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When PH and ILD meet: From overlap to a unified disease paradigm

Recent evidence has revealed an interconnected syndrome that requires a multidisciplinary approach

BY CONNI KOURY

The long-standing conceptual separation between pulmonary hypertension (PH) and interstitial lung disease (ILD) is rapidly dissolving.[1] What was once viewed as a coincidental overlap is now increasingly understood as a unified, pathobiologically interconnected syndrome—and one that demands a reassessment of diagnostic strategies, therapeutic models, and care delivery.

For clinicians, this shift represents more than semantic evolution. It reflects a fundamental transformation in how to detect, interpret, and treat disease at the intersection of parenchymal fibrosis and pulmonary vascular remodeling.[1]

"The field has undergone a fundamental transformation over the past few years, moving from a landscape of limited options to one in which PH is now recognized as a treatable complication of fibrotic lung disease," said Tejaswini Kulkarni, MD, MPH, FCCP, Director of the Interstitial Lung Disease Program and Associate Medical Director of the Lung Health Center at The University of Alabama at Birmingham.

// continued on page 10

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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]

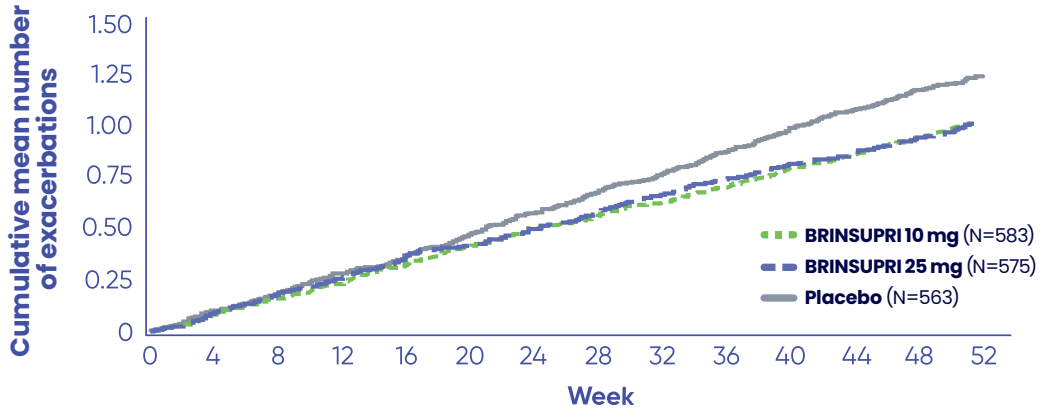
BRINSUPRI 25 mg

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.

insmed®

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®

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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.

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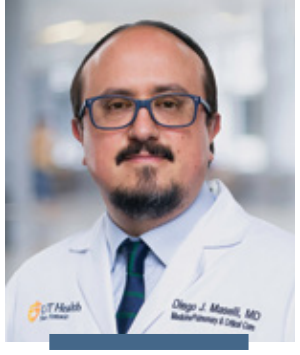
From the Editor



Welcome to another great issue of *CHEST Physician*!

We have a packed issue covering a wide range of topics that highlight the ever-evolving landscape of pulmonary, critical care, and sleep medicine. We explore the clinical consequences of sleep disruption in the critical care setting and strategies to promote restorative sleep. We examine how atelectasis can pose a significant challenge during robotic bronchoscopy for peripheral lung lesions and discuss practical approaches to overcoming this barrier.

We also take a closer look at the 2026 Surviving Sepsis Campaign guidelines and their recommendations for the management of this complex patient population. In addition, we explore the important intersection between pulmonary hypertension and interstitial lung disease and the multidisciplinary approach required to care for these challenging cases. Finally, we review the latest approaches to evaluating diaphragm dysfunction and share practical clinical pearls for the management of COPD.

Beyond this issue, our understanding of the impact of metabolic disease across pulmonary, critical care, and sleep medicine continues to grow. Diabetes is a well-established risk factor for poor outcomes in asthma, COPD, OSA, and sepsis, but what about bronchiectasis? In a study published in *Lancet Respiratory Medicine* in July, Hull and colleagues evaluated more than 30,000 patients with bronchiectasis from four registries across Europe, Asia, and Australia.[1] Patients with coexisting diabetes had a greater disease burden, including higher Bronchiectasis Severity Index and dyspnea scores, as well as worse clinical outcomes, with more frequent exacerbations and hospitalizations and higher five-year mortality. Importantly, these associations persisted after multivariable adjustment, suggesting that diabetes is independently associated with worse outcomes in patients with bronchiectasis. These patients also frequently had other comorbidities, including cardiovascular and renal disease. Although the mechanisms underlying these associations remain to be fully defined, diabetes may adversely affect host-pathogen interactions and impair immune responses to infection. Taken together, these findings suggest that diabetes should be considered an important factor in individualized risk assessment for patients with bronchiectasis and further highlight the need for a multidisciplinary approach to their care. More broadly, these results remind us that comorbid conditions continue to play an important role in the management and outcomes of patients with chronic respiratory disease.

Finally, I would like to extend a heartfelt invitation to all of you to join us for the 2026 CHEST Annual Meeting in Phoenix. Our annual meeting is always one of the highlights of the year! It will offer, once again, a unique opportunity to reconnect with colleagues and friends, exchange ideas, learn from one another, and celebrate the incredible work being done across our pulmonary, critical care, and sleep medicine community. Whether you are joining us for the latest scientific discoveries, outstanding educational sessions, or hands-on learning and simulations, there is truly something for everyone. You can register at **chestnet.org/annual-meeting**.

See you in Phoenix!

Warm regards,

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

1. Hull RC, Liu Y, Cao Z, et al. Comorbid diabetes disease severity and microbial changes in patients with bronchiectasis: a combined analysis of data from the EMBARC, EMBARC-India, Australian, and BE-China registries. *Lancet Respir Med*. 2026;14(7):620-632. doi:10.1016/S2213-2600(26)00057-3

In memoriam

CHEST has been informed of the death of a CHEST member.
We remember our colleague and extend our sincere condolences.

Robert J. Durkin, DO

Grow your career and your community at CHEST 2026

Every year, the CHEST Annual Meeting brings together pulmonary, critical care, and sleep medicine professionals with many backgrounds but the same passion: to advance knowledge of clinical practice for the benefit of patients.

During CHEST 2026, October 18 to 21 in Phoenix, CHEST Networks and Interest Groups will help attendees find their home within this vibrant community, contribute to impactful initiatives, and form bonds that outlast the meeting itself.

The seven CHEST Networks, organized around distinct educational curricula, provide a useful framework for anyone who is looking to expand their involvement, said Muhammad Adrish, MD, MBA, FCCP, Chair of the Council of Networks.

CAN'T-MISS EVENTS AT CHEST 2026

- ☑ **Opening Session**
  Sunday, October 18 | 8 AM
- ☑ **Welcome Reception**
  Sunday, October 18 | 7 PM
- ☑ **Career Fair**
  Monday, October 19 | 4 PM
- ☑ **Network Mixer**
  Monday, October 19 | 5:30 PM
- ☑ **Cultures and Communities Reception**
  Monday, October 19 | 6 PM
- ☑ **CHEST Challenge Championship**
  Tuesday, October 20 | 6 PM

"CHEST itself is a big organization, and if you try to navigate the organization by yourself, you could get really confused," Dr. Adrish said. "CHEST Networks are where you can identify the people who have the interests that you have."

Each of the Networks will host business meetings during CHEST 2026 to highlight current efforts and outline upcoming projects—from developing guidelines and submitting journal articles to designing educational events, podcasts, and webinars.

This year, the Network Open Forums will be split across two days in order to allow attendees to engage with multiple areas of interest. No prior involvement is necessary to attend, but showing up and speaking up is how many current leaders got their start, Dr. Adrish said. Additionally, members of CHEST's 22 Sections—subgroups within each Network—will present at Experience CHEST in the Exhibit Hall, Monday through Wednesday.

Attendees will also have an opportunity to mingle with Network leaders during the Network Mixer on Monday evening. Taking advantage of these opportunities can make a real difference at the meeting and down the line, no matter where someone ends up in their career, Dr. Adrish said.

"While I was moving from a community practice setting to an academic setting, the only thing that remained constant was my engagement with the Networks. The Networks didn't care which building I was walking into; they cared about what I was bringing to the organization, they provided me with the opportunities, and they gave me that same door into CHEST leadership, regardless of where I was," Dr. Adrish said. "If you share the CHEST mission of promoting education, you will find your home in CHEST Networks."

CHEST 2026 attendees will also have the chance to connect with one of the four CHEST Interest Groups, which unite members of shared identities and clinical interests.

Leaders from the Women in Chest Medicine, LGBTQ+ at CHEST, Citizens of the Global Majority, and Respiratory Care Interest Groups will be eager to speak about their overall missions, current initiatives, and available resources during the Cultures and Communities Reception on Monday evening.

"We're in a profession of lifelong learning," said David L. Vines, FAARC, PhD, FCCP, Chair of the Respiratory Care Interest Group Steering Committee. "We chose a profession where that knowledge continues to advance, and we all have different challenges in that process and continue to grow and learn. So to network with other individuals, to potentially develop collaborations, it's an amazing venue for that to happen."

Visit **chestnet.org/annual-meeting** to register today. ●

Don't Forget...

- ☑ Pick up your souvenir T-shirt at Experience CHEST
- ☑ Snap a new photo in the Headshot Lounge
- ☑ Sign up for a simulation course
- ☑ Visit with companies in the Exhibit Hall
- ☑ Check out the schedule of featured industry events

Inside

CHEST Puzzler Key

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

Column

Atelectasis in peripheral bronchoscopy

Understanding and mitigating this condition

BY CHRISTOPHER BERTINI, MD; ABDUL-RAHMAN HALAWA, MD; ROBERTO F. CASAL, MD, FCCP

For decades, bronchoscopy was limited in sampling peripheral lung lesions. With the recent advent of robotic bronchoscopy combined with cone beam computed tomography (CBCT) guidance, pulmonologists can now safely and accurately biopsy these targets. Nevertheless, when lesions are in dependent areas of the lungs, intraoperative development of atelectasis remains a significant challenge.

WHY ATELECTASIS OCCURS

The degree of lung insufflation is dependent on the transpulmonary gradient (pulmonary pressure [P_L] = alveolar pressure [P_a] – pleural pressure [P_{pl}]). General anesthesia (required for robotic bronchoscopy) causes an increase in P_{pl} relative to P_a due to loss of muscular tone of the diaphragm, generating abdominal compression of the lungs and other respiratory muscles (ie, intercostals, scalene). The weight of mediastinal structures upon the lung also generates atelectasis.[1] Furthermore, during bronchoscopy, airway obstruction due to bronchoscope insertion, blood clots, mucus plugging, or instillation of saline diminishes P_a and further contributes to the development of atelectasis.

WHY IT MATTERS

Atelectasis can cause false-positive radial probe endobronchial ultrasound (R-EBUS) images, leading to nondiagnostic samples. It is also partially responsible for the phenomenon of CT-to-body divergence during navigational bronchoscopy as atelectasis deforms the lungs. Although we can correct for CT-to-body divergence with intraoperative CBCT, the most feared outcome is when atelectasis completely obscures the target, preventing confirmation of tool-in-lesion and sampling. The description of atelectasis during bronchoscopy had an enormous clinical impact, leading to the reversal of the order of procedures in patients undergoing both mediastinal staging and diagnostic peripheral bronchoscopy, with the latter performed first (in patients without clear adenopathy).[2,3]

ATELECTASIS FREQUENCY AND AREAS AFFECTED

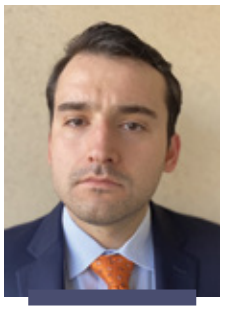
Published in 2020, the I-LOCATE (**I**ncidence and **Loc**ation of **Ate**lectasis) trial was an observational prospective study in which 57 patients undergoing bronchoscopy under general anesthesia were subject to an atelectasis survey carried out with R-EBUS at the end of bronchoscopy. Eight bronchial segments in dependent areas (right bronchus [RB] 2, RB6, RB9, RB10, and left bronchus [LB] 2, LB6, LB9, LB10) were assessed for atelectasis. At a median time of 33 minutes from anesthesia induction to atelectasis survey, 89% (95% CI, 78%-96%) of participants had atelectasis in at least one bronchial segment. The highest incidences occurred in dependent lung segments, with rates of 70% to 79% in LB6, LB10, and RB10. Not surprisingly, risk factors for atelectasis include higher BMI and longer procedural time.

To characterize by chest CT scan the areas of the lungs with increased risk of atelectasis, in a post hoc analysis Khan and colleagues studied the CBCT images obtained during the VESPA (**Ve**ntilatory **S**trategy to **P**revent **A**telectasis) trial.[4] To simplify their findings and provide our readers with a practical tip, if we draw a horizontal line at the anterior surface of the vertebral body in the CT slice corresponding to our target and our target is located posterior to this line, it is at high risk (greater than 50%) of being obscured by atelectasis. It is in these cases that a preventive strategy should be used, particularly in patients with high BMI and lower lobe lesions.

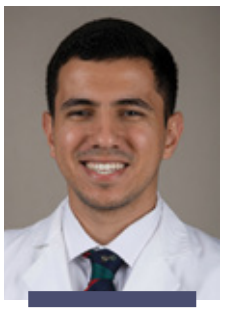
EFFECTIVE STRATEGIES TO MITIGATE ATELECTASIS

Ventilatory and positional strategies have been recently described. The VESPA trial was designed to prevent atelectasis during nodal sampling with a convex-probe endobronchial ultrasound (C-EBUS). Seventy-six patients undergoing C-EBUS were randomized 1:1 to a control group with standard ventilation (laryngeal mask airway, 100% FiO_2 and zero PEEP) or VESPA group (endotracheal intubation; FiO_2 titration as low as feasible to maintain oxygen saturation between 94% and 96%; PEEP between 8 and 10 cm H_2O; tidal volumes [VT] of 6-8 mL/kg ideal body weight [IBW]; and a recruitment maneuver of 10 breaths at a plateau pressure of 40 cm H_2O with 20 cm H_2O of PEEP). The proportion of patients with any atelectasis (unilateral or bilateral) on CBCT scan performed 40 to 45 minutes from induction of anesthesia was reduced from 84% (95% CI, 72.6%-95.8%) in the control group to 29% (95% CI, 15.4%-45.9%) in the VESPA group ($P < .001$).

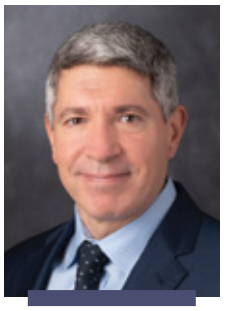
There were no significant differences between the two groups regarding complication rates, which were all minor; 24% of the control group experienced hypotension requiring intermittent doses of vasopressors compared with 29% of the VESPA group.[5] Retrospective reports of local experiences with other ventilatory strategies, with VT and PEEP twice as high as those in VESPA, and with prolonged breath-holds—likely used to compensate for the exaggerated target motion arising in the very high VT they selected—also reduced atelectasis rates to the 20% to 30% range but caused hemodynamic instability in up to 70% of the patients.[6]



Christopher Bertini, MD



Abdul-Rahman Halawa, MD



Roberto F. Casal, MD, FCCP

With the aim of fully eradicating atelectasis, the same group of investigators that carried out I-LOCATE and VESPA trials developed a positional strategy for robotic bronchoscopy, the Lateral Decubitus Strategy (LADS).[7] This approach involves placing patients in lateral decubitus position with the target lesion side up, along with standard ventilation, without the need for PEEP or recruiting maneuvers. Their initial report on this strategy was followed by a randomized controlled trial of LADS vs VESPA comparing these two approaches in patients undergoing robotic bronchoscopy for nodules measuring 3 cm or smaller located in dependent lung zones (at-risk zone as described previously).[8] Twenty-

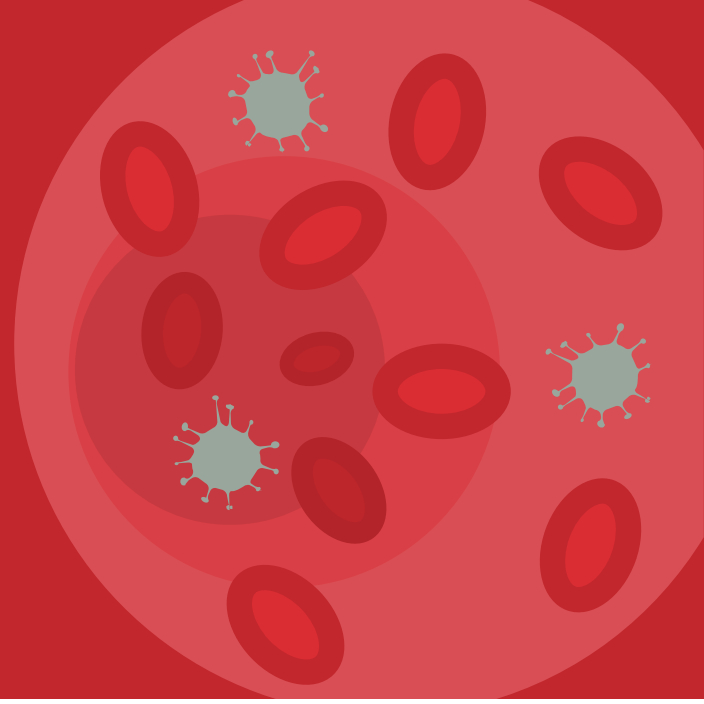
// continued on page 11

Column

The 2026 Surviving Sepsis Campaign

Applying guidelines at the bedside

BY ELIZABETH S. MUNROE, MD, MS



High-quality sepsis care hinges on early recognition and treatment. Sepsis management is both time-sensitive and complex, depending on streamlined processes that start before a patient arrives at the hospital, with prehospital sepsis screening, and continue through discharge. The Surviving Sepsis Campaign (SSC) guidelines distill available evidence into actionable recommendations aimed at helping clinicians navigate these complex processes and manage patients based on the most up-to-date evidence.[1] The new SSC guidelines, released in March 2026, provide 129 statements covering topics ranging from screening and early management to coordinating hospital discharge and addressing long-term outcomes.

UNDERSTANDING GUIDELINES

To understand how to apply the SSC guidelines in practice, it is important to understand why and how these guidelines are developed. The SSC guidelines, which are sponsored by the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) and endorsed by numerous multidisciplinary societies, are updated approximately every four years to capture new evidence and changing practices. The guidelines represent a massive undertaking by a diverse group of clinicians from around the world, including physicians across subspecialties, nurses, pharmacists, and physical therapists. For each selected topic, the committee conducts a systematic review of the literature and develops recommendations based on structured grading of the evidence, as outlined in the "Table of Statements" in the guideline publication.[1]

Despite this rigorous process for development, the SSC guidelines have been met with unfortunate backlash recently. In the United States, conditional recommendations from prior guidelines were translated into sepsis management bundles (SEP-1) that are now used as value-based purchasing, or pay-for-performance, measures by the US Centers for Medicare and Medicaid Services (CMS). This has blurred the line between guidelines and policy and resulted in accusations that the SSC guidelines are causing harm by mandating early antibiotics and aggressive fluid resuscitation.

Such framing misconstrues the intent of the SSC guidelines, which were developed to help bedside clinicians care for individual patients based on current evidence. The SSC guidelines aim to inform practice through feasible and broadly applicable recommendations that can be implemented across clinical settings.

These recommendations are not meant to be absolute. Rather, they often allow for nuance and acknowledge the realities of balancing complex factors involved in decision-making.

GUIDELINES BREAKDOWN

Most statements in the 2026 guidelines (63%) are "Conditional" recommendations, meaning they are based on low-to-moderate-quality evidence and are best framed as suggestions. Conceptually, it is reasonable to apply these recommendations for most patients, though shared decision-making and consideration of the clinical context may alter treatment.

In contrast, there are 19 "Strong" recommendations, which are typically based on higher-quality evidence and represent interventions that should be given to all, or nearly all, patients. For example, early antibiotic therapy and de-escalation of antibiotics after culture data return are both strong recommendations.

The 2026 SSC guidelines also offer a helpful new category of "In Our Practice" statements, which were made when there was very low certainty evidence for a topic. "In Our Practice" statements were developed by surveying the guideline panelists about their practices. For example, of the 69 panel members, 87% use peripheral vasopressors at least occasionally and 37% routinely treat patients with septic shock without invasive arterial blood pressure monitoring. While these statements in no way indicate that these are the best practices, they provide useful context to understand the clinical landscape in areas where evidence is less robust.

NOTABLE RECOMMENDATIONS

Overall, the updated SSC guidelines emphasize the importance of clinical evaluation, monitoring, and nuanced decision-making in the balance of risks and benefits of therapy. The guidelines encourage pairing proactive screening and early treatment with thoughtful approaches to diagnostic evaluation and antimicrobial stewardship. This helps clinicians navigate the challenge of time-sensitive management while avoiding overdiagnosis and overtreatment.

In particular, the guidelines highlight the importance of proactive screening and make a new conditional recommendation to screen patients for sepsis en route to the hospital (ie, in the ambulance or in flight). Simultaneously, the guidelines also acknowledge that there is no ideal sepsis screening tool, meaning not all patients with a positive screen have sepsis and should receive treatment. Therefore, the guidelines make a new conditional recommendation for the use of sepsis huddles or code sepsis teams—structured processes for responding to positive sepsis alerts—emphasizing that screening should prompt a clinical evaluation to inform treatment decisions.

Similarly, while the recommendation for time-to-antibiotics has not changed, the updated guidelines take two major steps to clarify this recommendation and minimize unwanted harms of antibiotic treatment.

First, the updated guidelines more clearly define "definite," "probable," and "possible" sepsis. Based on these definitions, the guidelines recommend antibiotics within one hour for all patients with definite sepsis (meaning sepsis is confirmed, eg, by positive blood cultures) or probable sepsis (meaning sepsis is number one on the differential), which aligns with clinical

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When PH and ILD meet // continued from cover

A COMMON AND CONSEQUENTIAL OVERLAP

PH is a frequent and clinically significant sequela of ILD. The development of PH in this population is associated with marked reductions in exercise capacity, increased hospitalization risk, and substantially worse survival outcomes compared with ILD alone.[1,2]

Studies have suggested that the prevalence of PH rises with disease severity, with reports suggesting it may occur in up to 86% of patients with end-stage idiopathic pulmonary fibrosis.[1] Despite this, diagnosis remains challenging, as symptoms such as dyspnea, fatigue, and reduced exercise tolerance overlap with those of ILD itself.

This diagnostic ambiguity often leads to delayed recognition.

"One of the biggest challenges is identifying which patients actually have PH, particularly given that definitive diagnosis still depends on invasive right heart catheterization," Dr. Kulkarni said.

Moreover, the severity of pulmonary vascular disease does not consistently correlate with the extent of fibrotic lung involvement.[1]

"We do not rely on echo for the diagnosis of PH, especially in group 3 disease, where echocardiographic estimates may mislead," said Todd M. Bull, MD, Director of the Center for Lungs and Breathing and the Pulmonary Vascular Disease Center at the University of Colorado Anschutz. "When suspicion is high and treatment is contemplated, invasive hemodynamic assessment remains essential."

This disconnect reinforces the need to move beyond a simplistic advanced ILD framework and instead recognize PH-ILD as a distinct entity.[1]

DISEASE OF DUAL PATHOBIOLOGY

At its core, PH-ILD reflects the convergence of two interrelated but partially independent processes: pulmonary fibrosis and vascular remodeling.[1] Chronic hypoxia, endothelial dysfunction, and inflammatory signaling contribute to progressive remodeling of small pulmonary arteries, increasing pulmonary vascular resistance and ultimately imposing strain on the right ventricle. At the same time, fibrotic pathways—driven by cytokines, growth factors, and extracellular matrix deposition—continue to reshape the lung parenchyma.

Profibrotic and vasoconstrictive mediators act in both domains, reinforcing what is increasingly recognized as a dual-pathway disease.[1] This challenges the notion that PH is merely a late manifestation of ILD. Rather, it positions PH-ILD as a distinct cardiopulmonary syndrome requiring targeted evaluation and management.

FROM SILOS TO SYNERGY

Historically, ILD and PH have been treated within parallel clinical silos—pulmonologists focusing on antifibrotic therapies and PH specialists targeting vascular dysfunction. That model is rapidly becoming obsolete.

For optimal care, Dr. Kulkarni said, it is important to bring together the ILD specialist, the PH expert, and, as the disease advances, lung transplant teams, so they can all work together.

Dr. Bull said this collaboration reflects a broader shift in care delivery and is essential to effective care. "It involves partnering PH specialists with other providers integral to the care of the patient to provide the best evidence-based care," he said.

Importantly, the push toward multidisciplinary care is not driven solely by pathophysiology; it is also shaped by patient priorities.

"In all ILD trials, we have physiologic outcomes. I'm making their lung function test look better, but that may not matter to the patient," said Corey Kershaw, MD, FCCP, Chair of CHEST's Diffuse Lung Disease and Lung Transplant Network and Clinical Services Chief of the Pulmonary and Critical Care Medicine at UT Southwestern Medical Center.

He recalled a patient who asked, "What about the fact that I can't play golf anymore? Is that test going to help me play golf?" That encounter changed Dr. Kershaw's care priorities.

"We need to think about comorbidity management and things that matter for the patient," he said. "It's so far beyond difficulty breathing. We need to have partners to help manage the things that matter the most to the patient."

THE IMPACT OF TREPROSTINIL

Few developments have reshaped PH-ILD management as dramatically as the emergence of inhaled treprostinil.[3,4] Historically, therapeutic progress in this space was limited, and there were significant concerns that pulmonary vasodilators might worsen ventilation-perfusion mismatch.

"For years, we didn't have anything," Dr. Kulkarni said. "Our treatment options for the past decade focused on antifibrotic therapies. But as the disease progressed and patients developed PH, therapeutic options were limited and lung transplantation remained the only curative strategy. It is now recognized as a treatable complication of fibrotic lung disease, particularly for patients who are not eligible for lung transplant."

The INCREASE trial demonstrated that inhaled treprostinil improves exercise capacity and reduces clinical worsening in PH-ILD—marking the first successful randomized trial in this population.[3] Dr. Bull described this milestone as "a huge step forward."

AN EXPANDING THERAPEUTIC PIPELINE

While inhaled treprostinil has become foundational, it is increasingly clear that it represents only the beginning of a wider therapeutic evolution. Emerging agents are targeting shared mechanisms across vascular and fibrotic pathways, reflecting a shift toward integrated disease modification.

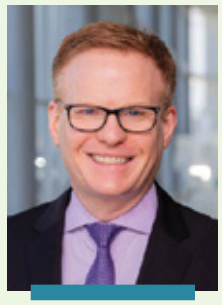
One example is CS014, an investigational oral histone deacetylase (HDAC) inhibitor.[5] By influencing gene expression pathways linked to tissue scarring, blood vessel abnormalities, and abnormal clotting, it aims to address multiple drivers of PH-ILD simultaneously. Dosing and participant visits in a phase 1 pharmacokinetic-bridging study have been completed, with top-line results anticipated later this year.[5]

Other approaches include mechanistic target of rapamycin (mTOR) inhibition with inhaled sirolimus (LAM-001). Data from a small phase 2a open-label study suggest improvements across multiple clinically relevant end points, including a 67.4-meter increase in 6-minute walk distance and a 33.9% reduction in pulmonary vascular resistance at 24 weeks in patients with PH-ILD.[6] LAM-001 targets the mTOR pathway, implicated in both pulmonary vascular remodeling and fibrotic processes, further reinforcing the convergence of vascular and fibrotic biology.[6]

The broader pipeline includes inhaled soluble guanylate cyclase activators, tyrosine kinase inhibitors such as seralutinib, and novel prostacyclin formulations.[1] While many remain investigational, the diversity of mechanisms reflects a shift toward combination and pathway-targeted therapies.

At the same time, drug delivery is evolving. Current inhaled therapies can be

Todd M. Bull, MD



Corey Kershaw, MD, FCCP

Tejaswini Kulkarni, MD, MPH, FCCP

burdensome, often requiring multiple daily doses. Although improvement in symptoms or exercise capacity is clinically meaningful for patients, treatment regimens requiring administration four times a day may present adherence challenges, Dr. Kulkarni said.

The PH-ILD experience has also highlighted an important cautionary lesson: Treatments that are effective in patients with pulmonary arterial hypertension cannot be assumed to translate to PH-ILD.[7] Endothelin receptor antagonists and riociguat have failed to demonstrate benefit. Similarly, phosphodiesterase-5 inhibitors have shown inconsistent results.[7]

Dr. Bull advised caution, noting that he generally does not recommend them because of a lack of evidence of efficacy and the potential for harm, particularly related to ventilation-perfusion mismatch.

THE PATH FORWARD

Despite meaningful progress, several critical challenges remain. One unresolved issue is the clinical significance of mild or "borderline" PH in ILD. As hemodynamic definitions evolve, determining when treatment is warranted remains uncertain.

Early detection is another unmet need. Drs. Kulkarni, Bull, and Kershaw all agreed that improved screening strategies to identify patients before advanced hemodynamic compromise develops are needed.

"One of the biggest challenges is identifying these patients sooner so we can start them on treatment sooner," Dr. Kulkarni said.

The PHINDER study aims to address this need by investigating a standardized evidence-based clinic screening algorithm for early identification of PH in patients who have ILD.[8]

Disease surrogates are another area of ongoing interest and research. This is perhaps where machine learning applied to larger physiologic data sets, such as PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) will be fruitful, Dr. Bull said.[9]

As the evidence evolves, capturing data on tolerability as well as measures such as time to clinical worsening will be important to better reflect the patient experience, Dr. Kershaw said.

For clinicians, the shift in this space demands a broader perspective that integrates vascular and parenchymal disease, emphasizes early detection, and prioritizes multidisciplinary care.

"We have gone from no specific treatments to an FDA-approved medication and multiple ongoing trials," Dr. Bull said. "It is an exciting time in PH-ILD research." ●

All references are available online at chestphysician.org.

Atelectasis in peripheral bronchoscopy

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nine patients were randomized to LADS and 33 to VESPA. The median BMI was 27.9 (IQR 23.8-32.7), the median target size was 1.6 cm (IQR 1.1-2.1), and 87.1% of the targets were in the lower lobes. The primary outcome was atelectasis obscuring target in CBCT, which was reduced from 27.3% (95% CI, 13.3%-45.5%) in the VESPA group to 0% in the LADS group (P = .002).

Additionally, the LADS group had higher tool-in-lesion confirmation (100% vs 72.7%, P = .002) and higher diagnostic yield (86.2% vs 57.6%, P = .013) compared with that of the VESPA group. Patients who crossed over from the VESPA arm to the LADS arm after developing atelectasis obscuring targets experienced complete resolution of atelectasis, with subsequent tool-in-lesion confirmation in all cases and diagnostic confirmation in 78% of crossover patients. Procedure times, radiation exposure, and complication rates (only minor) were comparable between groups. LADS was found to be a highly successful strategy to prevent and eradicate atelectasis, leading to better procedural outcomes.[8]

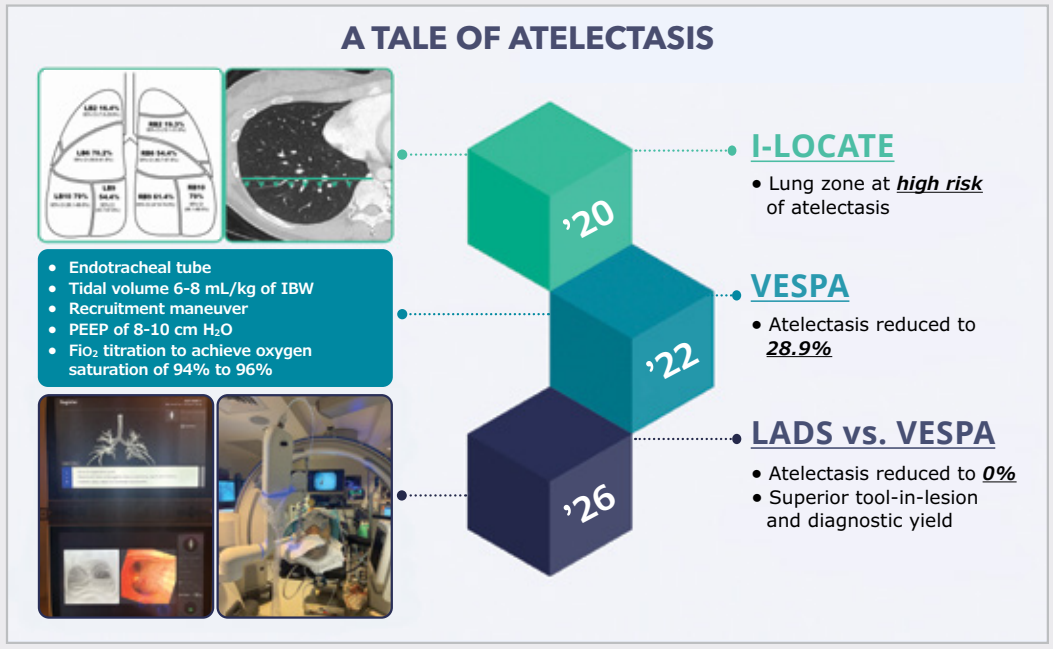
The use of prone positioning (PP) to prevent atelectasis has been retrospectively described in small case series.[9] While there is little doubt that PP would be effective (interventional radiologists commonly use PP for CT-guided percutaneous approach), it is evidently more complicated than LADS. PP requires an experienced team (typically not available in the bronchoscopy suite) to proceed with extreme caution and coordination. If any complication should arise (pneumothorax, bleeding, extubation, intravenous line dislodgement), these would all be harder to manage. Unlike in LADS where the target lung is free of atelectasis (shift of atelectasis to the dependent lung), in PP, atelectasis is shifted ventrally within the target lung, which can still cause CT-to-body divergence, being detrimental to navigational bronchoscopy.

Based on the available literature, LADS, when feasible, is the procedure of choice for patients with high BMI and lesions located in dependent areas.

INCORPORATING THESE CONSIDERATIONS EFFECTIVELY

With diagnostic accuracy, patient safety, and procedural efficiency in mind, we recommend a systematic approach to robotic bronchoscopy. A reasonable strategy that targets the vital components of the preparation for robotic bronchoscopy is the so-called A, B, C, D strategy.[10] In a nutshell, this includes **a**telectasis prevention, **a**rtificial **a**irway selection and **a**irway clearance, **b**ed adjustment and patient positioning on the bed, **C**-arm isocentering and **c**ollision check, and **d**ocking of the robot. Estimating the risk of atelectasis obscuring target (based on patient's BMI and target location), communicating with the anesthesia team, and selecting the most suitable prevention strategy, when needed, are cornerstone aspects of this approach.[10] ●

All references are available online at chestphysician.org.



Evolving biologic treatment options improving outcomes for patients with COPD

BY FARRUKH ABBAS, MD, FCCP; NICOLA ALEXANDER HANANIA, MD, MS, FCCP | EDITED BY TAYLOR FITHIAN

As the third leading cause of death worldwide, COPD remains a major public health concern even as treatment options improve.[1] Projections show an estimated 645.6 million people will have COPD by 2050, which equates to a 36% relative increase in global prevalence since 2020.[2]

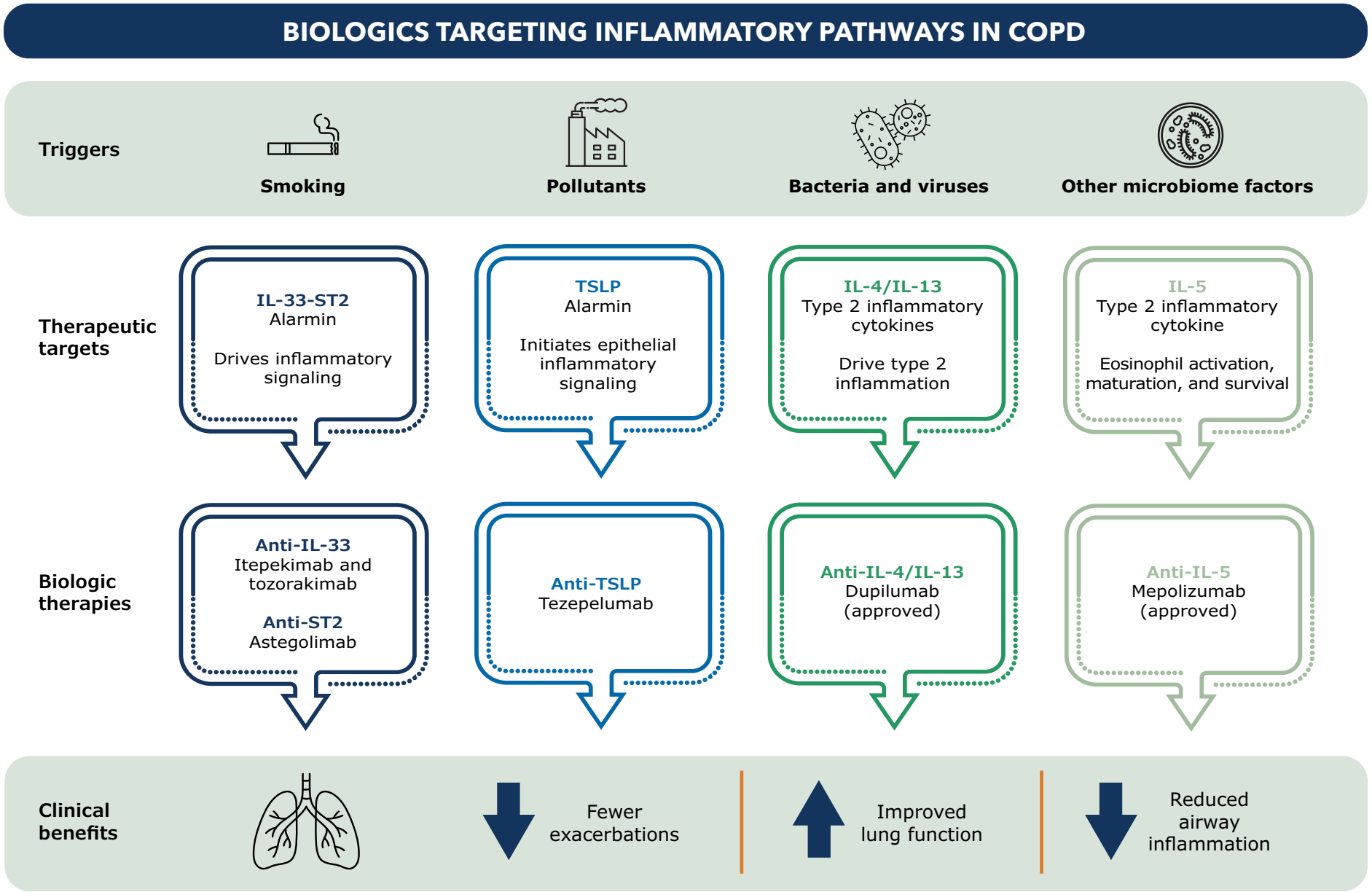
About one-half of patients with COPD continue to experience exacerbations despite adequate adherence to inhaled triple therapy with an inhaled corticosteroid (ICS), a long-acting β_2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA).[3] Additionally, 20% to 40% of patients with COPD have evidence of type 2 inflammation, which is associated with increased exacerbation risk and accelerated lung function decline.[4]

Building on the success of biologics in asthma, a similar precision medicine approach is improving outcomes for select patients with COPD, with blood eosinophils emerging as a key biomarker. The 2026 report from the Global Initiative for Chronic Obstructive Lung Disease recommends adding biologic therapy for patients with one severe or two moderate exacerbations despite adherence to triple therapy if the patient's absolute blood eosinophil count is 300 cells/μL or greater.[5]

Despite the recent approvals of dupilumab and mepolizumab, not all biologics targeting eosinophilic inflammation have demonstrated consistent benefit in COPD. Benralizumab, an interleukin (IL)-5 receptor α antagonist approved by the US Food and Drug Administration for severe eosinophilic asthma, did not meet the

COPD BIOLOGICS CLINICAL TRIAL LANDSCAPE

Drug and target	Phase 2a	Phase 2b	Phase 3	Status
Dupilumab (IL-4Rα)			BOREAS NOTUS	FDA-approved
Mepolizumab (IL-5)	ISS	COPD-HELP	METREX METREO MATINEE SUMMER	FDA-approved
Benralizumab (IL-5Rα)	ABRA		GALATHEA TERRANOVA RESOLUTE	Phase 3 trials did not meet primary end points
Tezepelumab (TSLP)	COURSE UPSTREAM-COPD		EMBARK JOURNEY	COURSE did not meet primary end point. Results of UPSTREAM-COPD expected in late 2027.
Itepekimab (IL-33)	POC AERIFY-3		AERIFY-1 AERIFY-2 AERIFY-4	AERIFY-1 met primary end point. AERIFY-2 did not meet primary end point. Results of AERIFY-4 expected in early 2027.
Tozorakimab (IL-33)	FRONTIER-4		OBERON TITANIA MIRANDA PROSPERO	Phase 3 trials met their primary end points. The regulatory submission and full data presentation process is ongoing.
Astegolimab (ST2)	COPD-ST2OP	ALIENTO	ARNASA	ALIENTO met its primary end point, however COPD-ST2OP and ARNASA did not.



primary end points in the phase 3 GALATHEA and TERRANOVA trials. Subsequent findings from the phase 2 ABRA trial suggested a potential role for benralizumab during acute eosinophilic exacerbations, with benralizumab demonstrating superiority to oral prednisolone.[6]

In addition, the results of the RESOLUTE study of benralizumab were announced in 2025. Despite showing numerical improvement compared with placebo, benralizumab did not achieve statistical significance for the primary end point—the annualized rate of moderate or severe COPD exacerbations over 56 weeks.[7]

Another inflammatory pathway under investigation is IL-33, with tozorakimab emerging as one of the leading investigational therapies. Positive findings from the OBERON and TITANIA trials, together with results from MIRANDA, have suggested potential benefit across a broader range of patients with COPD.[8] More recently, the phase 2a FRONTIER-4 trial further supported this by demonstrating encouraging efficacy among patients at high risk for exacerbations despite not meeting its primary end point.[9]

Other investigational agents targeting the IL-33 pathway include itepekimab and astegolimab. However, results have been mixed. AERIFY 1 showed a reduction in exacerbations, but the results were not reproduced in AERIFY 2.[10] In the phase 2 ALIENTO study, astegolimab was associated with lower exacerbations in patients with COPD, while in the phase 3 ARNASA trial, it did not reach statistical significance.[11,12] In addition, the phase 2a COPD-ST2OP evaluating astegolimab showed a nonsignificant reduction in exacerbation rates compared with placebo.[11]

Researchers have also investigated upstream inflammatory targets, including thymic stromal lymphopoietin (TSLP). Tezepelumab, a monoclonal antibody targeting TSLP, did not meet the primary end point in the phase 2a COURSE trial.[13] However, the results identified a subgroup of patients who may derive greater benefit, findings that have informed ongoing phase 3 studies.

Emerging next-generation therapies, including bispecific antibodies such as lunsekimig that simultaneously target TSLP and IL-13, reflect the continued evolution of biologic therapy beyond single-pathway inhibition.[14] ●

All references are available online at chestphysician.org.

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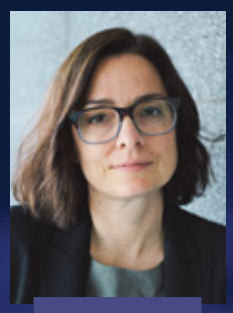


Sleep in the ICU

Why closed eyes do not mean rest

BY FAWAZ ALSHAMMARI, MD; MARY ELIZABETH WILCOX, MD, PHD

Many intensive care physicians have heard the comment, "At least the patient is asleep." Yet critically ill patients often experience fragmented sleep, circadian disruption, and loss of restorative slow-wave and rapid eye movement (REM) sleep despite appearing asleep or being sedated.[1,2] Increasing evidence suggests that sleep is a key component of recovery, with sleep disruption linked to delirium, delayed recovery, and long-term neurocognitive impairment.[1,3]

Understanding the unique nature of sleep disturbances in critical illness, the distinction between sedation and physiological sleep, and strategies to promote restorative sleep may provide an opportunity to improve both short- and long-term patient outcomes.

WHY SLEEP MATTERS

Sleep is a highly organized process involving cycles of nonrapid eye movement (NREM) and REM sleep. Slow-wave sleep, the deepest stage of NREM sleep, supports memory consolidation, immune regulation, and tissue repair.[4] It also enhances glymphatic clearance of metabolic waste products, including β-amyloid and tau proteins, which may help preserve cognitive function.[4,5] Sleep is also essential for maintaining circadian rhythms through interactions among the suprachiasmatic nucleus, melatonin secretion, light exposure, and homeostatic sleep drive. Critical illness disrupts these pathways, causing circadian dysregulation and abnormal sleep-wake patterns.[3,6]

While sleep deprivation in healthy individuals usually causes transient fatigue and impaired concentration, its effects in patients who are critically ill may be more serious. Combined with inflammation, organ dysfunction, medications, and physiological stress, sleep disruption has been linked to delirium, immune dysfunction, metabolic disturbances, delayed recovery, and long-term neurocognitive impairment.[1,3]

SEDATION IS NOT SLEEP

One of the most common misconceptions in critical care is that a sedated patient is a sleeping patient. From the bedside perspective, the distinction can seem academic. A patient receiving propofol, benzodiazepines, or opioid infusions may appear asleep and unresponsive. However, electrophysiological studies demonstrate that sedative-induced unconsciousness differs substantially from natural sleep. Natural sleep follows an organized architecture characterized by predictable cycling through NREM and REM stages. These stages are accompanied by coordinated neurochemical changes that regulate normal sleep architecture. Many commonly used ICU sedatives disrupt these normal physiological processes rather than reproducing them.[6,7]

Benzodiazepines suppress slow-wave sleep and REM sleep. Opioids fragment sleep architecture and reduce REM sleep.[6,7] Propofol induces unconsciousness but does not reliably reproduce the restorative physiological characteristics of natural sleep.[6,7] Consequently, a patient may spend hours appearing asleep while obtaining little of the biological benefits associated with restorative sleep. In short, unconsciousness is not synonymous with sleep.

WHY SLEEP BECOMES DISRUPTED IN THE ICU

Sleep disruption in the ICU is nearly universal and arises from a combination of environmental, physiological, and treatment-related factors. Noise from alarms, equipment, staff activity, and routine patient care frequently interrupts sleep, while nighttime light exposure and inadequate daytime light disrupt normal circadian rhythms.

Critical illness further impairs sleep through pain, dyspnea, anxiety, fever, inflammation, delirium, and organ dysfunction. Mechanical ventilation may contribute through patient-ventilator dyssynchrony, endotracheal tube discomfort, and recurrent respiratory-related arousals. Sedative medications, although often necessary, can also alter normal sleep architecture.[3]

As a result, patients who are critically ill commonly experience fragmented sleep, loss of circadian rhythmicity, and marked reductions in slow-wave and REM sleep.[2] Polysomnographic studies show that sleep is often redistributed across the entire 24-hour period, with patients spending most of their sleep time in lighter stages and experiencing substantial reductions—or even absence—of the restorative sleep stages most important for recovery.[2]

WHY SHOULD WE CARE?

Short-term consequences

Sleep deprivation affects nearly every organ system. Cognitively, sleep loss impairs attention, executive function, memory formation, and emotional regulation. These effects may contribute to the development and persistence of ICU delirium, one of the most common complications of critical illness. Delirium is associated with prolonged hospitalization, increased mortality, higher health care costs, and worse long-term cognitive outcomes.[3] Emerging evidence also suggests that disrupted sleep may contribute to the persistent cognitive impairment experienced by many survivors of critical illness.

Beyond its neurological effects, sleep deprivation has important consequences for immune, metabolic, cardiovascular, and respiratory function. Experimental studies have demonstrated alterations in both innate and adaptive immune responses, potentially impairing recovery from infection and systemic inflammation. Metabolic consequences include insulin resistance, impaired glucose regulation, and hormonal dysregulation, while cardiovascular effects include increased sympathetic activity, elevated catecholamine concentrations, and impaired autonomic control.[3,6] In patients who are mechanically ventilated, fragmented sleep may also contribute to respiratory muscle fatigue and difficulty weaning from ventilatory support.[1,3] Collectively, these observations highlight the broad physiological consequences of sleep disruption and reinforce the importance of sleep as a component of recovery from critical illness.

Long-term consequences

The consequences of sleep disruption often extend well beyond ICU discharge. Many survivors of critical illnesses report chronic insomnia, fragmented sleep, excessive daytime sleepiness, anxiety, depression, and symptoms consistent with posttraumatic stress disorder months to years after hospitalization.[1] These are increasingly recognized as important components of post-intensive care syndrome (PICS)—a constellation of physical, cognitive, and psychological impairments that persist following critical illness.

Particularly concerning is the association between sleep disruption and long-term cognitive impairment. Between 30% and 50% of patients who leave the ICU experience persistent deficits in memory, attention, and executive function that may last for years after recovery from critical illness.[1] Although multiple mechanisms likely contribute, including systemic inflammation, hypoxia, microvascular injury, delirium, and sedative exposure, sleep disruption may represent an important and potentially modifiable factor. Emerging evidence suggests that impaired slow-wave sleep may disrupt glymphatic function, reducing the clearance of neurotoxic proteins such as β-amyloid and tau.[4,8] While direct causal relationships remain to be established, these findings provide a biologically plausible framework linking sleep disruption during critical illness to persistent neurocognitive dysfunction.

WHAT CAN WE DO ABOUT IT?

Importantly, sleep disruption may be at least partially modifiable.

Nonpharmacologic interventions

The strongest evidence for improving sleep in the ICU supports multicomponent nonpharmacologic interventions.[3,6] Preserving normal circadian cues is a logical first step. During daytime hours, patients should be exposed to natural light whenever possible, encouraged to remain awake, and mobilized early. At night, lights should be dimmed, and unnecessary stimulation should be minimized to promote a more normal sleep-wake cycle.[3,6] Noise reduction is equally important. Alarm optimization, staff education, designated quiet hours, earplugs, and environmental modifications have all been associated with improvements in subjective sleep quality.[1,6]

Care clustering may be one of the simplest and most effective interventions available. Consolidating medication administration, laboratory testing, and routine nursing assessments can substantially reduce unnecessary nighttime awakenings.[3,6] Sleep promotion also requires attention to common clinical contributors to sleep disruption. Pain control should be optimized, recognizing that untreated pain remains a major cause of sleep fragmentation. Similarly, anxiety, dyspnea, and patient-ventilator dyssynchrony should be identified and addressed promptly.[3] Although evidence supporting individual interventions varies, bundled approaches appear to provide the greatest overall benefit.[3]

Pharmacologic approaches

Pharmacologic strategies for sleep promotion in the ICU remain considerably less well-supported than nonpharmacologic interventions. Melatonin is an attractive option because it targets circadian regulation rather than simply inducing sedation. Although clinical trials have yielded mixed results, melatonin is relatively safe, inexpensive, and biologically plausible as an adjunctive therapy for sleep promotion in critically ill patients.[3,6]

Dexmedetomidine has generated particular interest because of its ability to produce electroencephalographic patterns that more closely resemble physiological NREM sleep. Several studies have demonstrated improvements in sleep architecture and reductions in delirium compared with benzodiazepine-based sedation strategies. However, dexmedetomidine should not be viewed as a dedicated sleep medication and should be used within the context of individualized sedation goals.[3,6,7] In contrast, traditional hypnotic agents such as benzodiazepines, antihistamines, and antipsychotics lack strong evidence for routine sleep promotion in patients who are critically ill and may worsen delirium or further disrupt normal sleep architecture.[3,6]

THE BOTTOM LINE

Sleep disruption is one of the most common yet underrecognized complications of critical illness. Although many questions remain unanswered, the available evidence increasingly supports treating sleep as an essential component of ICU care rather than a secondary comfort measure. Strategies aimed at preserving circadian rhythms, minimizing nighttime disruptions, reducing unnecessary sedation, and promoting restorative sleep have the potential to improve both short- and long-term outcomes. As our understanding of ICU sleep continues to evolve, improving sleep quality may become an increasingly important therapeutic target. Perhaps the next frontier in critical care is not simply helping patients survive but helping them sleep well enough to recover. ●

All references are available online at chestphysician.org.

Advancing diaphragm dysfunction care

A team-based approach to evaluation and management

BY JASON DEAN, MSN, APRN, FNP-C

The overwhelming pressures of health care access, cost, reimbursement, and staffing made apparent during the outbreak of the COVID-19 pandemic have transformed the current health care climate. It has evolved to include advanced practice providers (APPs) in a multitude of settings. The implementation has led to numerous benefits including cost reduction, increased patient access, and improved patient satisfaction.[1] With a collaborative relationship and supportive leadership, APPs can not only gain expertise but also help establish and grow subspecialty clinics.[2]

IDENTIFY A NEED

One such specialty facility is the Cleveland Clinic Restrictive Thoracic Disorders Clinic, which allows us to focus on diaphragm dysfunction (DD). DD is often underrecognized and may be evaluated using a variety of assessment methods.[3] The condition may arise from underlying neuromuscular disease, late-stage obstructive lung disease, invasive surgical procedures, traumatic injury, prolonged hospitalization—with or without mechanical ventilation—or even cervical chiropractic manipulation.[4] Patient symptoms can be varied, with intensity ranging from milder positional intolerance to acute symptoms with life-threatening implications.

Patients with DD often present with reports of unexplained dyspnea, dyspnea on exertion, orthopnea, bendopnea, trepopnea, postprandial dyspnea, difficulty front-loading vs side-loading weight, trouble when submerged in water, or alterations to cough/sneeze strength.[5] In acute-onset DD, identifying the initiation of symptoms is vital. With iatrogenic or transient nerve palsy, such as in neuralgic amyotrophy, there can be spontaneous recovery with a time window extending to two years in some cases.

Pulmonary physicians and APPs can be instrumental in streamlining the assessment and management process for these patients. Though it is uncommon for institutions to have dedicated diaphragm-specific clinics for patients with DD, APPs can help fill the void to support these subspecialty clinics as they gain the appropriate training through both didactic and physician/APP-based mentorship pathways.

DD ASSESSMENT

Spirometry is the cornerstone of the assessment process in patients with suspected DD. Sitting-to-supine spirometry and maximal inspiratory pressure (MIP) testing are the two most common tests. While total lung capacity is often reduced in patients with bilateral dysfunction, vital capacity with the sit-to-supine transfer may be a more reliable measure in patients with unilateral dysfunction.[5] These tests not only serve as qualifying measures for noninvasive ventilation (NIV) support but also challenge the diaphragm to quantify the degree of weakness. A loss in FVC of greater than 20% in the supine position can be used as an indicator of diaphragm weakness.[5] An MIP of > -60 cm H_2O can raise the suspicion for nocturnal hypoventilation as muscle atonia occurs.

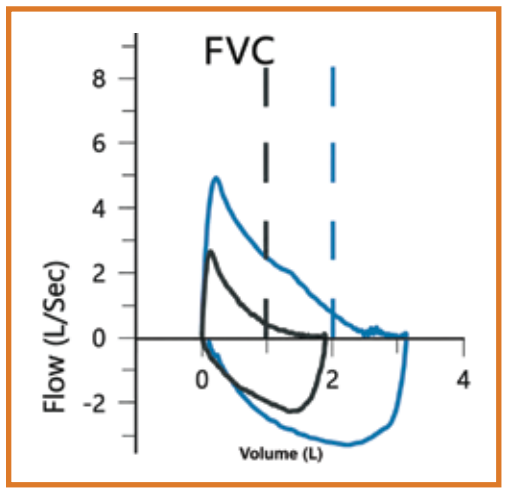


Figure 1. *Sitting-to-supine change in the FVC of a patient with bilateral hemi-diaphragm impairment.*

Chest X-ray is also a frequently used diagnostic tool to assess diaphragm dysfunction, and often, the incidental finding of an elevated hemidiaphragm triggers the pulmonary evaluation.[4] In addition to chest X-ray, other diagnostic methods that clinicians can use to build the diagnosis of DD include sniff fluoroscopy, electromyography, and phrenic nerve conduction studies. While these diagnostic methods are validated, their sensitivity and specificity are limited when compared with methods like diaphragm ultrasound.[6]

Lastly, point-of-care ultrasound (POCUS) is a useful tool that has multiple benefits when compared with other diagnostic methods when considering cost, ionizing radiation, ability to repeat, real-time assessment, and enhanced understanding for the patient. While many physicians receive training with diagnostic ultrasound during their residency and fellowship, diaphragm ultrasound remains a niche exam with limited implementation on a large-scale basis. Specially trained APPs can bridge the gap that exists surrounding outpatient POCUS assessment of DD.

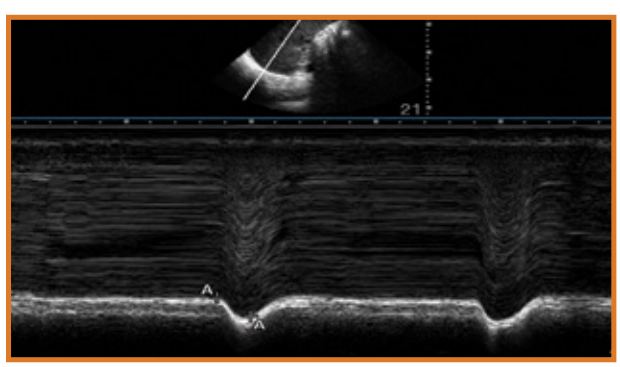


Figure 2. *Paradoxical motion in the right hemi-diaphragm with rapid sniff maneuver on ultrasound.*

DD can be treated conservatively with weight loss, positional therapy, or respiratory muscle training. Patients with an FVC <50% predicted, an MIP > -60 cm H_2O, a $Paco_2$ ≥45 mm Hg, or nocturnal oxygen desaturation to ≤88% for ≥5 minutes may benefit from NIV support.[7] Diaphragm pacing and surgical plication are options for managing DD. Surgical plication should not be considered prior to one year.[4] Plication should be reserved for unilateral diaphragm paralysis. Diaphragm pacing is most effective for patients with high-level spinal cord injury, but it has been used during the observation period for temporary paralysis.[4] Diaphragm pacing and surgical plication are available options for patients who do not have spontaneous recovery.

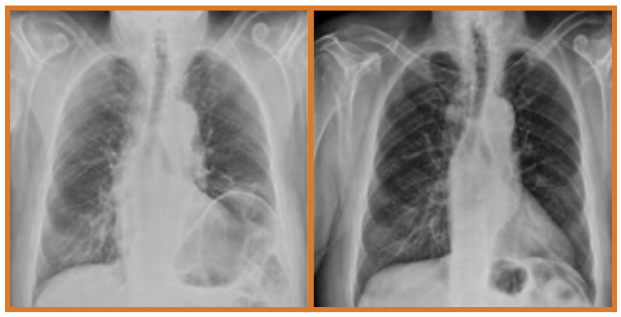


Figure 3. *Chest X-ray showing presurgical to post-surgical plication of the diaphragm.*

TRAINING, MENTORSHIP, GROWTH

As for my experience, I received initial training at the CHEST Annual Meeting. Following that specialized didactic training, physicians within our institution provided continuing mentorship to further grow my knowledge and skill. The use of POCUS has helped our team better diagnose, monitor, and educate patients presenting with DD. This has expanded the reach of our subspecialty clinic through referrals from both within our institution and outside institutions. POCUS assessments have increased to include all pretransplant patients, posttransplant assessment of patients with prolonged mechanical ventilation, cardiothoracic surgical patients with complications, autoimmune-mediated lung disease, and multiple upcoming funded studies. Performing diaphragm ultrasounds has become an essential component of our institution's approach to caring for highly complex medical and surgical cases.

Our institution's guiding principle has always been "patients first," and we are able to strive toward this goal because of the supportive leadership and dedication to framing health care models that put patients at the center. Our rapid growth has been made possible because of the close collaborative relationship between physicians and APPs within our institution. With an ever-changing health care environment, I hope that the bond between APPs and physicians continues to strengthen with our shared goal to provide high-quality care for our patients. ●

All references are available online at chestphysician.org.

Surviving Sepsis Campaign

// continued from page 9

decision-making. For patients with possible sepsis (meaning sepsis is one of several diagnoses on the differential), antibiotics are recommended only within one hour for patients in shock, where shorter time-to-antibiotics has a stronger association with mortality and there is less room for error.

Second, the guidelines balance the recommendation for rapid antibiotics with an increased focus on stewardship, emphasizing both appropriate upfront antibiotic selection and de-escalation of antibiotic therapy once culture data become available. While critics have raised concerns that the SSC recommendation for rapid antibiotics will lead to overprescription and increased resistance, this has not been borne out in the literature, where studies have found no evidence of overtreatment when hospitals or clinicians deliver antibiotics more quickly.[2,3] However, appropriate antibiotic selection is key to preventing unnecessary harms of treatment.

The 2026 guidelines include a new conditional recommendation against empiric antianaerobic coverage for infections unlikely to be caused by anaerobic pathogens—for example, respiratory and urinary tract infections, based on evidence that antianaerobic antibiotics alter the microbiome and may be associated with increased mortality.[4] The guidelines also suggest against empiric antifungal coverage, highlighting that fungal coverage should be considered on a case-by-case basis.

The 2026 SSC guidelines for fluid resuscitation also emphasize the need to balance the risks and benefits of fluid through thoughtful application and de-escalation. The updated guidelines make an unchanged conditional recommendation for 30 mL/kg initial IV fluid for patients with sepsis-induced hypoperfusion (hypotension or elevated lactate) or shock. While this fluid volume is reasonable in most patients, the guidelines highlight the importance of considering individual patient characteristics in fluid decisions and the need for frequent, ongoing reassessments, preferably using dynamic measures such as passive leg raise, to prevent fluid overload. The guidelines also make a new conditional recommendation for "active fluid removal"—the use of diuretics or ultrafiltration to remove excess fluid—following the acute resuscitation phase in patients with signs of fluid overload. Together, these updates acknowledge the potential risks of fluid and highlight the importance of close monitoring and active management.

ADDITIONAL CONSIDERATIONS

There are several other new and revised recommendations in the 2026 SSC guidelines that warrant brief mention. First is the conditional recommendation to target an initial mean arterial pressure (MAP) of 60-65 mmHg, rather than ≥65 mmHg, in patients over 65 years old. While this recommendation was made based on evidence that lower MAP targets can spare vasopressors and potentially improve mortality in older patients, for now CMS still requires a MAP goal of 65 mmHg, complicating the implementation of this recommendation.[5]

Second, the guidelines now make a strong recommendation for extended β-lactam infusions based on accruing moderate certainty evidence that extended infusions increase time above the minimum inhibitory concentration (MIC) and improve antibiotic efficacy.[6] This recommendation reflects an important opportunity for clinicians to review their local practice and consider modifications to antibiotic order sets to default β-lactam orders to extended infusions after the initial loading dose.

Finally, the guidelines make a conditional recommendation for selective decontamination of the digestive tract for mechanically ventilated patients in settings with low rates of antimicrobial resistance. Selective decontamination of the gut is an infection prevention strategy that involves the use of topical and targeted IV antibiotics aimed at eliminating pathogenic bacteria while maintaining the microbiome. While the data supporting selective decontamination are promising, with meta-analyses showing lower rates of infection and mortality, implementation warrants careful consideration at the local hospital level, in consultation with infection prevention specialists, to understand potential risks and benefits based on local epidemiology and resistance patterns.[7]

HIGH-QUALITY SEPSIS CARE

In summary, the 2026 SSC guidelines reaffirm that sepsis management is both time-sensitive and nuanced. The guidelines provide a practical framework to support early sepsis recognition and treatment, while emphasizing the importance of clinical evaluation, monitoring, and stewardship, providing a strong foundation for high-quality, patient-centered sepsis care. ●

All references are available online at chestphysician.org.

Column

Leadership begins before the title

The CHEST Annual Meeting is quickly approaching, and I am looking forward to seeing everyone in Phoenix (October 18 to 21). Every year, the meeting reminds me that some of our greatest opportunities for growth happen outside our own institutions. We come together to learn, exchange ideas, and develop as clinicians and as leaders.

I've been asked before how I became involved in leadership and my answer is always the same: There was no plan. I knew I wanted to take great care of patients and, along the way, opportunities arose.

If I have been successful in leadership, it is because I have been surrounded by really great people who have supported me and provided coaching and mentorship, while also providing honest, constructive feedback.

Neil Freedman, MD, FCCP

A consistent obstacle I see is that most clinicians are never formally taught how to lead. It's often assumed that if someone is an excellent clinician, they will naturally become an excellent leader, but those are different skill sets.

A title in and of itself does not make you a good leader. Leadership is a competency that develops over time and can be practiced anywhere, whether you are serving on a committee, mentoring a trainee, leading a multidisciplinary team, or volunteering in your community.

To me, the foundation of leadership is inspiring people to do great things, and, in doing so, building future leaders, supporting your colleagues, and helping others succeed.

Strong leadership also depends on creating environments where people feel safe to contribute and different perspectives are welcomed. Diversity of thought makes us stronger. Bringing together clinicians with different specialties, backgrounds, experiences, and viewpoints leads to better solutions for our patients and our profession.

As a leader, I want to hear what I don't know, but that mindset requires being humble, understanding that you have blind spots, and fostering a psychologically safe environment. People should feel comfortable sharing ideas, asking questions, and respectfully disagreeing. As I remind the groups I lead, everyone is encouraged to speak their mind, but that does not mean that you get your way. The goal is better decisions, not unanimous agreement.

What I've always loved about CHEST is that it is an organization that focuses on welcoming this diversity of thought. Our leaders—from the Board of Regents to the Networks to committees, task forces, and work groups—have a wide range of backgrounds, credentials, and specialties, and we are better for it.

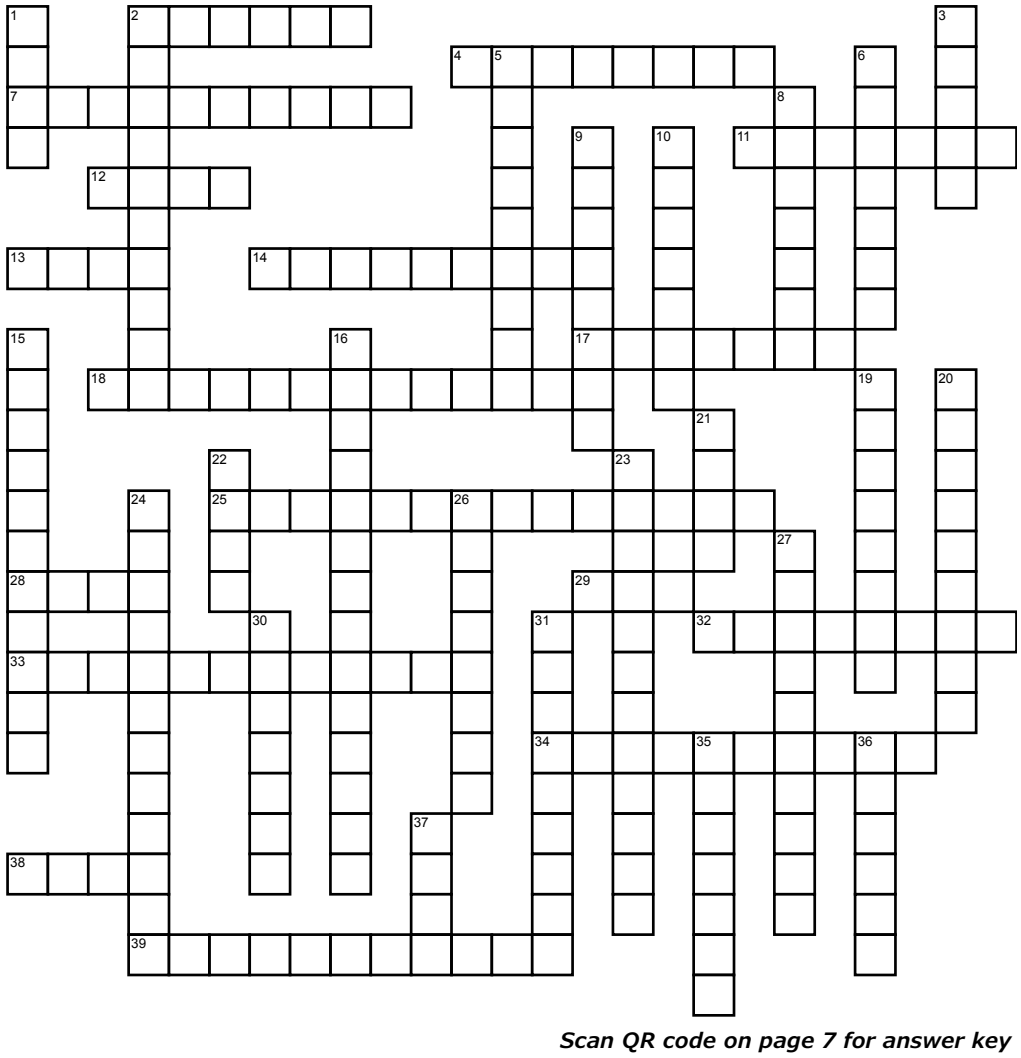
The organization is also uniquely positioned to help interested members develop into strong leaders. Beyond top-tier clinical education, we offer opportunities to build connections through mentorship, Network and Interest Group involvement, and more.

While in Phoenix, I encourage you to make the most of your time. Beyond attending the educational sessions, introduce yourself to someone new every day. Sign up for a simulation course. Attend a networking event. Seek out a mentor or become one.

Leadership does not begin with a title. It begins with curiosity, humility, and a willingness to learn from those around you. I hope you make the most of every opportunity that the CHEST Annual Meeting offers and leave Phoenix with not only new clinical knowledge but also new relationships and new leadership skills that will benefit your patients, your colleagues, and our profession. ●

CHEST Puzzler

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



Scan QR code on page 7 for answer key

ACROSS

2. _____ history is an unmodifiable, independent risk factor for the fifth-leading cause of cancer death (or lung cancer in individuals who never smoked) (May p.1174,1391)
4. In OSA, as with CPAP, discontinuation of oral appliances (which advance THIS bone) may approach 50%, inspiring hypoglossal nerve stimulation and medication options (May p.1171)
7. Drug class that has both anti-inflammatory and antimicrobial effects in bronchiectasis (Jun p.1427)
11. ECMO candidacy article reviews cognitive clinical biases. One is the _____ fallacy that if a random outcome recently has been infrequent, it is more likely to happen next (or vice versa). Clue for readers of a certain age: Kenny Rogers song. (Jun p.1653)
12. High-dose flu shots are recommended if older than 65 years and may also be better in patients with solid organ transplants. It has THIS many times the normal amount of antigen. (May p.1179)
13. Frontal chest X-rays can miss pleural effusions up to _____-hundred mL in volume (Jun p.1770)
14. Lung cancer screening prevalence in 2024 was 18%; less likely in adults without insurance and more likely in this region of the United States (Apr p.1148)
17. Echogenic pleural effusions by ultrasound are more likely to be classified as THIS type (Jun p.1770)
18. See review of fungal infections in patients who are immunocompetent. Think of this one in a hunter if his dog got sick first. Disseminated disease in up to 25%! (Jun p.1517)
25. Lung cancer in individuals who have never smoked affects females two-thirds of the time, is more common in Asian individuals, and is almost always THIS PATHOLOGY. Systematic review suggests TB and chronic bronchitis might also be risks. (Jun p.1717)
28. In a pragmatic randomized trial, a small number of patients enrolled in tobacco cessation if they got messages via THIS METHOD. Patients contacted more were more likely to join… but also more likely to opt out (30%). (Jun p.1462)
29. MIST2 trial showed that pleural tPA and DNase added sequentially, each with an hour dwell time, THIS number of times over three days improves parapneumonic effusions. Real-world data shows patients getting half as much. (Apr p.879,1115)
32. Intranasal flu vaccine is approved for ages 2 through 49 years without underlying medical conditions and who are not _____ (May p.1179)
33. Rhino-orbital fungal disease feared in patients with uncontrolled diabetes (Jun p.1515)
34. Review of pleural effusions: this hemothorax, exclusive to women, named from the Greek word for "monthly" (Jun p.1766)
38. Serologic diagnosis of fungal infections includes antibody testing, which is _____ [more or less?] sensitive in hosts who are immunosuppressed (Jun p.1518)
39. Novel PAH-specific therapy that is the "S" in PULSAR and STELLAR trials (May p.1313)

DOWN

1. Life-sustaining technology, a bridge to recovery, that can supply oxygenated blood to patients in refractory respiratory and/or circulatory failure (Jun p.1653)
2. Payer-driven drug formulary changes may deviate from asthma guidelines, such as maintenance and reliever therapy NOT containing THIS specific long-acting β-agonist (Apr p.868,1039)
3. Prediction models like THIS one will tell you a 65-year-old with peripheral lung adenocarcinoma may have occult malignancy by EBUS 5.8% of the time. Model is not named after *The Simpsons* patriarch. (Jun p.1454)
5. Use of these has increased 10%, subjecting participants to lower barometric pressure and hypoxic risks if there is underlying cardiopulmonary or neuromuscular disease (May p.1372)
6. A CHEST statement outlines gaps in research needed to have effective policies, since the FDA was granted control of THIS in products in 2009 (May p.1415)
8. A novel functional status questionnaire correlates better with symptoms and quality of life, perhaps because it is filled out by THIS PERSON (Apr p.870,1064)
9. Consumer sleep trackers include wearable devices as well as contactless ones that go underneath your _____ (Apr p.1101)
10. Both *Histoplasma* and *Coccidioides* fungal infections can, about 5% to 10% of the time, cause rheumatologic manifestations like erythema multiforme, erythema _____, and arthralgias (Jun p.1517)
15. Term given for a loculated pleural effusion within a lung fissure that appears mass-like (Jun p.1770)
16. B-D-glucan testing for candidemia can be false-positive after dialysis, shock, abdominal surgery, or some infusions, including THIS one (Jun p.1566)
19. The most common cause of drug-induced pleural effusions now is dasatinib, a first-generation _____-kinase inhibitor (Jun p.1767)
20. First-line therapy for hypersensitivity pneumonitis; visual fibrosis on CT scan may identify who also benefits from immunomodulatory treatment (Jun p.1580)
21. SwAB-IT trial shows in patients with CF age 12 years or older, sputum collection was feasible and acceptable when done in THIS location (Jun p.1430,1488)
22. Radiographic sign named for a circle of perilesional hemorrhage in invasive *Aspergillus* in patients with neutropenia (Jun p.1512)
23. Nebulized COPD medication that inhibits both phosphodiesterase-3 and -4 (Jun p.1437)
24. Lung cancer screening with low-dose CT scan can also identify this condition that 10 million US adults have, 80% of whom are women (May p.1382)
26. Benign, small, unilateral eosinophilic/hemorrhagic pleural effusion can occur 20 to 40 years after this occupational exposure (Jun p.1769)
27. Histoplasmosis is worldwide, occurs from inhalation of spores from soil with bird/bat guano, including during this recreational activity (Jun p.1517)
30. Prospective cohort study proposes OSA might be a cause of this common daytime pulmonary symptom (Apr p.873,1092)
31. Being analytic and not just intuitive can avoid diagnostic errors. Forced functions like timeouts and this type of tool (as among pilots) can help. (Jun p.1659)
35. _____-flavored aerosols in e-cigarettes can cause dose-dependent cell damage comparable to combustible smoke exposure (May p.1422)
36. Large language models did well on multiple-choice and OSCE-type questions for this condition, named from the Greek word "to breathe hard" (May p.1286)
37. FDG-PET has inadequate accuracy for identifying malignant pleural effusions. _____ pleurodesis can result in pleural thickening with significant PET uptake. (Jun p.1773)

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]

See where the journey leads at JASCAYDhcp.com

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.

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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