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

CORONAVIRUS
At the front lines of long COVID, local clinics prove vital // **8**

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Trials data leave primary care docs in the dark // **9**

PULMONARY MEDICINE
Home-based COPD rehab trial shows positive results // **11**

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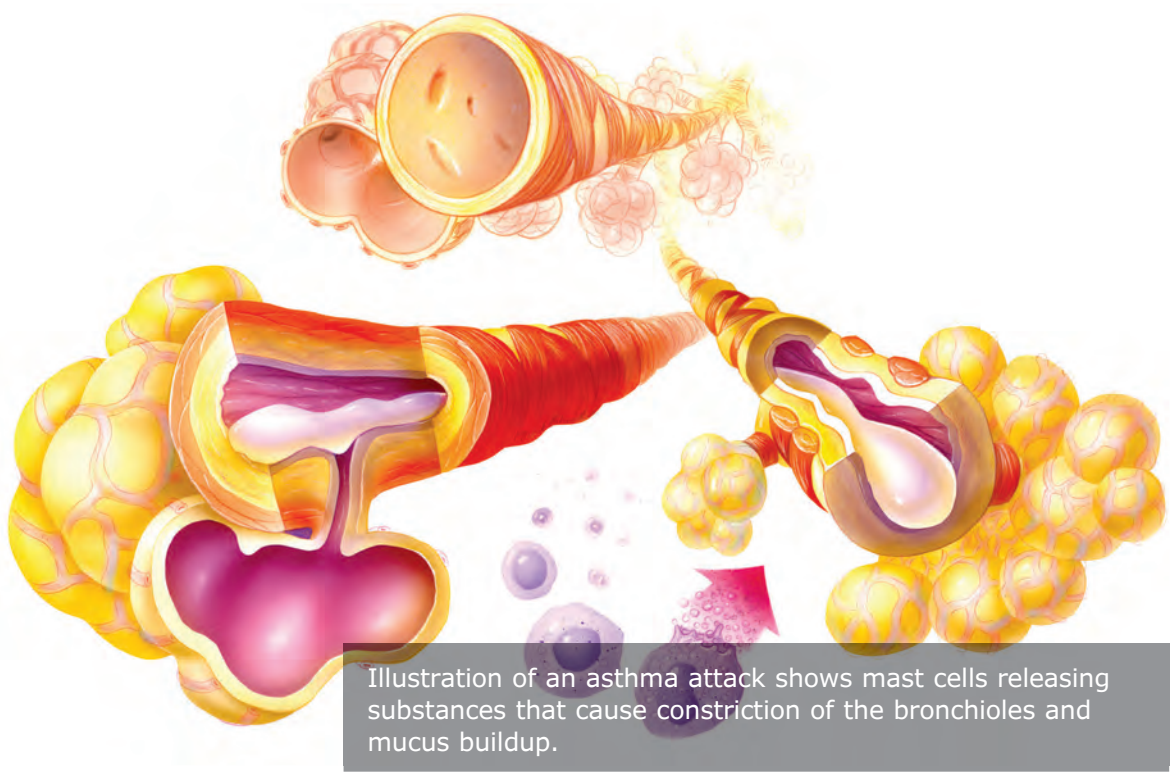
CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Patrick McDonnell/Science Source

Illustration of an asthma attack shows mast cells releasing substances that cause constriction of the bronchioles and mucus buildup.

Mucus unplugged

BY NEIL OSTERWEIL

Just uttering the word "mucus" is often sufficient to elicit amusement from those within earshot, but to patients with chronic inflammatory airway diseases, mucus is no laughing matter.

Under normal conditions, mucus plays an important protective role, trapping airway irritants such as smoke, pollen, and particulate matter, which are then moved by cilia out of the airways for expulsion through coughing.

But in cystic fibrosis (CF), for example, mucus hypersecretion can be deadly. The underlying pathology of CF – a mutation in the CFTR gene, which codes for the protein CF transmembrane conductance regulator – leads to buildup in the lungs of abnormally viscous and sticky mucus, resulting in frequent, severe infections (particularly with *Pseudomonas aeruginosa*), progressive lung damage, and prior to the development of effective disease management, significantly premature death.

Mucus hypersecretion is also a feature of chronic obstructive pulmonary disease (COPD), noted a team of editorialists in the American Journal of Respiratory and Critical Care Medicine (2019. doi: 10.1164/rccm.201808-1444ED).

In COPD, "mucus dysfunction arises from several mechanisms, including excess production due to inflammation, decreased elimination due to impaired ciliary clearance and reduced cough efficiency, and excessive concentration due to smoke-induced dysfunction of transepithelial anion transport resembling CF," the editorialists wrote.

In patients with idiopathic pulmonary fibrosis,

MUCUS UNPLUGGED // *continued on page 6*

Sepsis transition program may lower mortality rate in patients discharged to post–acute care

BY MARK S. LESNEY, PHD

FROM CHEST 2022 ▪ Sepsis survivors discharged to post–acute care facilities are at high risk for mortality and hospital readmission, according to Nicholas Colucciello, MD, and few interventions have been shown to reduce these adverse outcomes.

Dr. Colucciello and colleagues compared the effects of a Sepsis Transition And Recovery (STAR) program versus usual care (UC) alone on 30-day mortality and hospital readmission among sepsis survivors discharged to post-acute care.

In a study presented at the annual meeting of the American College of Chest Physicians (CHEST), Dr. Colucciello showed data suggesting that the STAR intervention program appears beneficial for patients discharged

SEPSIS TRANSITION // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Networks: Stella Ogake, MD, discusses firearm violence

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BATTLE TESTED IN EOS DISEASE

With proven results across **4 indications**—
our track record stands out

Severe eosinophilic asthma (SEA)

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Eosinophilic granulomatosis with polyangiitis (EGPA)

Hypereosinophilic syndrome (HES)

NUCALA is for the:

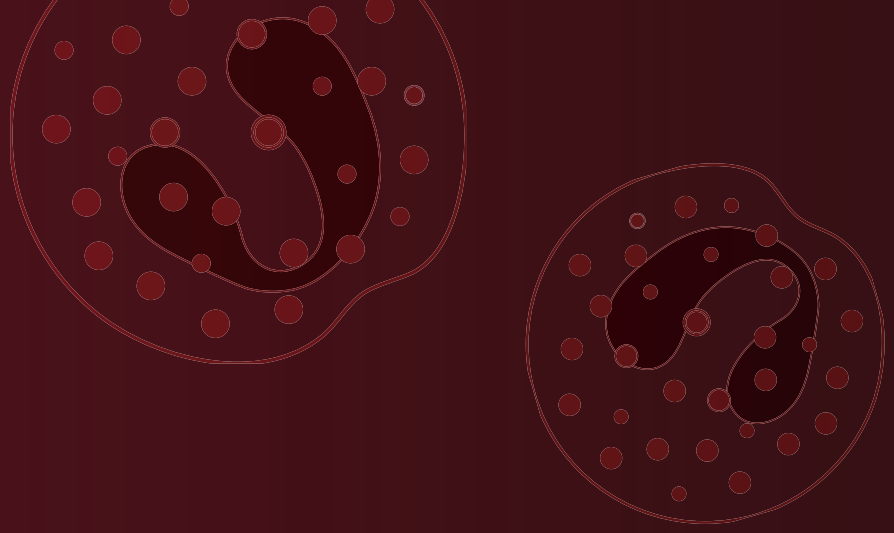
- add-on maintenance treatment of patients 6+ with SEA. Not for acute bronchospasm or status asthmaticus.
- add-on maintenance treatment of CRSwNP in patients 18+ with inadequate response to nasal corticosteroids.
- treatment of adult patients with EGPA.
- treatment of patients aged 12+ with HES for ≥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.

Visit **NucalaBattleTested.com** to learn more



Nucala (mepolizumab)

Injection 100 mg/mL

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.

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

MPLJRNA220004 August 2022
Produced in USA.

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.

13 NONCLINICAL TOXICOLOGY

13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
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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a polymorphism in the enhancer region of MUC5B, a gene that encodes for mucin glycoproteins, results in a 20-fold overexpression of the gene and prominent mucus production that has been shown to parallel lung inflammation and decline in forced vital capacity (FVC).

In patients with asthma, upregulation of MUC5AC and stimulated mucus secretion conspire to obstruct airways. In extreme cases this can lead to death, wrote the editorialsts, Victor Kim, MD, and colleagues from the University of Colorado at Denver, Aurora, and Burton F. Dickey, MD, of the University of Texas MD Anderson Cancer Center, Houston, and colleagues.

'Short shrift'

Yet until recently, the role of mucus hypersecretion in diseases such as COPD has been largely overlooked, or as Dr. Kim and colleagues put it, "airway mucus often receives short shrift from clinicians."

"It's a pretty hot topic in pulmonary medicine today because it has been so neglected for so long," Dr. Dickey said in an interview with CHEST Physician. "As clinicians, we haven't had a way to identify who needs treatment, which is ridiculous because many of the people who expectorate a lot, like those with chronic bronchitis, don't actually have small airway obstruction, and conversely, a lot of asthmatics, who have very serious small airway obstruction, don't expectorate, so you can't really tell from symptoms."

What has changed in recent years is the use of chest CT to image muco-obstructive pathology, commonly called "mucus plugging" in the peripheral airways of patients with COPD and asthma.

"In the last decade or so, we've seen the emergence in obstructive lung diseases such as asthma and COPD of the use of more objective measures on CT scans, including for the problem of mucus plugging, which is unfortunately very common," Dr. Kim said in an interview.

The discovery of the extent and severity of mucus in obstructive lung diseases has led to new strategies to combat mucus overconcentration, such as hydration, mucolytics, and an intriguing investigational approach to decrease calcium-induced hypersecretion with designer peptides.

Mighty mucins

Under normal physiologic conditions mucus is composed largely of water (97%) and salts (2%), with the remainder consisting of entrapped globular proteins (0.7%) and mucins (0.3%), Dr. Dickey explains.

Yet those meager mucins pack a real punch, with the ability to absorb 300 times their mass of water after secretion, creating mucus of optimal consistency and viscoelasticity.

"Personally, I've never understood – maybe I should have paid more attention in physics – how a compound can absorb 300-fold its mass, but it does," he said.

In a recent review article in the journal Clinical and Translational Medicine (2022 Jul 31 doi: 10.1002/ctm2.972), Dr. Dickey and colleagues described how good mucus can go bad.

"[H]igh levels of mucin production from inflammatory stimulation (termed 'mucous metaplasia'), followed by rapid release (together, termed 'mucus hypersecretion'), can plug airways due to mucus volume expansion. In addition, if available lumenal liquid is insufficient, concentrated mucus of excessive viscoelasticity and adhesivity can cause mucus stasis," they wrote.

Therapeutic strategies

In patients with CF, CFTR modulator therapy has markedly reduced but not eliminated the need for some patients to have mucolytic therapy, which may include dornase alfa, a recombinant human deoxyribonuclease that reduces the viscosity of lung secretions, hypertonic saline inhaled twice daily (for patients 12 and older), mannitol, and physical manipulations to help patients clear mucus. The manipulations can include both manual percussion and the use of devices for high-frequency chest wall oscillation.

Unlike in CF, where treating the underlying genetic pathology can help to resolve the thick, sticky mucus problems and thereby significantly reduce risk of infections and progressive lung damage, treatment of mucus metaplasia or hypersecretion in other diseases is aimed at symptomatic relief; it is still unclear whether symptomatic improvement of mucus overproduction would correlate with other disease-related outcomes, Dr. Kim and Dr. Dickey noted.

Potential therapeutic strategies to reduce excess mucus in the lungs include the use of mucolytic agents to thin secretions for more effective expulsion, decreasing mucus production through the use of an interleukin-13 (IL-13) inhibitor such as

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to post-acute care facilities and may lead to decreased 30-day mortality and readmission rates.

Study of IMPACTS

The study was a secondary analysis of patients from the IMPACTS (Improving Morbidity During Post–Acute Care Transitions for Sepsis) randomized clinical trial, focusing only on those patients who were discharged to a post–acute care facility. IMPACTS evaluated the effectiveness of STAR, a postsepsis transition program using nurse navigators to deliver best-practice postsepsis care during and after hospitalization, Dr. Colucciello, a primary care physician from Toledo, Ohio, said.

The interventions included comorbidity monitoring, medication review, evaluation for new impairments/symptoms, and goals of care assessment.

"Over one-third of sepsis survivors are discharged to post-acute care as they are not stable enough to go home," said Dr. Colucciello, and among these patients there is a high risk for mortality and hospital readmission.

Dr. Colucciello and his colleagues randomly assigned patients hospitalized with sepsis and deemed high risk for post-discharge readmission or mortality to either STAR or usual care. The primary outcome was a composite of 30-day readmission and mortality, which was assessed from the electronic health record and social security death master file.

Of the 175 (21%) IMPACTS patients discharged to post–acute care facilities, 143 (82%) were sent to skilled nursing facilities, and 12 (7%) were sent to long-term acute care hospitals. The remaining 20 patients (11%) were sent to inpatient rehabilitation. A total of 88 of these patients received the STAR intervention and 87 received usual care.

Suggestive results

The study showed that the composite primary endpoint occurred in 26 (30.6%) patients in the UC group versus 18 (20.7%) patients in the STAR group, for a risk difference of –9.9% (95% CI, –22.9 to 3.1), according to Dr. Colucciello. As individual factors, 30-day all-cause mortality was 8.2% in the UC group, compared with 5.8% in the STAR group, for a risk difference of –2.5% (95% CI, –10.1 to 5.0) and the 30-day all-cause readmission was 27.1% in the UC group, compared with 17.2% in the STAR program, for a risk difference of –9.8% (95% CI, –22.2 to 2.5). On average, patients receiving UC experienced 26.5 hospital-free days, compared with 27.4 hospital-free days in the STAR group, he added.

The biggest limitation of the study was the fact that it was underpowered to detect statistically significant differences, despite the suggestive results, said Dr. Colucciello. However: "This secondary analysis of the IMPACTS randomized trial found that the STAR intervention may decrease 30-day mortality and readmission rates among sepsis patients discharged to a post–acute care facility."

"This secondary analysis of the IMPACTS randomized trial found that the STAR intervention may decrease 30-day mortality and readmission rates among sepsis patients discharged to a post–acute care facility."

Dr. Colucciello and colleagues report no relevant financial relationships. ■

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the anti-asthma agent dupilumab (Dupixent), and a novel strategy, still in the experimental phase, aimed at "disrupting the fusion of mucin storage granules with the cell membrane, thereby blocking secretion," wrote Irina Gitlin, PhD, and John Fahy, MD, from the University of California, San Francisco, in Nature (2022 Mar 23;603:798-9).

They were referring to research by Dr. Dickey and colleagues described in the same issue of Nature (2022 Mar 23;603:949-56) focusing on the inhibition of calcium-triggered mucus secretion by the use of hydrocarbon-stapled peptides, short chains of amino acids stabilized with a chemical bridge to a hydrocarbon molecule.

Knocking secretion down, but not out

The work has centered on decreasing overproduction of mucins with a focus on the signals for mucin production, including IL-13 and interleukin-1 beta, and on the signals for rapid release of mucins, including adenosine 5'-triphosphate (ATP), best known as an intracellular energy-storage module.

"But ATP is also steadily released by ciliated cells in response to the shear stress of tidal breathing, and it tells the neighboring secretory cells to slowly and steadily release mucin. But if the ciliated cells get stressed by any of a number of mechanisms, it can release a lot of ATP, and then the secretory cell can explosively release essentially all of its mucin content," Dr. Dickey explained.

Other important signals for rapid release of mucins are acetylcholine and histamine, and all three of these agonists – ATP, acetylcholine, and histamine – cause a rise in intracellular calcium, which triggers calcium sensors that then lead to calcium-triggered membrane fusion and secretion.

Working as a postdoc in the Dickey laboratory, Dr. Evans had previously shown that deleting MUC5B in mice led to early development of serious lung abnormalities, some of which were fatal, indicating that MUC5B, a gene that is highly preserved in evolution, is essential for respiratory health.

This observation was later supported by a study of a family with a pattern of hereditary mucin deficiency (Am J Respir Crit Care Med. 2022;205[7]:761-8) caused by a homozygous loss-of-function mutation in MUC5B.

The main subject in this study was an adult woman with unexplained bronchiectasis, impaired pulmonary function, and repeated *Staphylococcus aureus* infections. Her sibling, who also had the biallelic mutation, had extensive sinus disease with nasal polyps. Other siblings who were heterozygous for the mutation were asymptomatic but had mild functional lung impairment.

The trick for the investigators, then, was to figure out how to reduce the stimulated release of stored mucins while still preserving normal release of mucins to allow for ciliary clearance of mucus, and Dr. Dickey and colleagues appear to have accomplished this, at least in mice.

They first validated as a potential therapeutic target a protein labeled synaptotagmin-2 (Syt2). Syt2 is a calcium sensor that is an essential part of the system that triggers calcium-regulated secretion.

In a model for allergic asthma, mice with Syt2 deleted from airway epithelia had marked reductions in both stimulated mucin secretion and in mucus occlusion in airway lumens, but remained otherwise healthy with normal lung function.

Working with structural biologist Axel Brunger, PhD, from Stanford (Calif.) University, Dr. Dickey and coinvestigators developed and validated a peptide that could specifically inhibit Syt2, and found that it mimicked the action of the Syt2 deletion, preventing mucus occlusion in the allergic asthma model without adversely affecting normal production.

Not ready for prime time

Dr. Dickey and colleagues are now working to translate the therapy into a form that can be used in humans, most likely as an aerosol that could be used for acute treatment of patients with mucus plugging from asthma and COPD, and also as a therapy for patients with chronic disease.

"In the chronic situation, what we would hope to do is identify patients with muco-obstructive lung disease – asthma, COPD, cystic fibrosis – who have airway mucus obstruction and then use the inhaled peptide on a regular basis as one part of a program to try to prevent this chronic mucus occlusion," according to Dr. Dickey.

As Dr. Gitlin and Dr. Fahy wrote in their editorial, "by confirming that it is possible to block calcium-regulated mucin secretion, Lai and colleagues have shown the potential of such an approach as a new therapeutic strategy for lung illnesses associated with mucus pathology, including diseases such as asthma and COPD, for which there is a large unmet medical need."

The study by Dr. Dickey and colleagues was supported by grants from the German Research Foundation, National Institutes of Health, and the Cystic Fibrosis Foundation

Dr. Dickey disclosed consulting for Arrowhead Pharmaceuticals. Dr. Kim disclosed personal fees from Medscape and others. Dr. Evans reported no relevant disclosures. Dr. Fahy and Dr. Gitlin are named inventors on patents for mucolytic drugs, and shareholders in Aer Therapeutics. ■

At the front lines of long COVID, local clinics prove vital

BY DEBORAH SCHOCH

Big-name hospital chains across the United States are opening dedicated centers to help patients dealing with long COVID. But so are the lower-profile clinics and hospitals run by cities, counties, and states – including Harborview Medical Center in Seattle.

The Harborview clinic, operated by King County, is an example of how public health agencies are stepping up to treat people experiencing long COVID.

They serve areas ranging from Campbell County, Wyo., with 47,000 residents, to New York City, with its 8.4 million people. Many providers working there are searching for innovative ways to approach this lingering illness with its variety of symptoms, from brain fog to shortness of breath to depression and more.

Their efforts often fall below the radar, with still-scant serious media attention to long COVID or the public health employees working to treat ailing patients.

Why are state and local health agencies taking on these duties?

They're leading the way in part because the federal government has made only limited efforts, said Lisa McCorkell, a cofounder of the Patient-Led Research Collaborative. The international group was founded in spring 2020 by researchers who are also long COVID patients.

"It's a big reason why long COVID isn't talked about as much," Ms. McCorkell said. "It's definitely a national issue. But it trickles down to state and local health departments, and there's not enough resources."

The government clinics may be accessible to people without insurance and often are cheaper than clinics at private hospitals.

Harborview has treated more than 1,000 patients with long COVID, and another 200 patients are awaiting treatment, said Jessica Bender, MD, a codirector of the University of Washington Post-COVID Rehabilitation and Recovery Clinic in Seattle's First Hill neighborhood.

The group Survivor Corps offers lists by states of clinics. While the publicly run clinics may be less expensive or even free for some patients, methods of payment vary from clinic to clinic. Federally qualified health clinics offer treatment on a sliding scale. For instance, the Riverside University Health System in California has federally qualified centers. And other providers who are not federally qualified also offer care paid for on a sliding scale. They include Campbell County Health, where some residents are eligible for discounts of 25%-100%, said spokesperson Norberto Orellana.

At Harborview, Dr. Bender said the public hospital's post-COVID clinic initially began with a staff of rehabilitation doctors but expanded in 2021 to include family and internal medicine doctors. And it offers mental health programs with rehabilitation psychologists who instruct on how to deal with doctors or loved ones who don't believe that long COVID exists.

"I have patients who really have been devastated by the lack of support from coworkers [and] family," Dr. Bender said.

In Campbell County, Wyo., the pandemic surge did not arrive in earnest until late 2021. Physical therapists at Campbell County's Health Rehabilitation Services organized a rehabilitation program for residents with long COVID after recognizing the need, said Shannon Sorensen, rehabilitation director at Campbell County Health.

> *"[Long COVID is] definitely a national issue. But it trickles down to state and local health departments, and there's not enough resources."*

"We had patients coming in showing chest pain, or heart palpitations. There were people trying to get back to work. They were frustrated," Ms. Sorensen said.

Myalgic encephalomyelitis and chronic fatigue syndrome activists have embraced the fight to recognize and help long-COVID patients, noting the similarities between the conditions, and hope to help kickstart more organized research, treatment and benefits for long-COVID sufferers and myalgic encephalomyelitis/chronic fatigue syndrome patients alike.

In Ft. Collins, Colo., disability activist Alison Sbrana has long had myalgic encephalomyelitis. She and other members of the local chapter of ME Action have met with state officials for several years and are finally seeing the results of those efforts.

Colorado Gov. Jared Polis has created the full-time position of policy adviser for long COVID and post–viral infection planning.

"This is one way forward of how state governments are (finally) paying attention to infection-triggered chronic illnesses and starting to think ahead on them," Ms. Sbrana said.

New York City's Health + Hospitals launched what may be the most expansive long-COVID treatment program in the nation in April 2021. Called AfterCare, it provides physical and mental health services as well as community support systems and financial assistance.

A persistent issue for patients is that there isn't yet a test for long COVID, like there is for COVID-19, said Amanda Johnson, MD, assistant vice president for ambulatory care and population health at New York Health + Hospitals. "It's in many ways a diagnosis of exclusion. You have to make sure their shortness of breath isn't caused by something else. The same with anemia," she said.

California's Department of Public Health has a detailed website devoted to the topic, including videos of "long haulers" describing their experiences.

Vermont is one of several states studying long COVID, said Mark Levine, MD, the state health commissioner. The state, in collaboration with the University of Vermont, has established a surveillance project to determine how many people have long COVID, as well as how severe it is, how long it lasts, and potential predispositions.

The University of Utah, Salt Lake City, established a comprehensive COVID-19 clinic more than a year ago that also handles long COVID patients, said Jeannette Brown, MD, PhD, an associate professor at the school and director of the COVID-19 clinic.

Jennifer Chevinsky, MD, MPH, already had a deep understanding of long COVID when she landed in Riverside County, Calif., in the summer of 2021. She came from Atlanta, where as part of her job as an epidemic intelligence service officer at the Centers for Disease Control and Prevention (CDC), she heard stories of COVID-19 patients who were not getting better.

Now she is a deputy public health officer for Riverside County, in a region known for its deserts, sizzling summer temperatures and diverse populations. She said her department has helped launch programs such as post–COVID-19 follow-up phone calls and long-COVID training programs that reach out to the many Latino residents in this county of 2.4 million people. It also includes Black and Native American residents.

"We're making sure information is circulated with community and faith-based organizations, and community health workers," she said.

Ms. McCorkell said there is still much work to do to raise public awareness of the risks of long COVID and how to obtain care for patients. She would like to see a national public health campaign about long COVID, possibly spearheaded by the CDC in partnership with local health workers and community-based organizations.

"That," she said, "could make a big difference." ■

Medscape Illustration/Dreamstime/Getty Images

Trials data leave primary care docs in the dark

BY MARY CHRIS JAKLEVIC

Primary care clinicians often struggle to care for their patients with chronic obstructive pulmonary disease (COPD), thanks to a lack of real-world evidence as to which treatments work best.

As a result, potentially preventable life-threatening exacerbations are common among people with the condition. Central to the problem, some experts believe, is that the average patient bears little resemblance to participants in clinical trials of the medications used to treat COPD.

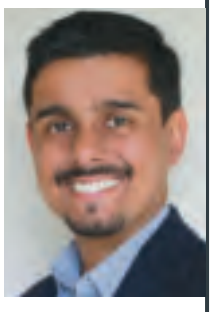
Indeed, a recent study showed that many COPD patients who were receiving maintenance therapy that should have been controlling their disease experienced severe flare-ups – a finding that caught the researchers by surprise.

"We know the benefit of COPD treatments in the context of clinical trials. However, the kinds of patients in primary care may not completely mimic those in clinical trials," one of the authors, MeiLan Han, MD, a professor of medicine in the division of pulmonary and critical care at the University of Michigan, Ann Arbor, told this news organization. Dr. Han, a volunteer medical spokesperson for the American Lung Association, added that patients "may not be as adherent to medications in real life as they are in clinical trials."

Randomized controlled trials that support regulatory drug approvals typically enroll patients who do not have comorbid conditions, who are younger than the average patient with COPD, and who typically are male. Patients are seen in resource-abundant settings designed to maximize adherence to treatment, with supports such as free medication and frequent monitoring – settings far different from those in which most primary care physicians practice.

The authors of the new article said trials conducted with typical patients in primary care settings could help physicians to optimize treatment.

Real-world evidence can shed light on physicians' intent and on barriers to following guidelines, as well as important patient factors, such as adherence and good inhaler technique, Barbara Yawn, MD, an adjunct professor in the department of family and community health at the University of Minnesota, Minneapolis, and a coauthor of the study, said in an interview.



Sachin Gupta, MD, FCCP, comments: The time from symptom recognition to diagnosis, as well as from diagnosis to full and appropriate management in chronic lung conditions like COPD, is concerningly prolonged. Concerns over the sensitivity of COPD screening tools (symptom scores, spirometry), lack of their timely widespread availability, and the incomplete adoption of formalized management checklists (such as with acute coronary syndrome and chronic heart failure) are some of the factors associated with persistently suboptimal long-term outcomes among patients with COPD. Time to adoption of new guideline-based recommendations in heart failure, for example, seems faster within primary care than what we see in COPD. Real-world evidence may be a piece of the solution as this article suggests; however, overall system-based changes in the processes for diagnosis and management, as well as better tools for screening/diagnosis, are likely to have greater benefit.

A window onto patient burden

According to the Centers for Disease Control and Prevention, an estimated $15 million Americans have COPD. Annual costs to the health care system approach $50 billion a year. The death rate for COPD has increased since 1969 as death rates of other major killers in the United States, such as heart disease and cancer, declined, according to a 2015 analysis of death records.

DATA *continued on following page*

COVID attacks DNA in heart, unlike flu, study says

BY CAROLYN CRIST

COVID-19 causes DNA damage to the heart, affecting the body in a completely different way than the flu does, according to a study published in Immunology (doi: 10.1111/imm.13577).

The study looked at the hearts of patients who died from COVID-19, the flu, and other causes. The findings could provide clues about why coronavirus has led to complications such as ongoing heart issues.

"We found a lot of DNA damage that was unique to the COVID-19 patients, which wasn't present in the flu patients," said Arutha Kulasinghe, one of the lead study authors and a research fellow at the University of Queensland, Brisbane, Australia, in the Brisbane Times.

"So in this study, COVID-19 and flu look very different in the way they affect the heart," he said.

Dr. Kulasinghe and colleagues analyzed the hearts of seven COVID-19 patients, two flu patients, and six patients who died from other causes. They used transcriptomic profiling, which looks at the DNA landscape of an organ, to investigate heart tissue from the patients.

"We found a lot of DNA damage that was unique to the COVID-19 patients, which wasn't present in the flu patients."

Because of previous studies about heart problems associated with COVID-19, he and colleagues expected to find extreme inflammation in the heart. Instead, they found that inflammation signals had been suppressed in the heart, and markers for DNA damage and repair were much higher. They're still unsure of the underlying cause.

"The indications here are that there's DNA damage here, it's not inflammation," Dr. Kulasinghe said. "There's something else going on that we need to figure out."

The damage was similar to the way chronic diseases such as diabetes and cancer appear in the heart, he said, with heart tissue showing DNA damage signals.

Dr. Kulasinghe said he hopes other studies can build on the findings to develop risk models to predict which patients may face a higher risk of serious COVID-19 complications. The research is a preliminary step, Dr. Kulasinghe said, because of the small sample size.

"Our challenge now is to draw a clinical finding from this, which we can't at this stage," he added. "But it's a really fundamental biological difference we're observing [between COVID-19 and flu], which we need to validate with larger studies." ■

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The new study, published in the July/August issue of the Annals of Family Medicine (2022;20[4]:319-27), provides a snapshot of COPD's toll on patients.

Researchers examined electronic health records of 17,192 patients treated at primary care clinics in five states using a dataset maintained by DARTNet Institute, a nonprofit organization that supports research and quality improvement. They also analyzed self-reported assessments from 1,354 patients in the dataset who are in a registry called Advancing the Patient Experience in COPD.

Over half (56%) of patients were female, White (64%), aged 55-84 years (81%), and current or exsmokers (80%). The vast majority had three or more comorbidities, including hypertension, diabetes, and depression.

Serious flare-ups were common; 38% of patients had experienced one or more exacerbations in the previous year. Of registry respondents, half said they had had at least one exacerbation, and 20% said they had been hospitalized for COPD during that period.

Among patients in the registry, 43% reported that COPD had a high or very high impact on their health, and 45% could not walk at a normal pace without losing their breath.

Almost 90% of patients were receiving a maintenance therapy regimen. The number of exacerbations was "somewhat surprising," the authors say. They write that the findings may indicate that patients were not receiving appropriate treatment or were not complying with their medication regimens and that there may be a need for nonpharmacologic interventions, such as smoking cessation. They also write that physician education is needed to support earlier diagnosis and treatment so as to delay declines in lung function.

The researchers say their findings highlight "the need for more real-life effectiveness trials to better support decision-making at the primary care level."

Dr. Yawn is a coinvestigator of one such study, called CAPTURE, which is assessing a screening tool for COPD in primary care practices.

At the University of Illinois, Chicago, Jerry Krishnan, MD, PhD, pulmonologist and professor of medicine and public health, is running the RELIANCE study, which is comparing the use of azithromycin and roflumilast in preventing hospitalization and death among patients with COPD who continue to have exacerbations.

Although RELIANCE involves pulmonologists, Dr. Krishnan told this news organization, it offers a model for building real-world evidence on questions relevant to primary care. "We don't really know if medications used by patients in my clinic are as effective as reported in clinical trials that were used to obtain regulatory approvals by the U.S. Food and Drug Administration," he said.

Wilson Pace, MD, a family physician and chief medical officer and chief technology officer of DARTNet, said funders of research are becoming aware of the need for real-world studies along with "gold standard" efficacy trials.

Dr. Pace, who helped conduct the new study, said a remaining obstacle to improving care is "a defeatist attitude of clinicians" who are skeptical about the ability of therapy to have an effect.

Real-world evidence could remedy clinician frustrations, he said. When clinicians are shown that they can improve patients' quality of life and maybe even reduce the cost of care, "then they will hopefully pay attention," he said.

Some experts who were not involved in the study said the findings offer an illuminating, although incomplete, picture. Nonpharmacologic interventions, the management of other health problems, and access to specialty care are not addressed, and the researchers didn't have data on treatment adherence, inhaler technique, and patients' peak inspiratory flow – factors that influence the effectiveness of medications. The study also lacked information on whether patients received pulmonary rehabilitation to help their heart and lungs work better.

Nicola Hanania, MD, a professor of medicine and director of the Airways Clinical Research Center at Baylor College of Medicine, Houston, said the study "adds a lot to what we have known" but pointed out that COPD is grossly underdiagnosed.

According to one analysis of National Health and Nutrition Examination Surveys, 72% of individuals with COPD don't know they have the condition. Such patients were not included in the study, Dr. Hanania noted.

"We need pragmatic studies over multiple years to better understand" the condition, Dr. Yawn said. Real-world evidence "based in an academic setting or specialty practices is not sufficient," she added. "We need to see results from patients and clinics that look like what we have."

The registry was established and funded by Optimum Patient Care Global, a nonprofit organization, and Boehringer Ingelheim. Dr. Han has consulted for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca and has received research support from Novartis and Sunovion. Dr. Yawn has served on advisory boards for GlaxoSmithKline, Astra-Zeneca, Novartis, and Boehringer Ingelheim and has received research funds from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, and Novartis. Dr. Krishnan has disclosed no relevant financial relationshps. Dr. Hanania has received honoraria for serving as consultant or advisory board member for GSK, Boehringer Ingelheim, Novartis, Sanofi, AstraZeneca, Teva, Genentech, and Amgen. His institution has received research grant support on his behalf from GSK, Sanofi, Boehringer Ingelheim, AstraZeneca, Genentech, Teva, and Novartis. Dr. Pace is on the advisory board for Mylan and has received stock from Novo Nordisk, Pfizer, Novartis, Johnson & Johnson, Stryker, Amgen, Gilead, and Sanofi. ■

Home-based COPD rehab trial shows positive results

BY TED BOSWORTH

AT CHEST 2022 ▪ NASHVILLE – The first multicenter randomized controlled trial of a home-based rehabilitation program for patients with chronic obstructive pulmonary disease (COPD) showed highly positive results, according to findings presented at the annual meeting of the American College of Chest Physicians (CHEST).

At the end of 12 weeks, those randomly assigned to the intervention had a significant and clinically meaningful improvement in all domains of the Chronic Respiratory Questionnaire (CRQ), including activity levels and emotional well-being, reported Roberto P. Benzo, MD, a consultant in the division of pulmonary and critical care medicine, Mayo Clinic, Rochester, Minn.

Presenting soon-to-be-published data, Dr. Benzo said that the intervention is based on a tablet-based app. On the tablet, the patient finds a daily schedule of exercises and videos to guide performance. The tablet is programmed to upload data captured from an activity monitor and pulse oximeter. Along with documentation of app usage, this information can then be downloaded for the remote coach to review with the patient.

The primary outcome of the randomized study were the physical and emotional domains of the CRQ quality of life, but a long list of secondary outcomes – including physical activity, symptoms of depression, sleep quality, and health care utilization, such as emergency room visits – was also analyzed.

In addition to the significant benefit on the primary outcomes, the home-based rehabilitation program relative to a wait list for intervention was associated with benefit or a trend for benefit on essentially every outcome measured. Health care utilization was a possible exception, but even then, the absolute number of visits was lower in the treatment arm.

"With a study period of only 12 weeks, we were limited to our ability to show a difference in emergency room visits," said Dr. Benzo, who also noted that the study was conducted during the COVID-19 pandemic, when hospital visits were already occurring at a lower than usual rate. Based on the other findings, he suspects that a reduction in health care utilization could also be shown in more typical circumstances, particularly with a longer follow-up.

COPD *continued on following page*

COPD *continued from previous page*

In the study, 375 patients with COPD were randomly assigned to a home health care regimen delivered by an app with remote coaching or to a wait list and usual care. The median age was 69 years. Fifty-nine percent were women. The median FEV_1 at enrollment was 45% of predicted.

The patients were able to access their own data to monitor their progress at any time, not just at the time of coaching, but contact with the remote coach occurred on a weekly basis. Patients rated their level of energy, how they felt generally, and their progress toward daily goals, which was also captured on the app and could be discussed with the coach during the review of the previous week's activity.

At 12 weeks, the favorable 0.54-point change ($P < .001$) and 0.51-point change ($P < .001$) in the physical and emotional summary scores, respectively, met the criteria for a clinically meaningful change, Dr. Benzo reported. There were also significantly favorable changes from baseline and relative to controls in CRQ domains of self-management, sleep quality, and depression (all $P \leq .01$).

Other data collected are supportive. For example, Dr. Benzo reported that those in the rehabilitation group took 624 more steps on average per day than those in the control group. The experimental group also spent nearly an hour more performing moderate or greater levels of activity.

"The app promotes behavioral change," said Dr. Benzo, who said that this "completely home-based model" of rehabilitation is likely to be cost effective given the relatively low costs of remote coaching and reasonable costs of the activity monitor, tablet, and other equipment.

Importantly, home-based rehabilitation is a billable practice under currently available CPT codes, according to Dr. Benzo, who believes this approach is not only effective but "feasible and practical."

Two clinicians active in the care of patients with COPD believe this approach could fulfill an unmet need if further validated. Andrew Berman, MD, professor of medicine, New Jersey Medical School, Newark, thinks the premise is sound.

"Digital competency is still a big issue as is access to adequate quality Internet, but this could be a very useful approach for many individuals, and it avoids visits to a center, which could be a big advantage for patients," Dr. Berman said.

Abebaw M. Johannes, PhD, a professor of physical therapy at Azusa Pacific University, Azusa, Calif., agreed. He said that home-based remote coaching could be a way of overcoming the current hurdles of participating in institutional-based programs

"This is clearly an unmet need in COPD," he said.

The development of more effective and patient-friendly programs is what was driving this research, according to Dr. Benzo. He cited data suggesting that only about 30% of patients with COPD are participating in rehabilitation programs once discharged from the hospital despite the evidence that they can improve quality of life. For many of these patients, a home-based program might be the answer.

Dr. Benzo, Dr. Berman, and Dr. Johannes reported no relevant financial relationships. ■

People of color more likely to be hospitalized for flu

BY LUCY HICKS

Black Americans are 80% more likely to be hospitalized for the flu, compared with White Americans, according to new federal data.

Black, Hispanic, and American Indian/Alaska Native (AI/AN) adults in the United States also have had lower influenza vaccination rates, compared with their White counterparts, since 2010, researchers at the Centers for Disease Control and Prevention revealed in a report. The inequalities are the result of barriers to care, distrust of the medical system, and misinformation, the report said.

"We have many of the tools we need to address inequities and flu vaccination coverage and outcomes," said CDC Acting Principal Deputy Director Debra Houry, MD, MPH,

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in a press call; "however, we must acknowledge that inequities in access to care continue to exist. To improve vaccine uptake, we must address the root causes of these ongoing disparities."

In the recent report on disparities by community published Oct. 18 in CDC Vital Signs, researchers looked at hospitalization rates from 2009 to 2022 and vaccination rates from 2010 to 2022 based on race and ethnicity using two national databases.

Compared with those for White adults, hospitalization rates were 80% higher for Black adults, 30% higher for Hispanic adults, and 20% higher for AI/AN adults. While flu vaccination rates were similar in White and Asian adults (about 54%), coverage was lower in Black (42%), Hispanic (38%), AI/AN (41%), and other/multiracial (43%) adults.

This disparity persisted even among individuals who had medical insurance, a personal health care provider, and a routine checkup within the last year.

"This report adds to the body of evidence that shows people from certain racial and ethnic minority groups have more severe outcomes at higher rates than White adults," Carla Black, PhD, MPH, an epidemiologist at the CDC's Immunization Services Division, said during the press call. ■

End the year on a wine note at the final Viva La Vino event of 2022


KIRBY HAMILTON/ISTOCKPHOTO

Don't miss your last chance to join the CHEST Foundation for a celebration of excellent initiatives – and equally excellent wines – at the last Viva La Vino event of 2022, happening on December 1 at 7:00 PM. This event will focus on white and red varietals from Piedmont, a

WINE *continued on following page*

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region of Northwest Italy. The Piedmont area is known for producing more wines classified as *Denominazione di Origine Controllata e Garantita*, the highest classification of quality for wines in Italy, than any other region.

With their ticket, attendees will receive one bottle of white wine and two bottles of red wine as well as an Italian-themed snack kit.

Join CHEST CEO Bob Musacchio, PhD, as he guides attendees through a virtual and interactive exploration of the history, varietals, and techniques of Piedmont wines.

Plus, hear from other CHEST leaders and friends of the Foundation about the important work currently being done and the evolution of the Foundation's many initiatives since its inception.

With their ticket, attendees will receive one bottle of white wine and two bottles of red wine – including

Paitin Starda Langhe Nebbiolo 2019, Michele Chiarlo Le Madri Roero Arneis 2020, and Massolino Barbera d'Alba 2019 – as well as an Italian-themed snack kit featuring cheese, salami, taralli, and other tasty treats, designed to complement their imbibes.

Funds raised from Viva La Vino benefit the Harold Amos Medical Faculty Development Program (AMFDP) and CHEST initiatives to improve patient care.

The AMFDP offers 4-year post-doctoral research awards to physicians, dentists, and nurses from historically marginalized backgrounds. Learn more about the recipient of this year's grant, George Alba, MD, in the September issue of CHEST PHYSICIAN.

To ensure your wine delivery reaches you before the event, purchase your ticket via the QR code shown by November 17, 2022. Those who wish to attend without the wine can opt for a "BYOB" ticket offering only access to the event. ■

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

NETWORKS

Firearms, off-label peds CPAP, and more ....

CHEST INFECTIONS & DISASTER RESPONSE NETWORK

Disaster Response & Global Health Section

Responding to the issue of firearm violence in America

We think of disasters as sudden, calamitous events, but it does not take much imagination to recognize the loss of lives in America from firearm violence as a type of disaster. In 2020, 45,222 people died of gun-related injuries, an increase of 5,155 (14%) since 2019 (Kegler, et al. *MMWR Morb Mortal Wkly Rep*. 2022;71[19]:656). This is the highest death rate since 1994, and includes increases in both homicides and suicides. Mass shootings constitute a fraction of this total, but there have already been 530 deaths from mass shooting incidents in 2022.

Opinions about the appropriate degree of firearm regulations remain divided, but the need to improve our response as clinicians is clear. The National Center for Disaster Medicine and Public Health recently published consensus recommendations for health care response in mass shootings (Goolsby, et al. *J Am Coll Surg*. 2022; published online July 18, 2022). These recommendations address readiness training, triage, communications, public education, patient tracking, family reunification, and mental health services.

Stop the Bleed is a program originally based on the military's Tactical Combat Casualty Care standards. It offers training on hemorrhage control for both the public and clinicians, similar to basic life support programs. It encourages bystanders to become trained and empowered to help in a bleeding emergency before professional help arrives. Opportunities for training are a frequent offering at the CHEST Annual Meeting, and additional information can be found at https://www.stopthebleed.org.

Dr. Ogake

Stella Ogake, MD
Member-at-Large

AIRWAYS DISORDERS NETWORK

Pediatric Chest Medicine Section

CPAP for pediatric OSA: "Off-label" use

Pediatric providers are well aware of the "off-label" uses of medications/devices. While it's not a stretch to apply "adult" diagnostic and therapeutic criteria to older adolescents, more careful consideration is needed for our younger patients. Typically, adenotonsillectomy is first-line treatment for pediatric OSA, but CPAP can be essential for those for whom surgical intervention is not an option, not an option yet, or has been insufficient (residual OSA). Unfortunately, standard

CPAP devices are not approved for use in children, and often have a minimum weight requirement of 30 kg. There are respiratory assist devices and home mechanical ventilators that are approved for use in pediatric patients (minimum weight 13 kg or 5 kg) and designed for more complex ventilatory support, and that also are capable of providing continuous pressure. Alternatively, pediatric providers may proceed with the "off-label" use of simpler CPAP-only medical devices and face obstacles in attaining insurance approval. The recent American Academy of Sleep Medicine position statement (Amos, et al. *J Clin Sleep Med*. 2022;18[8]:2041-2043) acknowledges that CPAP therapy can be safe and effective when management is guided by a pediatric specialist and is typically initiated in a monitored setting (inpatient or polysomnogram). The authors bring up excellent points regarding unique considerations for pediatric CPAP therapy, including the need for desensitization and facial development monitoring, lack of technology/software designed for younger/smaller patients, and limited published data (small and diverse cohorts). Ultimately, evaluation of effectiveness and safety, while distinct, must both be seriously considered in this risk-benefit analysis of care.

Pallavi P. Patwari, MD, FAAP, FAASM
Member-at-Large

DIFFUSE LUNG DISEASE & TRANSPLANT NETWORK

Pulmonary Physiology & Rehabilitation Section

Exercise tolerance in untreated sleep apnea

Numerous cardiovascular, respiratory, neuromuscular, and perceptual factors determine exercise tolerance. This makes designing a study to isolate the contribution of one factor difficult.

A recently published study (Elbehairy, et al. *Chest*. 2022; published online September 29, 2022) explores exercise tolerance in patients with untreated OSA compared with age- and weight-matched controls. The authors found that at an equivalent work rate, patients with OSA had greater minute ventilation, principally due to higher breathing frequency. Dead space volume, dead space ventilation, and dead space to tidal volume ratio (V_D/V_T) were higher in patients with OSA, likely due to a reduction in pulmonary vessel recruitment relative to ventilation. VD/VT decreased more from rest to peak in controls than in patients with OSA, an adaptation that is expected with exercise. Patients with OSA had greater arterial stiffness measured by pulse wave velocity and higher blood pressures, which may have affected cardiac output augmentation. Patients with OSA also had higher resting mean pulmonary artery pressures and exercise dyspnea scores. Regression models predicting peak oxygen uptake and peak work rate were statistically significant, with predictors being age, pulse wave velocity, and resting mean pulmonary artery pressure. The role of diastolic dysfunction remains to be determined.

Prior studies have shown that some effects of OSA on exercise may be reversed with CPAP treatment (Arias, et al. *Eur Heart J*. 2006;27[9]:1106-1113; Chalegre, et al. *Sleep Breath*. 2021;25[3]:1195-1202). Understanding the mechanisms of exercise limitation in OSA will help physicians address symptoms, reinforce CPAP adherence, and design tailored pulmonary rehabilitation programs.

Fatima Zeba, MD
Fellow-in-Training

PULMONARY VASCULAR & CARDIOVASCULAR NETWORK

Pulmonary Vascular Disease Section

Key messages from the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension

1. Per coverage by the American College of Cardiology, "Pulmonary hypertension (PH) is now defined by a mean pulmonary arterial pressure >20 mm Hg at rest. The definition of pulmonary arterial hypertension (PAH) also implies a pulmonary vascular resistance (PVR) >2 Wood units and pulmonary arterial wedge pressure ≤15 mm Hg."[1] These cut-off values do not translate into new therapeutic recommendations.

2. The diagnostic algorithm for PH now follows a simplified three-step approach, involving first **suspicion** by first-line physicians, then **detection** by echocardiography, and **confirmation** with right-sided heart catheterization, preferably in a PH center.

3. Pulmonary vasoreactivity testing is only recommended in patients with idiopathic PAH, heritable PAH, or drug/toxin associated PAH to identify potential candidates for calcium channel blocker therapy. Inhaled nitric oxide or inhaled iloprost are the recommended agents.

4. The role of cardiac MRI in prognostication of patients with PAH has been confirmed such that measures of right ventricular volume, right ventricular ejection fraction, and stroke volume are included as risk assessment variables.

Dr. Farmer

5. The primary limitation of the 2015 ESC/ERS three-strata risk-assessment tool is that 60% to 70% of the patients are classified as intermediate risk (IR). A four-strata risk stratification, dividing the IR group into IR "low" and IR "high" risk, is proposed at follow up.

6. No general recommendation is made for or against the use of anticoagulation in PAH given the absence of robust data and increased risk of bleeding.

7. In patients with PH-ILD, inhaled treprostinil may be considered based on findings from the INCREASE trial, but further long-term outcome data are needed.

8. Improved recognition of the signs of chronic thromboembolic pulmonary hypertension (CTEPH) on CT and echocardiographic imagery at the time of an acute pulmonary embolism (PE) event, along with systematic follow-up of patients with acute PE, is recommended to help mitigate the underdiagnosis of CTEPH.

9. The treatment algorithm for PAH has been simplified, and now includes a focus on cardiopulmonary comorbidities, risk assessment, and treatment goals. Current standards include initial combination therapy and treatment escalation at follow-up, when appropriate.

10. Per coverage by the American College of Cardiology, "The recommendations on sex-related issues in patients with PAH, including pregnancy, have been updated, with information and shared decision making as key points."[1] Calcium channel blockers, inhaled/IV/subcutaneous prostacyclin analogues, and phosphodiesterase 5 inhibitors all and are considered safe during pregnancy, despite limited data on this use.

11. Per the guideline, "Patients with PAH should be treated with the best standard of pharmacological treatment and be in stable clinical condition before embarking on a supervised rehabilitation program."[2] Additional studies have shown that exercise training has a beneficial impact on 6-minute walk distance, quality of life, World Health Organization function classification, and peak VO_2.

Dr. Balasubramanian

12. Immunization of PAH patients against SARS-CoV-2, influenza, and Streptococcus pneumoniae is recommended.

This edition of clinical practice guidelines focuses on early diagnosis of PAH and optimal treatments.

Vijay Balasubramanian MD, FCCP
Chair
Mary Jo S. Farmer, MD, PhD
Member-at-Large

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CRITICAL CARE NETWORK

Sepsis/Shock Section

Fluid Resuscitation – Back to BaSICS

The age-old debate regarding the appropriate timing, volume, and type of fluid resuscitation for patients in septic shock rages on – or does it? In October 2021, the Surviving Sepsis Campaign published updated guidelines for the management of sepsis. One of the biggest changes from prior versions was downgrading the recommendation for an initial 30mL/kg bolus of IV crystalloid for the initial resuscitation of a patient in septic shock to a *suggestion*, based on dynamic measures to assess individual patients' fluid balance (Evans, et al. *Crit Care Med*. 2021;49[11]:e1063-e1143).

Traditionally, 0.9% saline had been the resuscitative fluid of choice in sepsis. But it has a propensity to cause physiologic derangements such as hyperchloremic metabolic acidosis, renal afferent vasoconstriction, and reduced glomerular filtration

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rate – not to mention, can be a signal for possibly increased mortality, as seen in the SMART trial (Semler, et al. *N Engl J Med*. 2018;378[9]:829-839).

Normal saline had subsequently fallen from grace in favor of balanced crystalloids such as Lactated Ringer's and Plasma-Lyte. However, the recent PLUS and BaSICS trials showed no significant difference in 90-day mortality or secondary outcomes of acute kidney injury, need for renal replacement therapy, or ICU mortality (Finfer, et al. *N Engl J Med*. 2022;386[9]:815-826; Zampieri, et al. *JAMA*. 2021;326[9]:818-829).

While these are large randomized controlled trials, a major weakness is the administration of uncontrolled resuscitative fluids prior to randomization and even postenrollment, which may have biased results.


Dr. Agarwal

Ultimately, does the choice between salt water or balanced crystalloids matter? Despite the limitations in the newest trials, probably less than the timely administration of antibiotics and pressors, unless your patient also has a traumatic TBI – then go with the saline. But, in the everlasting quest for medical excellence, choosing the balanced fluid that causes the least physiologic derangement seems to make the most sense.

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The views expressed are those of the authors and do not reflect the official policy or position of the US Navy, Department of Defense, or the US Government.

THORACIC ONCOLOGY & CHEST IMAGING NETWORK

Ultrasound & Chest Imaging Section

VExUS scan: The missing piece of hemodynamic puzzle?

Volume status and tailoring the correct level of fluid resuscitation is challenging for the intensivist. Determining "fluid overload," especially in the setting of acute kidney injury, can be difficult. While a Swan-Ganz catheter, central venous pressure, or inferior vena cava (IVC) ultrasound measurement can suggest elevated right atrial pressure, the effect on organ level hemodynamics is unknown.

Abdominal venous Doppler is a method to view the effects of venous pressure on abdominal organ venous flow.

An application of this is the Venous Excess Ultrasound Score (VExUS) (Rola, et al. *Ultrasound J*. 2021;13[1]:32). VExUS uses IVC diameter and pulse wave Doppler waveforms from the hepatic, portal, and renal veins to grade venous congestion from none to severe.

VExUS has a strong physiologic basis, and early clinical experience indicates a strong role in improving assessment of venous congestion, an important aspect of volume status.

Studies demonstrate an association between venous congestion and renal dysfunction in cardiac surgery (Beaubien-Souligny, et al. *Ultrasound J*. 2020;12[1]:16) and general ICU patients (Spiegel, et al. *Crit Care*. 2020;24[1]:615).

This practice of identifying venous congestion and avoiding over-resuscitation could improve patient care. However, acquiring quality images and waveforms may prove to be difficult, and interpretation may be confounded by other disease states such as cirrhosis. Though it is postulated that removing fluid could be beneficial to patients with high VExUS scores, this has yet to be proven and may be difficult to prove.

While the score estimates volume status well, the source of venous congestion is not identified such that it should be used as a clinical supplement to other data.

VExUS has a strong physiologic basis, and early clinical experience indicates a strong role in improving assessment of venous congestion, an important aspect of volume status. This is an area of ongoing research to ensure appropriate and effective use.

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SLEEP STRATEGIES

Inpatient sleep medicine: An invaluable service for hospital medicine

BY CHRISTINE DEL PRADO RICO, MD, AND ROBERT C. STANSBURY, MD

Estimates suggest that nearly 1 billion adults worldwide could have sleep apnea (Benjafield AV, et al. *Lancet Respir Med*. 2019;7[8]:687-698). Even with the current widespread use of portable sleep testing, cheap and innovative models of OSA care will need to be developed to address this growing epidemic. This fact is particularly true for communities with significant health disparities, as the evidence suggests diagnostic rates for OSA are extremely poor in these areas (Stansbury R, et al. *J Clin Sleep Med*. 2022;18[3]:817-824). Current models of care for OSA are predominantly outpatient based. Hospital sleep medicine offers a potential mechanism to capture patients with OSA who would otherwise go undiagnosed and potentially suffer adverse health outcomes from untreated disease.

What is hospital sleep medicine?

Hospital sleep medicine includes the evaluation and management of sleep disorders, including, but not limited to, insomnia, restless legs syndrome, and circadian rhythm disorders, in hospitalized patients. Our program centers around proactive screening and early recognition of sleep-disordered breathing (SDB). Patients at high risk for SDB are identified upon entry to the hospital. These individuals are educated about the disease process and how it impacts comorbid health conditions. Recommendations are provided to the primary team regarding the appropriate screening test for SDB; positive airway pressure trials; mask fitting and acclimation; and coordination with care management in the discharge process, including scheduling follow-up care and diagnostic sleep studies. This program has become an integral part of our comprehensive sleep program, which includes inpatient, outpatient, and sleep center care and utilizes a multidisciplinary team approach including sleep specialists, sleep technologists, respiratory therapists, nurses, information technology professionals, and discharge planners, as well as ambulatory sleep clinics and sleep laboratories.

Evidence for hospital sleep medicine

While there has been interest in hospital-based sleep medicine since 2000, the most well-validated clinical pathway was first described by Sharma and colleagues in 2015 (Sharma, et al. *J Clin Sleep Med*. 2015;11[7]:717-723). This initial application of a formal sleep program demonstrated a high prevalence of SDB in hospitalized adult patients and led to a substantial increase in SDB diagnoses in the system. Subsequent studies have demonstrated improved outcomes, particularly in patients with cardiopulmonary disease. For example, there are data to suggest that hospitalized patients with congestive heart failure or COPD have increased rates of readmission, and early diagnosis and intervention are associated with decreased rates of subsequent readmission and ED visits (Konikkara J, et al. *Hosp Pract*. 2016;44[1]:41-47; Sharma S, et al. *Am J Cardiol*. 2016;117[6]:940-945). Long-term data also suggest survival benefit (Sharma S, et al. *Am J Med*. 2017;130[10]:1184-1191). Adherence to inpatient PAP trials has also been shown to predict outpatient follow-up and adherence to PAP therapy (Sharma S, et al. *Sleep Breath*. 2022; published online June 18, 2022).

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Establishing a team

Establishing a hospital sleep medicine program requires upfront investment and training and begins with educating key stakeholders. Support from executive administration and various

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Table 1. Description of individual components of SEAT-COM protocol for hospital sleep medicine

Component	Description
Screening	Use of EMR-generated reports and using STOP/STOP-BANG questionnaire for initial assessment in appropriate patients. Explain significance of OSA.
Evaluation	Individuals with positive screening findings undergo high-resolution pulse oximetry or portable sleep monitor assessment. Reports are downloaded and prepared for review. Results and recommendations made to primary service.
Acclimatization	Education on OSA and treatment with positive airway pressure (PAP) therapy. Appropriately introduce individuals to the PAP device and interface.
Treatment	Develop a plan with individuals to meet adherence guidelines for PAP therapy. Interrogate PAP devices to ensure therapy is optimized. Debrief and adjust PAP therapy based on individual's feedback.
Communications	Final recommendations communicated to members of the multidisciplinary team, including the discharge navigator, primary care team, sleep laboratory, and pulmonary/sleep team. Information is placed in an appropriate database for quality improvement and possible research purposes.

Note: SEAT-COM = Screening Evaluating Acclimatization Treatment and Communication Protocol; STOP = Snoring, Tiredness During Daytime, Observed Apnea, High BP; STOP-BANG = Snoring, Tiredness During Daytime, Observed Apnea, High BP, BMI, Age, Neck-collar size, Gender.

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departments including respiratory, sleep medicine, information technology, nursing, physicians, mid-level providers, and discharge planning is essential. Data are available, as outlined here, showing significant improvement in patient outcomes with a hospital sleep medicine program. This information can garner significant enthusiasm from leadership to support the initiation of a program. A more detailed account of key program elements, inpatient protocols, and technologies utilized is available in our recent review (Sharma S, Stansbury R. *Chest*. 2022;161[4]:1083-1091). Table 1 from this article is highlighted below and outlines the essential components (SEATCOM) of our hospital sleep medicine model. While each component of this model is important, we stress the importance of care coordination, timely diagnostic testing, and treatment, as significant delays can lead to inadequate time for acclimatization and optimization of therapy. It is important to note that the practice of hospital sleep medicine does not supplant clinic-based approaches, but rather serves to facilitate and enhance outpatient diagnosis and treatment.

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Current questions

Data to date suggest a hospital sleep medicine program positively influences important clinical endpoints in hospitalized patients identified to be at risk for SDB. However, much of the published research is based on retrospective and prospective analysis of established clinical programs. Further, most studies have been completed at large, urban-based academic medical centers. Our group has recently completed a validation study in our local rural population, but larger multicenter trials involving more diverse communities and health systems are needed to better understand outcomes and further refine the optimal timing of screening and intervention for SDB in hospitalized patients (Stansbury, et al. *Sleep Breath*. 2022; published online January 20, 2022).

A common question that arises is the program's impact regarding payment for rendered service in the context of Medicare's prospective payment system. Given that the program focuses on screening for SDB and does not utilize formal testing for diagnosis, there is no additional cost for diagnostic tests or procedural codes. Thus, the diagnosis-related group is not impacted (Sharma S, Stansbury R. Chest. 2022;161[4]:1083-1091). Importantly, hospital sleep medicine has the potential for cost savings given the reduction in hospital readmissions and decreased adverse events during a patient's hospital stay. The economics of the initial investment in a hospital sleep program versus potential savings from improved patient outcomes warrants evaluation.

Conclusion

SDB is a prevalent disorder with potential deleterious impacts on a patient's health. Despite this, it is underrecognized and, thus, undertreated. Hospital sleep medicine is a growing model of care that may expand our capability for early diagnosis and intervention. Studies have demonstrated benefits to patients, particularly those with cardiopulmonary disease. However, additional studies are required to further validate hospital-based sleep medicine in more diverse populations and environments. ■

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PRESIDENT'S REPORT

Time travel and thoughts on leadership

BY DAVID SCHULMAN, MD, MPH, FCCP


Dr. Schulman

This is an odd column for me to write. First, because of the nature of print publication, this writing for the November issue is being crafted just before the annual meeting is to be held in Nashville. Therefore, while I have a pretty good sense of what is in store for CHEST 2022, I have yet to see the final product, or the audience's reaction to it. However, I will make some bold predictions as to what occurred therein:

- Even in the context of 3 years of separation, thousands CHEST members gathered in droves to rekindle friendships and to experience the best education in pulmonary, critical care, and sleep medicine that the world has to offer, leading to our second-biggest meeting ever.
- Neil Pasricha's presentation helped attendees rekindle the "Art of Happiness."
- Hundreds of attendees participated in, and successfully solved, our newest escape room, "Starship Relics."
- Our valued CHEST members were able to successfully thwart Dr. Didactic and save the future of educational innovation.
- "CHEST After Hours" trended on social media and will become a normal and highly-anticipated part of the CHEST meeting moving forward.
- The most uncomfortable moment of the meeting centered on mayonnaise; for those of you who know what I am referencing, I am a little sorry…but only a little.
- Despite my best efforts, we were not able to recruit Neil Patrick Harris to participate.

Predicting the future of medical meetings is something we've spent a lot of time trying to do over the last year as we planned for CHEST 2022. But given the talented individuals involved in that planning, foreseeing the meeting's success did not require any time travel; it was hardly a difficult task at all. Program Chair Subani Chandra and Vice-Chair Aneesa Das were exactly the people we needed at the helm for this all-important return to in-person meetings, and I cannot thank them enough for their creativity, effort, and leadership in bringing CHEST 2022 to fruition. And while I expect to have been seven-for-seven in my predictions above, I do hope I got that NPH one wrong.

The other reason that this column was a challenge to craft is because it represents my final formal presidential missive in these esteemed pages. And as I planned this final walk of the path, I gave careful consideration to the message with which I wanted to conclude my year. And as I put together my predictions for the future, my mind also turned to the past, considering things I wish I had known (or spent more time considering) as I started this journey. Some of this information may prove useful to the next generation of CHEST leaders, and some may be already well engrained for those of you with leadership experience. Here, in no particular order, are some thoughts for those of you in the audience who are considering future leadership opportunities at CHEST (or elsewhere in life; I suspect some of this advice is applicable to other venues). That said, the recommendations also come from yours truly, so take them with an appropriately large grain of salt, as your mileage may vary, and reasonable people could take issue here or there.

- The most important conversations should happen in person. The past 3 years have shown us the amazing things that modern technology can accomplish, but when it comes to providing important information, asking for input on a crucial issue, or providing feedback on a sensitive matter, there is no adequate substitute for a discussion in which all parties are in the same room.
- You are going to get things wrong sometimes; sometimes, this is because there wasn't a way to get a right answer, and sometimes it will be because you tried something that didn't work. You will learn far more from one of these experiences than from a dozen things that went as well as (or better than) expected.
- It is profoundly difficult to change someone's mind if you aren't interacting with them. I believe there is no gap so large that warrants breakdown of communication. Going that extra mile to talk to people who have a drastically different opinion than your own is the only way that you might be able to change someone's mind and is a great way to ensure that your own opinion withstands pushback. With the growth of social media over the last decade, we've gotten very good at blocking people on social media; while this can sometimes be good (or even necessary) for emotional well-being, there can be value to interacting with such folks in a real-world environment.
- You do not have to bring everything to the table. The best leaders surround themselves with other really smart folks who, in aggregate, will provide support in areas in which you are deficient. That said, you need to know where these gaps in your knowledge and experience are, and when it is the right time to listen to those trusted advisors.
- When it comes time to identify folks for your "cabinet," make sure to choose people who think differently than you and who may disagree with you on some fundamental things. Surrounding yourself with friends and close colleagues can lead to groupthink and poor decision making. The best results often stem from challenging and difficult decision-making processes.
- As a corollary to the above, every leader will bring their own sensibility and personality to the role. Make sure to bring yours, even if it involves silly jokes about holding a medical meeting in a former President's basement or getting another former President to eat a big spoonful of the aforementioned condiment.
- Fun is important. Fun builds relationships, and teams, and trust. Make sure you are having it, as much as you possibly can, throughout your leadership tenure.

On that note, I will sign off for good, at least in these pages. I'll still be bumbling around, proposing new educational experiences, hosting Pardon the Interruption, and serving as a sounding board for anyone who wants to chat. But I cannot wait to see what the next 3 years bring for our organization, under the leadership of Drs. Addrizzo-Harris, Buckley, and Howington. And for those of you who are just taking your first steps in leadership, and who will be following in their footsteps years down the road, I hope that you get just as much enjoyment from and fulfilment in the role of President as I have. #SchulmanOut ■

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