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CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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The rate of workplace violence directed at U.S. health care workers is five times that in any other industry.

Citing workplace violence, 25% of critical care workers ready to quit

BY MAIYA FOCHT

A surgeon in Tulsa shot by a disgruntled patient. A doctor in India beaten by a group of bereaved family members. A general practitioner in the United Kingdom threatened with stabbing. The reality is grim: Health care workers across the globe experience violence while at work. A new study identifies this trend and finds that 25% of health care workers polled were willing to quit because of such violence.

"That was pretty appalling," Rahul Kashyap, MD, MBA, MBBS, recalled. Dr. Kashyap is one of the leaders of the Violence Study of Healthcare Workers and Systems (ViSHWaS), which polled an international sample of physicians, nurses, and hospital staff. This study has worrying implications, Dr. Kashyap said. In a time when hospital staff are reporting burnout in record numbers, further deterrents may be the last thing our health care system needs. But Dr. Kashyap hopes that bringing awareness to these trends may allow physicians, policymakers, and the public to mobilize and intervene before it's too late.

Previous studies have revealed similar trends. The rate of workplace violence directed at U.S. health care workers is five times that of workers in any other industry, according to the Bureau of Labor Statistics. The same study found that

VIOLENCE // *continued on page 6*

Restricted fluid failed to reduce mortality in sepsis-induced hypotension

BY HEIDI SPLETE
MDedge News

A restrictive fluid strategy had no significant impact on mortality in patients with sepsis-induced hypotension compared to the liberal fluid strategy, based on data from a randomized, controlled trial of 1,563 individuals.

Intravenous fluids are standard in the early resuscitation of sepsis patients, as are vasopressor agents, but data comparing restrictive or liberal use in these patients are limited, wrote Nathan I. Shapiro, MD, of Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, and colleagues.

In a study published in the New England Journal of Medicine (2023 Jan 21. doi: 10.1056/NEJMoa2212663), the researchers randomized 782 patients to the restrictive fluid group and 781 to the liberal fluid group. Patients aged 18 years and older were enrolled between March 7, 2018, and Jan. 31, 2022, at 60 centers in the

FLUID // *continued on page 6*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Introducing President-Designate John Howington

Page 20

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FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.
FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

2 ADMINISTRATION OPTIONS for FASENRA

At-home administration with FASENRA Pen

In-office administration with the prefilled syringe

FASENRA is the only respiratory biologic that combines Q8W dosing with at-home and in-office administration options[1]

Dosing comparisons do not imply comparable efficacy, safety, or FDA-approved indications.

FASENRA is for subcutaneous use only. The recommended dose of **FASENRA** is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter.

FASENRA is intended for use under the guidance of a healthcare professional to ensure appropriate initiation and follow-up of patients. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended.

FASENRA Pen is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare professional determines it is appropriate.[1]

Administer **FASENRA** into the thigh or abdomen. The upper arm can also be used if a healthcare professional or caregiver administers the injection.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

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

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed 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.

Please see additional Important Safety Information on back and Brief Summary of full Prescribing Information on adjacent page.

Parasitic (Helminth) Infection
It is unknown if FASENRA will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until infection resolves.

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

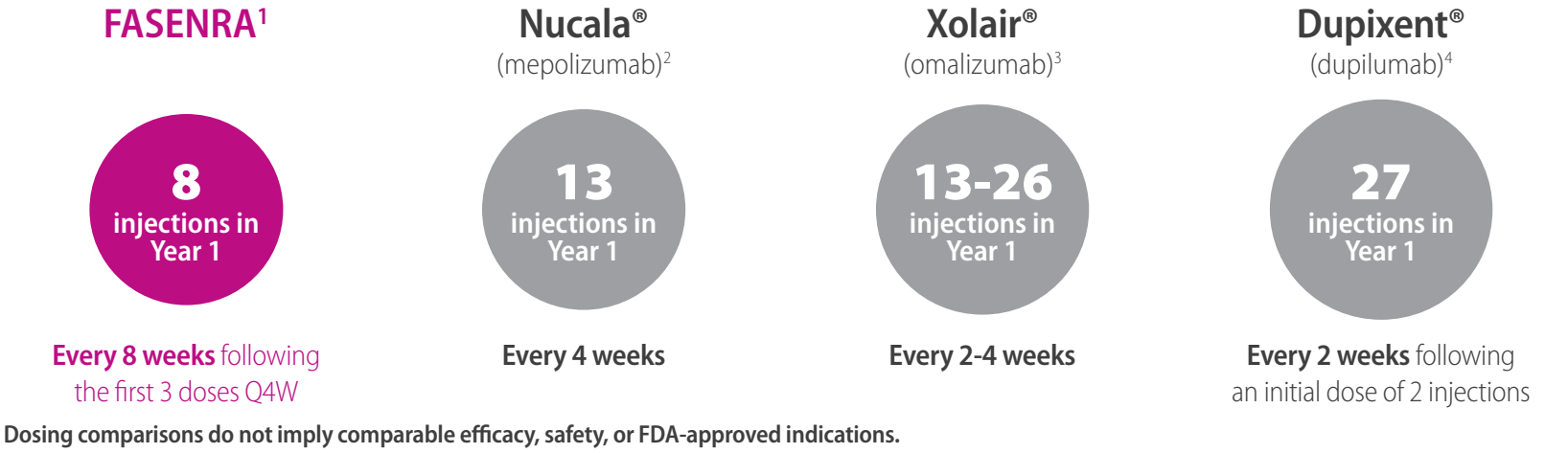
Scan the QR code or visit FasenraOptions.com to learn more

Fasenra® (benralizumab) Subcutaneous Injection 30 mg | Fasenra Pen® (benralizumab) Subcutaneous Injection 30 mg

FASENRA is indicated as an add-on maintenance treatment of patients 12 years and older with severe eosinophilic asthma.
FASENRA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

FASENRA is the only respiratory biologic that combines Q8W dosing with at-home and in-office administration options[1]

FASENRA offers patients the fewest injections per year



Dosing comparisons do not imply comparable efficacy, safety, or FDA-approved indications.

- **FASENRA** is for subcutaneous use only. The recommended dose of **FASENRA** is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter[1]
- **FASENRA** is intended for use under the guidance of a healthcare professional to ensure appropriate initiation and follow-up of patients. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended[1]
- **FASENRA Pen** is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare professional determines it is appropriate. Administer **FASENRA** into the thigh or abdomen. The upper arm can also be used if a healthcare professional or caregiver administers the injection[1]
- Prior to administration, warm **FASENRA** by leaving carton at room temperature for about 30 minutes. **FASENRA** may be left out of the refrigerator at room temperature for up to 14 days in the original carton[1]
- Administer **FASENRA** within 14 days of removing from the refrigerator or discard into sharps container[1]

Talk to your patients about the most convenient administration option for them

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS

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

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
- FASENRA is not indicated for treatment of other eosinophilic conditions
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus

References: 1. FASENRA® (benralizumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. **2.** Nucala [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; September 2019. **3.** Xolair [package insert]. South San Francisco, CA: Genentech Inc; May 2019. **4.** Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. and sanofi-aventis U.S. LLC; June 2019.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

Please see additional Important Safety Information on front and adjacent Brief Summary of full Prescribing Information.

Fasenra® (benralizumab) Subcutaneous Injection 30 mg | Fasenra Pen® (benralizumab) Subcutaneous Injection 30 mg

FASENRA® (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

General Administration Instructions

FASENRA is intended for use under the guidance of a healthcare provider. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Administer FASENRA into the thigh or abdomen. The upper arm can also be used if a healthcare provider or caregiver administers the injection. Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter.

Prefilled Syringe

The prefilled syringe is for administration by a healthcare provider.

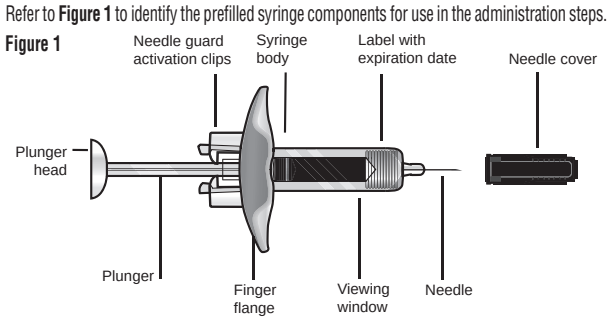
Autoinjector (FASENRA PEN™)

FASENRA PEN is intended for administration by patients/caregivers. Patients/caregivers may inject after proper training in subcutaneous injection technique, and after the healthcare provider determines it is appropriate.

Instructions for Administration of FASENRA Prefilled Syringe (Healthcare Providers)

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

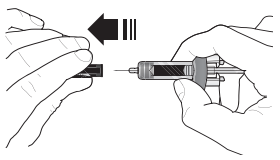
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

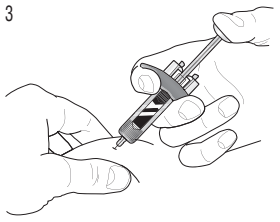
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. The syringe may contain small air bubbles; this is normal. **Do not** expel the air bubbles prior to administration.

2



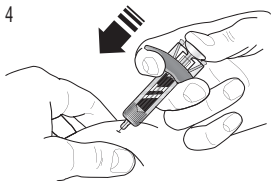
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3



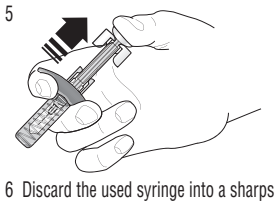
Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4



Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5



After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

Instructions for Administration of FASENRA PEN

Refer to the FASENRA PEN 'Instructions for Use' for more detailed instructions on the preparation and administration of FASENRA PEN *[See Instructions for Use in the full Prescribing Information]*. A patient may self-inject or the patient caregiver may administer FASENRA PEN subcutaneously after the healthcare provider determines it is appropriate.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed 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

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

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

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

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.

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two Phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n=841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n=822), and placebo (n=847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N=822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions†	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

† Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n=73) or placebo (n=75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of anti-body formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of FASENRA. 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 FASENRA or a combination of these factors.

Immune System Disorders: Hypersensitivity reactions, including anaphylaxis.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting mothertobaby.org/Fasenra.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the 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 benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [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 embryo/fetal 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 benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n=320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

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

PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use for FASENRA PEN) before the patient starts using FASENRA and each time the prescription is renewed as there may be new information they need to know.

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique using the FASENRA PEN, including aseptic technique, and the preparation and administration of FASENRA PEN prior to use. Advise patients to follow sharps disposal recommendations [*see Instructions for Use in the full Prescribing Information*].

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare provider if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA 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 FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

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 *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FASENRA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting mothertobaby.org/Fasenra *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

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COVID emergency orders ending: What's next?

BY DAMIAN MCNAMARA AND KELLY WAIRIMU DAVIS

The Biden administration announced that it will be ending the twin COVID-19 emergency declarations, marking a major change in the 3-year-old pandemic.

The orders spanned two presidencies. Health & Human Services Secretary Alex Azar issued a public health emergency in January 2020. Then-President Trump declared the COVID-19 pandemic a national emergency 2 months later. Both emergency declarations – which remained in effect under President Biden – will expire May 11.

Read on for an overview of how the end of the public health emergency will trigger multiple federal policy changes.

Changes that affect everyone

- There will be cost-sharing changes for COVID-19 vaccines, testing, and certain treatments. One hundred–percent coverage for COVID testing, including free at-home tests, will expire May 11.
- Telemedicine cannot be used to prescribe controlled substances after May 11.
- Enhanced federal funding will be phased down through Dec. 31, 2023. This extends the time states must receive federally matched funds for COVID-related services and products, through the Consolidated Appropriations Act of 2023. Otherwise, this would have expired June 30.
- Emergency use authorizations for COVID-19 treatments and vaccinations will not be affected and/or end on May 11.

Private health insurance

- Many will likely see higher costs for COVID-19 tests, as free testing expires and cost-sharing begins in the coming months.
- COVID-19 vaccinations and boosters will continue to be covered until the federal government's vaccination supply is depleted. If that happens, you will need an in-network provider.
- You will still have access to COVID-19 treatments – but that could change when the federal supply dwindles.

Medicare recipients

- Medicare telehealth flexibilities will be extended through Dec. 31, 2024, regardless of public health emergency status. This means people can access telehealth services from anywhere, not just rural areas; can use a smartphone for telehealth; and can access telehealth in their homes.
- Medicare cost-sharing for testing and treatments will expire May 11, except for oral antivirals.

Medicaid/CHIP recipients

- Medicaid and Children's Health Insurance Program (CHIP) recipients will continue to receive approved vaccinations free of charge, but testing and treatment without cost-sharing will expire during the third quarter of 2024.
- The Medicaid continuous enrollment provision will be separated from the public health emergency, and continuous enrollment will end March 31, 2023.

Uninsured people

- The uninsured will no longer have access to 100% coverage for these products and services (free COVID-19 treatments, vaccines, and testing).

Health care providers

- There will be changes to how much providers get paid for diagnosing people with COVID-19, ending the enhanced Inpatient Prospective Payment System reimbursement rate, as of May 11, 2023.
- Health Insurance Portability and Accountability Act (HIPAA) potential penalty waivers will end. This allows providers to communicate with patients through telehealth on a smartphone, for example, without violating privacy laws and incurring penalties.

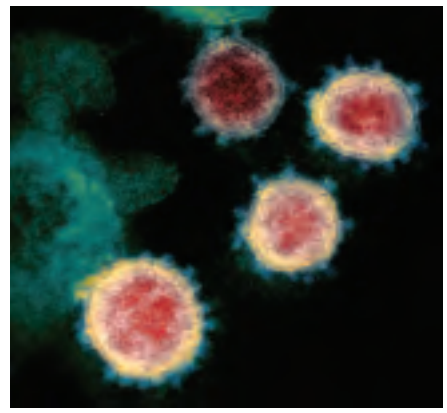
What the experts are saying

This news organization asked several health experts for their thoughts.

Question: Do you agree with the timing of the end to the emergency order?

Answer: Robert Atmar, MD, professor of infectious diseases at Baylor College of Medicine in Houston: "A lead time to prepare and anticipate these consequences may ease the transition, compared to an abrupt declaration that ends the declaration."

Answer: Georges C. Benjamin, MD, executive director of the American Public Health Association: "I think it's time to do so. It has to be done in a great, thoughtful, and organized way because we've attached so many different things to this public health emergency. It's going to take time for the system to adapt. Data collection most likely will continue. People are used to reporting now. The CDC needs to give guidance to the states so that we're clear about what we're reporting, what we're not."



Courtesy NIAID-RML

Answer: Bruce Farber, MD, chief public health and epidemiology officer at Northwell Health in Manhasset, N.Y.: "I would have hoped to see it delayed."

Answer: Steven Newmark, JD, chief legal officer and director of policy at the Global Healthy Living Foundation: "While we understand that an emergency cannot last forever, we hope that expanded services such as free vaccination, promotion of widespread vaccination, increased use of pharmacists to administer vaccines, telehealth availability and reimbursement, flexibility in work-from-home opportunities, and more continues. Access to equitable health care should never backtrack or be reduced."

Q: What will the end of free vaccinations and testing mean?

A: Dr. Farber: "There will likely be a decrease in vaccinations and testing. The vaccination rates are very low to begin with, and this will likely lower it further."

A: Dr. Benjamin: "For people who are uninsured and underinsured, we've got to make sure they have access to those. There's a lot of discussion and debate about what the cost of those tests and vaccines will be, and it looks like the companies are going to impose very steep, increasing costs."

Q: How will this affect higher-risk populations, like people with weakened immune systems?

A: Dr. Farber: "Without monoclonals [drugs to treat COVID] and free Paxlovid," people with weakened immune systems "may be undertreated."

A: Dr. Atmar: "The implications of ongoing widespread virus transmission are that immunocompromised individuals may be more likely to be exposed and infected and to suffer the consequences of such infection, including severe illness. However, to a certain degree, this may already be happening. We are still seeing about 500 deaths/day, primarily in persons at highest risk of severe disease."

A: Dr. Benjamin: "People who have good insurance can afford to get immunized. But lower-income individuals and people who really can't afford to get tested or get immunized would likely become underimmunized and more infected. So even though the federal emergency declaration will go away, I'm hoping that the federal government will continue to encourage all of us to emphasize those populations at the highest risk – those with chronic disease and those who are immunocompromised."

A: Mr. Newmark: "People who are immunocompromised by their chronic illness or the medicines they take to treat acute or chronic conditions remain at higher risk for COVID-19 and its serious complications. The administration needs to support continued development of effective treatments and updated vaccines to protect the individual and public health. We're also concerned that increased health care services – such as vaccination or telehealth – may fall back to prepandemic levels while the burden of protection, such as masking, may fall to chronic disease patients alone, which adds to the burden of living with disease."

Q: What effect will ending Medicaid expansion money have?

A: Dr. Benjamin: Anywhere from 16 to 20 million people are going to lose in coverage. I'm hoping that states will look at their experience over these last 2 years or so and come to the decision that there were improvements in healthier populations.

Q: Will this have any effect on how the public perceives the pandemic?

A: Dr. Farber: "It is likely to give the impression that COVID is gone, which clearly is not the case."

A: Dr. Benjamin: "It'll be another argument by some that the pandemic is over. I'm hoping people will realize ... that they still need to protect themselves, get vaccinated, and wear a mask when appropriate." ■

Fluid // *continued from page 1*

United States. Participants were randomized within 4 hours of meeting the criteria for sepsis-induced hypotension that was refractory to initial treatment with 1-3 L of intravenous fluid. Baseline characteristics were similar between the groups. At randomization, 21% of patients in the restrictive fluid group and 18% in the liberal fluid group received vasopressors.

The primary outcome was 90-day all-cause mortality, which occurred in 109 and 116 patients in the liberal and restricted groups, respectively (approximately 14% of each group). No significant differences were noted among subgroups based on factors including systolic blood pressure and the use of vasopressors at randomization, chronic heart failure, end-stage renal disease, and pneumonia.

The restrictive fluid protocol called for vasopressors as the primary treatment for sepsis-induced hypotension, with "rescue fluids" to be used for prespecified situations of severe intravascular volume depletion. The liberal fluid protocol was a recommended initial intravenous infusion of 2,000 mL of isotonic crystalloid, followed by fluid boluses given based on clinical triggers such as tachycardia, along with "rescue vasopressors," the researchers wrote.

The median volume of fluid administered in the first 24-hour period after randomization was 1,267 mL in the restrictive group and 3,400 mL in the liberal group. Adherence to the treatment protocols was greater than 90% for both groups.

The current study is distinct in its enrollment of patients with primary presentations of sepsis to a hospital emergency department, the researchers wrote in their discussion. "The patients who were enrolled in this trial were representative of the types of patients who present to the hospital with sepsis-induced hypotension; we expect our findings to be generalizable to these types of patients," they said.

Reported serious adverse events were similar between the groups, though fewer episodes of fluid overload and pulmonary edema occurred in the restricted group.

The findings were limited by several factors including some cases in which patients in the restrictive group received more fluid than called for by the protocol, the researchers noted. Other limitations included the lack of subgroups with different coexisting conditions, the lack of blinding, and the lack of a control with no instructions for treatment protocol, they said. However, the results suggest that a restrictive fluid strategy had no significant advantage over a liberal strategy in terms of mortality for patients with sepsis-induced hypotension, they concluded.

The study was supported by the National Heart, Lung, and Blood Institute. Dr. Shapiro disclosed serving as a consultant for and having stock options in Diagnostic Robotics, as well as grant support from Inflammatrix and Rapid Pathogen Screening, and serving as a consultant for Prenosis.

Violence // *continued from page 1*

attacks had increased 63% from 2011 to 2018. Other polls that focus on the pandemic show that nearly half of U.S. nurses believe that violence increased since the world shut down. Well before the pandemic, however, a study from the Indian Medical Association found that 75% of doctors experienced workplace violence.

With this history in mind, perhaps it's not surprising that the idea for the study came from the authors' personal experiences. They had seen coworkers go through attacks, or they had endured attacks themselves, Dr. Kashyap said. But they couldn't find any global data to back up these experiences. So Dr. Kashyap and his colleagues formed a web of volunteers dedicated to creating a cross-sectional study.

They got in touch with researchers from countries across Asia, the Middle East, South America, North America, and Africa. The initial group agreed to reach out to their contacts, casting a wide net. Researchers used WhatsApp, LinkedIn, and text messages to distribute the survey. Health care workers in each country completed the brief questionnaire, recalling their prepandemic world and evaluating their current one.

Within 2 months, they had reached health care workers in more than 100 countries. They concluded the study when they received about 5,000 results, according to Dr. Kashyap, and then began the process of stratifying the data. For this report, they focused on critical

Violence *continued on following page*

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Anne C. Coates, MD, FCCP, was born and raised in Montpelier, Vt. She attended the University of Vermont Larner College of Medicine for medical school, completed her pediatric residency at the University of Massachusetts and pediatric pulmonary fellowship at the Lucile Packard Children's Hospital of Stanford. She returned to Northern New England in 2013 to begin her practice at the Barbara Bush Children's Hospital in Portland, Maine. She loves being a pediatric pulmonologist and feels honored to serve the community at large where she is passionate about medical education and advocacy. She and her husband, a fellow Vermonter, feel blessed to raise their four young children in such a wonderful community.


Dr. Coates

Russell Miller, MD, is the Fellowship Program Director for Pulmonary and Critical Care Medicine and Director of Interventional Pulmonology at the Naval Medical Center, San Diego. Dr. Miller is a U.S. Navy physician with extensive experience in both military and academic settings. He has deployed to Afghanistan and served as the officer-in-charge during a COVID-19 domestic assistance deployment. He led the development of the American Association for Bronchology and Interventional Pulmonology's (AABIP) first consensus guideline on the post-insertion management of indwelling pleural catheters. Dr. Miller has published numerous peer-reviewed articles and book chapters, with a primary focus on interventional pulmonary procedures and lung cancer. He has received numerous military decorations for his service and holds academic appointments as an Assistant Professor of Medicine at the Uniformed Services University of Health Sciences and the University of California, San Diego.


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Dr. Naik

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Dr. Narendra

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Dr. Shojaee

Lisa Ulrich, MD, is a member of the Section of Pediatric Pulmonary Medicine at Nationwide Children's Hospital and an Assistant Professor of Pediatrics at the Ohio State University College of Medicine. She is the Associate Fellowship Director of the Pediatric Pulmonology Fellowship Program. She attended medical school at the University of Missouri–Kansas City School of Medicine. She completed her pediatric residency and pulmonary fellowship at Nationwide Children's Hospital. Currently, she is an attending in pediatric pulmonology, the Director of the Pulmonary Complex Asthma Clinic, and a collaborating pulmonologist in the Pulmonary Sickle Cell Combined Clinic at Nationwide Children's Hospital. ■


Dr. Ulrich

Violence *continued from previous page*

care, emergency medicine, and anesthesiology, which resulted in 598 responses from 69 countries. Of these, India and the United States had the highest number of participants.

In all, 73% of participants reported facing physical or verbal violence while in the hospital; 48% said they felt less motivated to work because of that violence; 39% of respondents believed that the amount of violence they experienced was the same as before the COVID-19 pandemic; and 36% of respondents believed that violence had increased. Even though they were trained on guidelines from the Occupational Safety and Health Administration, 20% of participants felt unprepared to face violence.

Although the study didn't analyze the reasons workers felt this way, Dr. Kashyap speculated that it could be related to the medical distrust that grew during the pandemic or the stress patients and health care professionals experienced during its peak.

Regardless, the researchers said their study is a starting point. Now that the trend has been highlighted, it may be acted on.

Moving forward, Dr. Kashyap believes that controlling for different variables could determine whether factors like gender or shift time put a worker at higher risk for violence. He hopes it's possible to interrupt these patterns and reestablish trust in the hospital environment. "It's aspirational, but you're hoping that through studies like ViSHWaS, which means trust in Hindi ... [we could restore] the trust and confidence among health care providers for the patients and family members." ■

LONG COVID

Inflammation and immunity troubles top list of causes

BY SOLARINA HO

Nonstop inflammation and immune problems top the list of potential causes of long COVID, but doctors say it's growing clear that more than one thing is to blame for the wide swath of often debilitating symptoms that could last months or even years.

"I think that it's a much more complex picture than just inflammation, or just autoimmunity, or just immune dysregulation. And it's probably a combination of all three causing a cascade of effects that then manifests itself as brain fog, or shortness of breath, or chronic fatigue," said Alexander Truong, MD, a pulmonologist and assistant professor at Emory University, Atlanta, who also runs a long-COVID clinic.

Long COVID, post–COVID-19 condition, and postacute sequelae of SARS-CoV-2 (PASC) are among the terms used by the National Institutes of Health to describe the long-term health issues faced by an estimated 10%-30% of people infected with COVID-19. Symptoms – as many as 200 – can range from inconvenient to crippling, damage multiple organ systems, come and go, and relapse. Long COVID increases the risk of worsening existing health problems

Long COVID *continued on following page*

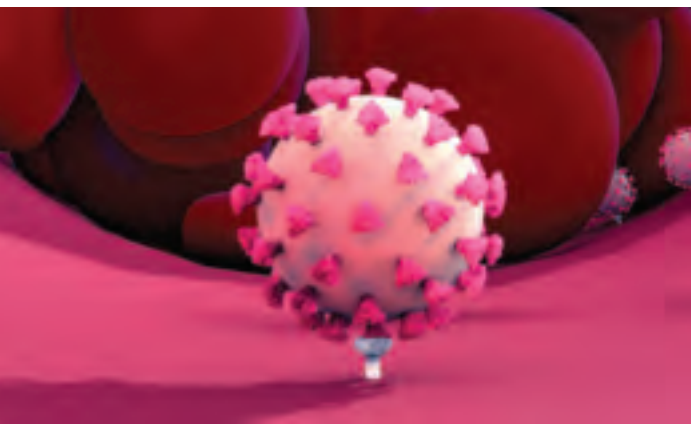
and triggering new ones, including cardiovascular disease and type 2 diabetes.

So far, research suggests there is no single cause, condition, or disease that explains why some people have an extensive range of symptoms long after the early COVID-19 infection has cleared up. Many experts believe some combination of biological processes – including the virus hanging around in our bodies, inflammation, autoimmunity, tiny blood clots, immune system problems, and even the reactivation of dormant viruses such as the Epstein-Barr virus – could be the culprit, a theory also supported by a comprehensive and in-depth review of long-COVID studies published in the journal Nature Reviews Microbiology (2023 Jan 13. doi: 10.1038/s41579-022-00846-2).

"It's become clear over the last couple of years that there are different [symptoms] of long COVID … that cannot all be lumped together," said Michael Peluso, MD, an assistant professor of medicine and an infectious diseases doctor at the University of California, San Francisco.

Inflammation and a lingering virus

Multiple studies have shown that the virus or pieces of it can remain in many parts of the body, including the kidneys, brain, heart, and gastrointestinal system, long after the early infection. "One major question that I think is the area of most intense investigation now is whether there is viral persistence that is driving immune dysregulation and therefore symptoms," says Dr. Peluso.



Design Cells/Getty Images

A small Harvard University study (Clin Infect Dis. 2022 Sep 2. doi: 10.1093/cid/ciac722), for example, found evidence that reservoirs of the coronavirus could linger in patients up to a year after they're first diagnosed.

An earlier German study (Cell Rep Med. 2022 Jun 21. doi: 10.1016/j.xcrm.2022.100663) found that patients with post–COVID-19 symptoms had higher levels of three cytokines – small proteins that tell the body's immune system what to do and are involved in the growth and activity of immune system cells and blood cells. Researchers said the results supported the theory that there is persistent reprogramming of certain immune cells, and that the uncontrolled "self-fueled hyperinflammation" during the early COVID-19 infection can become continued immune cell disruption that drives long-COVID symptoms.

"Long COVID is more likely due to either an inflammatory response by the body or reservoirs of virus that the body is still trying to clear … and the symptoms we're seeing are a side effect of that," said Rainu Kaushal, MD, senior associate dean for clinical research at Weill Cornell Medicine in New York.

Australian researchers found (Nat Immunol. 2022 Jan 13. doi: 10.1038/s41590-021-01113-x) that immune system recovery appeared different, compared with those who were infected with other common coronaviruses.

These findings also support concerns that some experts express over the long-term risks of COVID-19 infections in general, but especially repeat infections. "Anything that kind of revs up inflammation in the body can boil that pot over and make the symptoms worse. That's very easily an infection or some other insult to the body. So that's the generalized hypothesis as to why insults to the body may worsen the symptoms," said Dr. Truong.

An autoimmune condition?

But inflammation alone does not fully explain post–COVID-19 problems.

Dr. Truong and his team, for example, have been documenting inflammatory markers in patients at the post–COVID clinic he cofounded more than 2 years ago at Emory Executive Park in Atlanta. When the clinic was first launched, high-dose nonsteroidal anti-inflammatory drugs – including ibuprofen – and prednisone were prescribed to long–COVID patients.

"It didn't make a difference at all for any of these folks," he said, adding that there are signs that autoimmunity is at play. But he cautioned that it is still too early to suggest treating long-COVID patients with medications used for other autoimmune conditions.

In autoimmune conditions such as rheumatoid arthritis, lupus, and type 1 diabetes, a person's immune system can't tell normal cells from foreign pathogens and attacks healthy cells. There is typically no single diagnostic test, and many share similar symptoms, making detection and diagnosis potentially difficult, according to Johns Hopkins Medicine.

A small study published in the journal Science Translational Medicine (2022 Dec 21. doi: 10.1126/scitranslmed.add0484) found that, among patients who failed to regain their sense of smell long after their initial infection, there was inflammation in the nose tissue where smell nerve cells are found, even though no detectable virus remained. Fewer olfactory sensory neurons were seen, as well – findings that researchers said resembled some kind of "autoimmune-like process."

Meanwhile, scientists in Canada found signs of autoimmunity in blood samples taken from patients who still had fatigue and shortness of breath after their initial COVID-19 infection. Two specific proteins were present a year after infection in up to 30% of patients, many of whom still had shortness of breath and fatigue, the researchers reported in the Jan. 1 issue of the European Respiratory Journal (2023. doi: 10.1183/13993003.00970-2022). These patients had been healthy and had no autoimmune condition or other diseases before they were infected.

Immune system problems

A number of studies suggest that a problematic immune response could also explain why symptoms persist for some people.

Researchers in France (J Med Virol. 2022 Oct 13. doi: 10.1002/jmv.28209), for example, found that the immune response problems in those with severe COVID-19 infections caused exaggerated or uncontrolled formation of a type of bug-fighting defense mechanism called a neutrophil extracellular trap (NET), which in turn triggers harmful inflammation that can result in multiorgan damage. These traps are netlike structures made from fibers composed mostly of DNA strings that bind, or trap, pathogens.

Long COVID is not like an acute infectious disease, said Alexander Charney, MD, PhD, the lead principal investigator of the RECOVER adult cohort at Mount Sinai in New York, and an associate professor at Icahn School of Medicine at Mount Sinai. It is more similar to other complex chronic diseases that have taken decades to understand, such as heart disease, mental illness, and rheumatologic diseases, he says.

A number of studies suggest that a problematic immune response could also explain why symptoms persist for some people.

Biomarkers and blood clots

Scientists are honing in on biomarkers, or detectable and measurable traits – in this case, molecular indicators – that can make diagnosing long COVID easier and give better direction for treatment. These biomarkers are also key to helping sort out the complex biology of long COVID.

In one study, data from blood samples taken from hundreds of hospitalized COVID-19 patients suggest changes are happening at the molecular level during initial severe infections. These changes may be tied to the development of longer-term symptoms, according to the study by Dr. Charney and his team at Mount Sinai published in Nature Medicine (2022 Dec 8. doi: 10.1038/s41591-022-02107-4).

Blood clotting issues have also been detected in long–COVID patients. At least one study (J Med Virol, 2022 Oct 13. doi: 10.1002/jmv.28209) found signs that long-COVID patients had higher levels of a type of auto-antibody linked to the abnormal formation of clots. Researchers suspect that tiny, persistent microclots – undetectable via regular pathology tests – may be cutting off oxygen flow to tissue by blocking capillaries – and could explain many of the post-COVID symptoms described by patients.

While enormous progress has been made toward understanding long COVID, the research is still considered early and faces many challenges, including varying criteria used to define the condition, differences in patient recrutiing, the types and quality of data used, and the small size of many studies. Some research also appears to conflict with other studies. And while there are specialized tools for diagnosing some aspects of the condition, standard tests often don't detect many of the signs seen in long-COVID patients.

"People are suffering now, and they want answers now," said Dr. Charney. "It's going to be a long haul to figure out what is going on." ■

Pages 8a—8d ▸

Does less invasive surgery compromise outcomes?

BY LIAM DAVENPORT

For patients with early–stage non–small cell lung cancer (NSCLC), the survival outcomes appeared just as good with sublobar resection as with the more invasive lobar resection, suggested results from the CALGB 140503 trial.

These new results contrast with those from a previous study from 1995, which found that local recurrence was three times higher and cancer mortality was twice as high with the less invasive procedure.

Those results from nearly 30 years ago established lobectomy as the standard of surgical care in this patient population, but since then advances in imaging and staging have allowed the detection of smaller and earlier tumors, which has "rekindled interest in sublobar resection," the authors commented.

Hence, they conducted the new trial, which involved almost 700 U.S. patients with clinical T1aN0 NSCLC and a tumor size up to 2 cm, who were randomly assigned to lobar or sublobar tumor resection, and followed for 7 years.

"Thoracic surgeons will need to expand their expertise in sublobar resections, especially complex segmentectomies, and will need to collaborate closely with pathologists ...."

The rates of both disease-free and overall survival were similar between the two groups, with no significant differences observed. There were also no substantial differences in rates of distant and locoregional recurrence.

In addition, there was a suggestion of less reduction in pulmonary function following the less invasive procedure.

"These findings affirm that sublobar resection ... is an effective management approach for this subgroup of patients with NSCLC," said lead author Nasser Altorki, MD, Weill Cornell Medicine, NewYork–Presbyterian Hospital, New York.

"It is important that these results are interpreted strictly within the constraints of the eligibility criteria mandated by the trial, he emphasizes. "Specifically, the results are applicable only to a highly selected group of patients ... in whom the absence of metastases to hilar and mediastinal lymph nodes is pathologically confirmed."

Nevertheless, Dr. Altorki said that "these results will become increasingly relevant as the proportion of patients with early-stage lung cancer increases with expanded implementation of lung cancer screening, and as the number of older persons with early-stage disease in whom sublobar resection may be the preferred surgical option increases."

The study was published online in the New England Journal of Medicine (2023 Feb 9. doi: 10.1056/NEJMoa2212083).

In an accompanying editorial (2023 Feb 9. doi: 10.1056/NEJMe2215647), Valerie W. Rusch, MD, Thoracic Service, Memorial Sloan Kettering Cancer Center, New York, agreed. "As CT screening becomes more widespread, this patient population will increase in clinical practice," she explained.

However, Dr. Rusch also urged caution around patient selection, underlining that the results do not "provide a license for suboptimal surgical care." She said that "safeguards" such as the meticulous and strict patient criteria used in the trial "must be preserved in routine practice."

"Thoracic surgeons will need to expand their expertise in sublobar resections, especially complex segmentectomies, and will need to collaborate closely with pathologists in assessing margins of resection, adequacy of lymph-node staging, and tumor characteristics that may predict recurrence."

While emphasizing that lobectomy should still be performed when appropriate, Dr. Rusch nevertheless said: "The era of 'precision' surgery for NSCLC has arrived."

The investigators also point out that their findings are "consistent" with those of a recent Japanese study (Lancet. 2022 Apr 23. doi: 10.1016/S0140-6736[21]02333-3) that compared lobectomy with anatomical segmentectomy, which found that the 5-year overall survival was 91.1% for lobectomy and 94.3% for segmentectomy. The authors suggest that the difference in overall survival rates between the two trials might be due to anatomical segmentectomy being "considered by most surgeons to be more oncologically sound than wedge resection."

In the current trial, wedge resection was allowed, however, "because it is the most frequently practiced method of sublobar resection in North America and Europe; thus, its inclusion would make the trial more representative of a 'real world' setting."

Another important difference could be that more than 90% of the patients in the Japanese trial had adenocarcinoma, 45% with an associated ground-glass component, which is associated with better survival than a completely solid adenocarcinoma.

Dr. Rusch agrees that there are likely to be various factors related to the survival differences between the two trials, including patient selection, intraoperative management, and tumor characteristics.

"However, these two landmark trials are practice-changing because they establish sublobar resection as the standard of care for a select group of patients with NSCLC," Dr. Rusch concluded.

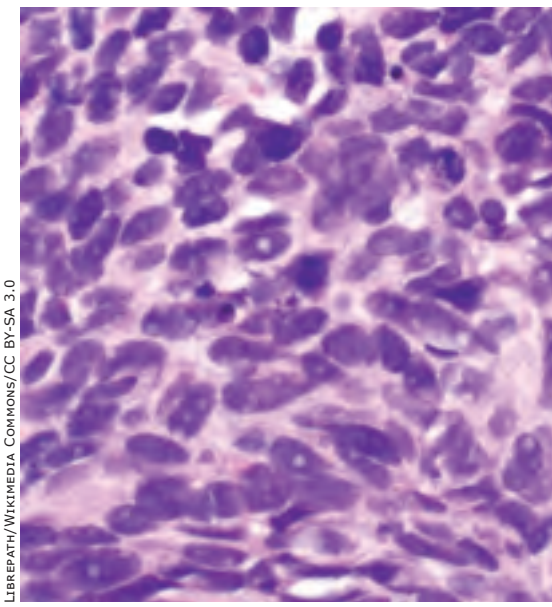
Dr. Altorki and colleagues conducted the multicenter, international, randomized, noninferiority, phase 3 trial in patients with clinically staged T1aN0 NSCLC from 83 academic and community-based institutions in the United States, Canada, and Australia.

Patients were required to have a peripheral lung nodule with a solid component of up to 2 cm on preoperative CT, a tumor center in the outer third of the lung, and a tumor location amenable to sublobar resection, whether wedge or segment, or lobar resection, among other criteria.

In all, 697 patients were randomly assigned to undergo either lobar resection or sublobar resection, of whom 59.1% had wedge resection and 37.9% anatomical segmental resection. The median age was 67.9 years, and 57.4% were female. The vast majority (90%) were White. After a median follow-up of 7 years, the 5-year disease-free survival was 63.6% with sublobar resection and 64.1% following lobar resection.

The team found that sublobar resection was not inferior to lobectomy for disease-free survival, at a hazard ratio for disease recurrence or death of 1.01 (90% confidence interval, 0.83-1.24), which adjusted to 0.99 after taking into account the site where the patient was treated.

The 5-year overall survival rate was 80.3% after sublobar resection, and 78.9% following lobar resection, at a hazard ratio for death of 0.95 (95% CI, 0.72-1.26). The results were "generally consistent" when accounting for factors such as age group, sex, tumor location, histologic type, smoking history, tumor size, and ECOG performance status.



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Micrograph shows NSCLC visualized with H&E stain.

The researchers showed that, among 687 patients eligible for assessment, 30.4% of those in the sublobar resection group and 29.3% of those assigned to lobar resection experienced disease recurrence, with 13.4% and 10%, respectively, having locoregional recurrence.

An exploratory analysis indicated that 5-year recurrence-free survival was similar in the two groups, at 70.2% vs. 71.2% or a hazard ratio for recurrence of 1.05 (95% CI, 0.80-1.39). The cumulative incidence of death was also similar.

It was also notable that reduction in predictive forced expiratory volume in 1 second from baseline was lower with sublobar than lobar resection, at –4.0 vs. –6.0, as was the reduction in predicted forced vital capacity, at –3.0 vs. –5.0.

"Although this difference is arguably not clinically meaningful in this patient population with normal baseline pulmonary functions," the team writes, "it may be more clinically relevant in patients with compromised pulmonary functions, or in those with lower-lobe disease in whom lobar resection may be associated with greater impairment of pulmonary function."

The study was supported by the National Cancer Institute and supported in part by Covidien and Ethicon. Dr. Altorki reported relationships with AstraZeneca, Genentech, Johnson & Johnson, and Regeneron. Dr. Rusch reported relationships with Genentech, and the National Cancer Institute.

Dapper homolog 2 shows promise for idiopathic pulmonary fibrosis

BY HEIDI SPLETE
MDedge News

Dapper homolog 2 attenuated pulmonary fibrosis development and suppressed glycosis in myofibroblasts, suggesting potential as a therapeutic target for idiopathic pulmonary fibrosis, based on data from mouse models.

Idiopathic pulmonary fibrosis (IPF) remains a challenge with poor prognosis, and current therapeutic options are limited, wrote Xiaofan Lai, of Sun Yat-sen University, Guangzhou, China, and colleagues. Previous studies suggest that myofibroblasts are key contributors to fibrosis in IPF, they said.

Dishevelled-associated antagonist of beta-catenin 2 (DACT2) is an antagonist in the DACT gene family and associated with tissue development and injury, but its function and potential therapeutic role in IPF has not been explored; specifically, "whether DACT2 participates in the dysregulated glycolysis of myofibroblasts remains unknown," they said.

In a study published in the International Journal of Biological Macromolecules (2022 Dec 6. doi.org/10.1016/j.ijbiomac.2022.11.324), the researchers examined adeno-associated virus serotype 6 (AAV6)-mediated DACT2 overexpression in experimental pulmonary fibrosis using mouse models.

DACT2 inhibited differentiation of lung myofibroblasts by downregulating lactate dehydrogenase A, which caused suppression of glycolysis.

The researchers injected AAV6 vectors into the lungs of mice to overexpress DACT2.

The DACT2 overexpression "effectively attenuated both bleomycin-induced and AdTGF-beta-1-induced pulmonary fibrosis murine models in vivo, as evidenced by the alleviation of myofibroblast differentiation and collagen accumulation," according to the researchers.

They found that overexpression of DACT2 was associated with glucose uptake, extracellular acidification rate, intracellular adenosine-triphosphate (ATP) level, and lactate levels of myofibroblasts.

The researchers also conducted in vitro experiments in which they treated lung fibroblasts with cycloheximide (CHX), a protein synthesis inhibitor. These experiments showed that DACT2 inhibited differentiation of lung myofibroblasts by downregulating lactate dehydrogenase A (LDHA), which caused suppression of glycolysis in myofibroblasts.

"We hope this research will lay the theoretical foundation for finding novel therapeutics to alleviate or reverse the development of pulmonary fibrosis."

"Aerobic glycolysis is an important method of energy generation, and several studies have shown that enhanced glycolysis facilitates the progression of pulmonary fibrosis," the researchers wrote in their discussion.

More research is needed outside of mouse models and in vitro studies, but the current study is the first known to explore the relationship between DACT2 and LDHA in pulmonary fibrosis, and the results provide evidence of the potential benefits of DACT2 in treating lung disorders, the researchers wrote.

"We hope this research will lay the theoretical foundation for finding novel therapeutics to alleviate or reverse the development of pulmonary fibrosis and other chronic lung disorders," the researchers concluded.

The study was supported by the National Natural Science Foundation of China and the Regional Joint Fund-Youth Fund projects of Guangdong Province. The researchers had no financial conflicts to disclose. ■

How much is enough for informed consent?

BY LAMBETH HOCHWALD

Sitting across from a patient explaining a complicated treatment proposal, protocol, or medication may be one of the most complex yet crucial tasks you have as a physician. Although informed consent is at the forefront of shared decisions between you and your patient, there's a fine line between providing enough information on the risks and benefits of a particular treatment and knowing you've explained it well enough to fully educate your patient about their choices.

According to the Medscape "Right and Wrong in Medicine: Life, Death, and Wrenching Choices" report, how you handle the informed consent process can be the difference between a positive outcome and a negative one.

"It is a bit of a fine line because unless your patient happens to be a health care provider, medicine is complicated for patients to understand," said David L. Feldman, MD, chief medical officer at The Doctors Company, the nation's largest medical malpractice insurer in New York.

In addition, documenting the interaction is critical, said James Giordano, PhD, MPhil, professor in the departments of neurology and biochemistry and chief of the neuroethics studies program at the Pellegrino Center for Clinical Bioethics at Georgetown University Medical Center, Washington.

"As with anything in medicine, the key rule is that, if it's not documented, it's not done," he said. "This also means diligent documentation in all aspects of the medical record, including the electronic medical record and the written one."

That said, it's important to know what's enough and what's too granular when you discuss a procedure with your patients, said Erum N. Ilyas, MD, a board-certified dermatologist at Schweiger Dermatology and a bioethicist near Philadelphia.

"One of the most challenging aspects of informed consent, especially for young physicians, is how to discuss a procedure or a medication in a manner that is both relevant and concise," Dr. llyas said. "I've had residents about to perform a skin biopsy spend several minutes covering every aspect of every potential outcome of a routine skin biopsy. The patient is left traumatized and confused as to whether they should proceed with the small procedure."

Instead, the goal of informed consent is to ensure that the patient has a general overview of the procedure and is empowered, knowing that the decision to proceed is, indeed, part of their decision-making process.

How long an informed consent discussion takes depends on the procedure.

"When I was in practice as a plastic surgeon, the conversations varied from the straightforward 'I'm taking this mole off your cheek, and there's a risk of scarring and bleeding' to talking about a mastectomy and breast reconstruction, which could take an hour or more to discuss," Dr. Feldman said.

To protect yourself, consider using technology to your advantage, especially since lawsuits over informed consent usually happen several years after the procedure.

Ultimately, it's as essential for doctors to explain the risks associated with a procedure as it is for patients to understand precisely what's involved, Dr. Ilyas added.

She also recommends creating a flow to the conversation that places the discussion of risks within the context of why the procedure is being performed. This way, clarity about both the risks and the need for the treatment or procedure can be achieved.

When doing so, it's critical to make sure you're speaking your patient's language – literally.

"Have a translator in the room if needed," Dr. Feldman added. "If your patient is hearing or sight impaired, you need to have every contingency ready to ensure that everyone is in complete communication."

Document, document, document!

To best protect yourself, the patient must consent to each procedure and intervention via active, informed consent, said Dr. Giordano.

"It's not enough to hand a patient a piece of paper and say sign it," he said. "There should be some documented evidence that the patient has not only read the document but that the key parts of the document have been explained and that the patient's level of comprehension has been assessed and verified."

It is vital if the patient has a disability, a neurological impairment, or a neurocognitive or psychiatric condition that might impede his or her ability to understand the consent that's being sought.

In addition, it's best if a "clinical proxy" handles the consent (for example, a nurse, office worker, or case manager).

"This can be very helpful because it means you've had third-party documentation of informed consent," Dr. Giordano said. "It should then be re-documented with you as the clinician and stated that the patient has affirmatively and actively agreed to treatment."

What happens when things go wrong?

If you're sued over informed consent, with the patient claiming that you didn't fully explain the potential risks, the first thing to consider is why this happened.

"Very often, these situations occur if there was some difficulty or competency of communication," Dr. Giordano said. "You may have done everything right, but somehow the patient hasn't gained an understanding of the procedure required."

Physicians must take a hard look at how they're explaining risks and possible side effects. For doctors who perform these procedures regularly, the risks may seem small, and they may unconsciously minimize them to the patient. But when something goes wrong, the patient may then feel that they didn't fully understand the frequency of poor outcomes, or the potential severity.

Next, it's important to perform a "gap analysis" to assess why something went awry. That means, look at all the potential factors involved to identify which one was the weak link.

"It might be that the patient was on a signing frenzy and signed away but didn't receive active and informed content," Dr. Giordano said. "The goal is to learn how to close the gap for this case and for future cases."

For protection, consider using technology to your advantage, especially since lawsuits over informed consent usually happen several years after the procedure. This is when a patient might argue that you didn't tell them about possible complications and that they might have

TERO VESALAINEN/GETTY IMAGES

opted out of the procedure if they had known about those issues ahead of time.

"Even before the statute of limitations is up for a lawsuit, it could be 5 years from the time the procedure occurred due to the length of time a lawsuit can take," Dr. Feldman said. "That's why it's important to take a video of your conversation or make a recording of the informed consent conversation. This way if there's a question of what you said, there's a video of it."

For many physicians, this would be a big change – to video record and then store all their informed consent conversations. It could most likely help you if a lawsuit occurs, but some physicians may feel that process to be cumbersome and time-consuming, and they'd rather find another way to ensure that patients understand the risks.

Ultimately, however, if there's a legal question involved with informed consent, the general thinking is that the effect on the patient must be harmful for it to stand up.

"The question becomes whether the outcome rendered that gap in the consenting process forgivable," Dr. Giordano said. "The hope is that there was nothing harmful to the patient and that the benefit of the procedure was demonstrable despite any gaps in the informed consent process."

In the end, informed consent should be a matter of good communication before, during, and after any treatment or procedure.

"When you form a relationship with a patient who needs any procedure, small or large, you're going to be guiding them through a very scary thing," Dr. Feldman said. "You want to make patients feel like you care about them and that, while neither you nor the system is perfect, you'll take care of them. That's the bottom line." ■

RSV MAY RAISE THE STAKES FOR OLDER ADULTS

Respiratory syncytial virus (RSV) is a common and contagious virus that typically produces mild, cold-like symptoms but can put older adults at risk for severe outcomes.[1,2,*]

Each year in the US, approximately 177,000 older adults are hospitalized and an estimated 14,000 of them die due to RSV infection.[2]

Those at high risk for severe illness from RSV include[2,3]:

Older adults, especially those aged 65 and older

Adults with chronic lung or heart disease

Adults with weakened immune systems

RSV may exacerbate serious conditions such as[4]:

Asthma

Chronic obstructive pulmonary disease

Congestive heart failure

Infection with RSV may put some older adults and adults with certain chronic medical conditions at increased risk.[2,3]

CDC=Centers for Disease Control and Prevention;
CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease.

Learn about the risks of RSV at RSVinAdults.com

*The CDC states that adults at highest risk for severe RSV infection include older adults, especially those 65 years and older, adults with chronic heart or lung disease, and adults with weakened immune systems. Data are limited in assessing the risk of severe outcomes due to RSV infection in adults 60-64 years of age.[5,6]

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SLEEP STRATEGIES

The triple overlap: COPD-OSA-OHS. Is it time for new definitions?

BY GORAV SHARMA, MD, AND ALEJANDRA C. LASTRA, MD, FCCP

In our current society, it is likely that the "skinny patient with COPD" who walks into your clinic is less and less your "traditional" patient with COPD. We are seeing in our health care systems more of the "blue bloaters" – patients with COPD and significant obesity. This phenotype is representing what we are seeing worldwide as a consequence of the rising obesity prevalence. In the United States, the prepandemic (2017-2020) estimated percentage of adults over the age of 40 with obesity, defined as a body mass index (BMI) of at least 30 kg/m^2, was over 40%. Moreover, the estimated percentage of adults with morbid obesity (BMI at least 40 kg/m2) is close to 10% (Akinbami, LJ et al. *Vital Health Stat*. 2022:190:1-36) and trending up. These patients with the "triple overlap" of morbid obesity, COPD, and awake daytime hypercapnia are being seen in clinics and in-hospital settings with increasing frequency, often presenting with complicating comorbidities such as acute respiratory failure, acute heart failure, kidney disease, or pulmonary hypertension. We are now faced with managing these patients with complex disease.

The obesity paradox does not seem applicable in the triple overlap phenotype. Patients with COPD who are overweight, defined as "mild obesity," have lower mortality when compared with normal weight and underweight patients with COPD; however, this effect diminishes when BMI increases beyond 32 kg/m^2. With increasing obesity severity and aging, the risk of both obstructive sleep apnea (OSA) and hypoventilation increases. It is well documented that COPD-OSA overlap is linked to worse outcomes and that continuous positive airway pressure (CPAP) as first-line therapy decreases readmission rates and mortality. The triple overlap phenotypic patients, however, are presenting with chronic hypercapnic respiratory failure in a backdrop of morbid obesity, unlike the stable COPD-OSA overlap. The pathophysiology of hypoventilation in obesity is complex and multifactorial, and, although significant overlaps likely exist with comorbid COPD, by current definitions, to establish a diagnosis of obesity hypoventilation syndrome (OHS), one must have excluded other causes of hypoventilation, such as COPD.

These patients with the triple overlap of morbid obesity, awake daytime hypercapnia, and COPD are the subset of patients that providers struggle to fit in a diagnosis or in clinical research trials.

The triple overlap is a distinct syndrome

Different labels have been used in the medical literature: hypercapnic OSA-COPD overlap, morbid obesity and OSA-COPD overlap, hypercapnic morbidly obese COPD and OHS-COPD overlap. A better characterization of this distinctive phenotype is much needed. Patients with OSA-COPD overlap, for example, have an increased propensity to develop hypercapnia at higher FEV_1 when compared with COPD without OSA – but this is thought to be a consequence of prolonged and frequent apneas and hypopneas compounded with obesity-related central hypoventilation. We found that morbidly obese patients with OSA-COPD overlap have a higher hypoxia burden, more severe OSA, and are frequently prescribed noninvasive ventilation after a failed titration polysomnogram (Htun ZM, et al. *Am J Respir Crit Care Med*. 2019;199:A1382), perhaps signaling a distinctive phenotype with worse outcomes, but the study had the inherent limitations of a single-center, retrospective design lacking data on awake hypercapnia. On the other side, the term OHS-COPD is contradictory and confusing based on current OHS diagnostic criteria.

How do we get these patients, who do not fit in any of the specified insurance criteria for PAP therapy approved for treatment?

In standardizing diagnostic criteria for patients with this triple overlap syndrome, challenges remain: would the patient with a BMI of 70 kg/m^2 and fixed chronic airflow obstruction with FEV_1 72% fall under the category of hypercapnic COPD vs OHS? Do these patients have worse outcomes regardless of their predominant feature? Would outcomes change if the apnea hypopnea index (AHI) is 10/h vs 65/h? More importantly, do patients with the triple overlap of COPD, morbid obesity, and daytime hypercapnia have worse outcomes when compared with hypercapnic COPD, or OHS with/without OSA? These questions can be better addressed once we agree on a definition. The patients with triple overlap syndrome have been traditionally excluded from clinical trials: the patient with morbid obesity has been excluded from chronic hypercapnic COPD clinical trials, and the patient with COPD has been excluded from OHS trials.

Dr. Sharma

Dr. Lastra

There are no specific clinical guidelines for this triple overlap phenotype. Positive airway pressure is the mainstay of treatment. CPAP is recommended as first-line therapy for patients with OSA-COPD overlap syndrome, while noninvasive ventilation (NIV) with bilevel positive airway pressure (BPAP) is recommended as first-line for the stable ambulatory hypercapnic patient with COPD. It is unclear if NIV is superior to CPAP in patients with triple overlap syndrome, although recently published data showed greater efficacy in reducing carbon dioxide ($PaCO_2$) and improving quality of life in a small group of subjects (Zheng et al. *J Clin Sleep Med*. 2022;18[1]:99-107). To take a step further, the subtleties of NIV set up, such as rise time and minimum inspiratory time, are contradictory: the goal in ventilating patients with COPD is to shorten inspiratory time, prolonging expiratory time, therefore allowing a shortened inspiratory cycle. In obesity, ventilation strategies aim to prolong and sustain inspiratory time to improve ventilation and dependent atelectasis. Another area of uncertainty is device selection. Should we aim to provide a respiratory assist device (RAD): the traditional, rent to own bilevel PAP without auto-expiratory positive airway pressure (EPAP) capabilities and lower maximum inspiratory pressure delivery capacity, vs a home mechanical ventilator at a higher expense, life-time rental, and one-way only data monitoring, which limits remote prescription adjustments, but allow auto-EPAP settings for patients with comorbid OSA? More importantly, how do we get these patients, who do not fit in any of the specified insurance criteria for PAP therapy approved for treatment?

A uniform diagnostic definition and clear taxonomy allows for resource allocation, from government funded grants for clinical trials to a better-informed distribution of health care systems resources and support health care policy changes to improve patient-centric outcomes. Here, we propose that the morbidly obese patient (BMI >40 kg/m2) with chronic airflow obstruction and a forced expiratory ratio (FEV_1/FVC) <0.7 with awake daytime hypercapnia ($PaCO_2$ > 45 mm Hg) represents a different entity/phenotype and fits best under the triple overlap syndrome taxonomy.

We suspect that these patients have worse outcomes, including comorbidity burden, quality of life, exacerbation rates, longer hospital length-of-stay, and respiratory and all-cause mortality. Large, multicenter, controlled trials comparing the long-term effectiveness of NIV and CPAP: measurements of

Triple overlap syndrome diagnostic criteria

Morbid obesity	≥ 40 kg/m^2
COPD	FEV_1/FVC = < 0.7
Daytime awake hypercapnia	$PaCO_2$ ≥ 45 mm Hg (pH ≥ 7.35)

Source: Dr. Sharma, Dr. Lastra

respiratory function, gas exchange, blood pressure, and health related quality of life are needed. This is a group of patients that may specifically benefit from volume-targeted pressure support mode ventilation with auto-EPAP capabilities upon discharge from the hospital after an acute exacerbation.

Inpatient (sleep medicine) and outpatient transitions

In patients hospitalized with the triple overlap syndrome, there are certain considerations that are of special interest. Given comorbid hypercapnia and limited data on NIV superiority over CPAP, a sleep study should not be needed for NIV qualification. In addition, the medical team may consider the following (Figure 1):

1. Noninvasive Ventilation:

a. Maintaining a high-pressure support differential between inspiratory positive airway pressure (IPAP) and EPAP. This can usually be achieved at 8-10 cm H_2O, further adjusting to target a tidal volume (Vt) of 8 mL/kg of ideal body weight (IBW).

b. Higher EPAP: To overcome dependent atelectasis, improve ventilation-perfusion (VQ) matching, and better treat upper airway resistance both during wakefulness and sleep. Also, adjustments of EPAP at bedside should be considered to counteract auto-PEEP-related ineffective triggering if observed.

c. OSA screening and EPAP adjustment: for high residual obstructive apneas or hypopneas if data are available on the NIV device, or with the use of peripheral arterial tonometry sleep testing devices with NIV on overnight before discharge.

d. Does the patient meet criteria for oxygen supplementation at home? Wean oxygen off, if possible.

2. Case-managers can help establish services with a durable medical equipment provider with expertise in advanced PAP devices.

3. Obesity management, Consider referral to an obesity management program for lifestyle/dietary modifications along with pharmacotherapy or bariatric surgery interventions.

4. Close follow-up, track exacerbations. Device download data are crucial to monitor adherence/tolerance and treatment effectiveness with particular interest in AHI, oximetry, and CO_2 trends monitoring. Some patients may need dedicated titration polysomnograms to adjust ventilation settings, for optimization of residual OSA or for oxygen addition or discontinuation.

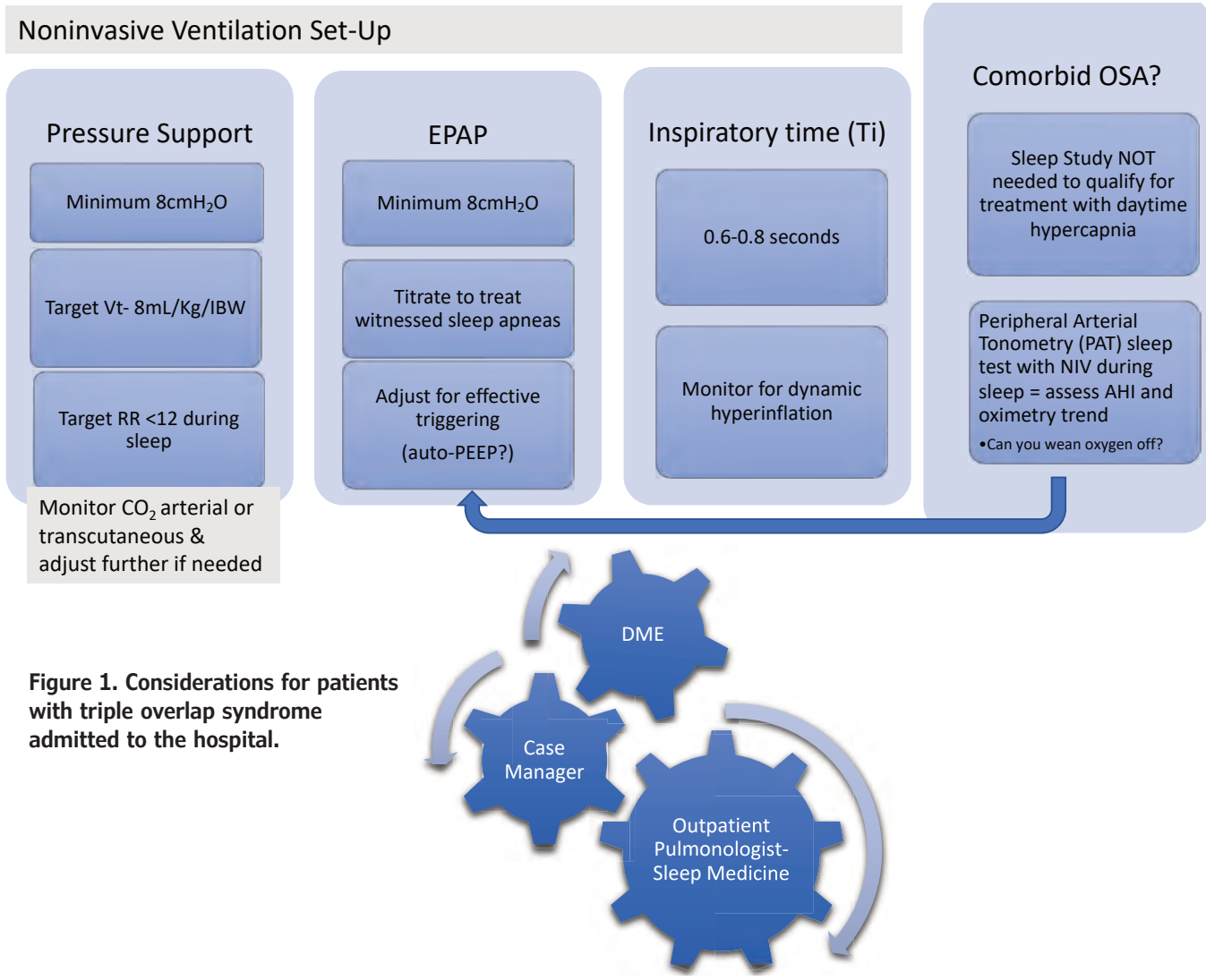


Figure 1. Considerations for patients with triple overlap syndrome admitted to the hospital.

Conclusion

Patients with the triple overlap phenotype have not been systematically defined, studied, or included in clinical trials. We anticipate that these patients have worse outcomes: quality of life, symptom and comorbidity burden, exacerbation rates, in-hospital mortality, longer hospital stay and ICU stay, and respiratory and all-cause mortality. This is a group of patients that may specifically benefit from domiciliary NIV set-up upon discharge from the hospital with close follow-up. Properly identifying these patients will help pulmonologists and health care systems direct resources to optimally manage this complex group of patients. Funding of research trials to support clinical guidelines development should be prioritized. Triple overlap syndrome is different from COPD-OSA overlap, OHS with moderate to severe OSA, or OHS without significant OSA. ■

Dr. Lastra is Program Director, Sleep Medicine Fellowships, Assistant Professor of Medicine, and Associate Medical Director, UChicago Sleep; and Dr. Sharma is a Sleep Medicine Fellow; Section of Pulmonary and Critical Care Medicine, The University of Chicago, Chicago, Illinois.

NETWORKS

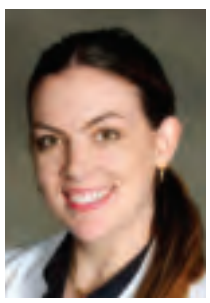
Tobramycin inhalation; neuromuscular disease; pleural catheters; and more ....

AIRWAYS DISORDERS NETWORK

Bronchiectasis Section

Tobramycin inhaled solution and quality of life in patients with bronchiectasis

Bronchiectasis is a condition of dilated, inflamed airways and mucous production caused by a myriad of diseases. Bronchiectasis entails chronic productive cough and an increased risk of infections leading to exacerbations. Chronic bacterial infections are often a hallmark of severe disease, especially with *Pseudomonas aeruginosa* (O'Donnell AE. *N Engl J Med*. 2022;387[6]:533). Prophylactic inhaled antibiotics have been used as off-label therapies with mixed evidence, particularly in non-cystic fibrosis bronchiectasis (Rubin BK, et al. *Respiration*. 2014;88[3]:177). As the incidence of bronchiectasis increases worldwide, the need for evidence- based therapies to reduce symptom burden is increasing.



Dr. Mirza

In a recent publication, Guan and colleagues evaluated the efficacy and safety of tobramycin inhaled solution (TIS) for bronchiectasis with chronic *P. aeruginosa* in a phase 3, 16-week, multicenter, double-blind randomized, controlled trial (Guan W-J, et al. *Chest*. 2023;163[1]:64). A regimen of twice-daily TIS, compared with nebulized normal saline, demonstrated a more significant reduction in *P. aeruginosa* sputum density after two cycles of 28 days on-treatment and 28 days off-treatment (adjusted mean difference, 1.74 log10 colony-forming units/g; 95% CI, 1.12-2.35; $P < .001$), and more patients became culture-negative for *P. aeruginosa* in the TIS group than in the placebo group on day 29 (29.3% vs 10.6%). Adverse events were similar in both groups. Importantly, there was an improvement in quality-of-life bronchiectasis respiratory symptom score by 7.91 points at day 29 and 6.72 points at day 85; all three were statistically significant but just below the minimal clinically important difference of 8 points.

Dr. Conroy Wong and Dr. Miguel Angel Martinez-Garcia (*Chest*. 2023 Jan;163[1]:3) highlighted in their accompanying editorial that use of health-related quality of life score was a "distinguishing feature" of the trial as "most studies have used the change in microbial density as the primary outcome measure alone."

Future studies evaluating cyclical vs continuous antibiotic administration, treatment duration, and impact on exacerbations continue to be needed.

Alicia Mirza, MD
Section Member-at-Large

SLEEP MEDICINE NETWORK

Home-Based Mechanical Ventilation & Neuromuscular Disease Section

Novel therapies for neuromuscular disease: What are the respiratory and sleep implications?

The natural history of respiratory impairment in children and adults with progressive neuromuscular disease (NMD) often follows a predictable progression. Muscle weakness leads to sleep-disordered breathing and sleep-related hypoventilation, followed by diurnal hypoventilation, and, ultimately leads to respiratory failure. A number of disease-specific and society guidelines provide protocols for anticipatory respiratory monitoring, such as the role of polysomnography, pulmonary function testing, and respiratory muscle strength testing. They also guide the treatment of respiratory symptoms, such as when to initiate cough augmentation and assisted ventilation.

The emergence of disease-modifying therapies over the last decade has changed the landscape of a number of neuromuscular diseases, including spinal muscular atrophy (SMA) and Duchenne muscular dystrophy. There are now cases of children with SMA type 1, who subsequent to treatment, are walking independently. Studies examining the impact of these therapies on motor function use standardized assessments, but there are limited studies assessing pulmonary and sleep outcomes (Gurbani N, et al. *Pediatr Pulmonol*. 2021;56[4]:700).

Researchers are also assessing the role of home testing to diagnose hypoventilation (Shi J, et al. *Sleep Med*. 2023;101:221) and using tools like positive airway pressure device data to guide treatment with noninvasive ventilation (Perrem L et al. *Pediatr Pulmonol*. 2020;55[1]:58). While these advances in therapy are exciting, we still do not know what the long-term respiratory function, prognosis, or disease progression may be. Questions remain regarding how to best monitor, and at what frequency to assess, the respiratory status in these patients.

Dr. Prero

Moshe Y. Prero, MD
Section Member-at-Large

THORACIC ONCOLOGY NETWORK

Interventional Procedures Section

Breathing easier: The growing adoption of indwelling pleural catheters

The management of recurrent pleural effusions is challenging. Indwelling tunneled pleural catheters (IPCs) have been shown to reduce the need for additional pleural procedures, admissions, and health care costs. These devices have become an important treatment option in patients with malignant pleural effusions (MPE), particularly those with a nonexpandable lung (Feller-Kopman DJ, et al. *Am J Respir Crit Care Med*. 2018;198[7]:839) and when talc pleurodesis is unsuccessful in patients with an expandable lung (Dresler CM, et al. *Chest*. 2005;127[3]:909).

Dr. Gupta

Dr. Avasarala

Over the last 5 years, studies evaluating the use of IPCs in treating nonmalignant pleural disease have proliferated. These studies have included and shown the successful treatment of pleural effusions due to end-stage renal disease, advanced heart failure (Walker SP, et al. *Eur Respir J*. 2022;59[2]:2101362), and cirrhosis, especially when a transjugular intrahepatic portosystemic shunt or liver transplant is not an option (Shojaee S et al., *Chest*. 2019;155[3]:546). Compared with MPE, the rate of pleurodesis is generally lower and takes longer when an IPC is used to manage a nonmalignant pleural disease. Infection is the most common complication; most cases can be managed without catheter removal.

With many cited advantages, the IPC is an essential tool in the armamentarium of the chest physician and interventional radiologist. Indwelling pleural catheters have proven applications beyond MPE. When applied in a multidisciplinary fashion involving subspecialists and considering the patient's goals, using an IPC can help achieve a crucial patient-centric goal in managing a recurrent nonmalignant pleural effusion.

Samiksha Gupta, MD
2nd Year Fellow
Sameer Kaushik Avasarala, MD
Section Member-at-Large

CRITICAL CARE NETWORK

Nonrespiratory Critical Care Section

Early mobility in the ICU: working with the TEAM

Advocating for early mobility for patients in the ICU seems like a no-brainer. This is especially true for critically ill patients, in which weakness is more common and can result in worse outcomes (Kress JP, et al. *N Engl J Med*. 2014;370:1626). This advocacy is endorsed by major societies and guidelines, like the ABCDEF bundle (Balas MC, et al. *Crit Care Med*. 2013;41:S116), in which "E" stands for Early mobility and exercise. In fact, the PADIS guidelines, addressing Pain, Agitation, Delirium, Immobility, and Sleep in the ICU, added Immobility and Sleep (the "I" and "S" in PADIS)

Networks *continued on following page*

De Marco gift to the CHEST Foundation makes more than one dream possible

As a member of the CHEST Foundation Board of Trustees for years, Bob De Marco, MD, FCCP, ruminated over new, exciting ways to increase support of the philanthropic efforts of the American College of Chest Physicians.

Dr. De Marco knows all too well growing the percent of CHEST members who donate to the Foundation in support of CHEST initiatives is – in a word – underwhelming. For those who are involved, they do so greatly and with their whole selves, but Dr. De Marco believed more could be done.

In the months leading up to the CHEST Annual Meeting 2022 in Nashville, Dr. De Marco discussed fundraising with CHEST staff and was already thinking ahead to CHEST 2023 in Hawaii.

Dr. De Marco

"That's when it hit me – we could leverage Hawaii to get donations and to expose people to the CHEST Foundation," said Dr. De Marco. "Hawaii is a dream destination and that might be the exact motivation it would take to get that first donation from someone."

Having a good idea is one thing, but making sure it happens requires individual commitment. Dr. DeMarco personally pledged to cover the cost of first-class airfare for two to Hawaii, hotel accommodations, and registration to CHEST 2023 in Honolulu. For a minimum donation of $250 to the CHEST Foundation between September and the end of 2022, each donor would be entered into a drawing for a chance to win this dream trip.

"I thought to myself, who wouldn't want this prize?" said Dr. De Marco.

"You get to go to paradise for free – with a guest – and attend a top tier educational conference. Knowing your entry supported an organization as deserving as the CHEST Foundation is the cherry on top," he added.

In launching the Hawaii trip fundraiser before and during CHEST 2022, attendees from around the world were introduced to the efforts the Foundation supported and its mission to champion lung health. Over $180,000 was donated during this time period, in no small part because of the Hawaii travel reward

"I'm happy to say that the fundraiser did a lot better than I expected, and I was elated to see all of the new donors," says De Marco.

"It's my hope that those first-time donors continue their support for all that we do to provide grants – community, research, and diversity – and support CHEST initiatives that impact patient care and change lives."

To all who donated to the CHEST Foundation in 2022, Dr. De Marco said, "A sincere thank you to each and every one of you for helping us fulfill our mission. To the first-time donors, hopefully this will inspire you and your friends to be an active part of the CHEST family."

During CHEST 2022, the CHEST Foundation celebrated its 25th anniversary by reflecting on its accomplishments and on its impact over the past 25 years.

Former grant recipients were invited to celebrate with donors and speak to what they were able to accomplish because of the support they received.

The anniversary celebration also introduced the new CHEST initiatives, the First 5 Minutes® program and Bridging Specialties™: Timely Diagnosis for ILD. The former improves patient care through strengthened patient/clinician relationships and the latter aims to eliminate gaps in diagnosing complex lung diseases like pulmonary fibrosis.

To all who donated to the CHEST Foundation in 2022, Dr. De Marco said, "A sincere thank you to each and every one of you for helping us fulfill our mission. To the first-time donors, hopefully this will inspire you and your friends to be an active part of the CHEST family."

And, to the winner of the trip, Dr. De Marco said, "A sincere congratulations and I hope you enjoy beautiful Hawaii and your time at the meeting."

Those who are interested in getting involved and supporting the philanthropic work of CHEST can contact us at chestfoundation@chestnet.org.

To support the mission by donating, visit foundation.chestnet.org. ■

Aloha to our foundation give-away winner

Out of the 150+ donors who gave $250 or more to the CHEST Foundation between September 2022 and the end of 2022, longtime friend of the Foundation, Noah Dorsky, was the recipient of two first-class tickets to Hawaii, hotel accommodation, and registration to CHEST 2023 in Honolulu.

Noah donated to the Foundation specifically to the Mark J. Rosen, MD Master FCCP Endowment in honor of his late friend, Dr. Mark Rosen who served as CHEST President from 2006-2007 and died in 2019.

"Mark [Rosen] was a remarkable doctor and valued life-long friend," said Noah, "My continued support for CHEST is my way of honoring his memory and how much he meant to me and others."

Dr. Rosen's distinguished career in pulmonary and critical care medicine spanned more than 4 decades, marked by his deep commitments to medical education and patient care. Before serving as President, Dr. Rosen served on the CHEST Board of Regents and the CHEST Foundation Board of Trustees for many years. He held positions as Chair or member on numerous CHEST committees, including Education, Nominations, Membership, Marketing, and Finance.

Following his passing, Dr. Rosen's wife, Ilene, stayed engaged with the College and the CHEST Foundation by creating the endowment in his name and attending the CHEST Annual Meeting every year to award the Rosen Cup to the winners of the annual CHEST Challenge.

Congratulations, Noah, and thank you for your faithful giving to support the work of CHEST.

Networks *continued from previous page*

to the prior PAD guidelines in the latest update in 2018, to stress the importance of early mobility in the ICU (Devlin JW, et al. *Crit Care Med*. 2018;46[9]:e825). Multiple studies have shown a positive impact of early mobility in the ICU on patients' outcomes (Tipping CJ, et al. *Intensive Care Med*. 2017;43:171).

The recent TEAM study examined an early mobility approach in mechanically ventilated patients and found no difference in the primary outcome of alive and out-of-hospital at 180 days (*N Engl J Med*. 2022;387:1747).

Before concluding, it is worth realizing that the usual care arm included mobilization that was otherwise normally provided. The intervention arm protocolized the early mobility to be done simultaneously with the minimization of sedation. Patients' assessment occurred in 81% in the usual care arm vs 94% in the intervention arm; both numbers are much higher than reported data in the ICU (Jolley SE et al. *Crit Care Med*. 2017;45:205).

Revisiting the question of early mobility in the ICU, more data are needed to clarify the best methodology, sedation, timing, amount, and type of patients who will benefit the most. Until then, it should remain a goal for ICUs and part of the daily discussion when caring for critically ill patients. ■

Mohammed J. Al-Jaghbeer, MBBS, FCCP – Section Member-at-Large
Salim Surani, MD, MPH, FCCP

Recognizing our 2022 Distinguished CHEST Educators

CHEST is pleased to recognize the 2022 Distinguished CHEST Educators (DCEs). These individuals have shown great commitment, involvement, and leadership in CHEST education programs and activities.

DCE recipients represent the top 4% of CHEST's international faculty and are recognized for their achievements and long-term contributions to the design and delivery of CHEST education. DCEs are selected on a yearly basis, based on the past 3 years of CHEST educational activities. It is a 1-year designation and can be received multiple times.

This year's elite group of 187 recipients include 25 individuals who are receiving the designation for the first time.

Sandra Adams, MD, MS, FCCP
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Abhinav Agrawal, MD, FCCP
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Nancy Collop, MD, Master FCCP
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Neha Dangayach, MD, FCCP
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Zachary DePew, MD, FCCP
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Daniel Dilling, MD, FCCP
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This month in the journal *CHEST*®

Editor's picks

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

Effect of Corticosteroids on Mortality and Clinical Cure in Community-Acquired Pneumonia: A Systematic Review, Meta-analysis, and Meta-regression of Randomized Control Trials.
By Naveed Saleem, MSc, et al.

Evaluation of an In-Home Virtual Pulmonary Rehabilitation Program for Respiratory Patients Delivered in Response to the COVID Pandemic.
By Virginia Huynh, MSc, PT, et al.

Prolonged Prone Position Ventilation Is Associated With Reduced Mortality in Intubated COVID-19 Patients.
By Daniel Okin, MD, PhD, et al.

Ventilatory Parameters in Obstetric Patients With COVID-19 and Impact of Delivery: A Multicenter Prospective Cohort Study.
By Daniela N. Vasquez, MD, et al.

How We Escalate Vasopressor and Corticosteroid Therapy in Patients With Septic Shock.
By Bijan Teja, MD, et al.

Consensus Statements on Deployment-Related Respiratory Disease, Inclusive of Constrictive Bronchiolitis: A Modified Delphi Study.
By Michael J. Falvo, PhD, et al.

Commonly Missed Findings on Chest Radiographs: Causes and Consequences.
By Warren B. Gefter, MD, et al.

Evidence of Advanced Pulmonary Vascular Remodeling in Obstructive Hypertrophic Cardiomyopathy With Pulmonary Hypertension.
By Bradley A. Maron, MD, et al.

Prevalence and Predictors of Sleep-Disordered Breathing in Men Participating in the Multicenter AIDS Cohort Study.
By Naresh M. Punjabi, MD, PhD, et al.

Patient and Clinician Recommendations to Improve Communication and Understanding of Lung Cancer Screening Results.
By Kristina Crothers, MD

Introducing CHEST President-Designate, John Howington, MD, MBA, FCCP

John Howington, MD, MBA, FCCP, is a cardiothoracic surgeon currently serving as Chief of Oncology Services and Chair of Thoracic Surgery at Ascension Saint Thomas Health and a professor at the University of Tennessee Health Sciences Center in Nashville, Tennessee.

Dr. Howington received his undergraduate degree from Tennessee Technological University and medical degree from the University of Tennessee. He completed his general surgery residency at the University of Missouri, Kansas City and thoracic surgery residency at Vanderbilt University Medical Center.

Most recently, he received his Physician Executive MBA from the University of Tennessee.

Dr. Howington has participated and published more than 46 research publications and guidelines, numerous book chapters, and has presented hundreds of lectures internationally.

As a passionate thoracic surgeon, he has lent his knowledge to the extensive CHEST lung cancer guideline portfolio for more than a decade. He offers regular leadership in multidisciplinary and executive forums and has spearheaded a series of quality improvement initiatives at Ascension. He has served in a variety of leadership roles with CHEST and with other national thoracic surgery societies.

Dr. Howington

Dr. Howington began his CHEST leadership journey with the Networks, as a member of the Interventional Chest Medicine Steering Committee and then as the Thoracic Oncology Network Chair (2008-2010).

Other leadership positions include serving as the President of the CHEST Foundation (2014-2016), member of the Scientific Program Committee and Membership Committee, and, recently, as the Chair of the Finance Committee from 2018-2021.

Since 2017, he has served on the Board of Regents as a Member at Large. Dr. Howington will serve as the 87th CHEST President in 2025. ■

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M. Patricia Rivera, MD, FCCP
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Obesity impacts peripheral airway reactivity

BY HEIDI SPLETE
Mdedge News

Peripheral airway response to methacholine was similar among obese adults with and without asthma, although forced expiratory volume was lower for those with asthma, based on data from 53 individuals.

Obesity remains a risk factor for asthma, and obese individuals with asthma tend to have worse control and more severe disease, wrote Anne E. Dixon, BM, BCh, of the University of Vermont, Burlington, and colleagues.

Previous studies have shown that airway reactivity can occur in obese individuals without airway inflammation, but studies characterizing obese asthma based on lung function are lacking, they said. "Combining spirometry and oscillometry might reveal abnormalities in lung mechanics particularly pertinent to people with obesity and asthma."

In a cross-sectional study published in the journal *Chest* (doi.org/10.1016/j.chest.2022.12.030), the researchers reviewed data from 31 obese adults with asthma and 22 obese adults without asthma. The participants were aged 18 years and older, with forced expiratory volume (FEV_1) of at least 60% of predicted. All had class III obesity, with an average BMI of 47.2 kg/m^2 for those with asthma and 46.7 kg/m^2 for nonasthma controls. Demographic characteristics were similar between the groups.

Airway reactivity was defined as a 20% decrease in FEV_1 and/or a 50% change in resistance or reactance at 5 Hz (R5 and X5), at a concentration of 16 mg/mL or less of methacholine. Patients were assessed using spirometry and oscillometry.

Most obese individuals with and without asthma showed significant changes in peripheral airway resistance. For those with asthma, the resistance at 5 Hz, measured by oscillometry, increased by 52% in response to the PC20 methacholine challenge, with an area under the reactance curve (AX) of 361%. For controls without asthma, the resistance at 5 Hz increased by 45%, with an AX of 268% in response to 16 mg/mL of methacholine.

This finding suggests that obesity predisposes individuals to peripheral airway reactivity regardless of asthma status, the researchers wrote.

They also identified two distinct groups of asthma patients categorized by respiratory system impedance based on more concordant vs. discordant bronchoconstriction in the central and peripheral airways. The baseline AX for these two groups was 11.8 and 46.7, respectively, with interquartile ranges of 9.9-23.4 and 23.2-53.7, respectively.

The discordant group included only women, and these patients reported significantly more gastroesophageal reflux, increased chest tightness, and more wheezing and asthma exacerbations than the concordant group, which may be related to air trapping, shown on previous studies of obese individuals with asthma.

The findings were limited by several factors, including the measurement of airway impedance only at the peak methacholine dose and the measurement of oscillometry after spirometry, the researchers noted. Other limitations included the relatively small study population at a single center, and the focus on obese individuals only. More research is needed in larger and more diverse patient populations, but the results support the characterization of a subgroup of obese asthma patients with significant peripheral airway dysfunction, the researchers wrote.

"Oscillometry testing can reveal a physiologic phenotype of asthma in obesity that may be related to worse symptoms and more severe disease, and also reveal subclinical abnormalities in people with obesity, but without clinically diagnosed lung disease," they concluded.

The study was supported in by the National Institutes of Health. The researchers reported no conflicts. ■

Muscle weakness predicts poor outcomes

BY HEIDI SPLETE
MDedge News

Lower muscle mass was significantly associated with more airway obstruction and reduced functional exercise capacity in adults with asthma, based on data from 114 individuals.

Previous studies have shown reduced muscle mass in asthma patients, but the impact on clinical and functional outcomes has not been well studied, wrote Edith Visser, MSc, of Medical Centre Leeuwarden (the Netherlands) and colleagues.

"Many asthma patients, especially those with severe disease, report exercise intolerance and limitations in daily activities, severely affecting their quality of life," they said. Research into the clinical consequences of low muscle mass and low muscle strength for patients with asthma and the role of inflammation could make muscle function a potential treatment target for those with asthma, they said.

In a study published in the Journal of Allergy and Clinical Immunology: In Practice (2023 Jan 20. doi: 10.1016/j.jaip.2022.12.043), the researchers recruited 114 consecutive adults aged 18 years and older with a diagnosis of moderate to severe asthma who were seen at a single center between Jun. 2019 and Oct. 2022. The mean age of the patients was 51.9 years, 36% were men, 70% were overweight or obese, and 34 were diagnosed with severe asthma.

Participants underwent clinical, functional, and laboratory assessments at one or two visits within a 2-week period. Assessment tools included the Asthma Quality of Life Questionnaire (AQLQ), the Asthma Control Questionnaire (ACQ-6), a questionnaire on health care use (HCU), and the 'short questionnaire to assess health-enhancing physical activity' (SQUASH).

Functional activity was based on the 6-minute walking distance (6MWD), and lung function tests included spirometry and fractional inhaled nitric oxide (FeNO). Muscle mass was based on fat-free mass index (FFMI) and urinary creatinine excretion rate (CER). Muscle strength was measured using handgrip strength (HGS).

The researchers examined levels of muscle mass and strength and their relation to functional and clinical outcomes.

Overall, the mean measures of muscle mass and strength were higher in males, who had average FFMI, CER, and HGS measures of 20.1 kg/m^2, 15.3 mmol/day, and 48.8 kg, respectively. These measures in women were 17.3 kg/m^2, 10.8 mmol/day, and 29.3 kg, respectively.

After adjusting for confounding factors, patients in the lowest tertile for muscle mass based on FFMI had significantly more severe asthma based on postbronchodilator forced expiratory volume in 1 second and FEV_1/forced vital capacity, as well as lower functional exercise capacity based on the 6MWD compared to those in the highest tertile. A similar association appeared between CER and FEV_1, but not FEV_1/FVC.

However, no significant associations appeared between the muscle mass measures of FFMI or CER and scores on the ACQ, AQLQ, emergency department visits, or asthma exacerbations, according to the researchers.

No relationship appeared between muscle strength and functional outcomes. However, patients in the lowest tertile of HGS had worse asthma control, worse quality of life, and a higher probability of at least one visit to the emergency department compared to patients in the highest HGS tertile.

Higher leukocyte levels were significantly associated with lower muscle mass after adjusting for age, sex, weight, and physical activity, but no other inflammatory markers were significantly associated with FFMI.

The association between lower muscle strength and poorer asthma control, lower quality of life, and greater odds of emergency department visits reflect findings from previous studies, the researchers said. The mechanisms behind the loss of muscle strength in asthma remain unclear, but physical inactivity and daily oral corticosteroid use may play a role, they added.

The study findings were limited by the cross-sectional design and the possibility that muscle weakness may instead stem from reduced physical activity associated with poor lung function and asthma control, the researchers noted.

Other limitations included the potential overestimation of FFMI and the lack of statistical power to show a relationship between FFMI and emergency department visits and asthma exacerbations, they said.

However, the current study is the first known to explore the relationship between lower muscle mass and strength and a range of both functional and clinical outcomes in patients with moderate to severe asthma, they said.

"Our findings encourage longitudinal studies into muscle function as a potential target for treatment to improve asthma outcomes," they concluded.

The study was supported by unrestricted grants from Medical Centre Leeuwarden research fund. Ms. Visser had no financial conflicts to disclose. ■

Six asthma subtypes may promote personalized therapy

BY HEIDI SPLETE
MDedge News

Six subtypes of asthma that may facilitate personalized treatment were identified and confirmed in a large database review of approximately 50,000 patients, according to a recent study.

Previous studies of asthma subtypes involved age of disease onset, the presence of allergies, and level of eosinophilic inflammation, and have been limited by factors including small sample size and lack of formal validation, Elsie M.F. Horne, MD, of the Asthma UK Centre for Applied Research, Edinburgh, and colleagues wrote.

In a study published in the International Journal of Medical Informatics (2022 Dec 7. doi: 10.1016/j.ijmedinf.2022.104942), the researchers used data from two databases in the United Kingdom: the Optimum Patient Care Research Database (OPCRD) and the Secure Anonymised Information Linkage Database (SAIL). Each dataset included 50,000 randomly selected nonoverlapping adult asthma patients. The researchers identified 45 categorical features from primary care electronic health records. The features included those directly linked to asthma, such as medications; and features indirectly linked to asthma, such as comorbidities.

The subtypes were defined by the clinically applicable features of level of inhaled corticosteroid use, level of health care use, and the presence of comorbidities, using multiple correspondence analysis and k-means cluster analysis.

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The six asthma subtypes were identified in the OPCRD study population as follows: low inhaled corticosteroid use and low health care utilization (30%); low to medium ICS use (36%); low to medium ICS use and comorbidities (12%); varied ICS use and comorbid chronic obstructive pulmonary disease (4%); high ICS use (10%); and very high ICS use (7%).

The researchers replicated the subtypes with 91%-92% accuracy in an internal dataset and 84%-86% accuracy in an external dataset. "These subtypes generalized well at two future time points, and in an additional EHR database from a different U.K. nation (the SAIL Databank)," they wrote in their discussion.

The findings were limited by the retrospective design, the possible inclusion of people without asthma because of the cohort selection criteria, and the possible biases associated with the use of EHRs; however, the results were strengthened by the large dataset and the additional validations, the researchers noted.

"Using these subtypes to summarize asthma populations could help with management and resource planning at the practice level, and could be useful for understanding regional differences in the asthma population," they noted. For example, key clinical implications for individuals in a low health care utilization subtype could include being flagged for barriers to care and misdiagnoses, while those in a high health care utilization subtype could be considered for reassessment of medication and other options.

The study received no outside funding. Dr. Horne had no financial conflicts to disclose. ■

Exacerbation history alone found flawed as risk predictor

BY RICHARD MARK KIRKNER

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FROM THE JOURNAL *CHEST*® ▪ Clinical guidelines recommend use of exacerbation history in choosing therapies to predict the risk for chronic obstructive pulmonary disease exacerbations, but an analysis of data from three different clinical studies has found that exacerbation history alone is not the most accurate risk-prediction tool – and that it may even cause harm in some situations.

"Our results present a cautionary tale for the potential risk of harm to patients when naively applying risk-stratification algorithms across different clinical settings," lead author Joseph Khoa Ho, PharmD, at the University of British Columbia, Vancouver, told this news organization.

"We show that risk-prediction models have better accuracy than exacerbation history alone for predicting the future risk of COPD exacerbations," he said. "However, the prediction models required re-evaluation and setting-specific recalibration in order to yield higher clinical utility."

The study, known as IMPACT, analyzed three trials that enrolled 4,107 patients at varying levels of moderate or severe exacerbation risks: the placebo arm of the Study to Understand Mortality and Morbidity in COPD (SUMMIT; N = 2,421); the Long-term Oxygen Treatment Trial (LOTT; N = 595); and the placebo arm of the Towards a Revolution in COPD Health trial (TORCH; N = 1,091). The exacerbation risks were low, medium, and high in the three respective trials.

The study, published online in the journal *CHEST* (2022 Dec 8. doi: 10.1016/j.chest.2022.11.041), compared the performance of three risk-stratification algorithms: exacerbation history; the model that Loes C.M. Bertens, PhD, and colleagues in the Netherlands developed in 2013; and the latest version of the Acute COPD Exacerbation Prediction Tool, known as ACCEPT.

Results of the analysis

The study used area under the curve (AUC), a method of evaluating effectiveness or efficiency, to compare performance of the prediction algorithms. ACCEPT outperformed exacerbation history and the Bertens algorithm in all the LOTT (medium risk) and TORCH (high risk) samples, both of which were statistically significant. In SUMMIT (low risk), Bertens and ACCEPT outperformed exacerbation history, which was statistically significant.

The AUC for exacerbation history alone in predicting future exacerbations in SUMMIT, LOTT, and TORCH was 0.59 (95% confidence interval, 0.57-0.61), 0.63 (95% CI, 0.59-0.67), and 0.65 (95% CI, 0.63-0.68), respectively. Bertens had a higher AUC, compared with exacerbation history alone in SUMMIT (increase of 0.10, $P < .001$), and TORCH (increase of 0.05, $P < .001$), but not in LOTT (increase of 0.01, $P = .84$).

ACCEPT had higher AUC, compared with exacerbation history alone in all study samples, by 0.08 ($P < .001$), 0.07 ($P = .001$), and 0.10 ($P < .001$), respectively. Compared with Bertens, ACCEPT had higher AUC by 0.06 ($P = .001$) in LOTT and 0.05 ($P < .001$) in TORCH; whereas the AUCs were not different in SUMMIT (change of –0.02, $P = .16$).

Study rationale

Senior author Mohsen Sadatsafavi, MD, PhD, associate professor of pharmaceutical sciences at the University of British Columbia, told this news organization that this study was inspired by a study in cardiology earlier in 2022 that found that the performance of the multitude of risk-prediction tools used to evaluate cardiovascular disease risk can vary widely if they're not calibrated for new patient populations.

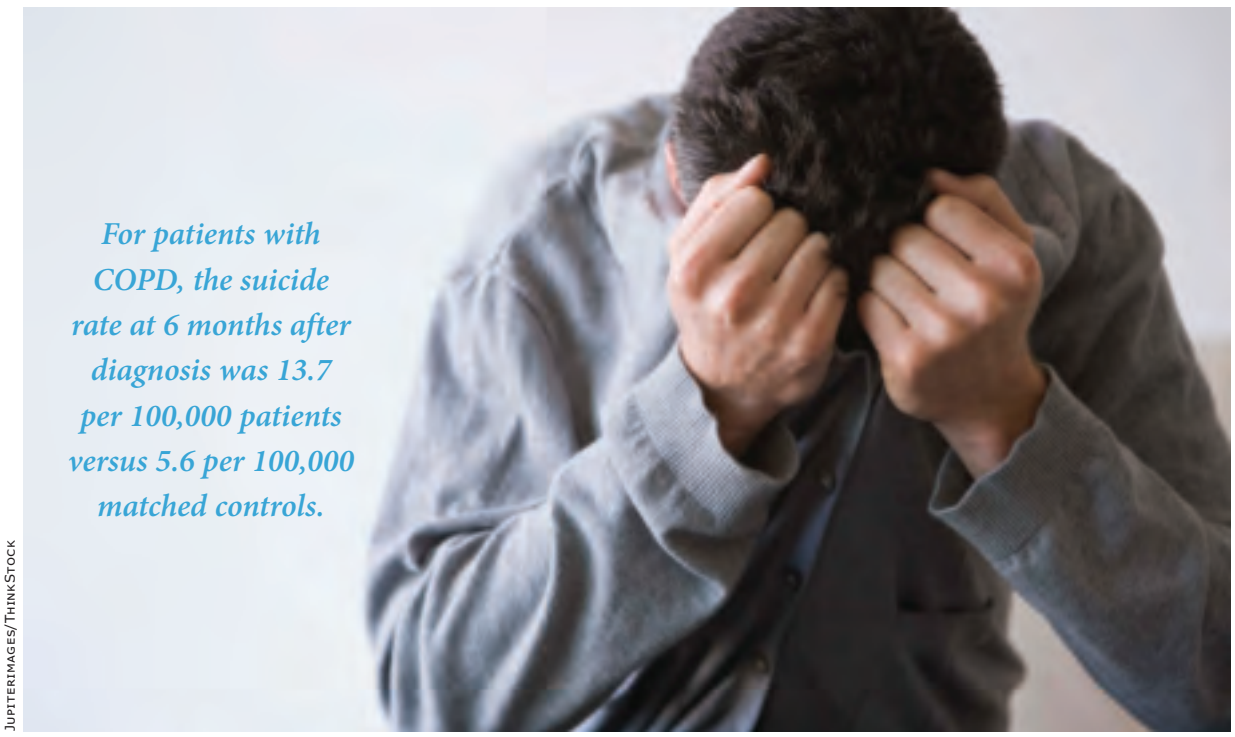
"We show that risk-prediction models have better accuracy than exacerbation history alone for predicting the future risk of COPD exacerbations."

"The main finding was that exacerbation history alone can be harmful even if it is applied at different risk levels," Dr. Sadatsafavi said of the IMPACT study. "No algorithm could be universally applicable, but exacerbation history has a very high chance of being worse than not doing any

COPD *continued on following page*

Severe health diagnoses drive suicide risk

BY HEIDI SPLETE
MDedge News



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Individuals diagnosed with a severe physical health condition were significantly more likely to commit suicide at 6 months and at 1 year later, based on data from more than 47 million individuals in a national database.

Previous smaller studies have shown a link between increased risk for suicide and a range of health conditions including cancer, coronary heart disease, neurologic conditions, diabetes, and osteoporosis, Vahé Nafilyan, PhD, of the Office for National Statistics, Newport, England, and colleagues wrote.

However, large-scale population-level studies of the association between specific diagnoses and suicide are lacking, they said.

In a study published in The Lancet Regional Health–Europe (2022 Dec 16. doi: 10.1016/j.lanepe.2022.100562), the researchers reviewed a dataset that combined the 2011 Census, death registration records, and the Hospital Episode Statistics. The study population included 47,354,696 individuals aged 6 years and older living in England in 2017. The mean age of the study population was 39.6 years, and 52% were female. The researchers examined deaths that occurred between Jan. 1, 2017, and Dec. 31, 2021.

The primary outcome was the time from the date of a diagnosis or first treatment of a severe physical health condition to a death by suicide. The health conditions included in the analysis were low-survival cancers, chronic ischemic heart disease, chronic obstructive pulmonary disease, and degenerative neurological disease.

The diagnosis of any of these conditions significantly increased the risk for suicide compared with controls. The highest risk appeared within 6 months of a diagnosis or first treatment, but the increased risk persisted at 1 year.

The suicide rate among low-survival cancer patients was 16.6 per 100,000 patients at 6 months, compared with 5.7 per 100,000 controls; at 1 year, these rates were 21.6 and 9.5 per 100,000 patients and controls, respectively.

For patients with COPD, the suicide rate at 6 months after diagnosis was 13.7 per 100,000 patients versus 5.6 per 100,000 matched controls; the suicide rates at 1 year were 22.4 per 100,000 patients and 10.6 per 100,000 matched controls.

The suicide rate at 6 months for individuals diagnosed with chronic ischemic heart disease was 11.0 per 100,000 patients and 4.2 per 100,000 matched controls; at 1 year, the suicide rates were 16.1 per 100,000 patients and 8.8 per 100,000 matched controls.

The 1-year suicide rate was especially high among patients with degenerative neurological conditions (114.5 per 100,000 patients); however, the estimate was considered imprecise because of the rarity of these diseases and subsequent low number of suicides, the researchers noted.

The results support data from previous studies showing links between increased risk of suicide and severe physical conditions, the researchers wrote. Patterns of suicide were similar between men and women and after adjusting for sociodemographic factors.

The findings were limited by the inability to fully control for a history of depression or self-harm, and by the imprecise estimates given the rare occurrence of suicide overall, the researchers noted. Other limitations included the late registration of deaths from external causes and the focus being only on suicides that occurred in England and Wales, meaning that individuals who traveled abroad for assisted suicide were not captured in the dataset.

"Further research is needed to understand the mechanisms driving the elevated risk of suicide and help provide the best support to these patients," the researchers concluded.

However, the current results enhance the literature with a large, population-based review of the elevated suicide risk among individuals newly diagnosed with severe health conditions, and reflect the need for better support for these patients to help with coping, they said.

The study was funded by the Office for National Statistics. The researchers reported no relevant financial relationships. ■

COPD *continued from previous page*

risk stratification at all and simply giving medication to all patients."

Exacerbation history was considered harmful because it generated a lower net benefit than the either Bertens or ACCEPT, the IMPACT study found.

The benefit of the two risk-prediction tools is that they can be recalibrated, Dr. Sadatsafavi said.

"You don't have that luxury with exacerbation history, because it's just a fixed positive or negative history," he added.

"We need to be quite cognizant of the difference in lung attacks in different populations and the fact that exacerbation history has very different performance in different groups and might be harmful when applied in certain populations. We suggest the use of the risk-stratification tools as a better proper statistical model."


Dr. Farmer

"As the authors point out, current guidelines for COPD management recommend preventive exacerbation therapy considering the patient's exacerbation history," Mary Jo S. Farmer, MD, PhD, FCCP, assistant professor at the University of Massachusetts Chan Medical School-Baystate, Worcester, said via email. "However, this strategy has demonstrated harm in some situations."

She noted that the multivariable prediction models were more accurate than exacerbation history alone for predicting 12-month risk of moderate/severe COPD exacerbations but that no algorithm was superior in clinical utility across all samples.

"The authors conclude that the highest accuracy of a risk prediction model can be achieved when the model is recalibrated based on the baseline exacerbation risk of the study population in question," Dr. Farmer added.

The study received funding from the Canadian Institutes of Health Research. Dr. Ho, Dr. Sadatsafavi, and Dr. Farmer all reported no relevant conflicts.

Dr. Farmer is a member of the *CHEST Physician* editorial advisory board. ■

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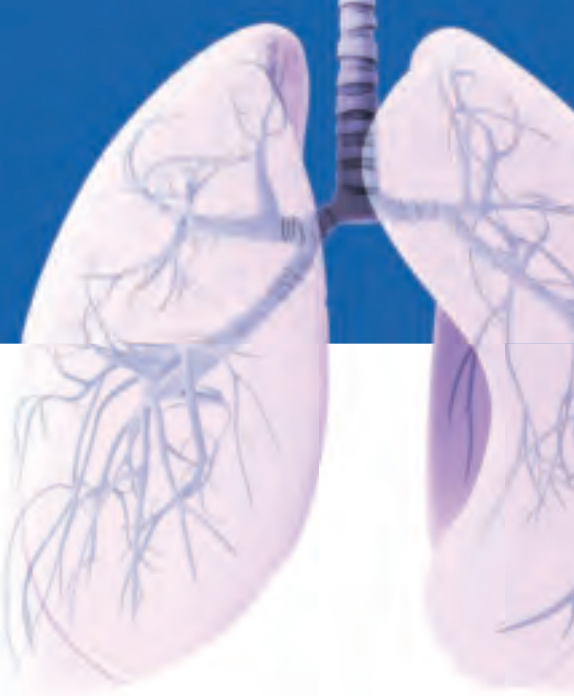
Do you recognize the signs of ILDs?



In a study* of individuals with interstitial lung disease (ILD), 41% of patients first had at least one alternate diagnosis, most commonly cardiac or obstructive lung disease. Ubiquitous symptoms make ILDs difficult to diagnose.

- Patients may be asymptomatic in early stages.
- Symptoms mirror other common conditions.
- ILDs are relatively rare.

CLASSIC SYMPTOM:

Have you heard this sound?

Crackles on auscultation is a tell-tale sign of ILDs. Listen at the bottom of the lungs to locate the sound where crackles are most commonly heard. **Learn how to identify the sound by scanning the QR code.**

Scan to Listen

Connect to the Toolkit

TAKE THE NEXT STEPS

Access our FREE ILD Clinician Toolkit for:

- Resources on identifying ILDs more quickly
- Steps to take when a patient displays signs of ILD
- ILD-specific patient questionnaire to use in practice
- Video and e-learning tools to advance your knowledge

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*Hoyer N, Prior TS, Bendstrup E, et al. Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. *Respir Res.* 2019;20(1):103.