schulman

far too few, and CHEST 2022 will include a number of ways to celebrate these reunions. Returning to in-person meetings has been too long in coming, and we will be sure not to squander a moment of our time together.

Something that has come to my attention over the last several weeks is that there may be efforts on the part of a still-unidentified group to capture what makes CHEST so special! Possibly, this is just my imagination, but I will be relying on each of you to keep your eyes open during CHEST 2022 for any atypical goings on, and to do your best to circumvent any potential "underhandedness"; there could be clues anywhere, and a generous reward awaits those who can successfully help us thwart the evil-doers! I expect you've noticed this column is a bit atypical compared with my previous *CHEST Physician* messages. Extreme care had to be taken to ensure that those qualified to help us in our mission to protect CHEST could receive instructions while making certain these directives didn't fall into the wrong hands. Since you likely noticed some odd linguistic choices, if you've gotten this far, I suspect you've found the secret message I've hidden herein; three randomly-selected members who email me at president@chestnet.org before October 1 with that message as the subject line will win free registration to CHEST 2022 (others will get a nice shout-out)!

Until next time,
David S.

Twenty-five years of life-changing grants

Realizing the impact of the CHEST Foundation

In 1996, the CHEST Foundation was just an idea. CHEST members all over the world had begun raising concerns to the Board of Regents over what their patients were experiencing – challenges like poverty and environmental factors. To Bart Chernow MD, Master FCCP, the founding father of the Foundation, that was the lightbulb moment that CHEST could do more. The Foundation's goal became serving patients by fighting against the global factors that contribute to disparities, focusing not just on clinical medicine but also the social, cultural, and environmental problems surrounding and impacting patient care.

A key driver of this mission was to provide financial grants to advance medicine and support those in need. Twenty-five years and 12 million

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The Foundation had an impact on the VACC Camp.

dollars later, the CHEST Foundation is proud to still be awarding grants to bolster the field of medicine and enhance patient care.

When asked about the grants awarded by the CHEST Foundation, CHEST Past President D. Robert McCaffree, MD, Master FCCP, recalls one that stuck with him because it gave children the gift of a childhood.

1998: Starting at the beginning

In 1998, the American College of Chest Physicians presented Dr. Moises Simpser, MD, FCCP, with its prestigious Governors Community Service Award in recognition of work he'd done to establish an overnight camp for ventilator-assisted children from all over the country.

Dr. Simpser created Ventilation Assisted Children's Center camp (VACC Camp) with the intention of giving families with ventilator-dependent children the "vacation of a lifetime" by offering unique opportunities for recreation and socialization.

"Dr. Simpser's goal was to give a break to the families caring for ventilator-dependent children; to provide respite for just a week where they wouldn't have to worry about anything," said Carlos Gallostra, a retired respiratory therapist and one of many medical volunteers at the camp. "For one week a year, the families didn't have to worry about therapies, administering medications, food, nothing."

With the assistance of the volunteers, VACC Camp was able to provide experiences for the children that would have been nearly impossible elsewhere, like getting into a swimming pool. "To see the pictures of these children with their tracheostomies on a ventilator floating in a pool ... you just had to smile or laugh. It was such a joyful picture," says Dr. McCaffree. "I will always remember that, not just because it was our first granting year but because it was such a great project."

Dr. Simpser died in 2017, but his legacy lives on through the camp, which is still operational. In its 30 years, VACC Camp has hosted more than 180 families for life-changing vacation experiences.

While the Foundation awarded its first grants to US-based projects, the program quickly expanded internationally.

2010: Running water in Peru

Robert Hyzy, MD, FCCP, medical director of the Critical Care Medicine Unit and co-chair of the Critical Care Committee at the University of Michigan Hospital in Ann Arbor, Michigan, also serves as medical director for Amazon Promise, a nonprofit organization that provides medical care to remote communities in the Upper Amazon Basin of northeastern Peru.

In 2010, Dr. Hyzy received a CHEST Foundation grant to fund plumbing improvements for an Amazon Promise free clinic in Belén, a poor community near the city of Iquitos. "Amazon Promise has a clinic on stilts in the air with a small waiting room," said Dr. Hyzy. "There's no running water, so … we built this clinic, but we really had no plumbing of any sort."

His proposal to the Foundation requested funding for a water purification system, composting toilet, and a shower in the back of the facility. After receiving the grant, Amazon Promise worked with Engineers Without Borders to install the components, which took less than a week to complete.

The funds also helped propel the clinic into a more fully functional center for local Peruvian staff, American staff, and the teams of University of Michigan medical students and residents who travel to Belén every year with Dr. Hyzy.

"It made a big difference for us to be able to use our clinic more fully [and] more comfortably…" he said. "It's been roughly 10 years, and that equipment is still in use today."

Since they made the system improvements, Dr. Hyzy and his teams have served thousands of people over the course of 10 trips. During each visit to Belén, they typically see 200 to 250 people a day for 1 or 2 days, often with a focus on deworming children and providing them with antiparasitic medications and multivitamins.

When Dr. Hyzy reflected on his opportunities to serve in the clinic, he said the most meaningful part was connecting with patients. "In a way, the greatest impact we have is on people who are largely forgotten knowing they're not forgotten," he said. "The third world deserves nothing less than university-based medical critical care."

2021: Offering a hand up, not a handout

Valerie Andrews, a community leader in south Sacramento, California, is using a recent grant to continue serving as a conduit between residents with asthma and their doctors.

She is the founder and program director of the JUDAHH Project, a nonprofit organization that works to help empower underserved residents of Sacramento with a "hand up" instead of a "handout." Andrews plans to use her grant funding from the CHEST Foundation to educate the community on asthma detection, treatment, and management.

Andrews will continue her work teaching residents how to use their inhaler, the importance of developing a personal asthma action plan, and the right questions to ask their doctor. JUDAHH also offers home visits to conduct an asthma trigger assessment and help remediate environmental triggers in partnership with Regional Asthma Mitigation Project (RAMP).

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The Foundation aided the JUDAHH Project.

"[Our goal is] just to bring the information because we know that health plays a significant part in continuing in the underserved community. If they have access to health, then the likelihood of them succeeding is better," said Andrews.

The work inspired Andrews to pursue other grant opportunities through the CHEST Foundation. Andrews plans to implement the project until June 2023. She hopes to help those who suffer from asthma identify household and environmental triggers and, ultimately, mitigate the need for ED visits, missed school, and work absences.

To the next 25

Twenty-five years ago, a handful of visionaries, including Dr. Bart Chernow, came together with a mission to give back to those who need it most. The CHEST Foundation is able fund projects dedicated to furthering this mission because of the continued support of those who donate. Looking ahead to the next 25 years, the Foundation will continue to advance medicine and public health through awarded grants, as well as support promising initiatives aimed at eliminating disparities.

In the words of one of the Foundation's trailblazers, Dr. McCaffree, "Awarding these grants is a great way for CHEST to not only support our members but to also thank our membership for ensuring the future of research and community involvement. Grants help us recognize the present and support the future."

To learn more about Amazon Promise, visit amazonpromise.org.

To learn more about the JUDAHH Project, visit thejudahhproject.com. ■

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