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VOL. 18 • NO. 8 • AUGUST 2023

CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Grafton Marshall Smith/Getty Images

Older adults admitted to the ICU today appear at greater risk for poor outcomes than those admitted in prior years.

Geriatric care principles should apply to ICUs as well, experts say

BY NEIL OSTERWEIL
MDedge News

Baseball legend Leroy "Satchel" Paige famously said that "age is a question of mind over matter: If you don't mind, it doesn't matter."

But even the strongest and most supple minds can't avoid the effects of advanced age and accompanying physical frailty, and for community-dwelling elderly with pulmonary diseases frailty is a predictor of both hospitalization and death, investigators have found.

For example, among 1,188 community-dwelling older adults enrolled in the Toledo (Spain) Study for Healthy Aging, declining pulmonary function measured by forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) was associated with increased risk for frailty and hospitalization, and a more than twofold greater risk for death in participants both with and without respiratory diseases. These findings were reported by Walter Sepulveda-Loyola, PhD, PT, MSC, from the Faculty of Health and Social Sciences at Universidad de Las Americas in Santiago, Chile, and colleagues in the journal Heart & Lung (2023 Feb 14. doi: 10.1016/j.hrtlng.2023.01.020).

Similarly, results of a meta-analysis performed by investigators at Jiangsu (China) University showed that, among 13,203 patients with chronic

GERIATRIC CARE // *continued on page 6*

Is ChatGPT a friend or foe of medical publishing?

BY LUCY HICKS

Researchers may use artificial intelligence (AI) language models such as ChatGPT to write and revise scientific manuscripts, according to a new announcement from the International Committee of Medical Journal Editors. These tools should not be listed as authors, and researchers must denote how AI-assisted technologies were used, the committee said.

These new guidelines are the latest effort for medical journals to define policies for using these large-scale language models (LLMs) in scientific publication. While these AI-assisted tools can help with tasks such as writing, analyzing data, catching mistakes, and much more, they are also prone to errors, noted Casey Greene, PhD, a professor of biomedical informatics at the University of Colorado at Denver, Aurora. It is also not totally clear how information is stored and processed in these kinds of tools, and who has access to that information, he noted.

At the same time, experts argue that these AI tools could have a positive impact on the field by

PUBLISHING // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Biologic therapy and asthma comorbidities

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Nucala
(mepolizumab)
Injection 100 mg/mL

BATTLE TESTED IN EOS DISEASE

Backed by real-world and clinical trial evidence—NUCALA protects SEA patients from exacerbations

INDICATION

NUCALA is indicated for the add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype. NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

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

Opportunistic Infections: Herpes Zoster
In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred with NUCALA compared to none with placebo. Consider vaccination if medically appropriate.

Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

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

Exacerbation reduction for SEA patients with NUCALA

Trial 2 (pivotal study): Exacerbations*/year at Week 32: NUCALA, 0.83 vs placebo, 1.74 (*P*<0.001, **primary endpoint**).
53% reduction in exacerbations vs placebo.[1]

REAL-WORLD STUDY: EXACERBATION* DATA OUT TO 2 YEARS[2]

AT 1 YEAR†
post-exposure (N=820)

71%
REDUCTION

Primary Objective:
1.24/year vs baseline 4.29/year
Rate ratio 0.29 (95% CI: 0.26, 0.32)

AT 2 YEARS‡
post-exposure (N=820)

74%
REDUCTION

Secondary Objective:
1.11/year vs baseline 4.29/year
Rate ratio 0.26 (95% CI: 0.24, 0.29)

Assessed vs 1-year† pre-exposure period (baseline), N=821. Results are descriptive.

Real-world study design: 2-year, single-arm, prospective, observational, cohort study assessing effectiveness/safety of NUCALA every 4 weeks in 822 adults with SEA initiated on NUCALA. Data collected prospectively at usual appointments; 1 year of prior medical data collected retrospectively at enrollment from medical records and patient recall. Baseline visit was first administration of NUCALA. **Safety:** At 2 years (N=822): 27% discontinued NUCALA (2% due to an AE; 9% lack of efficacy; 15% other). AEs (N=823): drug-related AEs 11%, serious AEs <1%, and most common AE was headache (4%). **Limitations:** Real-world studies are designed to evaluate associations among variables and not to definitively establish causality. Limitations important when interpreting results: no comparator arm; differences in patient populations and data collection vs randomized controlled trials.[2]

Trial 2 design: 32-week study comparing NUCALA to placebo, each added to SOC,[§] in 576 patients aged ≥12 years with SEA.

*Defined as worsening of asthma requiring: systemic corticosteroids or hospitalization or emergency department visit; or at least double the existing maintenance systemic corticosteroid dose for ≥3 days.
†1-year analysis model.
‡2-year analysis model.
§Defined as regular treatment with high-dose ICS and ≥1 other controller with or without OCS.
AE=adverse event; CI=confidence interval; ICS=inhaled corticosteroid; OCS=oral corticosteroid; SEA=severe eosinophilic asthma; SOC=standard of care.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Parasitic (Helminth) Infection

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

ADVERSE REACTIONS

In clinical trials in patients receiving NUCALA, the most common adverse reactions (≥5%) were headache, injection site reaction, back pain, and fatigue. Systemic reactions, including hypersensitivity, also occurred. Manifestations included rash, pruritus, headache, myalgia, and flushing; the majority were experienced the day of dosing.

USE IN SPECIFIC POPULATIONS

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

The data on pregnancy exposures are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

REFERENCES: 1. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13):1198-1207. **2.** Data on file, GSK.

See why NUCALA is BATTLE TESTED at **Nucala4SEA.com**

NUCALA (mepolizumab) for injection, for subcutaneous use
NUCALA (mepolizumab) injection, for subcutaneous use
The following is a brief summary only and is focused on the indication for maintenance treatment of severe asthma with an eosinophilic phenotype. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience in Severe Asthma

Adult and Adolescent Patients Aged 12 Years and Older

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

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

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

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

52-Week Trial: Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in patients receiving mepolizumab 75 mg IV compared with 2 patients in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions: In Trials 1, 2, and 3 described above, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 3% in the group receiving NUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving NUCALA 100 mg and 2% of patients in the placebo group. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving NUCALA 100 mg and 3% of patients in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in patients receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.
Injection Site Reactions: Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in patients receiving NUCALA 100 mg compared with 3% in patients receiving placebo.
Long-term Safety: Nine hundred ninety-eight patients received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

Pediatric Patients Aged 6 to 11 Years

The safety data for NUCALA is based upon 1 open-label clinical trial that enrolled 36 patients with severe asthma aged 6 to 11 years. Patients received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of NUCALA administered subcutaneously once every 4 weeks. Patients received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 patients received NUCALA for a further 52 weeks (long phase). The adverse reaction profile for patients aged 6 to 11 years was similar to that observed in patients aged 12 years and older.

6.5 Immunogenicity

In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 or 100 mg, 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.
The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.6 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to NUCALA or a combination of these factors.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg subcutaneous (*see Data*).
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an ACU basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.
In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.
Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT01691521) and had a mean age of 14.8 years. Patients had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Patients had a reduction in the rate of exacerbations that trended in favor of NUCALA.

(continued on next page)

8.4 Pediatric Use *(cont'd)*
Of the 19 adolescents who received NUCALA, 9 received 100 mg and the mean apparent clearance in these patients was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.
Use of NUCALA in pediatric patients aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in children aged 6 to 11 years. A single, open-label clinical trial (NCT02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneous every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg subcutaneous *[see Clinical Pharmacology (12.3) of full prescribing information]*.
The effectiveness of NUCALA in pediatric patients aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents *[see Clinical Pharmacology (12.3) of full prescribing information]*. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2) of full prescribing information]*.
The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.

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

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

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

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Research Triangle Park, NC 27709

Revised: 1/2022 NCL:9BRS

MPLJRNA220010 January 2023
Produced in USA.

GERIATRIC CARE // continued from page 1

obstructive pulmonary disease (COPD), frailty was associated with a more than 2.6-fold relative increase in risk for death from any cause, and "prefrailty," an intermediate state between frailty and "robustness," was associated with a 48% relative increase in all-cause mortality. Frailty was also associated with a 2.2-fold risk for COPD exacerbations of any severity, the authors reported in JAMDA: The Journal of Post-Acute and Long-Term Care Medicine (2023 May 4. doi: 10.1016/j.jamda.2023.03.032).

The good (old) USA

In June 2023 the U.S. Census Bureau announced that the median age of the U.S. population is now 38.9 years, and according to a 2016 Census Bureau report funded by the National Institutes of Health, "America's 65-and-over population is projected to nearly double over the next three decades, from 48 million to 88 million by 2050."

"These data show that increases in vulnerability are not simply due to chronological age, and they suggest that to identify those with greater baseline vulnerability, screening for geriatric syndromes at ICU admission may be warranted."

With the graying of the U.S. population the burden on pulmonary and critical care experts will almost inevitably increase, as evidenced by research from Julien Cobert, MD, from the University of California, San Francisco, and colleagues.

The investigators looked at trends over time in older adults admitted to ICUs from 1988 through 2015 using data from the Health and Retirement Study (HRS), a nationally representative, longitudinal study of older adults. They found that rates of preexisting frailty, disability, and multimorbidity increased over the study period.

"Our findings suggest a growing prevalence of geriatric conditions among older adults admitted to the ICU, suggesting a pressing need to integrate geriatric principles into critical care medicine. Further research could examine if early interventions emphasizing physical, cognitive, mental health, delirium prevention, advance care planning, and rehabilitation individualized to critically ill elderly patients with preexisting geriatric conditions could improve ICU outcomes and post-ICU recovery," they wrote in a study published in the journal *Chest* (2022 Jun; 161[6]:1555-65).

In an editorial accompanying the study by Dr. Cobert and colleagues, Nathan E. Brummel, MD, from the Ohio State University College of Medicine and Davis Heart and Lung Research Institute in Columbus, said "the finding that nearly 30% of overall HRS participants were admitted to the ICU provides novel data about the extent to which older Americans are affected by critical illness (*Chest*. 2022 Jun;161[6]:1436-7). Because the number of older Americans is projected to continue to increase for the next 30 years or more, these data make clear the ongoing importance of aging-focused research and clinical care."

Dr. Brummel also noted that older adults who are admitted to the ICU today are at greater risk for poor outcomes than those admitted in prior years, as evidenced by the increased prevalence of disability, frailty, and multimorbidity.

"Moreover, because the average age of those admitted to the ICU only changed by 1 year during the study, these data show that increases in vulnerability are not simply due to chronological age, and they suggest that to identify those with greater baseline vulnerability, screening for geriatric syndromes at ICU admission may be warranted," he wrote.

Geriatric principles in the ICU

"I think what's most important is that we think about patients from a geriatric principles standpoint, not just when they're admitted to the hospital but especially when they're admitted to the ICU," Dr. Cobert said in an interview.

"The first step is ensuring that we're asking questions about their underlying comorbidities, especially around frailty, hearing, vision loss, falls, multimorbidities, polypharmacy – things that are primarily done on the outpatient side in geriatric clinics, but things that we should probably be a little bit more cognizant of, given that we're starting to see higher rates of patients coming in with these issues," he said.

Critical care specialists need to take a more holistic approach and try to understand as best they can each patients' goals and then determine whether the ICU staff are acting in concordance with those goals, he emphasized.

GERIATRIC CARE *continued on following page*

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

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

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limiting some of the linguistic disparities in scientific publishing as well as alleviating the burden of some monotonous or mechanical tasks that come along with manuscript writing.

What experts can agree on, though, is that the use of AI tools is here to stay. "This is going to become a common tool," Dr. Greene said. "I don't think there's a way out of that at this point."

A change in medical publishing

OpenAI released ChatGPT in November 2022. In its own words, ChatGPT is "a deep learning model that has been trained on a massive amount of text data to understand and generate human-like text."

Enter a question or a prompt, and it will respond. For example, when asked how the AI tool can be used in scientific publishing, ChatGPT responded: "ChatGPT can aid scientific publishing by generating ideas, clarifying concepts, conducting preliminary literature reviews, providing proofreading and editing suggestions, and assisting with outlining and organizing scientific papers. However, it should be used as a supportive tool alongside domain expertise and validation from trusted scientific sources."

Just a few months after ChatGPT became available, researchers began using this tool in their own work. One individual, Som Biswas, MD, a radiologist at the University of Tennessee Health Science Center in Memphis, reportedly used ChatGPT to author 16 scientific articles in just 4 months, according to the Daily Beast. Five of these articles have been published in four different journals. Dr. Biswas declined to be interviewed for this article.

There were also reports of papers with ChatGPT as one of the listed authors, which sparked backlash. In response, JAMA, Nature, and Science all published editorials in January outlining their policies for using ChatGPT and other large language models in the scientific authoring process. Editors from the journals of the American College of Cardiology and the American College of Rheumatology also updated their policies to reflect the influence of AI authoring tools.

The consensus is that AI has no place on the author byline.

"We think that's not appropriate, because coauthorship means that you are taking responsibility for the analysis and the generation of data that are included in a manuscript. A machine that is dictated by AI can't take responsibility," said Daniel Solomon, MD, MPH, a rheumatologist at Brigham and Women's Hospital, Boston, and the editor in chief of the ACR journal Arthritis & Rheumatology.

Issues with AI

One of the big concerns around using AI in writing is that it can generate text that seems plausible but is untrue or not supported by data. For example, Dr. Greene and colleague Milton Pividori, PhD, also of the University of Colorado, were writing a journal article about new software they developed that uses a large language model to revise scientific manuscripts.

> *"The majority of research is published in English. Responsible use of LLMs can potentially reduce the burden of writing for busy scientists and improve equity for those who are not native English speakers."*

"We used the same software to revise that article and at one point, it added a line that noted that the large language model had been fine-tuned on a data set of manuscripts from within the same field. This makes a lot of sense, and is absolutely something you could do, but was not something that we did," Dr. Greene said. "Without a really careful review of the content, it becomes possible to invent things that were not actually done."

In another case, ChatGPT falsely stated that a prominent law professor had been accused of sexual assault, citing a Washington Post article that did not exist.

"We live in a society where we are extremely concerned about fake news," Dr. Pividori added, "and [these kinds of errors] could certainly exacerbate that in the scientific community, which is very concerning because science informs public policy."

Another issue is the lack of transparency around how large language models like ChatGPT process and store data used to make queries.

"We have no idea how they are recording all the prompts and things that we input into ChatGPT and their systems," Dr. Pividori said.

OpenAI recently addressed some privacy concerns by allowing users to turn off their chat history with the AI chatbot, so conversations cannot be used to train or improve the company's models. But Dr. Greene noted that the terms of service "still remain pretty nebulous."

Dr. Solomon is also concerned with researchers using these AI tools in authoring without knowing how they work. "The thing we are really concerned about is that fact that [LLMs] are a bit of a black box – people don't really understand the methodologies," he said.

A positive tool?

But despite these concerns, many think that these types of AI-assisted tools could have a positive impact on medical publishing, particularly for researchers for whom English is not their first language, noted Catherine Gao, MD, a pulmonary and critical care instructor at Northwestern University, Chicago. She recently led research comparing scientific abstracts written by ChatGPT and real abstracts and discovered that reviewers found it "surprisingly difficult" to differentiate the two.

"The majority of research is published in English," she said in an email. "Responsible use of LLMs can potentially reduce the burden of writing for busy scientists and improve equity for those who are not native English speakers."

Dr. Pividori agreed, adding that as a non-native English speaker, he spends much more time working on the structure and grammar of sentences when authoring a manuscript, compared with people who speak English as a first language. He noted that these tools can also be used to automate some of the more monotonous tasks that come along with writing manuscripts and allow researchers to focus on the more creative aspects.

In the future, "I want to focus more on the things that only a human can do and let these tools do all the rest of it," he said.

New rules

But despite how individual researchers feel about LLMs, they agree that these AI tools are here to stay.

"I think that we should anticipate that they will become part of the medical research

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GERIATRIC CARE *continued from previous page*

For example, ICU clinicians should try to understand whether patients were losing function or having mobility difficulties before hospital and ICU admission, and what they hope to retain when or if they are discharged. ICU staff can then try as much as reasonably possible to minimize interventions that could contribute to impairment after discharge.

Frailty and COPD in the ICU

There are special considerations for frail elderly with obstructive airway disease, Dr. Cobert noted.

Patients with advanced COPD, for example, are likely to be on home oxygen.

"Home oxygen is a big deal," he said. "It can definitely help with functioning and there's potentially a mortality benefit in certain populations. But that said, it's a flammable object that they have to carry around and lug with them all the time. It contributes to falls, it's tethering, it's life-limiting in many ways."

Many patients with COPD also have multiple rehospitalizations, and for clinicians the challenge is "understanding what their goals are, what their motivations are, especially when they live with dyspnea, with advanced lung disease. Is intubation within their goals of care? Has their functional status been declining over time? Are there things that we can optimize holistically and globally as their COPD advances over time?"

Another important component of critical care for the frail elderly is consideration of patients' palliative care needs and what their symptoms and symptom burdens were like prior to hospitalizations.

"The ICU experience and the critical illness experience may serve as an inflexion point – more likely a downward inflection point – whereby their needs increase, their symptoms can worsen, and their health, especially their global health, worsens. Their preexisting geriatric conditions might be a moving target after another hit and another traumatic stressor like the ICU setting," Dr. Cobert said.

The study by Dr. Cobert and colleagues was supported by the National Institute on Aging. Dr. Cobert had no reported conflicts of interest. ■

Real-world study widens benralizumab effectiveness

BY TERRY L. KAMPS, PHD

The real-world ZEPHYR 2 study, which assessed benralizumab for effectiveness in treating severe eosinophilic asthma, was extended with an analysis of a larger population stratified into three cohorts of participants who were aged 12 years or older. Pre- and posttreatment data showed an improvement in asthma control for each group.

Immunotherapy with monoclonal antibodies designed to block specific inflammatory pathways is a recommended add-on treatment for adults to manage severe, uncontrolled eosinophilic-dependent (> 150 cells/µl) and corticosteroid-dependent asthma. One such biologic, benralizumab, targets the interleukin-5 receptor alpha chain (IL-5Rα).

For asthma patients who had previously been treated with benralizumab, there were significant reductions in exacerbation rates in the ZEPHYR 1 study. However, information regarding benefit associated with specific profiles was limited, warranting a larger study to address effectiveness when considering various blood eosinophil counts, prior treatments with other biologics, or benralizumab use for up to 24 months, Donna Carstens, MD, of AstraZeneca, Wilmington, Del., and colleagues write.

Study details

In the retrospective cohort ZEPHYR 2 study, which was published in the Journal of Allergy and Clinical Immunology: In Practice (2023 May 2. doi: 10.1016/j.jaip.2023.04.029), the researchers retrieved deidentified patient information from medical, laboratory, and pharmacy U.S. insurance claims records from the PatientSource and DiagnosticSource databases and compared asthma exacerbation rates before and after treatment with benralizumab.

Age, asthma diagnosis, number of exacerbations, and number of benralizumab treatment records within specified periods were used to identify a total of 1,795 participants for inclusion in the study. The index date for establishing before-treatment and after-treatment index time intervals of 12 months each was defined as the day after the initial benralizumab treatment occurring between November 2017 and June 2019.

The cohort was stratified into three non-mutually exclusive groups consisting of 349 patients who had switched primarily from either omalizumab or mepolizumab biologics to benralizumab; 429 patients subdivided by closest to the index date blood eosinophil counts of less than 150, greater than or equal to 150, 150-299, less than 300, and greater than or equal to 300; and 419 patients with post data collection extended beyond 12 months to 18 or 24 months.

Similarities in baseline patient characteristics that were observed across the three cohorts included a mean age range of 51-53 years, preponderance of women (67%-69%), obesity diagnosis (31.5%-32.9%), and a mean Charlson Comorbidity Index of 1.47-1.52. Allergic rhinitis was the most frequently reported (60%-67%) comorbidity, followed by hypertension and gastroesophageal reflex.

Effectiveness

Benralizumab was found to be a significantly effective treatment for managing severe eosinophilic asthma for all three evaluated cohorts, as evidenced by reductions in asthma exacerbations post-index, compared with pre-index. Specifically, the exacerbation rate for all five subgroups of the blood eosinophil cohort significantly decreased from the pre-index 3.10-3.55 person per year (PPY) rate to a 1.11-1.72 PPY post-index rate, equivalent to a 52%-64% decrease in exacerbations ($P < .001$ for all pre-index vs. post-index comparisons).

Benralizumab was found to be a significantly effective treatment for managing severe eosinophilic asthma for all three evaluated cohorts, as evidenced by reductions in asthma exacerbations.

Comparable reductions also occurred with the cohort in which the biologic treatment was changed to benralizumab. A greater effect was observed when the switch was made from omalizumab to benralizumab with a pre-post PPY rate reduction of 3.25-1.25 (62%) than when the switch was made from mepolizumab (pre-post PPY rate reduction was 3.81-1.78 [53%], but both resulted in significant post-treatment improvements ($P < .001$).

Results from the extended follow-up analysis cohort showed consistency for significant exacerbation rate decline going from a pre-index rate of 3.38 PPY down to 1.34 PPY (60% rate reduction vs. pre-index) in the first 12 post-index months, continuing to decline to 1.18 PPY (65% reduction) over the following 6 months (both significant at $P < .001$).

Likewise, the results from the extended follow-up 24-month subgroup presented significant down trending exacerbation rates from pre-index 3.38 PPY to 1.38 (comparative 59% reduction) for the first 12 months continuing down to 1.08 PPY (68% reduction) over the 12to 24-month post-index period (both $P < .001$). In the first and second 12 post-index months for the 24-month subgroup, 39% and 49% of the patients, respectively, experienced no exacerbations.

Following treatment with benralizumab, in addition to the observed decline in asthma exacerbation rates, the need for concomitant asthma medications was also significantly reduced for all three cohorts.

This retrospective ZEPHYR 2 study contributes evidence supporting the significant effectiveness of benralizumab in improving disease management for "specific subsets of severe asthma patients that are frequently seen in real-world practice and may be excluded from clinical trials," according to the authors. The treatment resulted in reduced rates of asthma exacerbations with defined standards for hospitalizations, visits to emergency department or urgent care, or outpatient visits with separate exacerbations occurring at greater than or equal to 14 days, as reported in database records. Reduction in the rate of asthma exacerbations when benralizumab is switched for another biologic increases the disease management options for achieving optimal patient care, the authors add.

The authors have financial relationships with AstraZeneca, the source of funding for the study. ■

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establishment over time, when we figure out how to use them appropriately," Dr. Solomon said.

While the debate of how to best use AI in medical publications will continue, journal editors agree that all authors of a manuscript are solely responsible for content in articles that used AI-assisted technology. "Authors should carefully review and edit the result because AI can generate authoritative-sounding output that can be incorrect, incomplete, or biased," the ICMJE guidelines state.

"Authors should be able to assert that there is no plagiarism in their paper, including in text and images produced by the AI." This includes appropriate attribution of all cited materials.

The committee also recommends that authors write in both the cover letter and submitted work how AI was used in the manuscript writing process. Recently updated guidelines from the World Association of Medical Editors recommend that all prompts used to generate new text or analytical work should be provided in submitted work. Dr. Greene also noted that, if authors used an AI tool to revise their work, they can include a version of the manuscript untouched by LLMs.

It is similar to a preprint, he said, but rather than publishing a version of a paper prior to peer review, someone is showing a version of a manuscript before it was reviewed and revised by AI. "This type of practice could be a path that lets us benefit from these models," he said, "without having the drawbacks that many are concerned about."

Dr. Solomon has financial relationships with AbbVie, Amgen, Janssen, CorEvitas, and Moderna. Both Dr. Greene and Dr. Pividori are inventors in the U.S. Provisional Patent Application No. 63/486,706 that the University of Colorado has filed for the "Publishing Infrastructure For AI-Assisted Academic Authoring" invention with the U.S. Patent and Trademark Office. Dr. Greene and Dr. Pividori also received a grant from the Alfred P. Sloan Foundation to improve their AI-based manuscript revision tool. Dr. Gao reported no relevant financial relationships. ■

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Physician suicide roundtable: Here are 8 important initiatives that might make a difference

BY JENNIFER NELSON

Physician suicide continues to be a challenging problem in the United States. Each year, 1 in 10 doctors think about or attempt suicide, and 400 die by suicide each year. More than half of the doctors reading this know a colleague who has attempted or died by suicide.

This news organization recently sat down with three psychiatric experts to talk about the newest risk-reduction initiatives. These are part of a public health suicide prevention strategy, the preferred method for prevention, in hospitals and institutions around the country. A public health model for preventing suicide is a multifaceted approach that includes universal education, health promotion, selective and targeted prevention, and treatment and recovery.

These physicians hope to continue creating and implementing these and other risk-reduction measures across all health care organizations.

Our physician experts for this discussion

Mary Moffit, PhD, is an associate professor in the department of psychiatry at Oregon Health & Science University, Portland. She directs the resident and faculty wellness program and is director of the OHSU peer support program. She helped design and developed a comprehensive wellness program that is now a national model for academic medical centers.

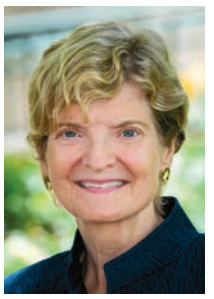
Christine Yu Moutier, MD, is the chief medical officer of the American Foundation for Suicide Prevention. She is the author of "Suicide Prevention," a Cambridge University Press clinical handbook. She has been a practicing psychiatrist, professor of psychiatry, dean in the medical school at the University of California, San Diego, and medical director of the inpatient psychiatric unit at the VA Medical Center in La Jolla, Calif.

Michael F. Myers, MD, is a professor of clinical psychiatry in the department of psychiatry & behavioral sciences at the State University of New York, Brooklyn. He is recent past vice-chair of education and director of training in the department of psychiatry & behavioral sciences at the university. He is the author of several books, including "Why Physicians Die by Suicide," "The Physician as Patient," and "Touched by Suicide."

The participants discussed these risk-reduction initiatives as having much potential for helping physicians at risk for suicide and suicidal ideations.

The importance of peer support programs

Peer support program models may differ across institutions but typically describe colleagues providing some degree of emotional first aid to peers who may be at risk.



Dr. Moffit

"The Pew support program that we have in place at OHSU ... trains individual physicians across multiple specialties in a peer support model. It's not specifically emotional first aid, although that's integral to it. It's also for adverse events: Having a tragic patient death, having learned that you will be named in a lawsuit ...."

Dr. Moffit: The Pew support program that we have in place at OHSU, similar to what's available in many hospitals and systems nationwide, trains individual physicians across multiple specialties in a peer support model. It's not specifically emotional first aid, although that's integral to it. It's also for adverse events: Having a tragic patient death, having learned that you will be named in a lawsuit, and exposure to trauma in the medical role.

Peer to peer is not where we anticipate physicians seeking someone to talk to about their marital relationship not going well. However, the peer supporter will know about resources throughout the university and the community for what is needed. We've got 20-30 peer supporters. We try to match them – for example, a surgeon with a surgeon, a primary care doc with a primary care doc. Physicians who use peer support aren't tracked, and no notes are taken or documented. It takes place informally but has changed the culture and lowered a barrier. We have a waiting list of people who want to be peer supporters.

Dr. Moutier: Peer-to-peer support is usually part of a multi-pronged program and is usually not the only effort going on. Depending on how they're set up, the goals may be slightly different for each program. Peer-to-peer can be one of the most powerful ways to augment awareness raising and education, which is almost always a basic first step.

Dr. Myers: It doesn't feel as threatening when people start in a peer-to-peer support group. Users may have been afraid of getting a mental health diagnosis, but with peers, many of whom are often not psychiatrists, that eases distress. Peer support can break down that sense of isolation and loneliness so that someone can take the next step.

Dr. Moutier: To be connected to family, to any community resource, frankly, is a protective factor that mitigates suicide risk. So that's the logic model from a suicide prevention standpoint. It may be the only opportunity for someone to start disclosing what they're experiencing, receive validation and support, and not a judgmental response. It can open up the avenue toward help-seeking.

Opt-in/opt-out support for medical residents

This initiative matches residents with a counselor as part of their orientation.

Dr. Moffit: Each resident has a meet and greet with a counselor when they arrive or in their first 6 months at their university. The resident can opt out and cancel the meeting, but they're scheduled for it as part of their "curriculum." Institutions like Michigan, Columbia, Montefiore, Mount Sinai, and the University of California, San Diego, have this in place. It starts something like: "Hello. Good afternoon. How's it going? I'm Dr. Moffitt, and here are the services available in this program."

Dr. Myers: It's another excellent example of normalizing the stress in the rigors of training and making it part of the wellness initiative.

Dr. Moutier: It's just a normal part of orientation. Again, as a universal strategy, one thing that I was doing at UCSD with a particular group of medical students, who were at higher risk, was a postbaccalaureate program that found students from under-represented, under-resourced backgrounds and brought them into this post-bacc year. I was directing it and mentoring these students.

So, I could afford a lot more intensive time and attention to them because it was a small group, but every one of them had regular meetings with me every 2 weeks. My approach was to help them uncover their unique strengths and vulnerabilities as they started this program. They all made it into med school.

It was a very intensive and more concierge-personalized approach. It's like personalized medicine. What specific self-care, mentoring, and mental health care plan would each student codesign with me to stay on track?

And it would involve very holistic things, like if part of their vulnerability was that leaving their Chicano family was creating stress because their father had said: "You're leaving our culture and our family by going into the profession of medicine," then we had specific plans around how to care for that aspect of their struggle. It was a much more informed, customized mentoring approach called the UCSD CAP (Conditional Acceptance Post-Baccalaureate Program). It could be a feature in a more specialized opt-in/opt-out program.

One-question survey: How full is your gas tank?

This initiative is a one-question survey emailed/texted to residents to check in on their wellness. We ask, how full is your gas tank? Select 1 to 5 (Empty to Full). If they flag low, they receive a follow-up.

Dr. Moffit: It's certainly a metaphor that we use. It's the idea of being depleted in combination with being extremely sleep deprived and the inability to access the usual sources of support or outlets, and how that can create a perfect storm of a level of distress that can put physicians at risk.

Dr. Moutier: It is a way to help people realize that there are things they can do proactively to keep that tank at least somewhat full enough.

Dr. Myers: Using colloquial or figurative language can get better buy-in than "Here's a PHQ-9." It also has a caring or intimate tone to

it. Somebody could feel they're a 1 in this rotation but a 4-5 the next. We know from a lot of the literature that when residents get a good, welcoming orientation, their satisfaction with that rotation is uniformly better than if they're thrown to the wolves. And we know trial by fire can put trainees at risk.

A buddy to check in with

This initiative is when you're assigned a buddy in or out of residency that you regularly check in with about how you're doing.

Dr. Moutier

"Our data show that 86% of a very high-risk group (currently having suicidal ideation, a recent attempt, or other high-risk factors for suicide) aren't in any form of treatment and have not disclosed their situation to anyone."

Dr. Myers: Not to be cynical, but there has been some mentor/mentee research that, if you're assigned a mentor, the results are not nearly as good. And if it's left to the individual to find a mentor, results could be marginal as well. You need a guide to say, "Here are some potential mentors for you, but you decide." We do a lot of that at (SUNY) Downstate instead of assigning a person. So, it may require some oversight. Picking a check-in buddy from a list provided rather than having one assigned may be more beneficial. A lot of what we're talking about are universal strategies that allow for increased interpersonal connection, which is a protective factor that normalizes help-seeking.

A platform or social media forum to share experiences

An online forum or platform permits medical students, residents, and physicians to discuss mental health and suicide prevention. Physicians with personal experience could provide testimonials.

Dr. Myers: I've recently signed a book contract, and the working title is "Physicians With Lived Experience: How Their Stories Give Clinical Guidance." When I talk with doctors who have published their personal stories in the New England Journal of Medicine, JAMA, or sometimes The Washington Post or The New York Times, many of them have said they had no idea at the beginning of their journey that they would do something like this: be transparent about their story. It's a measure of their health, growth, and grace.

Dr. Moutier: The current president of the Academic Association of Surgeons, Carrie Cunningham, MD, MPH, used her platform at the annual AAS conference in 2022 to focus on suicide prevention. She told her own recent story of having gotten into recovery after having been near suicide and struggling with addiction. It was a groundbreaking moment for the field of surgery and produced a ripple effect. She risked everything to tell her story, which was highly emotional since it was still raw. It got everyone engaged, a real turning point for that field. Storytelling and a place for trainees to discuss suicide prevention, and physicians to recall their lived experiences can be highly beneficial.

Interactive Screening Program

The Interactive Screening Program (ISP) is used in higher education to allow physicians to take a safe, confidential screening test and receive a personalized response that can connect them to mental health services before a crisis emerges.

Dr. Moutier: ISP is a tool within a public health model that can afford anonymity to the user so they can safely have their needs addressed. It's a way for high-risk individuals to sync up with treatment and support. It's sometimes used in the universal approach because it can be offered to everyone within the health system community of physicians and staff.

It can produce a ripple effect of normalizing that we all have mental health to take care of. Its intended value is in identifying those with a higher risk for suicide, but it doesn't stop at identifying those at risk. It helps physicians move past a stage of suffering in silence.

Our data show that 86% of a very high-risk group (currently having suicidal ideation, a recent attempt, or other high-risk factors for suicide) aren't in any form of treatment and have not disclosed their situation to anyone. A fairly high percentage of those going through ISP request a referral to treatment. It's a unique, very niche tool, and because users remain anonymous, that

ROUNDTABLE *continued on following page*

affords safety around confidentiality.

It's usually part of a multipronged approach with education, stigma reduction, storytelling, peer support, and other modalities. In my experience with the UCSD HEAR (Healer Assessment Education and Recovery) program, which is still going strong in about its 15th year, the program went from seeing 13 physicians die by suicide in the years leading up to its launch and in the 15 years since it's been going, 1 suicide. We all believe that the ISP is the heart of prevention.

Dr. Myers

Even though all of the universal strategies are important, they probably wouldn't be sufficient by themselves because the risk [for suicide] is dynamic, and you have to catch people when they are suffering and ready to seek treatment. Suicide prevention is challenging and must be strategic, multifaceted, and sustained over time.

"There is so much dated stuff out there, and it gets propagated by people who have had a bad experience. I'm not challenging the authenticity of that, but I feel like those are in the minority."

The importance of confidentiality for physicians

In the past, physicians may have been hesitant to seek treatment when struggling with mental health, substance use disorder, and suicidal ideations because they heard stories from doctors who said they had to disclose mental health treatment to medical and state licensing boards.

Dr. Myers: There is so much dated stuff out there, and it gets propagated by people who have had a bad experience. I'm not challenging the authenticity of that, but I feel like those are in the minority. The vast majority of people are seeking help. The Federation of State Physician Health Programs is working with state boards to update and get rid of antiquated questions, and they're working with credentialing groups.

When I was in practice and my patient was petrified of having to come into the hospital [because of confidentiality] I would just be their physician and say: "Look, I know that this is a worry for you [licensing and credentialing issues] but trust me, I'm going to help you get well; that's my job. And I'm going to help you sort all that out afterward." It was part of my work as their physician that, if they were going to have to jump through hurdles to get their license reinstated, etc., I could help. The Dr. Lorna Breen Heroes' Foundation is also doing so much good work in this area, especially with their toolkits to audit, change, remove, and communicate the changes about intrusive language in licensing applications and credentialing. (Dr. Breen was a New York City ED physician who died by suicide in April 2020 during the early days and height of the COVID-19 pandemic. Her father was quoted as saying: "She was in the trenches. She was a hero.")

Dr. Moutier: We're seeing hundreds of physicians get therapy and psychiatric treatment annually. And the advocacy effort is incredibly important, and I think we are

witnessing a swifter pace to eliminate those inappropriate and illegal questions about mental health and mental health treatment for physicians and nurses.

Dr. Moffit: We have lowered barriers, not only in individual institutions but also with programming. We have also worked with the Federation of State Medical Boards and the Breen Foundation to change the legislation. The Foundation has audited and changed 20 state medical boards to remove intrusive language from licensing applications.

Support for colleagues working to help each other

Dr. Myers: One final note for those physicians who need to take time out for medical leave: In my clinical experience, I find that they felt lonely as they were getting well. I can't tell you how much it made a difference for those who received a phone call, a card, or an email from their colleagues at work. It doesn't take long for a vibrant, active physician to feel out of the loop when ill.

We know from suicide literature that when somebody's discharged from the hospital or the emergency department, caring communications, brief expressions of care and concern by email, letter, card, text message, etc., can make all the difference to their recovery.

Reaching out to those struggling and those in recovery can help your fellow physician. ■

Circulatory support for RV failure caused by PE

BY JIM KLING
MDedge News

A new review article highlights approaches for mechanical circulatory support in patients with high-risk acute pulmonary embolism (PE). Mechanical support has become an important treatment option for refractory shock resulting from acute right ventricular failure (RVF).

Pulmonary embolism with hemodynamic significance is widely underdiagnosed, and the mortality rate can be as high as 30%, but new therapeutic developments offer promise. "Over the past few years, a renewed interest in mechanical circulatory support (MCS; both percutaneous and surgical) for acute RVF has emerged, increasing viable treatment options for high-risk acute PE," wrote the authors

of the review, which was published online in Interventional Cardiology Clinics (2023 Apr 27. doi: 10.1016/j.iccl.2023.03.004).

Poor outcomes are often driven by RVF, which is tricky to diagnose and manage, and it stems from a sudden increase in pulmonary vascular resistance (PVR) following PE. "The mechanism for increased PVR in acute PE is multifactorial, including direct blood flow impedance, local hypoxia-induced vasoconstriction, and platelet/thrombin-induced release of vasoactive peptides. The cascade of events that then leads to RVF includes decreased RV stoke volume, increased RV wall tension, and RV dilation," the authors wrote.

The authors noted that diuretics help to correct changes to RV geometry and can improve left ventricle filling, which improves hemodynamics. Diuretics can be used in patients who are hypotensive and volume overloaded, but vasopressors should be employed to support blood pressure.

When using mechanical ventilation, strategies such as low tidal volumes, minimization of positive end expiratory pressure, and prevention of hypoxemia and acidemia should be employed to prevent an increase of pulmonary vascular resistance, which can worsen RV failure.

Pulmonary vasodilators aren't recommended for acute PE, but inhaled pulmonary vasodilators may be considered in hemodynamically unstable patients.

Surgically implanted right ventricle assistance devices are generally not used for acute RV failure in high-risk PE, unless the patient has not improved after medical management.

Percutaneous devices

Percutaneous mechanical circulatory support devices can be used for patients experiencing refractory shock. The review highlighted three such devices, including the Impella RP, tandem-heart right ventricular assist devices (TH-RVAD)

Surgically implanted right ventricle assistance devices are generally not used for acute RV failure in high-risk PE, unless the patient has not improved after medical management.

or Protek Duo, and venoarterial extracorporeal membrane oxygenation (VA-ECMO), but they are not without limitations. "Challenges to using these devices in patients with acute PE include clot dislodgement, vascular complications, infections, device migration, and fracture of individual elements," the authors wrote.

The Impella RP is easy to deploy and bypasses the RV, but it can't provide blood oxygenation and may cause bleeding or hemolysis. TH-RVAD oxygenates the blood and bypasses the RV, but suffers from a large sheath size. VA-ECMO oxygenates the blood but may cause bleeding.

There are important differences among the mechanical support devices, according to Jonathan Ludmir, MD, who was asked to comment. "In reality, if someone has a large pulmonary embolism burden, to put in the Impella RP or the Protek Duo would be a little bit risky, because you'd be sometimes putting the device right where the clot is. At least what we do in our institution, when someone is in

SUPPORT *continued on following page*

Few of those eligible get lung cancer screening, despite USPSTF recommendations

BY MARCIA FRELLICK
MDedge News

Only 12.8% of eligible adults get CT screening for lung cancer, despite recommendations from the U.S. Preventive Services Task Force. Kristin G. Maki, PhD, with Karmanos Cancer Institute, Wayne State University, Detroit, led a team that estimated lung cancer screening (LCS) from the 2021 Behavioral Risk Factor Surveillance System in four states (Maine, Michigan, New Jersey, and Rhode Island).

"Increasing LCS among eligible adults is a national priority," the authors wrote in the study, published online in JAMA Network Open (2023 Jun 21. doi: 10.1001/jamanetworkopen.2023.19172). Lung cancer remains the top cause of cancer in the United States and smoking accounts for approximately 90% of cases.

The authors pointed out that screening rates for eligible people are much higher for other cancers. Melzer and colleagues wrote in a 2021 editorial (JAMA Netw Open. 2021;4[3]:e210275) that breast and colon cancer screening rates are near 70% "despite combined annual death rates less than two-thirds that of lung cancer."

The USPSTF updated its recommendations for lung cancer screening in March 2021.

Eligibility now includes anyone aged between 50 and 80 years who has smoked at least 20 pack-years and either still smokes or quit within the last 15 years.

The researchers found that, when comparing screening by health status, the highest odds for screening were seen in those who reported they were in poor health, which is concerning, the authors note, because those patients may not be healthy enough to benefit from treatment for their lung cancer. The odds ratio for getting screening was 2.88 (95% confidence interval, 0.85-9.77) times higher than that of the reference group, which reported excellent health.

Consistent with previous studies, this analysis found that screening rates differed by state. Their analysis, for example, showed a higher likelihood of screening for respondents in Rhode Island, compared with Maine (OR, 1.96; 95% CI, 1.05-3.67; $P = .03$).

Patients who reported having a primary health professional were more than five times more likely to undergo screening, compared with those without one (OR, 5.62; 95% CI, 1.19-26.49).

The authors said their results also highlight the need for Medicare coverage for screening as those with public insurance had lower odds of screening than those with private insurance (OR, 0.81; 95% CI, 0.42-1.56).

Neelima Navuluri, MD, assistant professor at Duke University and the Duke Global Health Institute, both in Durham, N.C., pointed out that the study highlights age, smoking status, and health care access as key factors associated with lack of uptake. Dr. Navuluri said in an interview that multifaceted patient-, provider- and also system-level interventions are needed to improve screening rates.

"For example, we need more community engagement to increase knowledge and awareness of eligibility for lung cancer screening," she said.

She highlighted the need for interventions around improving and streamlining shared decision-making conversations about screening (a CMS requirement that does not exist for other cancer screening).

Emphasis is needed on younger age groups, people who currently smoke, and communities of color as well as policy to improve insurance coverage of screening, she said.

Dr. Navuluri, who also works with the Durham Veterans Affairs Medical Center, was lead author on a study published in JAMA Network Open (2023 Jun 1. doi: 10.1001/jamanetworkopen.2023.18795) on racial disparities in screening among veterans.

"We demonstrate similar findings related to age, smoking status, and poor health status," she said. "We discuss the need for more qualitative studies to better understand the role of these factors as well as implementation studies to assess effectiveness of various interventions to improve disparities in lung cancer screening rates."

"Research to identify facilitators for LCS among persons who currently smoke is needed, including a focus on the role of stigma as a barrier to screening," they wrote.

One coauthor is supported by the cancer prevention program at the University of Texas MD Anderson Cancer Center. Dr. Navuluri receives funding from the National Comprehensive Cancer Network for work on lung cancer screening. ■

Russell Miller, MD, comments: Lung cancer screening has been proven to be our most effective method for diagnosing and treating lung cancer during its early stages when it's still potentially curable. However, despite the advantages of such screening, usage rates remain disappointingly low compared with other cancer screening programs. This report, which examined lung cancer screening utilization in 2021, showed that eligible patients with a private health plan were more likely to undergo lung cancer screening and argued that coverage by the Centers for Medicare and Medicaid Services would likely enhance screening usage. However, it's uncertain to what degree low utilization can be attributed to lack of coverage, as the study also found that screening usage remained low even among those with private insurance. In 2022, CMS expanded its coverage to include lung cancer screening for qualified patients. It's hoped this change will escalate screening uptake among eligible patients. Yet, it remains to be seen how much this adjustment will assist in improving the inferior utilization rates, even among patients with coverage. Nonetheless, observational studies like this one offer critical baseline data that can help evaluate the effects of policy changes on health care outcomes.

Dr. Miller is a member of the CHEST Physician *Editorial Board.*

SUPPORT *continued from previous page*

extremis despite using [intravenous] medications like vasopressors or inotropes, VA-ECMO is kind of the go to. This is both the quickest and probably most effective way to support the patient. I say the quickest because this is a procedure you can do at the bedside."

Benefits of PERT

One message that the review only briefly mentions, but Dr. Ludmir believes is key, is employing a pulmonary embolism response team.

"That's been looked at extensively, and it's a really key part of any decision-making. If someone presents to the emergency room or someone inside the hospital has an acute pulmonary embolism, you have a team of people that can respond and help assess the next step. Typically, that involves a cardiologist or an interventional cardiologist, a hematologist, vascular surgeon, often a cardiac surgeon, so it's a whole slew of people. Based on the patient assessment they can quickly decide, can this patient just be okay with a blood thinner like heparin? Does this patient need something more aggressive, like a thrombectomy? Or is this a serious case where you involve the shock team or the ECMO team, and you have to stabilize the patient on mechanical circulatory support, so you can accomplish what you need to do to get rid of the pulmonary embolism," said Dr. Ludmir, who is an assistant professor of medicine at Corrigan Minehan Heart Center at Massachusetts General Hospital and Harvard Medical School, both in Boston.

"Every case is individualized, hence the importance of having a team of a variety of different backgrounds and thoughts to approach it. And I think that's kind of like the key takeaway. Yes, you have to be familiar with all the therapies, but at the end of the day, not every patient is going to fit into the algorithm for how you approach pulmonary embolism," said Dr. Ludmir.

Dr. Ludmir has no relevant conflicts of interest. ■

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PIONEERING DIAGNOSTICS

NETWORKS

A bronchiectasis target, transplant frailty, and more

AIRWAYS DISORDERS NETWORK
Bronchiectasis Section
DPP1 a promising target for bronchiectasis

Bronchiectasis is a chronic inflammatory lung disease characterized by the progressive destruction of the airways and persistent inflammation. In bronchiectasis, excessive neutrophil accumulation in the airways leads to release of neutrophil serine proteases (NSPs), which contributes to tissue damage and perpetuates the inflammatory process in the lungs. The three main NSPs include neutrophil elastase (NE), proteinase3, and cathepsin G. Elevations in NE activity in sputum in NCFBE are associated with increased exacerbations and declines in lung function. Dipeptidyl peptidase 1 (DPP1), an enzyme primarily found in neutrophils, is responsible for activating NSPs during neutrophil maturation. In bronchiectasis, increased DPP1 activity results in an augmented production of active NSPs, exacerbating lung damage and inflammation. Brensocatib, an oral, reversible inhibitor of DPP1 is currently being developed as a novel approach to managing bronchiectasis. Brensocatib was evaluated in a phase 2 clinical trial (WILLOW), a randomized, double-blind, placebo-controlled trial involving adults with non–cystic fibrosis bronchiectasis (NCFBE). Treatment with brensocatib for 24 weeks significantly prolonged the time to the first exacerbation at both the 10 mg and 25 mg doses and lowered the risk of exacerbation by 40% relative to placebo. The treatment was well tolerated, with no significant safety concerns. Results of a recent post hoc analysis from the WILLOW study show that brensocatib effectively reduces exacerbations and slows lung function decline across different severities of bronchiectasis. These findings suggest that brensocatib holds potential as the 1st new therapeutic option for patients with NCFBE, with currently no FDA-approved drugs. Results of a larger-scale phase 3 trial are awaited later this year, which will hopefully confirm these results and ascertain the long-term safety.

Dr. Subramanian

Shyamsunder Subramanian, MD, MBBS, FCCP
Section Chair

DIFFUSE LUNG DISEASE & TRANSPLANT NETWORK
Lung Transplant Section
Use of frailty assessment in lung transplant evaluation

Frailty, a concept that originated in the geriatric population, is a state of vulnerability resulting from a decline in reserve and function across physiological systems. While it is more commonly observed in older adults, some aging-associated syndromes, such as sarcopenia, impaired cognition, inflammation, and malnutrition, may be present in younger patients with end-stage organ disease. These syndromes can be associated with biological age, as opposed to chronological age, which explains why younger patients with end-stage organ disease can develop frailty (Schaenman JM, et al. *Am J Transplant*. 2021 Jun;21[6]:2018-24). Frailty in the lung transplant population is associated with increased morbidity and mortality while on the waitlist and post-transplant (Montgomery E, et al. *J Transplant*. 2020 Aug 7:3239495). In 2021, the International Society of Heart and Lung Transplantation recommended including a frailty assessment to complete a patient's transplant evaluation. The committee cautioned using current assessment tools, as they are not yet accepted as the standard of care (Leard, et al. *J Heart Lung Transplant*. 2021 Nov;40[11]:1349-79). Existing tools being used evolved from studies of community-dwelling older adults with no predilection for distinct organ disease, which include the Fried Physical Frailty Phenotype (FPFP) and the Short Physical Performance Battery (SPPB). Along with physical limitations, frail patients tend to have abnormal biomarkers including higher inflammatory cytokines, such as plasma IL-6 and tumor necrosis factor receptor 1, and lower insulin-like growth factor I and leptin (Singer JP, et al. *Am J Respir Crit Care Med*. 2015;192[11]1325-34). The concept of a lung-focused approach to frailty, which considers biomarkers and body composition, is currently being researched (Singer JP, et al. *J Heart Lung Transplant*. 2023;S1053-S2498[23]00049-9). This disease-specific frailty scale would identify lung transplant candidates who may benefit from targeted interventions, and such frailty would also be expected to improve after transplant.

Erin Meier, MD
Section Fellow-in-Training
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CRITICAL CARE NETWORK
Nonrespiratory Critical Care Section
Addressing disparities in goals-of-care conversations

Goals-of-care discussions are essential to management of the intensive care unit (ICU) patient. Racial inequities in end-of-life decision making have been documented for many years, with literature demonstrating that marginalized populations are less likely to have EHR-documented goals-of-care discussions and more likely to have concerns regarding clinician communication.

A recently published randomized control trial in *JAMA* highlights an intervention that offers promise in addressing disparities in goals-of-care conversations. Curtis, et al. studied whether priming physicians with a communication guide advising on discussion prompts and language for goals-of-care could improve the rate of documented goals-of-care discussions among hospitalized older adults with serious illness. The study found that for patients in the intervention arm, there was a significant increase in proportion of goals-of-care discussions within 30 days. Notably, the difference in documented goals-of-care discussions between arms was greater in the subgroup of patients from underserved groups (Curtis JR, et al. *JAMA*. 2023;329[23]:2028-37).

Nevertheless, while interventions may help increase the rate of goals-of-care discussions, it is also important to address the content of discussions themselves. You and colleagues recently published

NETWORKS *continued on following page*

Celebrating the inaugural issues of CHEST's new open access journals

After much anticipation, the inaugural issues of both *CHEST® Critical Care* and *CHEST® Pulmonary* officially launched in late June. These new open access additions to the journal *CHEST®* portfolio feature content that is permanently and freely available online for all – promoting transparency, inclusiveness, and collaboration in research – and offer authors more avenues to share their practice-changing research.

The first issue of *CHEST Critical Care* featured research into ICU mortality across prepandemic and pandemic cohorts in resource-limited settings in South Africa, an exploration into symptom trajectory in recipients of hematopoietic stem-cell transplantation, a narrative review of post-intensive care syndrome, and an investigation into early echocardiographic and ultrasonographic findings in critically ill patients with COVID-19.

In addition, an editorial from Hayley Gershengorn, MD, Editor in Chief of *CHEST Critical Care*, offers readers more insights into the need for a publication focused on the breadth of clinical topics in critical care and her goals for the new publication.

"I'm ecstatic for this launch. We are grateful to our authors for the trust they put in us and are excited to share their work with our critical care colleagues around the world," Dr. Gershengorn said. "The editorial team and the American College of Chest Physicians staff have worked tirelessly on this journal, and it's incredibly gratifying to see the first issue publish."

Read the full issue and new research from the journal at www.chestcc.org.

In his own editorial featured in the inaugural issue of *CHEST Pulmonary*, Editor in Chief Matthew Miles, MD, MEd, FCCP, shares how the flagship journal's proud heritage of sharing impactful clinical research – and the need to target areas of pulmonary and sleep medicine research not covered by other journals – inspired the creation of this new publication.

The issue also includes research into mobile health opportunities for asthma management, an exploration into telemedicine for patients with interstitial lung diseases, an in-depth review into the rare and often underdiagnosed disorder primary ciliary dyskinesia, research on the impact of the social vulnerability index on pulmonary embolism mortality, and an investigation into pneumothorax complications after percutaneous lung biopsy.

"I am deeply grateful to our authors, reviewers, editorial board, and staff who have contributed to the launch of our first issue," Dr. Miles said. "The journal *CHEST* is known for excellence in clinically relevant research and patient management guidance. *CHEST Pulmonary* expands the *CHEST* portfolio with additional opportunity for researchers to share their work in an exclusively open access format to reach the broadest possible audience. I know our readers will enjoy learning from the research and reviews in issue one."

Review the full issue and new articles from *CHEST Pulmonary* at www.chestpulmonary.org. ■

NETWORKS *continued from previous page*

a mixed-methods study assessing the impact of race on shared decision-making behaviors during family/caregiver meetings. The authors found that while ICU physicians approached shared decision making with White and Black families similarly, Black families felt their physicians provided less validation of the family role in decision making than White families did (You H, et al. *Ann Am Thorac Soc*. 2023 May;20[5]:759-62). These findings highlight the importance of ongoing work that focuses not only on quantity but also on quality of communication regarding goals-of-care for patients from diverse backgrounds.

Divya Shankar MD
Section Fellow-in-Training
Muhammad Hayat-Syed MD
Section Vice Chair

THORACIC ONCOLOGY & CHEST PROCEDURES NETWORK

Ultrasound & Chest Imaging Section

Upper airway ultrasound: Easy to learn, facile to use!

Point-of-care ultrasound (POCUS) is integral to the delivery of high-quality patient care. The benefits of POCUS for timely diagnosis and procedural assistance are well documented. With continued innovation, its novel benefits can extend to the upper airway evaluation in both inpatient and outpatient settings.

Adi et al notes that POCUS can serve as an adjunct to traditional airway checklists and help intensivists/anesthesiologists identify potentially difficult laryngoscopies, choose the correct endotracheal tube size to reduce the risk of subglottic stenosis, and help confirm appropriate endotracheal tube placement (Adi, et al. *J Emerg Crit Care Med*. 2019;3:31).

The prediction of a difficult airway is a potentially lifesaving use for this technology. The authors note that smaller studies demonstrate promising results in four techniques: the inability to visualize the hyoid bone using the sublingual approach, a shorter hyomental distance in morbidly obese patients, anterior neck thickness at different anatomical levels (vocal cords, hyoid bone, and thyroid membrane), and a tongue thickness of more than 6.1 cm from the submental approach were all capable of predicting difficult tracheal intubation with varying degrees of sensitivity and specificity.

In the outpatient setting, an understanding of the upper airway anatomy can help with sleep apnea screenings. Korotun, et al. demonstrated in a small sample that ultrasound evaluation of hyoid bone excursion during hypoglossal nerve stimulation may be a useful tool to predict response to therapy and guide hypoglossal nerve stimulator settings (Korotun, et al. *Sleep*. 2020;43[Suppl_1]:A247-A248).

Upper airway ultrasound is easy to learn. The anatomical landmarks are similar in most patients. This convenient tool can be added to your patient care repertoire in a variety of clinical settings. ■

Sameer Khanijo, MD, FCCP
Section Member-at-Large
Navitha Ramesh, MD, FCCP
Section Vice-Chair

CRITICAL CARE COMMENTARY

Use the SCAI stages to identify and treat cardiogenic shock

BY JOHN P. GAILLARD, MD, FCCP

Cardiogenic shock (CS) is being recognized more often in critically ill patients. This increased prevalence is likely due to a better understanding of CS and the benefit of improving cardiac output (CO) to ensure adequate oxygen delivery (DO_2). There is no one specific definition of CS; rather, CS describes a clinical condition in which a patient is suffering from cellular hypoperfusion due to an ineffective CO with normal or elevating intravascular filling pressures.

CS is often, but not always, caused by a cardiac dysfunction. The heart is not able to provide adequate DO_2 to the tissues. Hypoperfusion ensues. The body attempts to compensate for the poor perfusion by increasing heart rate, vasoconstriction, and shunting blood flow to vital organs. These compensatory mechanisms worsen perfusion by increasing myocardial ischemia which further worsens cardiac dysfunction. This is known as the downward spiral of CS (*Ann Intern Med*. 1999 Jul 6;131[1]).

There is a number of different etiologies for CS. Historically, acute myocardial infarctions (AMI) was the most common cause. In the last 20 years, AMI-induced CS has become less prevalent due to more aggressive reperfusion strategies. CS due to etiologies such as cardiomyopathy, myocarditis, right ventricle failure, and valvular pathologies have become more common. While the overarching goal is to restore DO_2 to the tissue, the optimal treatment may differ based on the etiology of the CS. The Society for Cardiovascular Angiography and Intervention (SCAI) published CS classification stages in 2019 and then updated the stages 2022 (*J Am Coll Cardiol*. 2022 Mar 8;79[9]:933-46). In addition to the stages, there is now a three-axis model to address risk stratification. These classifications are a practically means of identifying and treating patients presenting with or concern for acute CS.

Stage A (At Risk) patients are not experiencing CS, but they are the at risk population. The patient's hemodynamics, physical exam, and markers of hypoperfusion are normal. Stage A includes patients who have had a recent AMI or have heart failure.

Stage B (Beginning) patients have evidence of hemodynamic instability but are able to maintain tissue perfusion. These patients will have true or relative hypotension or tachycardia (in an attempt to maintain CO). Distal perfusion is adequate, but signs of ensuing decompensation (eg, elevated jugular venous pressure [JVP]) are present. Lactate is <2.0 mmol/L. Clinicians must be vigilant and treat these patients aggressively, so they do not decompensate further. It can be difficult to identify these patients because their blood pressure may be "normal," but upon investigation,

SCAI *continued on following page*

Dr. Gaillard is Associate Professor in the Departments of Anesthesiology, Section on Critical Care; Internal Medicine, Section on Pulmonology, Critical Care, Allergy, and Immunologic Diseases; and Emergency Medicine; Wake Forest School of Medicine, Winston-Salem, NC.

Add hands-on and interactive learning opportunities to your CHEST 2023 schedule

BY KATLYN CAMPBELL
Communications Coordinator

As part of the 300+ educational sessions attendees will find at CHEST 2023 in Hawai'i, ticketed sessions are available for learners looking to attend smaller group sessions or experience hands-on learning.

Explore the many ticketed sessions, and sign up early in case they sell out.

Simulation sessions

If you're looking to gain hands-on exposure to equipment and tools that may not be available at your home institution, look no further than these simulation sessions. Choose from 25 different sessions offering firsthand experience with procedures relevant to your clinical practice.

"It's a great opportunity to teach higher stakes procedures in a very low stakes environment where everybody's comfortable and everybody's learning from each other," said Live Learning Subcommittee Chair, Nicholas Pastis, MD, FCCP.

CHEST 2023 simulation sessions will address clinical topics, including endobronchial ultrasound, cardiopulmonary exercise testing (CPET), intubation and cricothyrotomy, bronchoscopy management, and more. These sessions are taught by experts who use these real-world strategies in their daily practice.

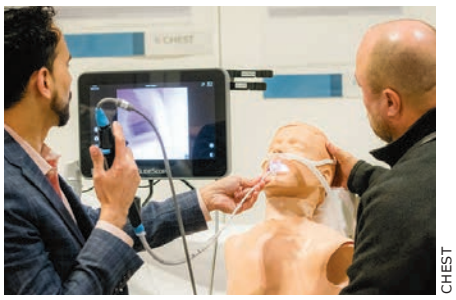
CHEST 2022 attendee, Weston Bowker, MD, found value in the simulation courses he was able to attend in Nashville.

"It's fantastic just to work with some of the leading experts in the field, especially from an interventional pulmonology standpoint. And, you truly get a different experience than maybe what your home institution offers," he said.

Problem-based learning sessions

Exercise your critical thinking skills by working to resolve real-world clinical problems during these small group sessions. Refine your expertise on topics like lung cancer screening and staging, biologics in asthma, pneumonia, and more.

"Problem-based learning courses



CHEST

take a clinical problem or case study that is somewhat controversial to create a learning environment where the problem itself drives the learning with participants," said CHEST 2023 Scientific Program Committee Chair, Aneesa Das, MD, FCCP. "These are small group sessions where learners can actively participate and collaborate to discuss various perspectives on the issue and work toward potential solutions."

This year's problem-based learning courses were chosen based on common controversies in chest medicine and current hot topics in medicine.

Dr. Das is excited for the Using CPET to Solve Your Difficult Cases course. "Cardiopulmonary exercise tests can sometimes be difficult even for seasoned physicians. This is always an amazing problem-based learning topic," she added.

Meet the Professor sessions

Connect with leading chest medicine experts during these limited-capacity discussions capped at 24 registrants per session. Meet the Professor attendees will have the opportunity to engage in stimulating conversations on bronchiectasis, central airway obstructions, obesity hypoventilation, and sublobar resection.

"Meet the Professor sessions are a unique opportunity to interact and learn from a leader in the field in a very small group setting on a high-yield topic," said Dr. Das. "These sessions allow for a learning environment that is personalized and intimate."

Ready to sign up? Scan the QR code to learn more about CHEST 2023 and to register. ■

SCAI *continued from previous page*

the blood pressure is actually a drop from the patient's baseline.

Chronic heart failure patients with a history of depressed cardiac function will often have periods of cardiac decompensation between stages A and B. These patients are able to maintain perfusion for longer periods of time before further decompensation with hypoperfusion. If and when they do decompensate, they will often have a steep downward trajectory, so it is advantageous to the patient to be aggressive early.

SCAI developed the three-axis model of risk stratification as a conceptual model to be used for evaluation and prognostication. This model is a way to individualize treatment to a specific patient.

Stage C (Classic) patients have evidence of tissue hypoperfusion. While these patients will often have true or relative hypotension, it is not a definition of stage C. These patients have evidence of volume overload with elevated JVP and rales throughout their lung fields. They will have poor distal perfusion and cool extremities that may become mottled. Lactate is ≥ 2 mmol/L. B-type natriuretic peptide (BNP) and liver function test (LFTs) results are elevated, and urine output is diminished. If a pulmonary arterial catheter is placed (highly recommended), the cardiac index (CI) is < 2.2 L/min/m^2 and the pulmonary capillary wedge pressure (PCWP) is > 15 mm Hg. These patients look like what many clinicians think of when they think of CS.

These patients need better tissue perfusion. Inotropic support is needed to augment CO and DO_2. Pharmacologic support is often the initial step. These patients also benefit from volume removal. This is usually accomplished with aggressive diuresis with a loop diuretic.

Stage D (Deteriorating) patients have failed initial treatment with single inotropic support. Hypoperfusion is not getting better and is often worsening. Lactate is staying > 2 mmol/L or rising. BNP and LFTs are also rising. These patients require additional inotropes and usually need vasopressors. Mechanical cardiac support (MCS) is often needed in addition to pharmacologic inotropic support.

Stage E (Extremis) patients have actual or impending circulatory collapse. These patients are peri-arrest with profound hypotension, lactic acidosis (often > 8 mmol/L), and unconsciousness. These patients are worsening despite multiple strategies to augment CO and DO_2. These patients will likely die without emergent veno-arterial (VA) extracorporeal membrane oxygenation (ECMO). The goal of treatment is to stabilize the patient as quickly as possible to prevent cardiac arrest.

In addition to the stage of CS, SCAI developed the three-axis model of risk stratification as a conceptual model to be used for evaluation and prognostication. Etiology and phenotype, shock severity, and risk modifiers are factors related to patient outcomes from CS. This model is a way to individualize treatment to a specific patient.

Shock severity: What is the patient's shock stage? What are the hemodynamics and metabolic abnormalities? What are the doses of the inotropes or vasopressors? Risk goes up with higher shock stages and vasoactive agent doses and worsening metabolic disturbances or hemodynamics.

Phenotype and etiology: what is the clinical etiology of the patient's CS? Is this acute or acute on chronic? Which ventricle is involved? Is this cardiac driven or are other organs the driving factor? Single ventricle involvement is better than bi-ventricular failure. Cardiogenic collapse due to an overdose may have a better outcome than a massive AMI.

Risk modifiers: how old is the patient? What are the comorbidities? Did the patient have a cardiac arrest? What is the patient's mental status? Some factors are modifiable, but others are not. The concept of chronologic vs. physiologic age may come into play. A frail 40 year old with stage 4 cancer and end stage renal failure may be assessed differently than a 70 year old with mild hypertension and an AMI.

The SCAI stages of CS are a pragmatic way to assess patients with an acute presentation of CS. These stages have defined criteria and treatment recommendations for all patients. The three-axis model allows the clinician to individualize patient care based on shock severity, etiology/phenotype, and risk modification. The goal of these stages is to identify and aggressively treat patients with CS, as well as identify when treatment is failing and additional therapies may be needed. ■

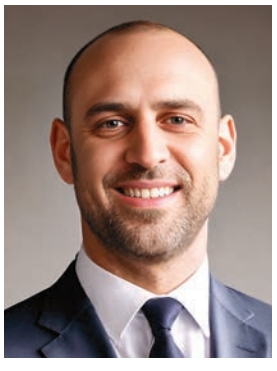
PULMONARY PERSPECTIVES®

Which biologic therapy should I use in patients who have moderate to severe asthma with associated comorbidities?

BY SAMI HOSSRI, MD, AND HALYNA IVASHCHUK, MD

As new treatments for specific moderate to severe asthma phenotypes have been developed, management decisions have grown more complicated. The treatment indications for asthma are clear; however, there is overlap with certain therapeutics that target the same pathway with similar end results. In the past decade, research to help providers decide which biologic therapy to use for defined cases has increased. It is now customary to call such treatment "tailored therapy" because it is not a one-size-fits-all approach that follows a rigid algorithm. Instead, it is a customized treatment plan that accounts for patient-specific risk factors and comorbidities.

Comorbidities commonly associated with asthma include atopic dermatitis, chronic rhinosinusitis with nasal polyposis, eosinophilic granulomatosis with polyangiitis, eosinophilic esophagitis, bronchiectasis and allergic bronchopulmonary aspergillosis. While we lack consensus or a universally accepted treatment algorithm for treating asthma when these comorbidities are present, recent evidence helps guide us to which therapies work best.



Dr. Hossri and Dr. Ivashchuk are with UTHealth Houston –Texas Medical Center, Department of Internal Medicine; Division of Pulmonary, Critical Care, and Sleep Medicine.

Atopic dermatitis

There is a higher prevalence of asthma in patients with atopic dermatitis. A concept called the "atopic march" refers to the progression of childhood atopic dermatitis to manifestations such as asthma, food allergies, and hay fever. The more severe the atopic dermatitis is in childhood, the higher the risk for asthma later on in life. The data on the biologic pathogenesis of atopic dermatitis point to the involvement of interleukins – interleukin (IL)-4 and IL 13 (Silverberg JI. *Ann Allergy Asthma Immunol.* 2019;123[2]:144-51). These same interleukins are active in what is called "Th2-high" asthma. The activation of Th2 cells in the inflammatory pathway occurs in atopic dermatitis and asthma irrespective of immunoglobulin E levels. Preliminary data show therapies that target IL-13 alone are effective for treating asthma with comorbid atopic dermatitis but those blocking both IL-4 and IL-13, like dupilumab, are superior. Both interleukins are considered pivotal in the Th-2 pathway. This suggests that dual inhibition is an

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integral component in the treatment of moderate to severe atopic dermatitis with asthma. Analysis of other Th2 mediators, such as mepolizumab (IL-5 antagonist) and omalizumab (anti-IgE) have shown minimal efficacy, further supporting the use of dupilumab (Guttman-Yassky E, et al. *J Allergy Clin. Immunol*. 2019 Jan;143[1]:155-72).

Chronic rhinosinusitis with nasal polyposis

The "unified airway" concept holds that because the upper airways (nasal mucosa, pharynx, and larynx) are in direct communication with the lower airways (bronchi and bronchioles). This would explain the correlation between chronic rhinosinusitis with nasal polyposis (CRSwNP) and asthma. Many studies also show the severity of one disease increases the severity of the other. Patients with both CRSwNP and asthma typically experience a more treatment-resistant course characterized by higher rates of corticosteroid dependence and nasal polyposis recurrences when compared with asthma alone (Laidlaw TM, et al. *J Allergy Clin Immunol Pract*. 2021 Mar;9[3]:1133-41). They typically have Th2-high asthma and are usually eosinophilic. The optimal treatment approach is mindful of the unified airway concept. Large-scale studies demonstrate significant benefit when targeting IL-5, especially in those with bilateral nasal polyps, need for systemic steroids in the past 2 years, significant impairment in quality of life, loss of smell, and a concomitant diagnosis of asthma (Fokkens WJ, et al. *Allergy*. 2019 Dec;74[12]:2312). Although data are inconsistent, there is enough evidence to suggest dupilumab be considered for those with eosinophilic asthma and CRSwNP along with atopy, atopic dermatitis, and/or high FeNO levels. In those without atopic symptoms, an anti-IL5/anti-IL5R (mainly mepolizumab and benralizumab) is preferred. Having said this, direct comparative analyses between biologics are lacking, and the above approach relies on an indirect assessment of existing data coupled with clinical experience. The approach may change as new data become available.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is a vasculitis characterized by disseminated necrotizing eosinophilic granulomas. EGPA is driven by a response similar to that seen in Th2-high asthma. Adult-onset asthma with sinusitis and allergic rhinitis is the most common EGPA presentation. Of all the biologics, mepolizumab has been best studied as treatment for those with EGPA and asthma symptoms. One small study demonstrated disease remission in 8 of 10 cases (Moosig F, et al. *Ann Intern Med*. 2011 Sep 6;155[5]:341-3). However, many of these patients relapsed after discontinuing therapy.

Eosinophilic esophagitis

Recent reports demonstrated a large portion of adults with a diagnosis of eosinophilic esophagitis (EoE) also have a history of asthma. Currently, standard treatment is proton pump inhibitors and diet modifications. The prevalence of EoE has increased with growing awareness of the disease. Unrecognized and untreated EoE can lead to devastating complications such as esophageal fibrosis, strictures, and food impaction. Similar to some of the above-mentioned syndromes, EoE is also driven by a Th2 response and eosinophilic inflammation. A recent study in 2022 showed that 31% to 38% of people with EoE had concomitant asthma (Dellon ES, et al. *N Engl J Med*. 2022 Dec 22;387 [25]:2317-30). In this population, a weekly dose of dupilumab, 300 mg, led to a significant improvement in dysphagia symptoms and histology when compared with placebo.

Allergic bronchopulmonary aspergillosis

Despite its low prevalence worldwide, allergic bronchopulmonary aspergillosis (ABPA) is frequently encountered when managing severe asthma. Current treatment is long-term, relatively high dose systemic corticosteroids. In light of their unfavorable side effect profile, steroid-sparing approaches are being sought. Dupilumab, omalizumab, mepolizumab, and benralizumab have all been tested for their effects on ABPA. Thus far, mepolizumab has the most convincing evidence to support its use for asthma with concomitant ABPA, mainly because it has the most rapid onset of action. Up to 90% of patients with ABPA were able to stop systemic steroids between 2 and 14 months after starting mepolizumab (Schleich F, et al. *J Allergy Clin Immunol*. 2020 Jul-Aug;8[7]:2412-3.e2).

Bronchiectasis

Asthma and bronchiectasis can coexist in up to 77% of patients. Typically, the pathophysiology behind bronchiectasis is focused around neutrophilic inflammation. New evidence suggests some patients with bronchiectasis, usually in the setting of comorbid adult-onset asthma, demonstrate an eosinophilic Th-2 response. The association is seen more commonly in female patients, the elderly, and nonsmokers. A small prospective study with four patients with severe asthma and bronchiectasis showed significant improvement with less exacerbations, increased pre-bronchodilator FEV_1, and a reduction of serum and sputum eosinophils after starting mepolizumab treatment (Carpagnano GE, et al. *J Asthma Allergy*. 2019 Mar 5;12:83-90). Clinical trials designed to clarify the role for biologics for asthma with co-morbid bronchiectasis are currently underway. ■

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BY PETER J. MAZZONE, MD, MPH, FCCP
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