AN OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

CHEST Physician®

VOL. 21 | NO. 2 | SUMMER 2026

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The evolution of interventional pulmonology

Practicing medicine at the intersection of groundbreaking technology and complex thoracic care

BY KRITHIKA SUBRAMANIAN, PHD

It is prime time for interventional pulmonology (IP), a relatively young subspecialty formally described about 25 years ago. An expanding arsenal of novel bronchoscopy innovations and advanced imaging, along with minimally invasive approaches for managing pleural disease and standardized training, have enabled this maturation.

"IP has evolved significantly from rigid bronchoscopes and cryoprobes to endobronchial ultrasound [EBUS] and contemporary advanced modalities," said Yaron Gesthalter, MD, Associate Professor of Medicine at the University of California, San Francisco. "With recent innovations, the two major domains in IP—diagnostic and therapeutic—can now often be combined in one procedure or visit."

While rigid bronchoscopes have been available since the 1800s, the field was propelled forward by the introduction of the dedicated silicone airway stent in the 1990s. And today, IP is in high demand.

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Brinsupri®
(brensocatib) tablets, 10 mg·25 mg

THE FIRST FDA-APPROVED TREATMENT INDICATED FOR

NON-CYSTIC FIBROSIS BRONCHIECTASIS: PROVEN TO REDUCE EXACERBATIONS

Primary endpoint: In a 52-week study, BRINSUPRI reduced the annualized rate of pulmonary exacerbations vs placebo (10 mg: 1.02 [rate ratio=0.79; 95% CI: 0.68-0.92]; 25 mg: 1.04 [rate ratio=0.81; 95% CI: 0.69-0.94]; placebo: 1.29)[1]

BRINSUPRI is one pill, once a day[1]

BRINSUPRI targets a key driver of inflammation in bronchiectasis[1,2]

INDICATION

BRINSUPRI is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Dermatologic Adverse Reactions
Treatment with BRINSUPRI is associated with an increase in dermatologic adverse reactions, including rash, dry skin, and hyperkeratosis. Monitor patients for development of new rashes or skin conditions and refer patients to a dermatologist for evaluation of new dermatologic findings.

Gingival and Periodontal Adverse Reactions
Treatment with BRINSUPRI is associated with an increase in gingival and periodontal adverse reactions. Refer patients to dental care services for regular dental checkups while taking BRINSUPRI. Advise patients to perform routine dental hygiene.

Live Attenuated Vaccines
It is unknown whether administration of live attenuated vaccines during BRINSUPRI treatment will affect the safety or effectiveness of these vaccines. The use of live attenuated vaccines should be avoided in patients receiving BRINSUPRI.

ADVERSE REACTIONS

The most common adverse reactions ≥2% in the ASPEN trial included upper respiratory tract infection, headache, rash, dry skin, hyperkeratosis, and hypertension. The safety profile for adult patients with NCFB in WILLOW was generally similar to ASPEN, except for a higher incidence of gingival and periodontal adverse reactions.

Less Common Adverse Reactions

Liver Function Test Elevations
In ASPEN, there was an increase from baseline in average ALT, AST, and alkaline phosphatase levels at all time points from Week 4 through Week 56 in both BRINSUPRI 10 mg and 25 mg arms compared to placebo. The incidence of ALT >3X upper limit of normal (ULN) was 0%, 1.2%, and 0.9%; the incidence of AST >3X ULN was 0.2%, 0.3%, and 0.5%; and the incidence of alkaline phosphatase >1.5X ULN was 2.5%, 4.1%, and 4.0% in patients treated with placebo and BRINSUPRI 10 mg and 25 mg, respectively.

PRIMARY ENDPOINT

Proven to reduce the risk of bronchiectasis exacerbations[1,3,a]

BRINSUPRI 10 mg

21.1%

reduction in exacerbation risk over 52 weeks

Rate ratio vs placebo (95% CI): 0.79 (0.68-0.92); *P*=0.004.[b]

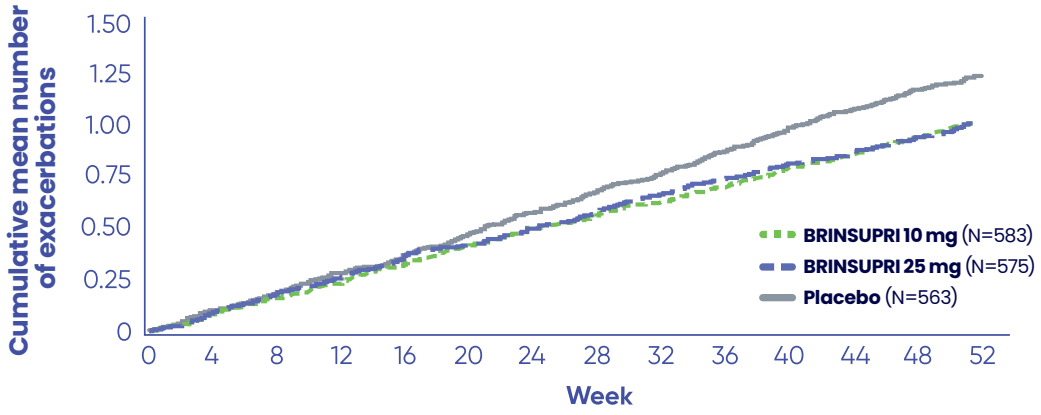
BRINSUPRI 25 mg

19.4%

reduction in exacerbation risk over 52 weeks

Rate ratio vs placebo (95% CI): 0.81 (0.69-0.94); *P*=0.005.[b]

BRINSUPRI demonstrated a significant reduction in exacerbation risk over 52 weeks



Annualized exacerbation rate: BRINSUPRI 10 mg: 1.02, BRINSUPRI 25 mg: 1.04, placebo: 1.29.

Pulmonary exacerbations were defined as a worsening of ≥3 major symptoms over 48 hours resulting in a healthcare provider's decision to prescribe systemic antibiotics. Symptoms included increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness and/or decreased exercise tolerance, fatigue and/or malaise, and hemoptysis.[1]

Study design

The ASPEN study was an international, multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 clinical trial. Patients were 12 to 85 years of age (41 adolescents and 1680 adults) and received 1 of 2 doses of BRINSUPRI (10 mg: n=583; 25 mg: n=575) or placebo (n=563), administered orally once daily for 52 weeks. Patients in all arms were permitted to continue using their existing concomitant therapy.[1,3,4]

[a]Annualized rate.[1]
[b]*P* value was adjusted for multiplicity.[3]
CI=confidence interval.

Explore more efficacy and safety data at BRINSUPRIhcp.com

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

Less Common Adverse Reactions (cont'd)

Skin Cancers

In ASPEN, the incidence of skin cancers among patients treated with BRINSUPRI 10 mg and 25 mg was 0.5% and 1.9%, respectively, compared to 1.1% in placebo-treated patients.

Alopecia

In ASPEN, the incidence of alopecia among patients treated with BRINSUPRI 10 mg and 25 mg was 1.5% and 1.6% respectively, compared to 0.4% in placebo-treated patients.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no clinical data on the use of BRINSUPRI in pregnant women.

Lactation: There is no information regarding the presence of BRINSUPRI and/or its metabolite(s) in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRINSUPRI and any potential adverse effects on the breastfed child from BRINSUPRI or from the underlying maternal condition.

Pediatric use: The safety and effectiveness of BRINSUPRI for the treatment of NCFB have been established in pediatric patients aged 12 years and older. Common adverse reactions in pediatric patients aged 12 years and older enrolled in ASPEN were consistent with those in adults. The safety and effectiveness of BRINSUPRI have not been established in pediatric patients younger than 12 years of age.

Please see additional Important Safety Information and the Brief Summary on the following pages.

References: 1. BRINSUPRI [package insert]. Bridgewater, NJ: Insmed Incorporated; 2025. **2.** Chalmers JD, et al. *Am J Respir Crit Care Med*. 2017;195(10):1384-1393. **3.** Chalmers JD, et al. *N Engl J Med*. 2025;392(16):1569-1581. **4.** Chalmers JD, et al. *N Engl J Med*. 2025;392(16)(suppl appendix):1-53.

BRINSUPRI® (brensocatib)
BRIEF SUMMARY: For complete safety, please consult the full Prescribing Information.

1 INDICATIONS AND USAGE
BRINSUPRI is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
The recommended dosage of BRINSUPRI is as follows:
• 10 mg orally once daily with or without food
or
• 25 mg orally once daily with or without food

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Dermatologic Adverse Reactions
Treatment with BRINSUPRI is associated with an increase in dermatologic adverse reactions, including rash, dry skin, and hyperkeratosis. Monitor patients for development of new rashes or skin conditions and refer patients to a dermatologist for evaluation of new dermatologic findings.

5.2 Gingival and Periodontal Adverse Reactions
Treatment with BRINSUPRI is associated with an increase in gingival and periodontal adverse reactions. Refer patients to dental care services for regular dental checkups while taking BRINSUPRI. Advise patients to perform routine dental hygiene.

5.3 Live Attenuated Vaccines
The concomitant use of BRINSUPRI and live attenuated vaccines has not been evaluated. It is unknown whether administration of live attenuated vaccines during BRINSUPRI treatment will affect the safety or effectiveness of these vaccines. The use of live attenuated vaccines should be avoided in patients receiving BRINSUPRI.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
The safety data below reflect the safety of BRINSUPRI in adult and pediatric patients aged 12 years and older with NCFB. A total of 1721 patients with NCFB were randomized in a double-blind, placebo-controlled clinical trial of 52 weeks' duration (ASPEN). The safety of BRINSUPRI was based on data from 1719 adult and pediatric patients aged 12 years and older who received at least one dose of BRINSUPRI or placebo. A total of 1156 patients received at least one dose of BRINSUPRI 10 mg or 25 mg orally once daily.

Table 1 shows the adverse reactions occurring at an incidence of ≥2% and higher in BRINSUPRI-treated patients compared to placebo in the safety population from ASPEN.

Table 1 Adverse Reactions with BRINSUPRI with an Incidence of ≥2% and More Common than Placebo in ASPEN

Adverse Reaction	Placebo (N=563) n (%)	BRINSUPRI 10 mg QD (N=582) n (%)	BRINSUPRI 25 mg QD (N=574) n (%)
Upper respiratory tract infection[1]	141 (25)	157 (27)	169 (29)
Headache	39 (7)	39 (7)	49 (9)
Rash[2]	22 (4)	25 (4)	35 (6)
Dry skin[3]	8 (1)	17 (3)	25 (4)
Hyperkeratosis[4]	5 (1)	8 (1)	16 (3)
Hypertension	17 (3)	28 (5)	13 (2)

[1] Upper respiratory tract infection includes coronavirus infection, COVID-19, influenza, upper respiratory tract infection, viral infection, and viral upper respiratory tract infection.
[2] Rash includes rash, rash maculo-papular, rash pruritic, rash erythematous, dermatitis, and erythema.
[3] Dry skin includes dry skin, chapped lips, cheilitis, lip dry, skin exfoliation, skin fissures, xeroderma, and xerosis.
[4] Hyperkeratosis includes hyperkeratosis, palmoplantar keratoderma, and skin hypertrophy.

Adverse Reactions in WILLOW
A total of 256 adult patients with NCFB were randomized in the 24-week, double-blind, placebo-controlled clinical trial (WILLOW). Of those randomized, 255 adult patients received BRINSUPRI 10 mg, BRINSUPRI 25 mg, or placebo, which consisted of 170 adults treated with at least one dose of BRINSUPRI 10 mg or 25 mg orally once daily. The safety profile for adult patients with NCFB in WILLOW was generally similar to ASPEN, with the exception of a higher incidence of gingival and periodontal adverse reactions. The incidence of gingival and periodontal adverse reactions in WILLOW among patients treated with BRINSUPRI 10 mg and 25 mg were 9.9% and 10.1%, respectively, compared to 2.4% in placebo-treated patients.

Less Common Adverse Reactions

Liver Function Test Elevations
In ASPEN, there was an increase from baseline in average ALT, AST, and alkaline phosphatase levels at all time points from Week 4 through Week 56 in both BRINSUPRI 10 mg and 25 mg arms compared to placebo. The incidence of ALT >3X upper limit of normal (ULN) was 0%, 1.2%, and 0.9%, in patients treated with placebo and BRINSUPRI 10 mg and 25 mg, respectively. The incidence of AST >3X ULN was 0.2%, 0.3%, and 0.5% in patients treated with placebo and BRINSUPRI 10 mg and 25 mg, respectively. The incidence of alkaline phosphatase >1.5X ULN was 2.5%, 4.1%, and 4.0% in patients treated with placebo and BRINSUPRI 10 mg and 25 mg, respectively.

Skin Cancers
In ASPEN, the incidence of skin cancers among patients treated with BRINSUPRI 10 mg and 25 mg was 0.5% and 1.9%, respectively, compared to 1.1% in placebo-treated patients.

Alopecia
In ASPEN, the incidence of alopecia among patients treated with BRINSUPRI 10 mg and 25 mg was 1.5% and 1.6%, respectively, compared to 0.4% in placebo-treated patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on BRINSUPRI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

8.2 Lactation

Risk Summary
There are no data on the presence of brensocatib and/or its metabolite(s) in human milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRINSUPRI and any potential adverse effects on the breastfed child from BRINSUPRI or from the underlying maternal condition.

8.4 Pediatric Use
The safety and effectiveness of BRINSUPRI for the treatment of NCFB have been established in pediatric patients aged 12 years and older. Use of BRINSUPRI for this indication is supported by evidence from an adequate and well-controlled trial (ASPEN), which enrolled 41 pediatric patients aged 12 years and older, and additional pharmacokinetic data in pediatric patients aged 12 to 17 years.

Common adverse reactions in pediatric patients aged 12 years and older enrolled in ASPEN were consistent with those in adults.

The safety and effectiveness of BRINSUPRI have not been established in pediatric patients younger than 12 years of age.

8.5 Geriatric Use
There were 988 patients 65 years of age and older in the clinical studies for non-cystic fibrosis bronchiectasis. Of the total number of BRINSUPRI-treated patients in these studies, 676 (51%) were 65 years of age and older while 201 (15%) were 75 years of age and older. No observed differences in safety and/or effectiveness in geriatric patients compared to younger adult patients.

10 OVERDOSAGE
Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for overdose management recommendations.

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

Dermatologic Adverse Reactions
Inform patients that BRINSUPRI is associated with a risk of adverse skin reactions including rash, dry skin, and hyperkeratosis. Advise patients to monitor their skin and report any new rash or skin condition.

Gingival and Periodontal Adverse Reactions
Inform patients that BRINSUPRI is associated with a risk of gingival and periodontal adverse reactions. Advise patients to have regular dental checkups while taking BRINSUPRI. Advise patients to perform routine dental hygiene.

Live Attenuated Vaccines
Instruct patients to inform the healthcare provider that they are taking BRINSUPRI prior to a potential vaccination.

CHEST Physician®

American College of Chest Physicians (CHEST)

chestphysician@chestnet.org

CHEST Physician, an official publication of the American College of Chest Physicians, provides cutting-edge reports on timely news, research, and clinical advances in the world of chest medicine. Regular columns feature the areas of pulmonary, critical care, and sleep medicine, as well as association news and updates from CHEST leadership.

CHEST Physician (ISSN 1558-6200) is published quarterly for the American College of Chest Physicians by TriStar Event Media, LLC.

Subscription price is $251.00 per year.

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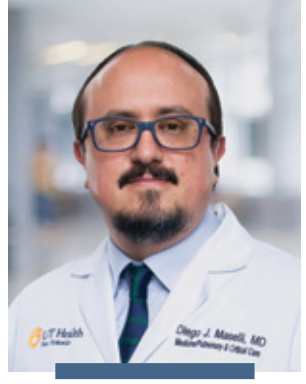
From the Editor



Welcome to another exciting issue of *CHEST Physician*! In this issue, we highlight a spectrum of topics that reflect both the complexity and rapid evolution of pulmonary, critical care, and sleep medicine—from the nuanced role of antibiotics and biomarkers in postcardiac arrest care to updated guidance on the management of acute pulmonary embolism and OSA in hospitalized patients. We also explore emerging technologies in interventional pulmonology and examine the growing clinical experience with DPP-1 inhibitors in bronchiectasis.

Beyond this issue, notable work continues to shape our understanding of airway disease. Can we reverse airway remodeling? The recent REMOMEPO study, published in April in the journal *CHEST®*, suggests that anti-IL-5 therapy in severe eosinophilic asthma may extend beyond controlling inflammation to attenuate key features of airway remodeling.[1] These findings build on the results from the MESILICO study, the effects of mucus plugging and lung function by inhibition of TSLP and IL-4Rα, and reinforce the concept that targeted biologic therapies may influence the structural components of disease.[2] Although these observations require confirmation in larger cohorts and longer studies, they point toward an evolving paradigm in which biologic therapy moves closer to disease modification rather than symptom control alone. Ongoing studies in asthma, as well as in other airway diseases such as COPD and bronchiectasis, will further define whether aspects of airway remodeling are reversible, or at least partially reversible, when inflammation is effectively controlled. This paradigm has the potential to slow disease progression and improve symptom control. Additionally, emerging targets such as IL-33 have now shown promise in COPD and highlight the expanding range of pathways that may be therapeutically relevant in airway disease.

In just a few months, we will gather in Phoenix for CHEST 2026. With an expanded program and more learning opportunities than ever before, the meeting offers a valuable opportunity to engage with the latest advances in pulmonary, critical care, and sleep medicine. I am especially looking forward to the interactive sessions, hands-on simulations, and the opportunity to connect with colleagues from across the field. I encourage you to register and join us in Phoenix! (Visit **chestnet.org/annual-meeting** for all the details.)

Warm regards,

Diego J. Maselli, MD, FCCP
Editor in Chief, *CHEST Physician*

1. Taillé C, Hamidi F, Heddebaut N, et al. Impact of mepolizumab on airway remodeling and inflammation in severe eosinophilic asthma. *Chest*. 2026;169(4):890-901. doi:10.1016/j.chest.2025.10.047
2. Domvri K, Tsiouprou I, Bakakos P, et al. Effect of mepolizumab in airway remodeling in patients with late-onset severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol*. 2025;155(2):425-435. doi:10.1016/j.jaci.2024.10.024

In memoriam

CHEST has been informed of the following deaths of CHEST members. We remember our colleagues and extend our sincere condolences.

Siraj Ahmed, MD, MBBS
Allan R. Glanville, MD, MBBS
Bimalin Lahiri, MD, MBBS
A. David Russakoff, MD, FCCP

Biologic therapy for severe asthma

Time for precision, access, and accountability

BY RAJU REDDY, MD, FCCP; IOANA AGACHE, MD, PHD; FREDERIC F. LITTLE, MD; MAHESH PADUKUDRU ANAND, MBBS, DTCD, DNB; NEHA SOLANKI, MD; AMBER J. OBERLE, MD

ASTHMA EPIDEMIOLOGY AND ECONOMIC IMPACT

Approximately 260 million individuals globally have asthma, with an age-standardized prevalence rate of 3,340 per 100,000 people. In the United States, asthma affects approximately 20 million adults, 5% to 10% of whom have severe uncontrolled asthma. The economic costs of asthma exceed $50 billion annually in the United States. Approximately 8.8 per 100 people with asthma per year have an emergency department visit, resulting in 450,000 hospitalizations in the United States. It is estimated that 15% to 50% of asthma-related hospitalizations are preventable through education, lifestyle management, and medications, including biologics.

PATIENT SELECTION FOR BIOLOGICS (WHO, WHEN, HOW)

Biologic therapy is recommended for patients with severe asthma who have uncontrolled symptoms despite optimized comorbidities and adherence to high-dose inhaled corticosteroid plus long-acting β_2-agonist therapy. Candidates predominantly demonstrate a type 2 inflammatory profile, defined by presence of one or more of these findings: blood eosinophil count of ≥ 300 cells/μL, elevated immunoglobulin E, or F_{ENO} of ≥ 25 ppb.

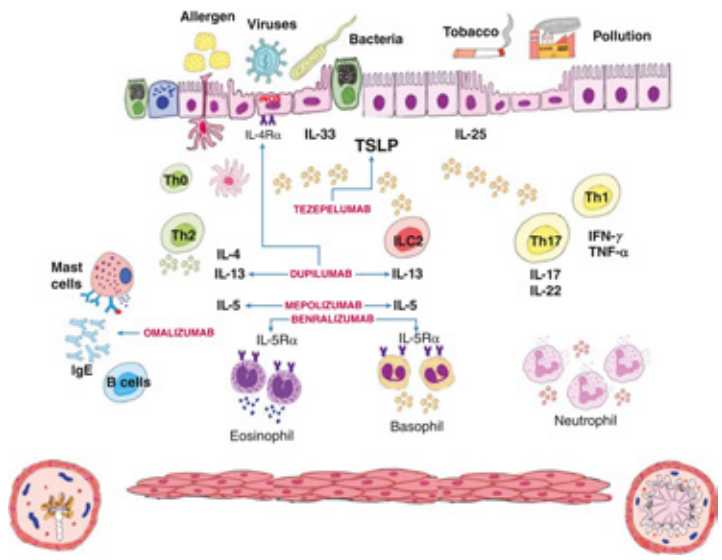
However, there are also treatment options for patients with a non-type 2 inflammatory profile. Recurrent exacerbations (two or more annually) or oral corticosteroid (OCS) dependence strengthen eligibility. Selection should integrate biomarker profile, comorbidities, and exacerbation burden using a structured algorithm, with reassessment at four to six months to confirm clinical response and justify continuation or therapeutic modification.

CHOOSING THE RIGHT BIOLOGIC

A) Asthma with comorbidities

Patients with severe asthma frequently present with comorbid conditions such as chronic rhinosinusitis with nasal polyps, atopic dermatitis, or eosinophilic esophagitis, all of which have a significant effect on achieving asthma control. There is overall agreement that the assessment of comorbidities in addition to biomarkers is essential for tailoring biologic therapies for severe asthma.

FIGURE 1. PATHOPHYSIOLOGY OF ASTHMA, BIOLOGICS, AND THERAPEUTIC TARGETS



Cytokines and receptors involved in the T2 inflammatory pathway and therapeutic targets for the various biologic agents used in the management of severe asthma, as outlined in "Biologic Management in Severe Asthma for Adults: An American College of Chest Physicians Clinical Practice Guideline."

Image adapted from Sardon-Prado O, et al. J Clin Med. 2023;12(18):5846.

Clinical decision-making in patients with comorbidities should incorporate:

1. Analysis of the shared pathogenetic pathways
2. Availability of an approved biologic targeting both conditions
3. Defining response by combining asthma and comorbidity-relevant outcomes

There are no randomized controlled trials in which biologics address both asthma and its comorbidities as a primary outcome. Most of the data collected are from either post hoc analysis or disease registries. Therefore, the current CHEST guideline provides guidance on treating comorbidities in the format of conditional recommendations.[1]

B) Asthma with OCS dependence

Given the well-described adverse effects of OCS, they need to be considered not just for those on daily OCS but also for those prescribed OCS during exacerbations. There is good evidence for reducing OCS burden with dupilumab, specifically for patients who are "steroid-dependent" on daily OCS. Additionally, anti-interleukin-5 (anti-IL-5)/5Rα agents also show

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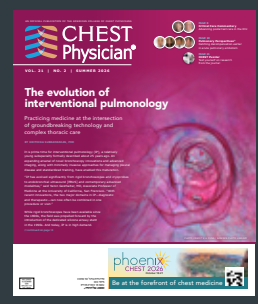
Inside



ON THE COVER
Virtual bronchoscopy view looking down the trachea towards the carina, the point where it divides into the two bronchi to the lungs.

CHEST PUZZLER KEY
Scan the QR code to access the answer key to the crossword puzzle on page 21.

Column

Advancing postarrest care in the ICU

Emerging roles for antibiotics and biomarkers

BY JORDAN E. NOGLE, DO; RYAN C. MAVES, MD, FCCP

Despite significant advances in care, survival to discharge for patients who experience cardiac arrest remains dismal, at 10.5% for out-of-hospital cardiac arrest (OHCA) and 23.5% for in-hospital cardiac arrest (IHCA).[1] Minimizing infectious complications in patients following cardiac arrest in the ICU is crucial to reducing the risks of morbidity and mortality.

Pneumonia is the most common infection in patients postarrest, with attributable mortality rates of between 21% and 45%.[2] Empiric broad-spectrum antibiotic administration for patients postarrest is not well-supported by the current literature, however, and may contribute to antibiotic resistance.

The use of prophylactic antibiotics in patients who are mechanically ventilated has a mixed history, with interventions such as inhaled antibiotics and selective digestive decontamination failing to reduce mortality on a consistent basis. Given the particularly high risk of pneumonia following IHCA and OHCA, there remains an interest in finding a role for prevention in this vulnerable patient population.

ANTIBIOTICS IN POSTARREST CARE

The 2019 Antibiotherapy During Therapeutic Hypothermia to Prevent Infectious Complications (ANTHARTIC) trial randomized patients following cardiac arrest with shockable rhythms to a two-day course of amoxicillin-clavulanate vs placebo, leading to a reduction in rates of ventilator-associated pneumonia in the intervention arm. However, ANTHARTIC failed to show a reduction in overall mortality or ICU length of stay.[3]

More recently, the Prevention of Early Ventilation-Acquired Pneumonia in Brain-Injured Patients by a Single Dose of Ceftriaxone (PROPHY-VAP) trial identified a mortality benefit in patients who are neurologically injured who require mechanical ventilation from a single dose of prophylactic ceftriaxone following endotracheal intubation.[4] Independent of the PROPHY-VAP trial but similar in concept, the Ceftriaxone to PRevent pneumOnia and inflammatTion aftEr Cardiac arresT (PROTECT) trial studied prophylactic ceftriaxone following OHCA. PROTECT randomized 52 patients with any underlying initial heart rhythm who had suffered an OHCA to receive 2 grams intravenously every 12 hours for three days vs a matching placebo dose of 0.9% sodium chloride.[2] The primary outcome was to evaluate the development of early-onset pneumonia using a standardized definition. Notable secondary outcomes included late-onset pneumonia (more than four days following intubation), nonpulmonary infections, ICU-free days, ventilator-free days, and mortality at 28 days.

PROTECT failed to show a statistically significant decrease in the rate of early-onset pneumonia. However, there was a significant reduction in the use of open-label antibiotics; the treatment arm also notably had significantly fewer antibiotic resistance genes to common ICU antibiotics identified on surveillance testing when compared with the placebo arm. In-hospital mortality was also lower in the ceftriaxone group (42% vs 73%; RR, 0.58, 95% CI, 0.35-0.96). It is noteworthy that the treatment group had a notably higher rate of bystander CPR (85% vs 62%) and a notably lower average APACHE IV score (71 vs 102), potentially confounding these results.

Given the results of PROPHY-VAP, ANTHARTIC, and PROTECT, we may soon reach a point where it is reasonable to provide a brief duration of prophylactic, relatively narrow-spectrum antibiotics to prevent pneumonia and reduce mortality in patients who are neurologically injured or have recently suffered cardiac arrest. Conceptually, it may be useful to consider this not as empiric therapy but rather as peri-procedural prophylaxis, similar to peri-operative cefazolin before a major surgical procedure. The doses and durations used vary across these studies, although the long half-life of ceftriaxone may lend itself to a single dose for prophylaxis. Further studies will be needed to confirm and refine these findings.

BIOMARKERS IN POSTARREST CARE

Another potentially practice-changing update in postarrest management is the use of neuron-specific enolase (NSE) as an adjunct for neuroprognostication. NSE is an isomer of enolase found in neurons that correlates with the degree of neuronal apoptosis secondary to hypoxic-ischemic cerebral injury. In the current European guidelines on postarrest

care, an NSE level > 60 at 48 to 72 hours postarrest is recommended as a predictor of poor neurologic outcomes.[5] However, the use of NSE is not currently widespread in North America; most neuroprognostication relies on physical examination, neuroimaging, and electroencephalography (EEG).

NSE has shown reasonable predictive value in the postarrest period. In a retrospective study looking at both patients who experienced IHCA and OHCA with an initial GCS of < 8, the combination of malignant EEG findings and an NSE of > 42 was found to be 100% specific in predicting an unfavorable outcome.[5] Even with a benign EEG pattern, an NSE of > 78.2 remained 100% specific for predicting an unfavorable neurologic outcome. Similarly, a prospective observational study published in 2025 including 120 postarrest cases reported that an NSE of > 68 ng/mL at 72 hours postarrest was 82% sensitive and 90% specific for predicting an unfavorable outcome.[6]

While potentially valuable, it remains unclear to what extent NSE could improve our existing practices in patients postarrest. Biomarkers have received a great deal of attention in other areas of critical care such as sepsis diagnosis, but these biomarkers have had variable impacts on actual management. It remains unclear, for example, whether an elevated NSE value in a patient who is persistently comatose with malignant EEG findings would meaningfully alter such a patient's prognosis (or persuade a family to alter goals of care). However, there are few decisions more fraught in the ICU than neuroprognostication, and it could be that every additional piece of data would help.

A NEW FRONTIER

While caring for patients following cardiac arrest in the ICU poses significant challenges, ongoing research continues to improve our understanding and hopefully our management. Prophylactic pneumonia coverage may present a potential mortality benefit without significantly increasing antibiotic resistance within the ICU; and advances in neuron-derived biomarkers, such as NSE, may provide an objective measurement for neuroprognostication.

It is easy to fall into the trap of fatalism when caring for patients postarrest, but the advances in cardiac care over the past several years have nonetheless been meaningful: fever avoidance and temperature management, hemodynamic and respiratory optimization, and—above all else—improvements in CPR and advanced cardiac life support. Prophylactic antibiotics and biomarkers may also have a role to play as we learn more about these most challenging and vulnerable cases. ●

All references are available online at chestphysician.org.

Asthma guideline

// continued from page 7

reductions in daily OCS use. And for patients with significant peripheral eosinophilia (especially despite daily OCS use), the effect may be even more pronounced. Notably, despite improvement in key asthma-related outcomes, some other biologics do not show consistent improvement in cumulative OCS use (eg, tezepelumab).

When deciding which biologic agent to start in patients who do not require daily OCS, the clinician must consider exacerbation frequency and select the biologic agent that is most likely to decrease annual exacerbations based on biomarker assessment. If a patient response is deemed inadequate based on usual criteria after four to six months, change to an alternate agent is indicated.

BIOLOGIC SWITCHING

Despite careful patient selection for clinical trials, a subset of patients continue to demonstrate suboptimal response to initial biologic therapy. Reasons include heterogeneity of inflammatory pathways, overlapping endotypes, or non-type 2 disease. Biologic switching has emerged as a pragmatic strategy in patients who are not responding to treatment. Patients who do not demonstrate the desired response to the first-choice biologic are likely to be eligible for others. Ongoing steroid dependence should prompt the clinician to consider those biologics shown to reduced overall systemic OCS exposure first. Additionally, the use of FeNO can help select the next best potential agent with both anti-IL-4/anti-IL-13 and anti-thymic stromal lymphopoietin, showing a positive response in those with elevated FeNO levels.

Guidelines recommend reassessment after four to six months of therapy using objective outcomes such as exacerbation reduction, steroid requirement, symptom control, and biomarkers. Lack of clinically meaningful improvement should prompt reconsideration of adherence, comorbidities, and potentially switching biologics.

ROLE OF FeNO

Elevated FeNO reflects IL-4/13-mediated stimulation of inducible nitric oxide synthase in airway epithelium and is a useful biomarker in severe asthma. FeNO can guide biologic selection when patients do not respond to anti-IL5/5Rα after four to six months. Higher FeNO levels predict greater reductions in exacerbations with dupilumab, but not with anti-IL-5/IL-5Rα therapy. Tezepelumab also reduces exacerbations in patients with elevated or low FeNO levels, but the effect is more pronounced in those with elevated FeNO levels. Implementation of FeNO testing in clinical practice depends on equipment availability, trained staff, and insurance coverage.

CHALLENGES WITH OBTAINING BIOLOGICS

The challenges to obtain biologics for patients are multifactorial. The need for prior authorizations can pose a major barrier to treatment. In a survey of 259 health care professionals, 71% of the respondents described the burden of prior authorizations as extremely high. Other barriers include patient costs, lack of commercial insurance, and lack of access to a specialist. In a study by Inselman and colleagues, biologic use was higher in those with household incomes of more than $75,000 per year compared with those making less than $40,000 per year: 24.3% vs 9.7%, respectively.[2] Similarly, having commercial insurance and an asthma exacerbation requiring hospitalization in the past 12 months were associated with higher rates of obtaining biologics. Those who do not have commercial insurance are likely to have undertreated asthma.

CALL TO ACTION AND FUTURE DIRECTIONS

Despite these challenges, increased access to appropriate biologics could be achieved in several ways. First, insurers should expedite the prior authorization process, which can take up to two weeks or even longer when denials are issued. In addition, the need for repeated authorization every six to 12 months should be removed, as this often leads to interruptions in therapy. Second, cost reduction is imperative. The Institute for Clinical and Economic Review in 2018 estimated that biologics would need 62% to 80% cost reduction to achieve cost-effectiveness. Therefore, these costs could be shared between governmental agencies, insurance companies, and pharmaceutical companies.

CONCLUSION

Asthma remains widely prevalent in the United States and globally, and it imposes a significant economic burden. The advent of biologic therapy has been shown to improve patient outcomes and could potentially lower economic costs. Choosing the appropriate initial biologic and having the ability to implement timely changes in therapy, if needed, can lead to improved patient-centered outcomes in severe asthma. ●

READ THE FULL GUIDELINE

All references are available online at chestphysician.org.

Column

Catching decompensation earlier in acute pulmonary embolism

The shift toward physiological precision

BY PARTH RALI, MD, FCCP; DEEPIKA POTARAZU, MD; ANIKET S. RALI, MD, FCCP; LISA K. MOORES, MD, FCCP

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The latest guidelines from the American Heart Association (AHA) and the American College of Cardiology focus on the evaluation and management of acute pulmonary embolism (PE) in adults. They come nearly a decade after the previous set of AHA guidelines. The current guidelines are endorsed by nine other societies, including CHEST, which had representatives on the writing panel and peer review group.[1] These guidelines are being published at the dawn of several randomized controlled trials in acute PE, albeit only one (the PEERLESS trial) was published prior to the release of the guidelines.[2] Others, including Hi-PEITHO, STORM-PE, PEITHO-3, and PEERLESS 2, are ongoing or were published afterward.[2-6]

The AHA guidelines focus on diagnosis, risk stratification, and management of acute PE. Unlike the 2021 CHEST guidelines, they do not address deep vein thrombosis (DVT) or the prevention and recurrence of VTE.[7]

A key feature of the AHA guidelines is the panel's proposed new classification of acute PE severity. This classification parallels the Society of Cardiovascular Angiography and Interventions' (SCAI) stages for cardiogenic shock (CS), which in recent years have found wide acceptance. The SCAI system divides CS into stages A through E: A (at risk), B (beginning), C (classic), D (deteriorating), and E (extremis).

Our review focuses primarily on this proposed classification and its ability to risk-stratify patients. The specifics of proposed treatment algorithms will be deferred to a subsequent review.

INTRODUCTION OF NEW PE CLASSIFICATION

The current classification most widely used and endorsed is that proposed by the European Society of Cardiology (ESC), which classifies PE into low, intermediate-low, intermediate-high, and high-risk categories. These categories are based on expected short-term (30-day) mortality. Intermediate-risk PE encompasses a very heterogeneous group, as patients may present anywhere on the spectrum of clinically stable to nearing hemodynamic collapse.

The new AHA classification adopts the SCAI framework, grouping patients into Categories A through E with respiratory modifiers. Unlike prior systems, this model incorporates respiratory decompensation specifically in Categories C through E. Notably, SCAI Stage C represents classic CS, while in this new classification for PE, Category E represents classic obstructive shock. The hope is that this new framework will better define the dynamic spectrum between intermediate and high-risk PE.

Category A includes incidental PE. Categories B1 and B2 include patients with a low clinical severity score (such as the Pulmonary Embolism Severity Index [PESI] or its simplified version [sPESI]) presenting with either subsegmental or nonsubsegmental PE. These patients would have been considered low-risk PE in the ESC classification. Category B highlights that some patients with symptoms may have proximal clots but lack abnormal risk scores or biomarkers, requiring only anticoagulation.

Category C has three subcategories. Patients in Category C1 present with an elevated severity score but normal right ventricular (RV) function and cardiac biomarkers, such as troponin or brain natriuretic peptides (BNP). The presence of either RV dysfunction on imaging or abnormal biomarkers leads to a C2 categorization. Patients in Category C3 have both RV dysfunction and abnormal biomarkers. The inclusion of BNP alongside troponin is a new feature of the updated guidelines, although the ESC guidelines do note that an elevated BNP may provide additional prognostic information. Respiratory modifiers are to be applied in Categories C1 through C3 if oxygen saturation drops below 90%, respiratory rate is high, or supplemental oxygen is required.

Category D introduces a new hemodynamic category of incipient cardiopulmonary failure. Patients in Category D1 experience transient hypotension, while patients in Category D2 have evidence of systemic hypoperfusion (elevated lactate, acute kidney injury, low urine output, or elevated Composite Pulmonary Embolism Shock [CPES] score). The inclusion of transient hypotension as a preshock stage (D1)

ESC 2019 VS AHA 2026 CLASSIFICATION IN ACUTE PE

A Case-Based Comparison

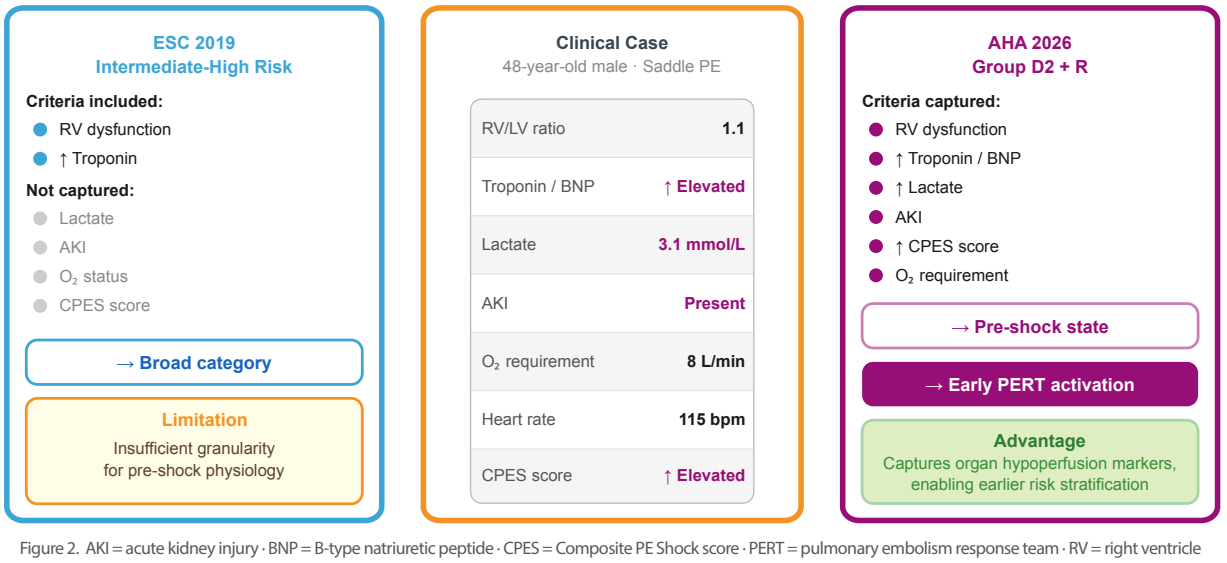


Figure 2. AKI = acute kidney injury · BNP = B-type natriuretic peptide · CPES = Composite PE Shock score · PERT = pulmonary embolism response team · RV = right ventricle

is a new addition. D2 builds on the concept of normotensive shock. In Category D, respiratory modifiers include high oxygen needs (> 6 L/min) or escalation to nonrebreather mask.

Category E represents true obstructive shock. Stage E1 includes those with recurrent or persistent hypotension (classic high-risk PE). Stage E2 represents catastrophic PE, characterized by refractory cardiogenic shock or cardiac arrest due to PE. Category E also includes a respiratory modifier for patients requiring ventilatory support. **Figure 1** illustrates the acute PE clinical categories, emphasizing the continuum of physiologic severity captured by the new classification.

NEW PARAMETERS IN THIS CLASSIFICATION

The 2026 AHA classification incorporates additional risk scores and physiologic markers—including the CPES score, National Early Warning Score 2 (NEWS2), serum lactate, and recognition of normotensive shock—reflecting a shift toward earlier identification of decompensation in acute PE. Recognition of normotensive shock addresses a key limitation of prior classifications by identifying patients with preserved systemic BP but impaired perfusion.

The CPES score was derived from the FlowTriever All-Comer Registry for Patient Safety and Hemodynamics registry to identify normotensive patients with acute PE and low cardiac index.[8] It incorporates markers of RV dysfunction (imaging and biomarkers), ischemia, central clot burden, risk of further embolization (eg, concomitant DVT), and cardiovascular compensation (eg, tachycardia). The score was subsequently validated in an independent cohort of normotensive patients with acute symptomatic PE from the PROTECT study.[9] Alongside the CPES score, the Bova, PESI, and sPESI scores have been validated in hemodynamically stable patients to identify those at higher risk of adverse outcomes; however, no single score demonstrates clear superiority, and clinicians are encouraged to apply judgment when selecting among tools.[1,10-11]

Similarly, NEWS2, a generic early-warning system based on dynamic vital sign assessment, has shown performance comparable to PE-specific scores with the added advantage of enabling serial assessment.[1] The recently published Hi-PEITHO trial underscores the relevance of physiologic risk markers such as NEWS2, demonstrating that ultrasound-facilitated catheter-directed thrombolysis plus anticoagulation reduced the composite outcome vs anticoagulation alone. This was primarily driven by reductions in hemodynamic collapse, with analysis suggesting a key contribution of NEWS2-defined risk.[3] Serum lactate further refines risk assessment, with elevated levels associated with a 4.54-fold increase in all-cause mortality in normotensive PE.[12]

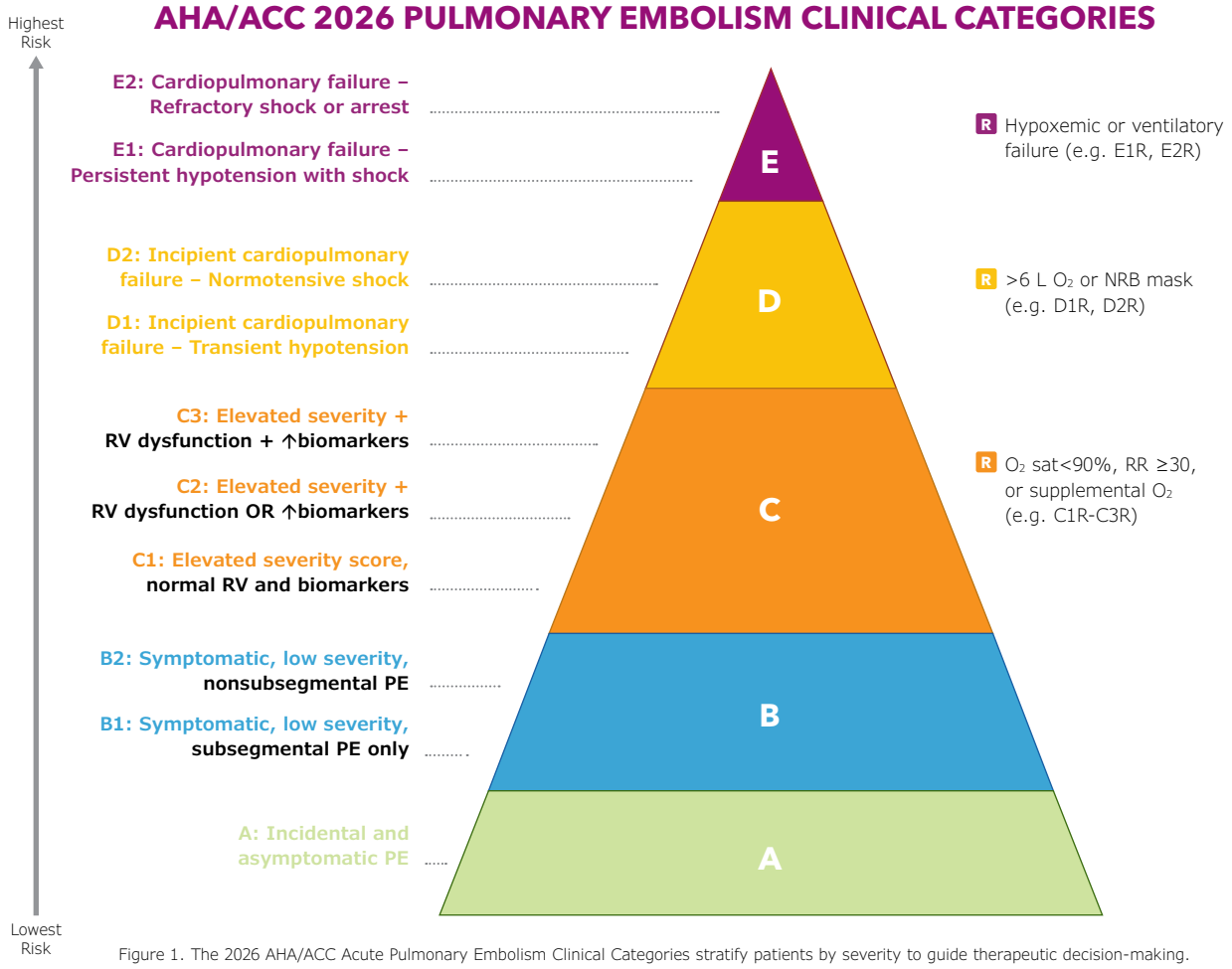


Figure 1. The 2026 AHA/ACC Acute Pulmonary Embolism Clinical Categories stratify patients by severity to guide therapeutic decision-making. The respiratory modifier (R) may be applied to categories C, D, and E when supplemental oxygen or respiratory support is required.[1]

REFLECTIONS AND DIRECTIONS: A BALANCED PERSPECTIVE

The new classification system represents a sophisticated shift toward a more granular understanding of acute PE, moving beyond binary risk models into a spectrum of physiological decompensation. By integrating markers like serum lactate, CPES score, and the recognition of normotensive shock, this framework offers the promise of identifying patients who may benefit from closer monitoring and early interventions to restore perfusion before overt collapse occurs. It elegantly bridges the gap between intermediate and high-risk categories by using a language of shock stages (the A through E framework) already familiar to many pulmonary and cardiovascular clinicians.

Figure 2 demonstrates a representative case that highlights the added granularity of the AHA classification compared with the previous ESC framework. However, a note of caution is warranted. While this system is rooted in published literature regarding prognostic markers, the classification itself remains largely expert opinion-based. Unlike the ESC classification, which has undergone extensive validation, this new AHA model has yet to be tested for its real-world predictive accuracy. Furthermore, while the guidelines tie specific treatment recommendations to these proposed categories, such a leap may be premature until the framework is rigorously vetted.

MOVING FORWARD

To move this classification from a conceptual framework to a clinical standard, several steps are essential. Retrospective validation utilizing large-scale databases and existing registries (such as the Pulmonary Embolism Response Team or Registro Informatizado de Enfermedad TromboEmbólica) to determine if these specific categories accurately predict clinical outcomes would be the first step.

Next, investigators should incorporate the A through E stages into the design of future management trials to see whether category-specific interventions truly improve survival or reduce morbidity. Conducting well-designed meta-analyses to harmonize the data emerging from recently published and ongoing randomized controlled trials soon to be completed may also increase our understanding.

Ultimately, while the 2026 AHA guidelines provide a much-needed physiological road map for the modern PE specialist, clinicians must continue to apply sound bedside judgment while the evidence base catches up to expert consensus. ●

All references are available online at chestphysician.org.

DPP-1 inhibitors enter clinical practice

A targeted, disease-based approach to bronchiectasis

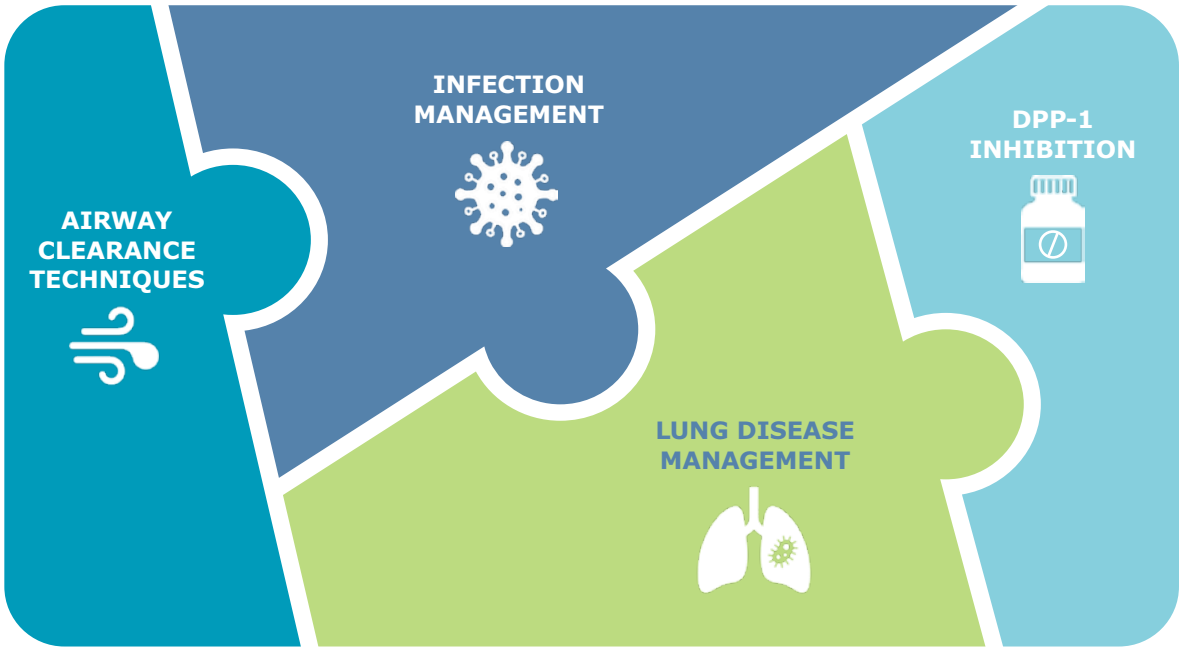
BY SUNJAY R. DEVARAJAN, MD, FCCP; ANAS HADEH, MD, FCCP

The US Food and Drug Administration's approval of brensocatib in 2025 marked the first potential disease-modifying therapy for noncystic fibrosis (non-CF) bronchiectasis and the first approved dipeptidyl peptidase 1 (DPP-1) inhibitor.[1-2] Unlike traditional symptomatic care, DPP-1 inhibition targets the underlying driver of disease: neutrophilic airway inflammation. Reversibly blocking the DPP-1 enzyme (cathepsin C) in the bone marrow impairs the activation of neutrophil serine proteases (NSPs), including neutrophil elastase (NE), while preserving other neutrophil functions. This treatment "defangs" the developing neutrophils, reducing the release of harmful proteolytic enzymes at disease sites like the lungs, thereby attenuating inflammation.[3-8]

In the phase 3 ASPEN and phase 2 WILLOW trials, once-daily oral brensocatib significantly reduced pulmonary exacerbations compared with placebo, with the 25 mg dose also slowing lung function decline (FEV_1) in patients 12 years or older.[1,9] Although guidelines are still evolving, DPP-1 inhibitors are expected to become a new standard of care, with ongoing studies further defining their role in bronchiectasis management.

All references are available online at chestphysician.org.

DPP-1 INHIBITION: A COMPLEMENT TO EXISTING BRONCHIECTASIS TREATMENT STRATEGIES



EARLY CLINICAL EXPERIENCE WITH DPP-1 INHIBITION

Though longer-term data are needed, early real-world and observational clinical experience suggests DPP-1 inhibition:

- Reduces health care use
- Decreases antibiotic use
- Improves respiratory symptoms and patient-reported outcomes
- Is generally well-tolerated

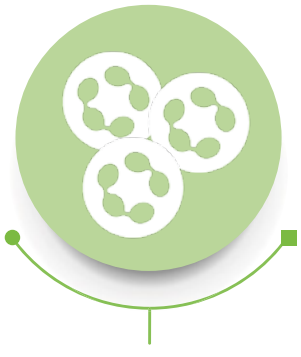
Although no validated biomarker currently guides therapy in bronchiectasis, clinical decision-making is supported by well-established disease characteristics. Unlike asthma or COPD, where blood eosinophils and other biomarkers inform biologic use, bronchiectasis management relies on a comprehensive clinical assessment of neutrophilic activity. In practice, treatment decisions are informed by:

- Exacerbation frequency
- Symptom burden
- Overall clinical impact

This clinically driven approach enables individualized patient selection, with therapeutic positioning expected to further evolve as emerging evidence and biomarker development advance.

TARGETING NEUTROPHILIC AIRWAY INFLAMMATION IN BRONCHIECTASIS

Neutrophils mediate innate immunity via phagocytosis, degranulation, and reactive oxygen species generation.



Rapidly recruited to sites of infection, neutrophils accumulate and contribute to purulent inflammation.

Excess neutrophil activation drives tissue injury and chronic inflammation; deficiency increases infection risk.

DPP-1 inhibition attenuates protease-mediated airway injury while preserving antimicrobial function.

By reversibly blocking the DPP-1 enzyme (cathepsin C), DPP-1 inhibitors target neutrophil serine protease activation, including NE, during myelopoiesis in the bone marrow.

Chronic airway neutrophilia with elastase release leads to impaired clearance, tissue damage, and a self-perpetuating cycle of infection and inflammation.

CURRENT, FUTURE TRIALS EXPAND ELIGIBLE PATIENT POPULATIONS

Ongoing studies are expanding the clinical scope of cathepsin C/DPP-1 inhibition across a broader spectrum of patients (see Table 1). Compared with earlier trials, emerging programs are evaluating use in:

- Patients with lower exacerbation burden, supporting earlier intervention in the disease course
- Parallel populations such as CF, extending evaluation beyond non-CF bronchiectasis
- Diverse clinical phenotypes, reflecting real-world heterogeneity of bronchiectasis

This evolution reflects a shift toward earlier and more individualized treatment strategies, with ongoing studies expected to further refine patient selection and therapeutic positioning.

	NCT06660992[10]	AIRTIVITY™ (NCT06872892)[11]
DPP-1 inhibitor	HSK3185810	Verducatib
Stage	Phase 2 complete; phase 3 underway	Phase 2 complete; phase 3 underway
Primary indications	Non-CF bronchiectasis	Bronchiectasis, including both non-CF bronchiectasis and CF-related bronchiectasis
Efficacy	Reduced exacerbation rates vs placebo	Reduced exacerbation risk
	Benefit at 20 mg and 40 mg QD	Prolonged time to first exacerbation
Optimal dose	20 mg and 40 mg PO both effective	2.5 mg PO appeared most favorable
Safety & tolerability	Favorable short-term safety profile	Safety profile similar to placebo
		Generally well-tolerated

Table 1: Ongoing trials

Interventional pulmonology

// continued from cover

While IP was initially developed primarily as a therapeutic modality, particularly for managing central airway obstruction (CAO) via rigid bronchoscopy, its role has expanded significantly beyond CAO and into diagnostics—spurring increasing demand.

Yaron Gesthalter, MD

Septimiu D. Murgu, MD, FCCP

Sujith V. Cherian, MD, FCCP

ADVANCES IN BRONCHOSCOPY

Two key technological advances in bronchoscopic airway navigation are electromagnetic navigation (EMN) and robotic bronchoscopy (RAB), a safer and more effective artificial intelligence-guided, human-operated approach that evolved from EMN.

Septimiu D. Murgu, MD, FCCP, Professor of Medicine at the University of Chicago Medicine, said the TARGET study is an example of how RAB has improved access and diagnostic yield for peripheral lung lesions.[1] In the TARGET trial, RAB-guided peripheral lung lesion sampling was shown to be safe, with a lower incidence of complications, including pneumothorax, bleeding requiring intervention, and respiratory failure compared with conventional bronchoscopic approaches.[1]

"We learned that we could get further into the lung and sample smaller lesions, and that RAB offers the stability to operate and perform biopsies in a safer way," Dr. Murgu said. Additionally, based on evidence from recent studies such as VERITAS and RELIANT, interventional pulmonologists can now access peripheral airways with greater precision, Dr. Gesthalter said.

The VERITAS study compared navigational bronchoscopy with radial EBUS and optional integrated digital tomosynthesis to conventional CT-scan-guided transthoracic needle biopsy.[2] The data demonstrated the noninferiority of navigational bronchoscopy, with diagnostic accuracy comparable to that of CT-scan-guided biopsy. The safety profile favored navigational bronchoscopy, with a significantly lower pneumothorax rate (3.3% vs 28.3%).

The RELIANT bronchoscopy study compared the diagnostic yield of EMN with RAB.[3]

"The RELIANT data showed that EMN and RAB are equivalent from a diagnostic perspective," Dr. Gesthalter said. "VERITAS, RELIANT, and other studies of diagnostic approaches are potentiating early and timely diagnosis for patients who might otherwise not receive further assessments. With advances in RAB, we have the stability and articulation to not only know where we are in the periphery spatially but also target different areas accurately."

LEVERAGING IMAGING ADVANCES

Integrating conventional approaches like radial EBUS or cryoscopy with newer tools, such as digital tomosynthesis, cone-beam CT (CBCT) imaging, and augmented fluoroscopy, has transformed IP, increasing both accuracy and reach and enabling exploration of ablative and other therapeutic strategies.

Dr. Murgu said newer technologies can also provide a 3D view of the lung, enabling precise pathway mapping and in-lesion confirmation of the scope's position.

The FRONTIER study, for instance, combined EMN with integrated digital tomosynthesis, resulting in a strict diagnostic yield of 89.5% in 18 patients with 19 nodules.[4]

"We would like to see larger studies in many centers to confirm these results, but the initial reports and our own experience are very promising," Dr. Murgu said.

With improved diagnostic yield, newer modalities can help sample lymph nodes during the same procedure, enabling concurrent staging. Moreover, advanced bronchoscopic modalities carry a low risk of seeding the tumor in the pleural space, a risk associated with percutaneous transthoracic needle biopsies.[5-7]

"For all these reasons, if patients present with a lung nodule or mass suspected of being lung cancer, we favor going directly for bronchoscopic intervention," he said.

BEYOND NODULE MANAGEMENT

An important development in IP for nonmalignant disease management is the development of clinical practice guidelines, including CHEST's 2025 guideline on CAO management.[8] The World Association for Bronchology and Interventional Pulmonology has published guidance on stenting for the management of benign and malignant airway obstruction.[9-10] In addition, CHEST and the American Thoracic Society released consensus criteria and reporting guidance for diagnostic yields in bronchoscopy.[11]

"These guidelines represent the accumulated evidence throughout recent decades, culminating in data-driven recommendations for the community on the type and timing of bronchoscopic procedures, using clinical, context-appropriate, patient-centered, safe, and effective approaches," Dr. Murgu said.

Dr. Gesthalter concurred. "It is an exciting time for IP management of benign disease, especially in patients who have sequelae related to smoking history or pollutant exposure, such as emphysema," he said. "There is room for optimism."

Dr. Gesthalter pointed to the emerging potential of individualized stent design and 3D-printed stents—with less granulation and mucus impaction, and improved tolerability—for patients with benign airway disease.

IP APPLICATIONS IN CRITICAL CARE

"Any patient who is in the ICU on a ventilator due to CAO should not have care withdrawal considered before an interventional pulmonologist is consulted," said Sujith V. Cherian MD, FCCP, highlighting the fundamental role of interventional pulmonologists in the ICU.

CAO remains a significant concern in patients with thoracic malignancies, with 13% presenting with the condition at diagnosis and an additional 5% developing it within a year following diagnosis.[12] Rigid bronchoscopy remains a critical and technically successful procedure for relieving CAO, said Dr. Cherian, who is Associate Professor and Director of Interventional Pulmonology and Pleural diseases at Lyndon B. Johnson Hospital at the University of Texas Health McGovern Medical School.

During the past decade, interventional pulmonologists have been increasingly tasked with diagnostics in the ICU as well. For instance, although not widely practiced, interventional pulmonologists now perform EBUS-facilitated diagnosis of pulmonary embolism in the ICU for patients in whom an emergent CT scan is not feasible because of mobility limitations or critical illness, Dr. Cherian said.

Another diagnostic application is thoracoscopy, for complex pleural effusions or early management of empyema.[13] Interventional pulmonologists also perform endobronchial/intrabronchial valve

placement to manage persistent pneumothorax with a persistent air leak and manage hemoptysis.[13] Percutaneous ultrasound gastrostomy and combined tracheostomy and gastrostomy in a single procedure are also increasingly being performed by interventional pulmonologists in the ICU.[13]

During and since the outbreak of the COVID-19 pandemic, the utilization of single-use flexible bronchoscopes (SUFBs) has been increasing in and out of ICUs.[14-15] SUFBs offer significant advantages, including a range of sizes, suction capabilities, and options for ablative tools to relieve airway obstruction, Dr. Cherian said. Most importantly, SUFBs do not have the processing burden and costs associated with conventional reusable flexible bronchoscopes.

TRAINING INTERVENTIONAL PULMONOLOGISTS

IP is a growing specialty, with more than 40 IP training programs offered in the United States. In 2020, there were more than 300 American Association for Bronchology and Interventional Pulmonology (AABIP) board-certified US specialists, of whom 43% had completed an additional fellowship in IP.[16] Dr. Murgu, who serves as the Clinical Simulation Oversight Director of CHEST's Live Learning Subcommittee, said that number has grown to 605 in 2026.

Many professional organizations, including CHEST, offer education courses focused on these technologies, he said. AABIP also offers educational programs focused on advanced bronchoscopic procedures.

"Most people are getting their training through the IP fellowship," Dr. Murgu said. "Device manufacturers also offer training programs conducted by expert faculty and in-house educational divisions.

"But IP training is not just about RAB and EBUS. It includes advanced therapeutic interventions in the central airways and pleural spaces. Especially because of these high-impact, relatively low-frequency procedures, a dedicated interventional pulmonology training is necessary to assure enough exposure, opportunities for deliberate practice, quality feedback, and thus a competency-oriented education." •

All references are available online at chestphysician.org.

Honoring a legacy, empowering the future

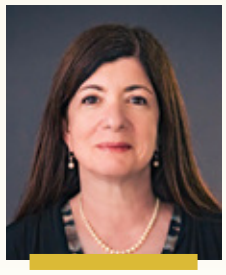
Passion lives on through the John R. Addrizzo, MD, FCCP, Endowed Research Grant in Sarcoidosis

"All for one, and one for all."

For John R. Addrizzo, MD, FCCP, this simple phrase was more than words; it was a way of life. When he was with his family, it meant loyalty and unity. In his work, it meant passion, persistence, and a commitment to advancing knowledge for the greater good.

Dr. Addrizzo's career in pulmonary medicine spanned four decades, yet he never strayed far from his earliest research passion: sarcoidosis. From his first presentation in 1969 at the International Conference on Sarcoidosis in Prague, through his training in pulmonary medicine at Kings County/Downstate Medical Center in Brooklyn, New York, to founding a sarcoidosis clinic following his training, he was struck by both the rarity of the disease and the outsized effect it took on his patients, many of whom were from minority communities. For Dr. Addrizzo, something about sarcoidosis always called him back.

Today, his family honors that dedication through the John R. Addrizzo, MD, FCCP, Endowed Research Grant in Sarcoidosis, a transformative and permanent fund dedicated to advancing sarcoidosis research. This endowment is not only a tribute to a beloved husband, father, grandfather, and physician but also a beacon for progress and discovery.



Doreen Addrizzo-Harris, MD, FCCP

"CHEST is a phenomenal place for this endowment to be because my father was first and foremost a clinician," said CHEST Past President Doreen Addrizzo-Harris, MD, FCCP. "It is a really great place for his memory to live on and in an area where he wished he could have done more."

ENDURING IMPACT

An endowment is more than a gift for today; it is an investment in tomorrow. Endowments provide a steady, reliable foundation for innovation, discovery, and impact year after year. With each breakthrough supported, each researcher empowered, and each family given new hope, an endowment ensures that the legacy of one person's passion can echo for generations.

"I wanted something that would live forever, beyond my involvement with CHEST and our family's involvement with CHEST," Dr. Addrizzo-Harris said.

The John R. Addrizzo, MD, FCCP, Endowed Research Grant in Sarcoidosis will continue to expand on its meaningful, early-stage progress, which included projects such as:

- Helping Divya Patel, DO, (2019 recipient) uncover an unpredicted response to sarcoidosis treatment with methotrexate and inspiring colleagues to explore new therapeutic approaches
- Backing Maneesh Bhargava, MD, PhD, FCCP, (2021 recipient) in identifying inflammatory proteins to distinguish multiorgan sarcoidosis from pulmonary sarcoidosis
- Supporting Michelle Sharp, MD, MHS, FCCP, (2023 recipient) in evaluating the feasibility of home air quality monitoring in a diverse cohort of individuals with pulmonary sarcoidosis

These are not just scientific milestones. They represent lives changed, possibilities opened, and a community strengthened.

A LEGACY THAT LIVES ON

The John R. Addrizzo, MD, FCCP, Endowed Research Grant in Sarcoidosis reflects the heart of CHEST philanthropy: advancing bold ideas, shaping the future of chest medicine, and improving the lives of patients worldwide.

One man's curiosity became a life's passion. That passion inspired a family's generosity. And now, through an endowment, it will empower generations of researchers to come. •

Learn more at ***chestnet.org/philanthropy***.

The measurable medical and financial benefits of transitional care

Proof of concept from an APP-led COPD clinic

BY JOHN "KENNY" LARSEN, PA-C

The term "zebra" in health care originates from the medical adage, "When you hear hoofbeats, think horses, not zebras." Coined by Dr. Theodore Woodward, this phrase warns against overdiagnosing rare conditions.[1] But just as practitioners sometimes encounter unexpected diagnoses in clinical practice, an unexpected scenario in health care administration began nearly 15 years ago. This uncommon scenario involves navigating unprecedented regulatory changes and taking advantage of new revenue sources. It was this "zebra" in health care administration that was the catalyst for an exciting and fulfilling professional experience—and one that I am eager to share.

HOSPITAL READMISSION REDUCTION AND TRANSITIONAL CARE BILLING

The Hospital Readmissions Reduction Program (HRRP) was established by Congress in 2010 as part of the Affordable Care Act (ACA) to incentivize reduced readmissions for Medicare beneficiaries. The program reduces payments to hospitals with higher-than-expected 30-day readmission rates for specific conditions. The program originally targeted heart failure, acute myocardial infarction, and pneumonia. It has since expanded to include COPD, hip/knee replacements, and coronary artery bypass graft surgeries. Since 2010, the program has been credited with preventing more than 565,000 readmissions.[2]

Transitional care management (TCM) billing was established by the Centers for Medicare and Medicaid Services (CMS) three years later. These codes (CPT 99495 and 99496) were introduced to reimburse physicians and qualified practitioners for care coordination services provided to patients transitioning from an inpatient setting back to the community.[3] The initiative was created to improve patient follow-up care.

The combination of the HRRP and TCM billing created a "zebra" in the patient, practitioner, and payor relationship—specifically, the rare instance where the best interests of the patient, the practitioner, and the payor all align.

COPD TRANSITIONAL CARE CLINIC STRUCTURE

In August 2018, I helped organize a COPD transitional care clinic in Carson City, Nevada, led by advanced practice providers (APP), with the mission of lowering readmissions for patients discharged with acute exacerbation of COPD. Acute exacerbations alone are responsible for up to 70% of COPD-related health care costs, and hospital readmissions alone account for more than $15 billion annually.[2] Fewer than half of these patients are alive at five years following their initial exacerbation requiring hospitalization, driving a clear use case for more effective postdischarge intervention.[2]

The clinic's team included an APP, a registered nurse (RN), and a medical assistant (MA). The APP rounded at the hospital in the mornings and worked in the outpatient clinic in the afternoons. The RN arranged follow-up appointments and managed prescriptions, as well as tracked patient outcomes including readmissions. The MA handled triage calls, prepared charts, and supported clinic operations.

Rounding in the hospital by the APP helped connect patients with outpatient providers for continued care and supported best-practice discharge planning. The nurse navigator contacted patients within two days of discharge and scheduled follow-ups within one to two weeks, both important for TCM billing. They also assessed patient needs such as access to inhaled medications, providing samples if needed, and coordinated with the APP to determine long-term solutions, including identifying patient assistance programs and local charities. Along with the MA, they arranged durable medical equipment orders like oxygen and nebulizers, as indicated.

The initial outpatient hospital follow-up visits with the APP typically lasted 60 minutes and included assessing patient recovery, determining medication and therapy compliance, and addressing immediate concerns. They also reviewed events before hospitalization to identify early signs of exacerbation and explain the process, discussed imaging and lab results, and answered lingering questions pertaining to hospitalization.

Patients were reminded they could contact the clinic if recovery issues arose, and they were given a direct phone number for the clinic MA's desk. Follow-up appointments were scheduled in two or four weeks based on readmission risk. Office notes were sent to the primary care provider and pulmonologist, or a referral to outpatient pulmonary was provided, if needed.

"The combination of the HRRP and TCM billing created a 'zebra' in the patient, practitioner, and payor relationship—specifically, the rare instance where the best interests of the patient, the practitioner, and the payor all align."

John "Kenny" Larsen, PA-C

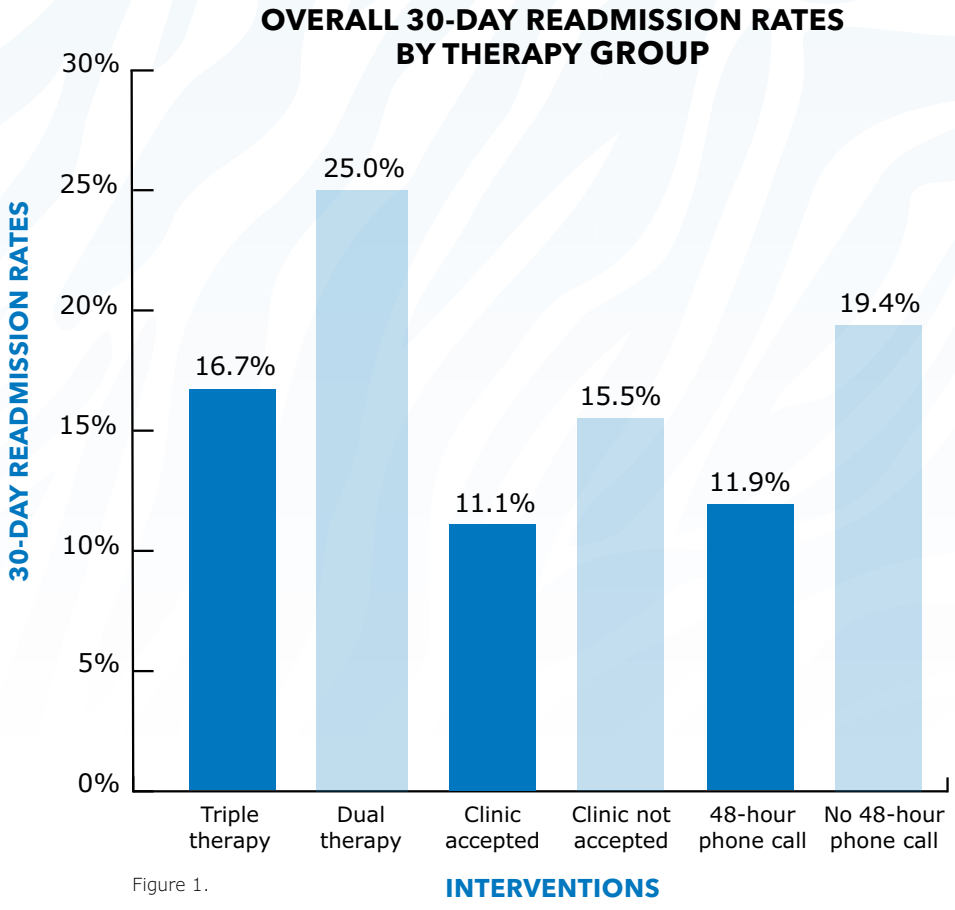


Figure 1.

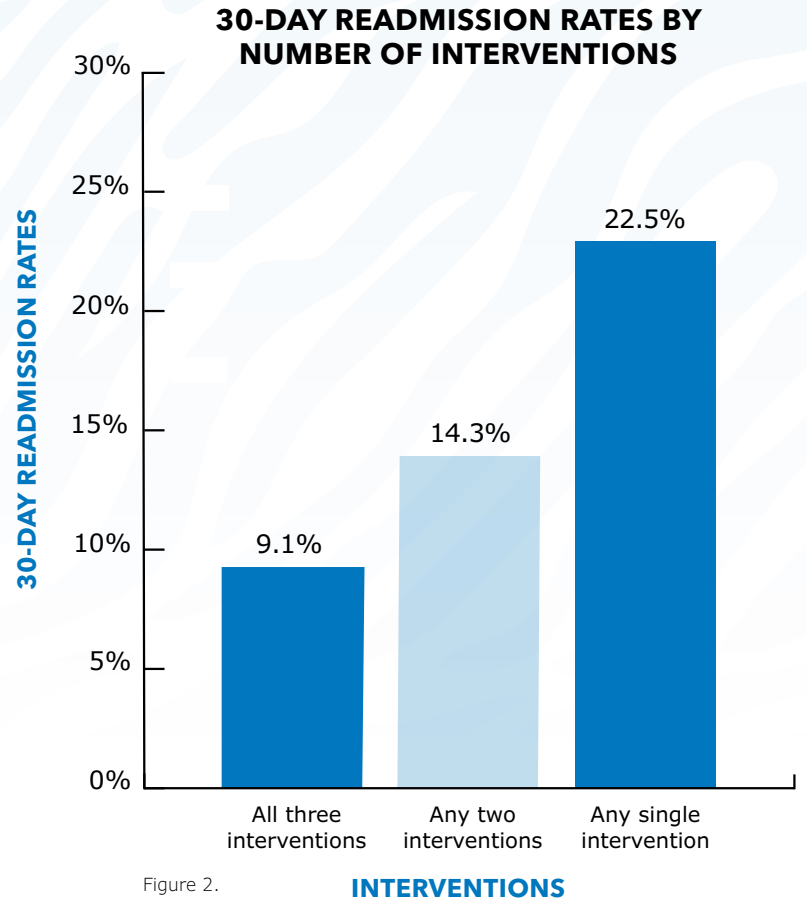


Figure 2.

The relationship between the patient and the clinic lasted between 30 and 90 days following hospital discharge with the intent to provide education and encouragement to the patient and their caregivers. If everything went well, the patient would have access to strategies, medications, and interventions that would keep them from another hospitalization or—at the very least—delay their next exacerbation beyond the 30- to 60-day period that would qualify for CMS penalties.

STATISTICAL ANALYSIS OF THE DATA

A longitudinal study of the spreadsheet kept by this clinic from 2019 to 2025 tracked a total of 2,305 hospital events and revealed value to several interventions, including early contact, education-focused visits, care coordination, and continuity. Patients contacted by the clinic within 48 hours had a readmission rate of 11.9% compared with 19.4% in patients who were not contacted within 48 hours. Patients who accepted engagement with the clinic had an average 30-day readmission rate of 11.1% compared with 15.5% for those who chose not to engage.

In 2020, discharge medications were tracked along with severity of COPD in patients who had prehospital spirometry. In patients with moderate to severe COPD who were discharged on long-acting muscarinic antagonist (LAMA)/long-acting β-agonist (LABA) therapy alone, the readmission rate was 25% vs 16.7% for patients on inhaled corticosteroid/LAMA/LABA therapy. (See **Figure 1**)

While any of these interventions were better than no intervention, the combination of these interventions showed that bundled transitional care far outweighed any intervention by itself. Patients who experienced any one intervention had a readmission rate of 22.5%, compared with 14.3% for patients who experienced any two interventions and 9.1% for patients who experienced all three interventions. (See **Figure 2**)

Clinic implementation costs included hiring a full-time APP, RN, and MA, plus added overhead. Within six years, the health system eliminated HRRP penalties, increased revenue reimbursement, and began TCM and standard outpatient billing. The APP generated 3,000 work relative value units (wRVUs) in 2022, which increased yearly, up to 4,500 wRVUs in 2025. Revenue for RN services was not pursued due to billing barriers, though codes exist for telephone calls (CPT 98966-98968) and nurse-only visits (CPT 99211), which could supplement APP visits for ongoing patient needs beyond 30 to 60 days postdischarge.[6-7]

The data show that dynamic transitional care clinics provided with adequate resources are effective. They work for the best interests of all involved.

FINAL THOUGHTS

There is still plenty to learn from this "zebra" in health care. There are several other examples of successful APP-led transitional care clinics in the United States, each of which has its own experience with improving outcomes for patients with COPD.[8-10]

Nationwide readmission rates have improved with the implementation of HRRP and TCM billing; but where are the other "zebras" in American health care? What strategies can be devised? What legislation needs to be passed?

We can look to the HRRP with TCM billing as a model to improve health care delivery in America and, hopefully, get to the point where universal interest alignment is no longer a "zebra." ●

All references are available online at chestphysician.org.

The evaluation and management of OSA in medically hospitalized patients

Review of guidelines from the AASM Task Force

BY DENNIS AUCKLEY, MD, FCCP; REENA MEHRA, MD, MS, FCCP

The evaluation and management of OSA have traditionally taken place in the outpatient setting. During the past couple of decades, however, an increasing number of studies suggest that OSA is highly prevalent among medically hospitalized patients, can be feasibly screened for or diagnosed during admission, and may present an opportunity to initiate therapy, all with the intent of improving clinical outcomes.

Dennis Auckley, MD, FCCP

Reena Mehra, MD, MS, FCCP

Roughly 80% of patients with OSA are undiagnosed, suggesting an ongoing failure of the outpatient setting to identify and diagnose these individuals. Studies have reported that inpatient populations have prevalence rates of (mostly undiagnosed) moderate to severe OSA ranging from 25% to 84%, depending on the medical population studied. And while not consistent across all studies, a growing number of observational studies suggest worse inpatient outcomes for patients with undiagnosed OSA, particularly in those receiving opioids during admission.

In addition, higher one-to-three-month readmission rates have been reported in patients with cardiopulmonary disease and previously undiagnosed OSA compared with those without OSA. And finally, OSA is associated with a 17% increased length of stay per whole day increment and 67% higher costs, even after accounting for potential confounding factors. However, the impact of diagnosing OSA and intervening (ie, via sleep medicine consultation, enhanced monitoring, initiation of therapy, ensuring follow-up, etc) on inpatient outcomes has not been critically analyzed.

As a result of growing interest in this field and the concerns described, the American Academy of Sleep Medicine (AASM) convened a multidisciplinary task force of experts and methodologists to conduct a systematic review of the literature using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to develop, analyze, and assign strengths to recommendations. Following nearly five years of work, the AASM Task Force on the Evaluation and Management of OSA in Medically Hospitalized Patients published its systematic review and clinical practice guidelines (CPG) in December 2025.[1]

"Roughly 80% of patients with OSA are undiagnosed, suggesting an ongoing failure of the outpatient setting to identify and diagnose these individuals."

A Good Practice Statement, based on expert consensus, preceded the recommendations. This statement specifies that, "For medically hospitalized adults with an established diagnosis of sleep-disordered breathing and on active treatment, existing treatment should be continued rather than withheld, unless contraindicated." This was thought to be consistent with good patient care and should be the standard of care.

The subsequent recommendations are as follows:

1 For medically hospitalized adults at increased risk for OSA, the AASM suggests in-hospital screening for OSA as part of an evaluation and management pathway that incorporates diagnosis and treatment with PAP rather than no in-hospital screening.

CONDITIONAL RECOMMENDATION, LOW CERTAINTY OF EVIDENCE

Remarks: Screening may include validated questionnaires and/or screening with overnight high-resolution pulse oximetry (HRPO). High risk for OSA is defined by signs and symptoms that suggest moderate to severe OSA (eg, excessive daytime somnolence of more than two of the following: diagnosed hypertension; habitual loud snoring; witnessed apnea, gasping, or choking and/or association of high-risk comorbidities).

2 For medically hospitalized adults with newly diagnosed OSA or with a prior established diagnosis of moderate to severe OSA but not currently on treatment, the AASM suggests the use of inpatient treatment with PAP rather than no PAP.

CONDITIONAL RECOMMENDATION, LOW CERTAINTY OF EVIDENCE

3 For medically hospitalized adults at increased risk for or with an established diagnosis of OSA, the AASM suggests that sleep medicine consultation be available as part of an evaluation and management pathway, rather than no sleep medicine consultation.

CONDITIONAL RECOMMENDATION, VERY LOW CERTAINTY OF EVIDENCE

Remarks: It is recognized that there will be variability in the availability of hospital-based expertise and resources specific to sleep medicine consultation; therefore, suggestions are provided in terms of the construct of the model of care, which will need to be tailored according to resources and personnel available.

4 For medically hospitalized adults at increased risk for or with an established diagnosis of OSA, the AASM suggests a discharge management plan to ensure timely diagnosis and effective management of OSA, rather than no plan.

CONDITIONAL RECOMMENDATION, VERY LOW CERTAINTY OF EVIDENCE

There was insufficient data to make a recommendation regarding enhanced inpatient physiological monitoring for medically hospitalized patients with known or suspected OSA.

The conditional nature of the recommendations was made based on the low degree of certainty about the evidence resulting from imprecision and potential for bias, as the randomized studies evaluated were small in nature, used different methodologies, and reported variable outcomes. Observational studies considered were generally consistent in terms of direction of the outcomes but lacked adequate controls, which contributed to the weak strength of the recommendations.

There are some additional caveats to be considered:

1. The initial charter was to address sleep-disordered breathing (SDB), ie, inclusive of disorders such as central sleep apnea and sleep-related hypoventilation, in addition to OSA. However, most of the evidence was focused on OSA; limited and generally low-quality data addressed other forms of SDB in medically hospitalized patients. Thus, the task force did not believe it was appropriate to extrapolate evidence from OSA to non-OSA sleep-related breathing disorders.

2. The guideline is not intended to provide guidance on management of hospitalized patients with acute or chronic respiratory failure requiring noninvasive ventilatory support, nor are the recommendations crafted to address OSA considerations in the peri-operative surgical or procedural inpatient population.

3. It is recognized that the hospital environment can be disruptive to sleep in terms of interruptions of sleep, light exposures, and noise; however, these aspects and the consideration of sleep disorders other than SDB (eg, parasomnias, restless legs syndrome) are not addressed by this guideline.

The hope is that these recommendations will prompt institutions and inpatient/sleep providers to begin to consider and develop, if not already doing so, processes and protocols for screening, diagnosing, and potentially offering PAP therapy in medically hospitalized patient populations, particularly those considered at increased risk for OSA (ie, cardiac units, respiratory units, neurologic units). The default of not considering OSA in these inpatient populations may contribute to the status quo of persistently high rates of undiagnosed OSA and fail to improve patient outcomes.

Recognizing that a formal overarching protocol of screening for OSA, diagnosing OSA, and implementing therapy for previously unrecognized OSA may require significant resource investment and personnel that may not be available at many institutions, the task force discussed various models of how this process could be realized in real-world practice. A process as simple as a nursing-driven screening protocol using standardized questionnaires, with subsequent care coordination to ensure that those identified as high risk for OSA receive appropriate outpatient follow-up for testing and treatment, could suffice based on current recommendations.

Conversely, some institutions may be well-situated to offer a full inpatient sleep consult service with a team of consultants, standardized screening, an array of diagnostic options, and well-supported patient-centered inpatient initiation of PAP therapy with transition to outpatient care. It is expected that there will be variable institutional approaches to this, and there will be numerous local factors that will influence decision-making, but the AASM believes it is time to begin to address this issue in clinical practice.

There are many opportunities for future investigation to better inform the benefits and values of various approaches to diagnosis and management of SDB in the inpatient setting. The field needs large, rigorously conducted studies to examine optimal objective and subjective screening approaches, diagnostic testing approaches, and OSA interventions in the inpatient setting. Approaches to care for those with highly complex cardiopulmonary pathophysiology and SDB (eg, hypoventilation syndromes and central sleep apnea) are warranted.

The role of the inpatient sleep consultation service needs to be further explored. The utility of enhanced inpatient physiological monitoring to detect early warning signs of a deteriorating clinical state, cost benefit analyses, and models of workflow processes and consultative and peri-discharge care are also high priority areas for future studies. Last but not least, improved coverage of inpatient sleep testing and services will be key to addressing gaps in inpatient sleep medicine care. ●

All references are available online at chestphysician.org.

Column

Opportunity, leadership, and the mindset for change

Neil Freedman, MD, FCCP

The summer months, particularly as we approach July, are a season of transition in medicine. New residents and fellows step into their roles—bringing energy, curiosity, and potential—and graduating trainees advance into the world of the attending. Across our profession, careers quietly but meaningfully move forward. These moments offer us an opportunity to reflect—not just on progress but on how that progress happens.

At its core, leadership is not about titles or authority. Leadership is the ability to inspire others to do great things; it is distinct from management. While management ensures execution, leadership builds people. It is about lifting others up, building the bench for the future, and having the integrity to do the right thing, especially when it is difficult. It also requires the humility and awareness to know when to lead, when to partner, and when to step back and be led.

In many ways, mentorship is where leadership becomes real.

At CHEST, mentorship is not passive—it is an active commitment. Through our programs, committee engagement, and opportunities surrounding the annual meeting, we intentionally connect early career clinicians with experienced leaders who can guide, challenge, and support them.

I am a product of CHEST's leadership and mentorship, and I credit a large part of my personal and professional success to the organization. In 1999, I left my academic job and joined a private practice in the suburbs north of Chicago. By chance, I was contacted by Nancy Collop, MD, Master FCCP, at CHEST to participate in an upcoming sleep-related educational program. And the rest is history.

Formal and informal mentoring and coaching by senior leaders and clinicians helped me develop skills in how to develop and present a lecture, organize a meeting, and accept and provide constructive feedback. These opportunities eventually led me to participation in the Networks, committees, and eventually, Board of Regents. It's as simple as that. And if can happen to me, it can happen to anyone who is willing to engage with the organization.

The CHEST Travel Grants program, supported by our donors, is another strong example of how CHEST helps many clinicians develop. These grants do more than support attendance; they create relationships. Each recipient is paired with a mentor who helps shape their experience during the meeting and beyond. In 2025, to celebrate CHEST's 90th anniversary, we awarded 90 travel grants. (And this year, we're awarding 91 travel grants!) That represented 90 opportunities for connection, for guidance, and, potentially, for transformation. Because sometimes, a single conversation can change the trajectory of someone's career. I have served as a mentor for this program for the past three years, and I continue to learn and be inspired by every mentee with whom I work.

This is how we build the next generation of leaders—not by chance but by design.

To succeed in the years ahead, we must embrace a learning mindset. We must be willing to think differently and remain open to change. The pace of medicine is accelerating, and expectations are evolving just as quickly. Those who thrive will be the ones who remain curious, adaptable, and committed to growth. And within that change lies tremendous opportunity.

At CHEST, we are committed to creating that opportunity. We continue to invest in mentorship while strengthening the pipeline of future clinicians through partnerships. One such partnership is our work with the Association of Pulmonary and Critical Care Medicine Program Directors. We are also advancing team-based care by supporting advanced practice providers through initiatives like the Critical Care Advanced Practice Provider Certification and expanding critical care education. And we will continue formal and informal mentorship programs through CHEST Travel Grants, Networks, and committees.

These efforts are important—but organizations alone do not create opportunity. People do. Leaders do.

So I will close with a simple call to action.

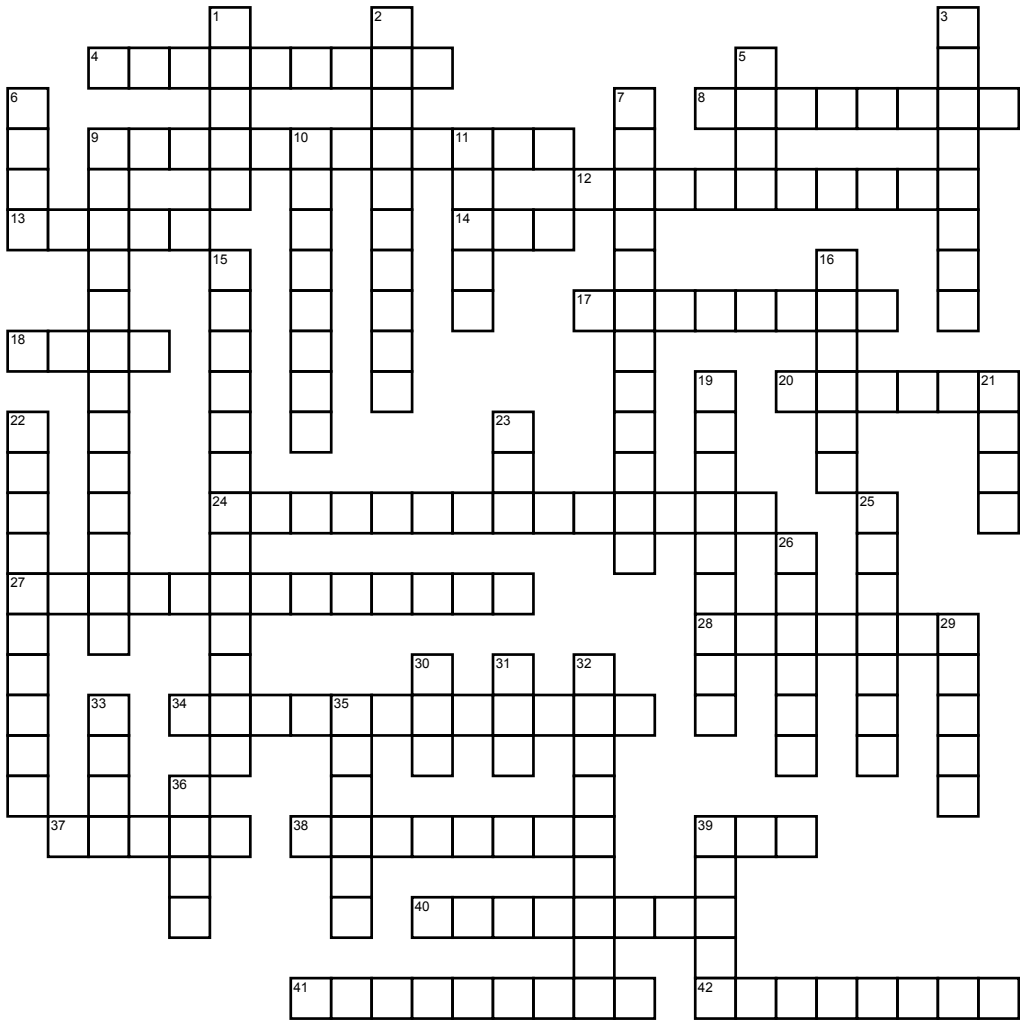
Reach out to your mentees. If it has been a while, reconnect. Send a message. Schedule a conversation. Offer guidance, encouragement, or simply your time. Also, reach out to your own mentors and coaches and thank them for their time, commitment, and wisdom.

Because leadership is not defined by what we accomplish alone but by what we enable others to become.

And often, it starts with a single conversation.

CHEST Puzzler

Test yourself with these clues from the January, February, and March 2026 issues of the journal *CHEST*®—compiled by William Kelly, MD, FCCP.



Scan QR code on page 7 for answer key

ACROSS

4. Inhaled treprostinil benefits fibrotic PH-ILD, but avoid it in patients with combined pulmonary fibrosis and _____ (Jan p.227)
8. In this study, patients with lung cancer who smoked _____ AND tobacco (39%) were younger, with more emphysema and rare/aggressive types (Mar p.819)
9. Digital respiratory technologies, including video-observed therapy, showed promising results for treatment of this infection, known worldwide (Jan p.55)
12. Pulmonary vascular _____ = (mean PA pressure - wedge pressure) / (stroke volume x heart rate) (Feb p.509)
13. Color of light with 20X more absorption than red and the focus of SpO_2 device research (Feb p.406)
14. Highly vascular body part used to check SpO_2 since the 1970s (Feb p.402)
17. Where many of us work; etymology from "host" (Mar p.757)
18. Sustained instant messaging with a _____ who formerly smoked improves tobacco cessation engagement; from the verb to look narrowly or closely (Jan p.21)
20. Pulmonary alveolar proteinosis' ground glass opacities and interlobular septal thickening = crazy _____ pattern (Feb p.441)
24. More than 400,000 patients in the US have this destructive disease, frequently with non-TB mycobacteria (Jan p.34)
27. First used in the 1930s to target fibrin in empyema, from streptococcal bacteria (Feb p.361)
28. _____-dose inhalers generate 13 billion tons of CO_2 equivalents annually (Feb p.326)
34. Patients with this pneumonia who are NOT living with HIV have more respiratory failure, mortality (Mar p.568)
37. In a large North American cohort, this was most common organ for additional sarcoid to develop (Jan p.169)
38. Measuring pleural _____ can facilitate large volume drainage, diagnose nonexpandable lung, and predict pleurodesis success (Mar p.589)
39. Radiation-free imaging modality that may have a role in longitudinal follow-up of ILD, including check of PH, inflammation, nodules, and gas exchange (Mar p.706)
40. 5% to 10% of asthma is severe; see CHEST clinical practice guideline for use of _____ agents (Feb p.337)
41. The R in RECITAL trial; as effective and better tolerated vs cyclophosphamide (Feb p.429)
42. Bronchoscopic diagnostic yield is strictly defined as getting either a malignant or a _____ benign diagnosis (Mar p.600)

DOWN

1. Lung development starts at _____ weeks postconception and continues to early adulthood (Jan p.180)
2. The most studied asthma biologic in pregnancy (Mar p.610)
3. Pulse _____, introduced in 1974, can vary with ambient light, perfusion, skin pigmentation, fever, and device brand (Jan p.245)
5. "FIVER_____," a multicenter trial comparing the _____ procedure to intrapleural fibrinolytic therapy, is expected to be complete by CHEST 2028 (Feb p.364)
6. In a novel CPET study, this dyspnea scale was reported as a probability of normality, not an absolute value. Resistance is futile! (Feb p.318)
7. This small observational series directly measured pleural pressures in _____, showing high values are necessary (but perhaps not always sufficient) for tension physiology (Mar p.830)
9. A patient position (named for a German surgeon born in 1844) that can, when safe, help lung secretion clearance (Mar p.573)
10. _____ a chest tube placed for spontaneous pneumothorax before removal did not reduce repeat collapse/procedures in a retrospective analysis (Mar p.850)
11. Loss of this is associated with neurodegenerative disease and COVID-19, and now also with lower pulmonary function, which really stinks (Mar p.577)
15. 2025 GOLD Report references biologics since 30% to 40% of patients suffer moderate to severe _____ despite triple inhaler therapy (Feb p.385)
16. Whole lung _____ is the primary treatment for alveolar proteinosis; a "How I Do It" article provides step-by-step suggestions (Feb p.440)
19. Asthma biologic that requires monitoring for hypereosinophilia at initial use (Feb p.346)
21. Popular Italian name meaning queen; also a group that says to avoid short-acting β-agonists alone, even in mild intermittent asthma (Jan p.1)
22. Preferred inhaled corticosteroid in pregnancy (Mar p.609)
23. Unannounced cardiac arrest simulation in clinical settings (in situ) identifies care delays, improves teams, and can be done multiple times a day. This is the number of hospital-wide alerts done to avoid response fatigue. (Feb p.480)
25. This sleep apnea symptom is twice as common (and peaks five years earlier) in men, so additional screening for women may be warranted (Mar p.804)
26. Most common respiratory condition in pregnancy (12%) (Mar p.605)
29. The landmark MIST-2 trial showed synergy of TPA plus _____ for empyema therapy (Feb p.360)
30. Inhibition of this enzyme was associated with increased IPF survival (Jan p.140)
31. 93% of women and 83% of men with moderate to severe _____ don't know it (Mar p.804)
32. Emergent variceal bleeding treatment may include a Sengstaken-Blakemore tube, or its variant named after the state of 1,000 lakes (Mar p.732)
33. IL-___ (or its receptor) are targeted by mepolizumab, reslizumab, and benralizumab (Feb p.338)
35. Regurgitation of this valve can cause pansystolic apex murmur, right upper lobe consolidation with hemoptysis (Mar p.750)
36. Cancers with this mutant (first identified in the rat sarcoma virus) were associated with poorer early-stage outcomes in lung cancer (Mar p.603)
39. Bronchial rheoplasty delivers pulsed electrical fields, which is being studied to reduce _____ plugs in COPD (Jan p.74)

JASCAYD® (nerandomilast tablets), for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

1 INDICATIONS AND USAGE: 1.1 Idiopathic Pulmonary Fibrosis: JASCAYD is indicated for the treatment of idiopathic pulmonary fibrosis (IPF) in adult patients. **1.2 Progressive Pulmonary Fibrosis:** JASCAYD is indicated for the treatment of progressive pulmonary fibrosis (PPF) in adult patients.

2 DOSAGE AND ADMINISTRATION: 2.1 Recommended Dosage: The recommended dosage of JASCAYD is 18 mg twice daily, administered orally (swallow tablets whole or dispersed in water) approximately 12 hours apart, with or without food. Reduce JASCAYD to 9 mg twice daily for patients who are unable to tolerate 18 mg twice daily, except in patients who concomitantly use JASCAYD with pirfenidone. Recommended Dosage for Concomitant Use with Pirfenidone: Recommended dosage of JASCAYD is 18 mg twice daily when used concomitantly with pirfenidone. Do not reduce dosage to 9 mg twice daily *[see Drug Interactions (7.1)]*. Administration Instructions: Swallow JASCAYD tablets whole or dispersed in water *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Missed Dose(s): If a dose of JASCAYD is missed, advise the patient to take the next dose at the next scheduled time. Advise the patient to not make up for a missed dose. Maximum Recommended Dosage: The maximum recommended dosage of JASCAYD is 18 mg twice daily. **2.2 Dosage Modification of JASCAYD for Concomitant Use With CYP3A Inhibitors:** Strong CYP3A Inhibitors: Reduce JASCAYD dosage to 9 mg twice daily when used concomitantly with strong CYP3A inhibitors *[see Drug Interactions (7.1)]*. Moderate and Weak CYP3A Inhibitors: No dosage modification is recommended for JASCAYD when used concomitantly with moderate or weak CYP3A inhibitors. **2.3 Administration Instructions for Patients Who Have Difficulty Swallowing Tablets:** Disperse JASCAYD tablet in water and administer as follows: Place approximately 100 mL (3 to 4 ounces) of non-carbonated, room temperature water in a glass. Do not use any other liquids; Place a JASCAYD tablet in the water, without crushing, and stir regularly for approximately 15 to 20 minutes until the tablet is dispersed into very small pieces (the tablet will not completely dissolve); Drink the dispersion within 2 hours of mixing; If the dispersion is not drunk immediately, stir again before drinking; Rinse the glass with approximately 100 mL (3 to 4 ounces) of water and drink to ensure the full dose is administered.

4 CONTRAINDICATIONS: None.

6 ADVERSE REACTIONS: 6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. Adverse Reactions for Idiopathic Pulmonary Fibrosis: The safety of JASCAYD was based on a randomized, placebo-controlled, double-blind trial (FIBRONEER-IPF), which included 1,177 adult patients with IPF who were randomized in a 1:1:1 ratio to receive JASCAYD 9 mg twice daily, JASCAYD 18 mg twice daily, or matching placebo. Patients received JASCAYD or placebo with or without background antifibrotic treatment (nintedanib or pirfenidone) for at least 52 weeks *[see Clinical Studies (14.1)]*. The median duration of exposure was 14 months in each treatment arm. Discontinuation due to adverse reactions occurred more frequently in patients treated with JASCAYD (with or without background antifibrotic treatment) 18 mg (15%) and 9 mg (12%) compared to placebo (11%). The most frequent adverse reaction leading to discontinuation of JASCAYD 18 mg and 9 mg was diarrhea (6% and 2%, respectively). Table 1 lists the most common adverse reactions from the studied population with an incidence of greater than or equal to 5% in JASCAYD-treated patients and more common than the placebo group.

Table 1 Adverse Reactions with JASCAYD with Incidence of ≥5% and More Common than Placebo in Patients[1] with IPF (FIBRONEER-IPF Trial)

	JASCAYD 18 mg BID n=392	JASCAYD 9 mg BID n=392	Placebo n=393
Diarrhea	42%	31%	17%
COVID-19	13%	16%	12%
Upper respiratory tract infection	13%	11%	10%
Depression[2]	12%	11%	10%
Weight decreased	11%	10%	8%
Decreased appetite	9%	9%	5%
Nausea	8%	9%	7%
Fatigue	7%	8%	6%
Headache	7%	6%	5%
Vomiting	6%	5%	5%
Back pain	6%	5%	4%
Dizziness	5%	6%	5%

[1]Studied population including patients who received JASCAYD with or without background antifibrotic treatment (nintedanib or pirfenidone)
[2]Includes depression, depressed mood, depression rating scale score increased, suicidal ideation, adjustment disorder with depressed mood, depressive symptom
BID: twice daily; COVID-19: infection with SARS-CoV-2 virus

Specific Adverse Reactions of JASCAYD for IPF with or without Concomitant Use of Nintedanib or Pirfenidone: *Diarrhea:* Diarrhea was more common in patients using JASCAYD with concomitant nintedanib. In patients taking nintedanib, diarrhea occurred in 62%, 50%, and 28% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. In patients using concomitant pirfenidone, diarrhea occurred in 24% and 8% of patients treated with JASCAYD 18 mg twice daily and placebo, respectively. In patients without concomitant antifibrotic treatment, diarrhea occurred in 26%, 17%, and 8% of patients using JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. Diarrhea was the most common adverse reaction associated with treatment discontinuation, and most common with JASCAYD used concomitantly with nintedanib: discontinuation occurred in 13%, 2%, and 1% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily and placebo, respectively. No treatment discontinuations due to diarrhea occurred in patients treated with background pirfenidone and JASCAYD 18 mg twice daily or background pirfenidone with placebo. Diarrhea leading to treatment discontinuation occurred in 1% of patients treated with JASCAYD 18 mg twice daily and in no patients treated with JASCAYD 9 mg or placebo without concomitant antifibrotic treatment. In most patients treated with JASCAYD, diarrhea was of mild to moderate intensity and generally occurred within the first 3 months of treatment. *Weight Decrease:* Weight decrease was most common in patients who received JASCAYD concomitantly with nintedanib in the studied population: in patients taking nintedanib, weight decrease occurred in 16%, 14%, and 12% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. In patients using concomitant pirfenidone, weight decrease occurred in 6% and 5% of patients treated with JASCAYD 18 mg twice daily and placebo, respectively. In patients without background antifibrotic therapy, weight decrease occurred in 8%, 2%, and 6% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. *Decreased Appetite:* In patients taking nintedanib, decreased appetite occurred in 7%, 10%, and 4% in JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. In patients using concomitant pirfenidone, decreased appetite occurred in 13% and 10% of patients treated with JASCAYD 18 mg twice daily and placebo, respectively. In patients without concomitant antifibrotic treatment, decreased appetite occurred in 9%, 6%, and 0% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. *Less Common Adverse Reactions in IPF*: Less common adverse reactions in the IPF population following administration of JASCAYD included asthenia (5% JASCAYD 18 mg twice daily, 4% JASCAYD 9 mg twice daily, and 2% placebo), amylase increased (1% JASCAYD 18 mg twice daily, 1% JASCAYD 9 mg twice daily, and 0% placebo), and vasculitis (1% JASCAYD 18 mg twice daily, 1% JASCAYD 9 mg twice daily, and 0% placebo). Adverse Reactions for Progressive Pulmonary Fibrosis: The safety of JASCAYD was based on a randomized, placebo-controlled, double-blind trial (FIBRONEER-ILD), in which 1,178 adult patients with PPF were randomized in a 1:1:1 ratio to receive JASCAYD 9 mg twice daily, JASCAYD 18 mg twice daily, or matching placebo. Patients received JASCAYD or placebo with or without background nintedanib treatment for at least 52 weeks *[see Clinical Studies (14.2)]*. The median duration of exposure was 15 months in each treatment arm. The most common adverse reactions in patients with PPF treated with JASCAYD were generally consistent with those observed in patients with IPF. Specific Adverse Reactions of JASCAYD for PPF with or without Concomitant Use of Nintedanib: *Diarrhea:* Diarrhea was more common in patients using JASCAYD with concomitant nintedanib. In patients taking nintedanib, diarrhea occurred in 49%, 50%, and 37% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. In patients without concomitant use of nintedanib, diarrhea occurred in 27%, 16%, and 16% of patients using JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. Diarrhea was the most common adverse reaction associated with treatment discontinuation, and most common with JASCAYD used concomitantly with nintedanib: discontinuation occurred in 4%, 3%, and 1% in patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. Diarrhea leading to treatment discontinuation occurred in 1% of patients treated with JASCAYD 18 mg twice daily and in no patients treated with JASCAYD 9 mg or placebo without concomitant use of nintedanib. In most patients treated with JASCAYD, diarrhea was of mild to moderate

intensity and generally occurred within the first 3 months of treatment. *Weight Decrease:* Weight decrease was more common in patients who received JASCAYD concomitantly with nintedanib, which occurred in 12%, 10%, and 9% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. In patients without concomitant use of nintedanib, weight decrease occurred in 13%, 8%, and 5% of patients treated with JASCAYD 18 mg twice daily, JASCAYD 9 mg twice daily, and placebo, respectively. *Malignancies:* Among patients with PPF, neoplasms (benign, malignant, or unspecified) were reported in more patients with PPF treated with JASCAYD than placebo over the entire study duration of FIBRONEER-ILD (5% JASCAYD 18 mg, 5% JASCAYD 9 mg, and 3% placebo). Malignancies such as non-melanoma skin cancers and small cell lung cancer were observed in patients who received JASCAYD (basal cell carcinoma: JASCAYD 18 mg n=2 [1%] vs. JASCAYD 9 mg n=3 [1%] vs. placebo n=1 [0.3%]; squamous cell carcinoma of skin: JASCAYD 18 mg n=4 [1%] vs. JASCAYD 9 mg n=2 [0.5%] vs. placebo n=0; and small cell lung cancer: JASCAYD 18 mg n=4 [1%] vs. JASCAYD 9 mg and placebo n=0). *Less Common Adverse Reaction(s) in PPF:* Less common adverse reactions in the PPF population following administration of JASCAYD include atrial fibrillation (3% JASCAYD 18 mg twice daily, 2% JASCAYD 9 mg twice daily, and <1% placebo).

7 DRUG INTERACTIONS: 7.1 Effects of Other Drugs on JASCAYD: Strong CYP3A Inhibitors: Reduce the dosage of JASCAYD to 9 mg twice daily when used concomitantly with strong CYP3A inhibitors *[see Dosage and Administration (2.2)]*. Nerandomilast is a CYP3A substrate. Concomitant use of JASCAYD with a strong CYP3A inhibitor increases exposure of nerandomilast, which may increase the risk of JASCAYD adverse reactions *[see Clinical Pharmacology (12.3)]*. Moderate or Strong CYP3A Inducers: Avoid use of JASCAYD with strong or moderate CYP3A inducers. Nerandomilast is a CYP3A substrate. Concomitant use of JASCAYD with moderate or strong CYP3A inducers is expected to decrease exposure of nerandomilast, which may decrease the efficacy of JASCAYD *[see Clinical Pharmacology (12.3)]*. Pirfenidone: Recommended dosage of JASCAYD is 18 mg twice daily when used concomitantly with pirfenidone. Do not reduce the dosage to 9 mg twice daily *[see Dosage and Administration (2.1)]*. Concomitant use of JASCAYD with pirfenidone decreases exposure of nerandomilast *[see Clinical Pharmacology (12.3)]*. When JASCAYD was used concomitantly with pirfenidone in patients with IPF in FIBRONEER-IPF, efficacy was not observed with the JASCAYD 9 mg twice daily dosage *[see Clinical Studies (14.1)]*.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: There are no available data on JASCAYD use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are maternal and fetal risks associated with untreated idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) during pregnancy *(Clinical Considerations)*. Based on findings from animal reproduction studies, JASCAYD may increase the risk for fetal loss. In an embryo-fetal development study in rats, oral administration of nerandomilast to pregnant rats during organogenesis at an exposure approximately 5 times the maximum recommended human dose (MRHD) of 36 mg/day resulted in an increase in embryo-fetal losses *(see Data)*. Advise pregnant women and females of reproductive potential of the potential risk of fetal loss. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%. Clinical Considerations: *Disease-Associated Maternal and/or Embryo/Fetal Risk:* Untreated IPF or PPF can lead to respiratory failure and mortality in the mother and intrauterine growth restriction, preterm birth, fetal hypoxia, and neonatal death. Data: *Animal Data:* In an embryo-fetal development study in pregnant rats dosed by the oral route during the period of organogenesis from gestation days 6 to 17, nerandomilast caused an increase in embryo-fetal losses (pre- and post-implantation loss and decreased mean number of live fetuses) at an exposure that was approximately 5 times the MRHD (on an AUC basis with a maternal oral dose of 6 mg/kg/day). Maternal toxicity, as evidenced by decreased body weight gains and adverse clinical signs, was observed at exposures approximately 7 times the MRHD (on an AUC basis with a maternal oral dose of 9 mg/kg/day). No fetal or maternal toxicities were observed at exposures up to 3 and 5 times the MRHD (on an AUC basis with maternal oral doses of 3 mg/kg/day and 6 mg/kg/day), respectively. In an embryo-fetal development study in pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 7 to 19, no effects on maternal or fetal development were observed at an exposure that was approximately 4 times the MRHD (on an AUC basis with a maternal oral dose of 15 mg/kg/day). In a prenatal and postnatal development study in pregnant rats dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, nerandomilast had no effects on delivery or the growth and development of offspring at an exposure that was approximately 2 times the MRHD (on an AUC basis with a maternal oral dose of 3 mg/kg/day). **8.2 Lactation:** Risk Summary: There are no data on the presence of nerandomilast or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. Nerandomilast is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JASCAYD and any potential adverse effects on the breastfed infant from JASCAYD or from the underlying maternal condition. Data: In a prenatal and postnatal development study in pregnant rats dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, nerandomilast was present in the plasma of rat pups during the lactation period. In a single dose milk secretion study in lactating rats dosed with radiolabeled nerandomilast by the oral route, similar concentrations of total radioactivity were observed in the milk and plasma of lactating females, with the maximum radioactive concentration observed at 1 hour post dose that was significantly reduced by 24 hours post dose. The concentration of total radioactivity in animal milk does not necessarily predict the concentration of drug in human milk. **8.4 Pediatric Use:** The safety and effectiveness of JASCAYD for the treatment of idiopathic pulmonary fibrosis or progressive pulmonary fibrosis have not been established in pediatric patients. **8.5 Geriatric Use:** There were 930 patients 65 years of age and older in the FIBRONEER-IPF trial *[see Clinical Studies (14.1)]*. Of the total number of JASCAYD-treated patients with idiopathic pulmonary fibrosis in this trial, 623 (79%) were 65 years of age and older, while 251 (32%) were 75 years of age and older. There were 733 patients 65 years of age and older in the FIBRONEER-ILD trial *[see Clinical Studies (14.2)]*. Of the total number of JASCAYD-treated patients with progressive pulmonary fibrosis in this trial, 490 (63%) were 65 years of age and older, while 150 (19%) were 75 years of age and older. No overall differences in safety or effectiveness of JASCAYD have been observed between patients 65 years of age and older and younger adult patients. **8.6 Renal Impairment:** JASCAYD has not been investigated in patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2). Use of JASCAYD is not recommended in patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2). The recommended dosage in patients with mild (eGFR ≥60 to <90 mL/min/1.73 m^2 according to CKD-EPI), moderate (eGFR ≥30 to <60 mL/min/1.73 m^2), or severe renal impairment (eGFR ≥15 to <30 mL/min/1.73 m^2) is the same as that in patients with normal renal function *[see Clinical Pharmacology (12.3)]*. **8.7 Hepatic Impairment:** JASCAYD has not been investigated in patients with severe (Child-Pugh Class C) hepatic impairment. Use of JASCAYD is not recommended in patients with severe (Child-Pugh Class C) hepatic impairment. The recommended dosage in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment is the same as that in patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE: In the event of an overdosage with JASCAYD, monitor the patient for any signs or symptoms of adverse reactions and provide appropriate symptomatic treatment. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

17 PATIENT COUNSELING INFORMATION: *Advise the patient to read the FDA-approved patient labeling (Patient Information).* Pregnancy: Advise female patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant during treatment with JASCAYD. Advise female patients of the potential risk of fetal loss *[see Use in Specific Populations (8.1)]*. Missed Dose: Inform patients that if they miss a dose of JASCAYD, they should take the next dose at the next scheduled time. Advise patients to not make up for a missed dose or exceed the recommended dosage of 18 mg twice daily *[see Dosage and Administration (2.1)]*.

COL11694DB272026 (04/26) CL-JS-100018

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JASCAYD®
(nerandomilast)
tablets 18 mg

A LANDMARK MOMENT IN PPF AND IPF CARE[1-5]

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INDICATIONS

JASCAYD is indicated for:

- the treatment of idiopathic pulmonary fibrosis (IPF) in adult patients.
- the treatment of progressive pulmonary fibrosis (PPF) in adult patients.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- The most common adverse reactions with an incidence of ≥5% in patients treated with JASCAYD were diarrhea, COVID-19, upper respiratory tract infection, depression, weight decreased, decreased appetite, nausea, fatigue, headache, vomiting, back pain, and dizziness.

DRUG INTERACTIONS

Effects of Other Drugs on JASCAYD

- **Strong CYP3A Inhibitors:** Reduce the dosage of JASCAYD to 9 mg twice daily when used concomitantly with strong CYP3A inhibitors. Nerandomilast is a CYP3A substrate. Concomitant use of JASCAYD with a strong CYP3A inhibitor increases exposure of nerandomilast, which may increase the risk of JASCAYD adverse reactions.
- **Moderate or Strong CYP3A Inducers:** Avoid use of JASCAYD with strong or moderate CYP3A inducers. Nerandomilast is a CYP3A substrate. Concomitant use of JASCAYD with moderate or strong CYP3A inducers is expected to decrease exposure of nerandomilast, which may decrease the efficacy of JASCAYD.
- **Pirfenidone:** Recommended dosage of JASCAYD is 18 mg twice daily when used concomitantly with pirfenidone. Do not reduce the dosage to 9 mg twice daily. Concomitant use of JASCAYD with pirfenidone decreases exposure of nerandomilast. When JASCAYD was used concomitantly with pirfenidone in patients with IPF in FIBRONEER-IPF, efficacy was not observed with the JASCAYD 9 mg twice daily dosage.

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Advise pregnant women and females of reproductive potential of the potential risk of fetal loss. Advise female patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant during treatment with JASCAYD.
- **Lactation:** The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JASCAYD and any potential adverse effects on the breastfed infant from JASCAYD or from the underlying maternal condition.
- **Renal Impairment:** Use of JASCAYD is not recommended in patients with end stage renal disease (eGFR <15 mL/minute/1.73 m^2).
- **Hepatic Impairment:** Use of JASCAYD is not recommended in patients with severe (Child-Pugh Class C) hepatic impairment.

CL-JS-100019 4.17.2026

Please see the Brief Summary of Prescribing Information on the preceding pages.

IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

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