Scientists use mRNA technology for universal flu vaccine

BY ALICE MCCARTHY

Two years ago, when the first COVID-19 vaccines were administered, marked a game-changing moment in the fight against the pandemic. But it also was a significant moment for messenger RNA (mRNA) technology, which up until then had shown promise but had never quite broken through.

Now, scientists hope to use this technology to develop more vaccines, with those at the University of Pennsylvania hoping to use that technology to pioneer yet another first: a universal flu vaccine that can protect us against all flu types, not just a select few.

It’s the latest advance in a new age of vaccinology, where vaccines are easier and faster to produce, as well as more flexible and customizable.

“It’s all about covering the different flavors of flu in a way the current vaccines cannot do,” said Ofer Levy, MD, PhD, director of the Precision Vaccines Program at Boston Children’s Hospital, who is not involved with the UPenn research.

“The mRNA platform is attractive here given its scalability and modularity, where you can mix and match different mRNAs.”

A recent paper, published in Science (2022 Nov 24. doi: 10.1126/science.abm0271), reports successful animal tests of the experimental vaccine, which, like the Pfizer-BioNTech and...
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.
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BATTLE TESTED
IN EOS DISEASE

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

SEVERE EOSINOPHILIC ASTHMA (SEA)
• add-on maintenance treatment of patients 6+ with SEA. Not for acute bronchospasm or status asthmaticus.

CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)
• add-on maintenance treatment of CRSwNP in patients 18+ with inadequate response to nasal corticosteroids.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)
• treatment of adult patients with EGPA.

HYPEREOSINOPHILIC SYNDROME (HES)
• treatment of patients aged 12+ with HES for ≥6 months without an identifiable non-hematologic secondary cause.

IMPORTANT SAFETY INFORMATION (cont’d)
WARNINGS AND PRECAUTIONS (cont’d)
Acute Asthma Symptoms or Deteriorating Disease
NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster
Herpes zoster infections have occurred in patients receiving NUCALA. Consider vaccination if medically appropriate.

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

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

ADVERSE REACTIONS
Most common adverse reactions (≥5%) in patients receiving NUCALA:
• Severe asthma trials: headache, injection site reaction, back pain, fatigue
• CRSwNP trial: oropharyngeal pain, arthralgia
• EGPA and HES trials (300 mg of NUCALA): no additional adverse reactions were identified to those reported in severe asthma clinical trials

Systemic reactions, including hypersensitivity, occurred in clinical trials in patients receiving NUCALA. Manifestations included rash, pruritus, headache, myalgia, flushing, urticaria, erythema, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, stridor, angioedema, and multifocal skin reaction. A majority of systemic reactions were experienced the day of dosing.

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

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

Visit NucalaBattleTested.com to learn more
NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP) and with disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day for at least 12 weeks prior to study entry. The safety and effectiveness of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established.

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with eosinophilic granulomatosis with polyangiitis (EGPA).

NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

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].

NUCALA should be used only when the benefit outweighs the risk for a given patient.

NUCALA is not for use in patients with active systemic infection.

NUCALA is not for use as a prophylaxis for acute exacerbations of asthma.

NUCALA is not for use in pediatric patients aged younger than 6 years with severe asthma.

The total dose of NUCALA administered was 600 mg in all patients who received NUCALA 100 mg or placebo. There was no significant difference in the incidence of adverse events between patients on NUCALA or placebo.

In the 52-week trial, the percentage of patients who experienced systemic allergic (type I hypersensitivity) and other reactions was <1% in the group receiving NUCALA 100 mg and <1% in the placebo group. Systemic allergic (type I hypersensitivity) reactions were reported by <1% of patients in the group receiving NUCALA 100 mg and <1% 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, 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.

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6 ADVERSE REACTIONS (cont’d)
Injection Site Reactions
Injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of NUCALA compared with 4% in patients receiving placebo.

6.5 Immunogenicity
In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody levels and changes 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 40 or 100 mg (n=153) NUCALA, 7/153 (5%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.

In patients with CSRWP receiving NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies.

No neutralizing antibodies were detected in any patients with CSRWP.

In patients with EGPA receiving NUCALA 100 mg, 2/153 (1%) had detectable anti-mepolizumab antibodies.

No neutralizing antibodies were detected in any patients with EGPA.

In adult and adolescent patients with HES receiving 300 mg of NUCALA 1/53 (2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with HES.

The reported frequency of anti-mepolizumab antibodies may understate 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.

6.7 Drug Interactions
Formal drug interaction trials have not been performed with NUCALA.

7 USE IN SPECIFIC POPULATIONS
8 Pregnancy
8.1 Pregnancy
Pregnancy 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 pre-eclampsia in the mother and preterm delivery, 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 day 20 to 140 after the mid-point of gestation exposure, up to approximately 9 times the exposure with the MRHD (on an ASCII 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. Examination 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 the HES cytokine IL-5. In the analogous antibody, the antibody was 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 (IgG3 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy (see Use In Specific Populations (8.1)). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use
Severe Asthma
The safety and efficacy of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older. Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 26 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 eosinophil of ≥150 cells/μl at screening or ≥300 cells/μl within 12 months prior to enrolment. (See Clinical Studies (14.4) full prescribing information.) 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.

The safety profile 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 (12.3) of full prescribing information). The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.

Steroid Reversal of Pseudohypoparathyroidism
The safety and effectiveness in patients aged younger than 18 years with CRSwNP have not been established. Eosinophil Granulomatosis with Polyangiitis
The safety and effectiveness in patients aged younger than 18 years with EGPA have not been established.

Hyper eosinophilic Syndrome
The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older.

8.5 match not found

8.6 Geriatric Use

8.7 Pregnancy

8.8 Nursing Mothers

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

Hyper-sensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after initiation of treatment with NUCALA. Instruct patients to contact their physicians if such reactions occur.

For Acute Symptoms or Determining 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.

Dysfunctional Infection: 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 who are pregnant 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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MIR®/KAI200000G September 2022
Produced in USA.
Autopsies show COVID virus invades entire body

BY LISA O’MARRY

The SARS-CoV-2 virus can be found throughout the entire body and remain present for more than 7 months, researchers discovered.

A study on the subject was published in the journal Nature (2022 Dec 22. doi: 10.1038/s41586-022-05542-y). The researchers completed autopsies from April 2020 to March 2021 of 44 unvaccinated people who had severe COVID-19. The median age was 62.5 years old, and 30% were female. Extensive brain sampling was done for 11 cases.

Because of its nature as a respiratory illness, SARS-CoV-2 was most widespread in the respiratory system such as in the lungs. But it was also found in 79 other body locations, including the heart, kidneys, liver, muscles, nerves, reproductive tract, and eyes.

Vaccine // continued from page 1

Modern COVID vaccines, relies on mRNA. But the idea is not to replace the annual flu shot. It’s to develop a primer that could be administered in childhood, readying the body’s B cells and T cells to react quickly if faced with a flu virus.

It’s all part of a National Institutes of Health–funded effort to develop a universal flu vaccine, with hopes of heading off future flu pandemics. Annual shots protect against flu subtypes known to spread in humans. But many subtypes circulate in animals, like birds and pigs, and occasion-ally jump to humans, causing pandemics.

“The current vaccines provide very little protection against these other subtypes,” said lead study author Scott Hensley, PhD, a professor of microbiology at UPenn. “We set out to make a vaccine that would provide some level of immunity against essentially every influenza subtype we know about.”

That’s 20 subtypes altogether. The unique properties of mRNA vaccines make immune responses against all those antigens possible, Dr. Hensley said.

Old-school vaccines introduce a weakened or dead bacteria or virus into the body, but mRNA vaccines use mRNA encoded with a protein from the virus. That’s the “spike” protein for COVID, and for the experimental vaccine, it’s hemagglutinin, the major protein found on the surface of all flu viruses.

Mice and ferrets that had never been exposed to the flu were given the vaccine and produced high levels of antibodies against all 20 flu subtypes. Vaccinated mice exposed to the exact strains in the vaccine stayed pretty healthy, while those exposed to strains not found in the vaccine got sick but recovered quickly and survived. Unvaccinated mice exposed to the flu strain died.

The vaccine seems to be able to “induce broad immunity against all the different influenza subtypes,” Dr. Hensley said, preventing severe illness if not infection overall.

Still, whether it could truly stave off a pandemic that hasn’t happened yet is hard to say, Dr. Levy said.

“We are going to need to better learn the molecular rules by which these vaccines protect,” he said.

But the UPenn team is forging ahead, with plans to test their vaccine in human adults in 2023 to determine safety, dosing, and antibody response.
**PULMONARY MEDICINE**

**Comorbidities and the prognosis of chronic obstructive pulmonary disease**

**BY JAVIER COTELO, MD**

Strict control of comorbidities in patients with chronic obstructive pulmonary disease decreases exacerbations and mortality, and avoids readmissions. An increasing number of women have the disease, which progresses differently in women than in men and even has different comorbidities.

“Comorbidities in patients with chronic obstructive pulmonary disease are more common in older adults, in those with more advanced pulmonary disease, and in those that are hospitalized for an acute exacerbation,” said Belén Alonso, MD, PhD, coordinator of the COPD Working Group of the Spanish Society of Internal Medicine. Up to 73 comorbidities associated with chronic obstructive pulmonary disease have been described. Dr. Alonso made these remarks during her presentation at the Comorbidities in Chronic Obstructive Pulmonary Disease Panel, which took place during the 43rd Conference of the Spanish Society of Internal Medicine (SEMI), in Gijón, Spain.

According to the scientific society’s press release, moderator María Gómez Antúnez, MD, stated, “The correct approach and treatment of these comorbidities is fundamental to improve the quality of life of the patient, decrease exacerbations, avoid readmissions, and decrease morbimortality in people with chronic obstructive pulmonary disease.”

The different works published, two of them by the SEMI COPD Working Group (ECCO and ESMI studies), indicate that the main comorbidities of patients with that pneumopathy are arterial hypertension, dyslipidemia, diabetes, heart failure, atrial fibrillation, ischemic heart disease, chronic kidney disease, peripheral arterial disease, and osteoporosis. Chronic hepatopathy, pulmonary neoplasm, depression, and cerebrovascular disease are less common.

**73 comorbidities described**

Dr. Alonso told this news organization, “Of those 73 comorbidities, some of the lesser known or less attention grabbing, according to a paper that we brought to the panel, include sleep disorders that encompass insomnia, nightmares, night terrors, sleep apneas, or hypopneas. Other lesser-known comorbidities related to cognitive decline, with patterns that reflect that up to 60% [of patients] may create to some degree of deterioration, and may involve the disease phase, hypoxemia, or degree of inflammation. On the other hand, there are also links to Parkinson’s disease and gastroesophageal reflux, among many more that arise from the cardiovascular sphere.”

One paper reveals that more than 78% of COPD patients have a significant bronchodilator response. Four puffs of albuterol (100 mcg each for a total of 400 mcg) with a 15- to 20-minute wait before repeat spirometry is also suggested.

The 2005 iteration acknowledges that a significant bronchodilator response isn’t a very accurate predictor of, well, anything. It doesn’t reliably differentiate COPD from asthma and it’s never been as sensitive as bronchoprovocation testing for diagnosing airway reactivity. The absence of a significant bronchodilator response does not preclude a 2-month trial of the same medicine used to test for response. Given these problems with standardization and accuracy, I was left wondering why anyone bothers ordering the test at all.

In my own practice, I continued to order, conduct, and interpret bronchodilator response according to the suggestions made by the ERS/ATS in 2005 when trying to diagnose asthma. I recognized that a nonsignificant response meant nothing, but bronchodilator response testing was easier to obtain than bronchoprovocation at my hospital. It was a matter of convenience for me and the patient. According to the Global Initiative for Asthma (GINA) Guidelines, a significant bronchodilator response conducted and interpreted as recommended by the ERS/ATS 2005 standard provides objective confirmation of asthma in the presence of characteristic clinical symptoms.

The headline from the ERS/ATS 2022 Technical Standard is that the 12% and 200-cc criteria suggested in 2005 are being retired. Why? Well, much of the variability in the 2005 criteria is explained by height, age, sex, and baseline lung function. These factors obscure change related to intrinsic airway abnormalities. Instead, the authors suggest using a threshold change in the predicted values of FEV1 and FVC to determine a significant response. Because predicted values incorporate age, height, and sex, the impact from these variables is minimized. Using a percent predicted (PPD) threshold will also minimize the effect from the inverse relationship between measured values and bronchodilator response.

A 10% change in the PPD value for either FEV1 or FVC constitutes a significant bronchodilator response. Ten percent was chosen because it represents the statistically defined upper limit of normal response; and a greater than 8% change in bronchodilator response is associated with mortality, implying that values above this threshold connote disease. The technical standard seems to be on solid ground here; the rationale is mathematically appropriate and evidence based. The new definition will certainly improve precision.

There’s really no progress on accuracy, though. There are no comments on the protocol to be followed or clinical indications. The reader is referred to the ERS/ATS 2019 technical statement on standardization of spirometry. The statement on standardization is short on details, too, and refers the reader to an online supplement for a suggested protocol. The suggested protocol is identical to that presented in 2005.

In summary, not a lot is different in the world of bronchodilator response testing. The definition is different now, and though it’s likely to be more precise, we still don’t know enough about accuracy. It’s nice to know that the new criteria will predict mortality; but in clinical practice we don’t use the test for that purpose. The 2022 technical standard acknowledges this and other limitations in a “future directions” paragraph. Perhaps we’ll know more when the next iteration is published.
patients with chronic obstructive pulmonary disease have one associated comorbidity, almost 69% have two, and 47.9% have three. "Based on gender, comorbidities are different. In women, it is well observed that anxiety, depression, and osteoporosis are more common. However, hypertension, ischemic heart disease, and diabetes are more common in men with chronic obstructive pulmonary disease," she stated.

"The pulmonary disease in question also progresses differently in men and women. In women, onset is at younger ages – between 40 and 50 years – and in men, after 50. Likewise, it appears that the disease progresses more quickly, which coincides with a worse quality of life (since dyspnea is tolerated less) and exceeds the anatomical differences, where hormonal influences play a dominant role," Dr. Alonso stressed.

Reciprocal prognosis
Dr. Alonso stated, "The prognostic importance of comorbidities in the disease is reciprocal. In other words, if there are comorbidities that we do not look for or treat, they are going to have a negative influence on the chronic obstructive pulmonary disease. The disease will progress more and elevate the risk of exacerbations (the most important prognostic factor of that disease). In turn, if we are not treating the disease well, not only pharmacologically, it will have negative repercussions on the comorbidities. It will progress and have negative connotations, such as diabetes or ischemic heart disease."

The aforementioned ECCO and ESMI studies include patients in internal medicine with exacerbations where the most common comorbidities have been mapped out, although there is also extensive research on comorbidities in patients who are admitted to departments other than internal medicine. "With regard to prognostic implications, our working group very clearly observed the comorbidities and the comorbidome, that solar system that appears so much in medical conferences and forums, which implies that proximity to the center of that solar system is related more to mortality, anxiety, depression, and breast cancer. Other pathologies, such as ischemic heart disease or dyslipidemia, are outside of that territory of greater risk, in which we have been more pioneering than other groups," said Dr. Alonso.

The current trend is that the age of these patients is increasing, and there are more and more women with this pathology. According to the latest report from the Ministry of Health on respiratory diseases, the prevalence of chronic obstructive pulmonary disease among the population 40 years and older is around 33.9 cases per 1,000 inhabitants, more than twice as common in men than in women (47.7 vs. 21.3). Prevalence increases with age after 40 years progressively until reaching the greatest frequency in the 80- to 84-year-old age group.

In 2019, the number of deaths due to chronic obstructive pulmonary disease in Spain was 13,808 (9,907 men and 3,901 women), with a crude mortality rate of 29.3 deaths per 100,000 inhabitants. This toll decreased in comparison with that of 2018. Chronic obstructive pulmonary disease causes 2.5 times more deaths in men than in women. From 2001 to 2019, mortality due to that pathology declined by 43% in men and women. The decrease was almost 50% in men and 33% in women.

Overlap syndrome prevalent
Javier Sánchez Lora, MD, of the internal medicine department of the Virgen de la Victoria de Málaga University Clinical Hospital, discussed chronic obstructive pulmonary disease and sleep disorders. More concretely, he spoke about overlap syndrome: chronic obstructive pulmonary disease plus obstructive sleep apnea. According to the international consensus document on obstructive sleep apnea, the diagnosis requires an apnea-hypopnea index (AHI) equal to or greater than 15 per hour or equal to or greater than 5. The patient must also have one or more of the following factors: excessive daytime sleepiness, sleep that is not restful, excessive fatigue, and deterioration in quality of life related to sleep and not justified by other causes. "The overlap syndrome affects 3%-66% of chronic obstructive pulmonary diseases and 7%-55% of obstructive sleep apnea," said Dr. Sánchez Lora. This syndrome has important effects on different systems: at the cardiovascular level (arterial and pulmonary hypertension, heart failure, stroke, arrhythmias, ischemic heart disease, pulmonary thromboembolism), metabolic (insulin resistance, diabetes, metabolic syndrome), neurocognitive (dementia, depression), and sleep with hypoxemia and hypercapnia (lung, pancreas, esophagus) effects. "These patients have a worse prognosis than those that have these pathologies alone. During sleep, they experience more frequent episodes of oxygen desaturation and they have a longer total period of sleep with hypoxemia and hypercapnia than those with obstructive apnea alone without chronic obstructive pulmonary disease," said Dr. Sánchez Lora.

The apneic events of patients with the syndrome have a more profound hypoxemia and more arrhythmias, in addition to their being more susceptible to developing pulmonary hypertension than those with chronic obstructive pulmonary disease or sleep apnea alone. "The good news is that, in patients with overlap, the use of ventilation with positive pressure reduces all causes of hospitalization and the visits to the emergency room, as well as the moderate and severe exacerbations of the disease."

Dr. Sánchez Lora referred to a series of recommendations in clinical practice for the diagnosis and treatment of overlap syndrome: screening, combined therapy of hygienic–dietary measures, and the use of continuous positive respiratory pressure. Oxygen therapy to correct isolated nocturnal desaturations has not shown benefits in survival, although a benefit trial of symptoms attributed to nocturnal hypoxemia in patients with significant comorbidity can be conducted.

Underdiagnosis
"During the panel, we also spoke about the importance that as part of internal medicine we need to make an effort to reduce the underdiagnosis of chronic pulmonary disease and its comorbidities. Specialists in internal medicine need to become aware that this pathology is not only pulmonary, but also multisystemic, complex, heterogeneous, and very variable even in the same patient," said Dr. Sánchez Lora.

Dr. Alonso said, "Regarding the importance of diagnosis of this disease, we continue with an underdiagnosis greater than 70% for men and 80% for women. Secondly, we need to actively seek out the comorbidities associated with chronic obstructive pulmonary disease, even taking advantage of the admission of these patients with exacerbations, which are undesired and common."

"Regarding ongoing trials, we have a study that started during the COVID-19 pandemic, ADEG-EPOC, that involves the adaptation to and impact of severe and very severe exacerbations in patients admitted to our departments," the specialist indicated.

"In the group, we are also planning to publish an updated agreement, which we already made in 2014, on the most common and important comorbidities associated with chronic obstructive pulmonary disease. The agreement discusses the 20 most important comorbidities. In addition, the 2023 GOLD Guide, which appeared in November 2022, includes a new chapter on updated treatment and the latest developments.

In the last 5 years, Dr. Sánchez Alonso has collaborated with Abbott, AstraZeneca, Boehringer Ingelheim, Chiesi, FAES, Ferrer, Fresenius Kabi, GSK, Nestlé, Novo Nordisk, Nutricia, and Menarini. Dr. Sánchez Lora has collaborated with AstraZeneca, Boehringer Ingelheim, Chiesi, FAES, GSK, and Menarini."
LUNG CANCER

Immunotherapy target may aid in NSCLC treatment

BY JIM KLING
MDedge News

In a phase 2 clinical trial of the soluble lymphocyte-activation gene 3 (LAG-3) as a potential treatment for non–small cell lung cancer (NSCLC), the drug performed well across all levels of PD-L1 expression.

“We observed a very encouraging response rate. Responses were seen across PD-L1 status,” said Wade Iams, MD, at a press conference held in advance of the annual meeting of the Society for Immunotherapy of Cancer. Dr. Iams is a professor of medicine at Vanderbilt University Medical Center, Nashville, Tenn.

“The study was not loaded to PD-L1–high patients. We had a good breakdown across all of our three typical groups in the [NSCLC] treatment setting. Across histology types between squamous and nonsquamous, the median duration of response was almost 22 months. This is very encouraging compared to historical controls,” he said.

Eftilagimod alpha is a soluble form of the LAG-3 protein, which is a stimulator of antigen-presenting cells and CD8+ T cells through its action on MHC class 2 molecules. It suppresses the activation of T cells and therefore has the potential to boost the effect of anti–PD-1 therapy. LAG-3 can have both stimulatory and inhibitor immune effects, leading Immutep, which sponsored the study with Merck Sharp and Dohme, to pursue it in both cancer immunotherapy and autoimmune diseases.

The drug is a departure from other drugs which are LAG-3 antagonists. Those therapies interfere with the interaction between LAG-3 on the surface of activated T cells and MHC class 2 molecules on the surface of resting dendritic cells, which would otherwise dampen immune response in the tumor microenvironment. On the other hand, LAG-3 (or eftilagimod alpha) interacts with MHC class 2 on the surface of activated dendritic cells and monocytes to stimulate production of cytotoxic CD8+ T cells. These in turn can be unleashed further by the downstream action of pembrolizumab.

The phase 2 trial included three parts: In part A, 114 patients with NSCLC received the combination of eftilagimod alpha and pembrolizumab being given as a first-line therapy. Part B looked at the combination in 36 patients who were resistant to PD-1/PD-L1 therapies. Part C included 39 patients with head and neck squamous cell carcinoma who had previously received platinum-based chemotherapy. Patients received combination therapy for up to 1 year, then monotherapy with pembrolizumab for up to another year.

The primary endpoint of the study was a comparison of overall response rate to historical controls, with success set at 35% or higher. In the intent-to-treat analysis of the treatment-naive NSCLC population, ORR was 39.5% (95% confidence interval, 30.5%-49.1%) and the interim median progression-free survival was 6.9 months (95% CI, 4.9-9.3 months). Among 40 responders, the median duration of response was 21.6 months (95% CI, 17.3-30.0 months). ORRs were similar between squamous and nonsquamous subtypes.

In his presentation of the results, Dr. Iams said that 75% of participants had PD-L1 levels below 50%. The ORR was highest at 55% in the PD-L1 greater than 50% group, 44.7% in the PD-L1 1%-49% group, and 31.1% in the PD-L1 less than 1% group. It was a “very impressive response rate” for the low PD-L1 group, Dr. Iams said. Interim median progression-free survival followed a similar trend, with values of 11.4 months, 8.3 months, and 4.2 months, respectively.

Asking about the efficacy across subgroups, Dr. Iams responded that other immune-stimulating agents have shown a stepwise improvement across PD-L1 expression levels, similar to what was observed in the current study. “My personal opinion as to why it was still effective at low PD-L1 is in part that PD-L1 is an imperfect biomarker. We know that there’s tumor heterogeneity, and perhaps it’s not fully representative of a one-site evaluation, but also in combination, and we have seen this in patients with [NSCLC] treated with both PD-L1 and CTLA-4 agents of increased efficacy in the PD-L1–low patients. So these combination immunotherapy strategies may be uniquely opportune for the low PD-L1 patients,” Dr. Iams said.

The study was funded by Immutep and Merck Sharp and Dohme. Dr. Iams has financial relationships with Merck.
Trace metals may be tied to risk of sleep disorders

BY HEIDI SPLETE
MDedge News

Higher concentrations of serum zinc, alone and in combination with copper or selenium, were inversely related to an increased risk of sleep disorders in adults, based on data from 3,660 individuals. Previous research has shown an association between trace metals and sleep and sleep patterns, but data on the impact of serum trace metals on sleep disorders have been limited, wrote Ming-Gang Deng, MD, of Wuhan (China) University and colleagues.

In a study published in the Journal of Affective Disorders (2022 Dec 7. doi: 10.1016/j.jad.2022.11.088), the researchers reviewed data from the National Health and Nutrition Examination Survey (NHANES) 2011-2016 to calculate the odds ratios of sleep disorders and serum zinc (Zn), copper (Cu), and selenium (Se). The study population included adults aged 18 years and older, with an average age of 47.6 years. Approximately half of the participants were men, and the majority was non-Hispanic white. Serum Zn, Cu, and Se were identified at the Environmental Health Sciences Laboratory of the Centers for Disease Control and Prevention National Center for Environmental Health. The lower limits of detection for Zn, Cu, and Se were 2.9 mcg/dL, 2.5 mcg/dL, and 4.5 mcg/L, respectively. Sleep disorders were assessed based on self-reports of discussions with health professionals about sleep disorders, and via the Sleep Disorder Questionnaire.

After adjusting for sociodemographic, behavioral characteristics, and health characteristics, adults in the highest tertiles of serum Zn had a 30% reduced risk of sleep disorders, compared with those in the lowest tertiles of serum Zn (odds ratio, 0.70; P = .035).

In measures of trace metals ratios, serum Zn/Cu and Zn/Se were significantly associated with reduced risk of sleep disorders for individuals in the highest tertiles, compared with those in the lowest tertiles (OR, 0.62 and OR, 0.68, respectively).

However, the serum Cu, Zn, and Cu/Se were not associated with sleep-disorder risk. Sociodemographic factors included age, sex, race, education level, family income level; behavioral characteristics included smoking, alcohol consumption, physical activity, and caffeine intake. The researchers also used a restricted cubic spline model to examine the dose-response relationships between serum trace metals, serum trace metals ratios, and sleep disorders. In this analysis, higher levels of serum Zn, Zn/Cu, and Zn/Se were related to reduced risk of sleep disorders, while no significant association appeared between serum Cu, Se, or Cu/Se and sleep disorders risk.

The findings showing a lack of association between Se and sleep disorders were not consistent with previous studies, the researchers wrote in their discussion.

Previous research has shown that a higher Se was less likely to be associated with trouble falling asleep, and has shown a potential treatment effect of Se on obstructive sleep apnea, they said. “Although serum Cu and Se levels were not correlated to sleep disorders in our study, the Zn/Cu and Zn/Se may provide some novel insights,” they wrote. For example, Zn/Cu has been used as a predictor of several clinical complications related to an increased risk of sleep disorders including cardiovascular disease, cancer, and major depressive disorder, they noted.

The findings were limited by several factors including the cross-sectional design, use of self-reports, and the inability to examine relationships between trace metals and specific sleep-disorder symptoms, such as restless legs syndrome, insomnia, and obstructive sleep apnea, the researchers noted.

However, the results were strengthened by the large national sample, and support data from previous studies, they said. “The inverse associations of serum Zn, and Zn/Cu, Zn/Se with sleep disorders enlightened us that increasing Zn intake may be an excellent approach to prevent sleep disorders,” they wrote.

Severe OSA associated with poor prognoses in stroke

BY HEIDI SPLETE
MDedge News

Patients with acute ischemic stroke had a worse prognosis if they had also experienced severe obstructive sleep apnea (OSA), based on data from 125 individuals. OSA is on the rise, and is associated with pathophysiological changes, and data from previous studies suggest that severe OSA doubles the risk of stroke and increases risk of stroke recurrence, according to Juan Xu, PhD, of Soochow University, Suzhou, China, and colleagues. “There is a high comorbidity between stroke and OSA,” and effective sleep is important to cerebral function recovery, the researchers wrote. Early prediction of stroke prognosis may inform treatment in stroke patients, but the value of OSA as a predictor of functional prognosis has not been explored.

In a study published in Sleep Medicine (2022 Dec 5. doi: 10.1016/j.sleep.2022.11.035), the researchers analyzed data from 125 adults with mild to moderate ischemic stroke and OSA. The participants underwent polysomnography within a week of stroke onset between January 2015 and June 2020 and were grouped by severity according to apnea-hypopnea index (AHI) of either less than 30/h (not severe) or 30/h or higher (severe). The mean age of the patients was 58 years, and 87% were men. Approximately one-third of the participants met the criteria for severe OSA. The researchers assessed the impact of OSA on functional prognosis in the acute phase of stroke, and reviewed quantitative electroencephalography (EEG) markers in stroke patients during sleep.

Overall, individuals with severe OSA were significantly more likely than those with less severe OSA to have comorbid hypertension (85.4% vs. 56%; P = .002) and a higher body mass index (28 vs. 24; P < .001). Other factors including blood pressure, smoking history, alcohol use, and comorbid diabetes were similar between the groups.

Quantitative EEG among patients with severe OSA showed lower relative power of high-frequency bands (alpha, beta, and gamma). The EEG also showed higher delta/alpha power ratio and slowing ratio, and higher delta relative power (delta RP) in severe OSA (P < .05 for all).

In addition, severe OSA was associated with more than triple the risk (3.6-fold increase) of poor prognosis, defined as a Modified Rankin Scale score of 3 or higher (24.4% for severe OSA vs. 8.3% for nonsevere OSA; P = .03). “Our study confirmed that severe OSA is an independent risk factor for poor functional prognosis in the acute phase of ischemic stroke,” the researchers wrote. “Integrating the alteration of quantitative EEG parameters may improve the accuracy of early predictions of functional prognosis in patients with stroke.”

The findings were limited by factors including the retrospective design and the lack of a sizable non-OSA control group, the researchers noted. Other limitations included the use of an AHI of 30/h or higher to define severity and the use of data from medical histories, with the potential for information bias, and the use of only 30-second continuous polysomnography segments.

However, the results suggest that increased delta RP and TSR, and decreased alpha, beta, and sigma RP, may be independent predictors of a poor functional prognosis in stroke patients with OSA, and that the prognosis could be improved by treating the OSA, they concluded.

The study was supported by the Natural Science Foundation of China and the Discipline Construction Program of the Second Affiliated Hospital of Soochow University. The researchers reported no financial conflicts.
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OVID-19 has lifted the lid on the risks of secondary pulmonary fungal infections in patients with severe respiratory viral illness – even previously immunocompetent individuals – and highlighted the importance of vigilant investigation to achieve early diagnoses, leading experts say.

Most fungi are not under surveillance in the United States, leaving experts without a national picture of the true burden of infection through the pandemic. However, a collection of published case series, cohort studies, and reviews from Europe, the United States, and throughout the world – mainly pre-Omicron – show that fungal disease has affected a significant portion of critically ill patients with COVID-19, with concerning excess mortality, these experts say.

COVID-associated pulmonary aspergillosis (CAPA) has been the predominant fungal coinfection in the United States and internationally. But COVID-associated mucormycosis (CAM) – the infection that surged in India in early 2021 – has also affected some patients in the United States, published data show. So have *Pneumocystis* pneumonia, cryptococcosis, histoplasmosis, and *Candida* infections (which mainly affect the bloodstream and abdomen), say the experts who were interviewed.

“We had predicted [a rise in] aspergillosis, but we saw more than we thought we’d see. Most fungal infections became more common with COVID-19,” said George Thompson, MD, professor of clinical medicine at the University of California, Davis, and cochair of the University of Alabama–based Mycoses Study Group Education Committee, a group of experts in medical mycology. *Pneumocystis*, for instance, “has historically been associated with AIDS or different types of leukemia or lymphoma, and is not an infection we’ve typically seen in our otherwise healthy ICU patients,” he noted. “But we did see more of it [with COVID-19].”

More recently, with fewer patients during the Omicron phase in intensive care units with acute respiratory failure, the profile of fungal disease secondary to COVID-19 has changed. Increasing proportions of patients have traditional risk factors for aspergillosis, such as hematologic malignancies and longer-term, pre-COVID use of systemic corticosteroids – a change that makes the contribution of the viral illness harder to distinguish.

Moving forward, the lessons of the COVID era – the fungal risks to patients with serious viral infections and the persistence needed to diagnose aspergillosis and other pulmonary fungal infections using bronchoscopy and imperfect noninvasive tests – should be taken to heart, experts say.

“Fungal diseases are not rare. They’re just not diagnosed because no one thinks to look for them,” said Dr. Thompson, a contributor to a recently released World Health Organization report naming a “fungal priority pathogens” list.

“We’re going to continue to see [secondary fungal infections] with other respiratory viruses,” he said. And overall, given environmental and other changes, “we’re going to see more and more fungal disease in the patients we take care of.”

**CAPA not a surprise**

CAPA is “not an unfamiliar story” in the world of fungal disease, given a history of influenza-associated pulmonary aspergillosis (IAPA), said Kieren A. Marr, MD, MBA, adjunct professor of medicine and past director of the transplant and oncology infectious diseases program at Johns Hopkins University, Baltimore, who has long researched invasive fungal disease.

European researchers, she said, have led the way in describing a high incidence of IAPA in patients admitted to ICUs with influenza. In a retrospective multicenter cohort study (Lancet Respir Med. 2018 Oct. 10:1016/S2213-2600[18],30274-1) reported in 2018 by the Dutch-Belgian Mycosis Study group, for instance, almost 20% of 432 influenza patients admitted to the ICU, including patients who were otherwise healthy and not immunocompromised, had the diagnosis a median of 3 days after ICU admission. (Across other cohort studies, rates of IAPA have ranged from 7% to 30%.)

Mortality was significant: 51% of patients with influenza and invasive pulmonary aspergillosis died within 90 days, compared with 28% of patients with influenza and no invasive pulmonary aspergillosis.

Reports from Europe early in the pandemic indicated that CAPA was a similarly serious problem, prompting establishment at Johns Hopkins University of an aggressive screening program using biomarker-based testing of blood and bronchoalveolar lavage (BAL) fluid. Of 396 mechanically ventilated COVID-19 patients admitted to Johns Hopkins University hospitals between March and August 2020, 39 met the institution’s criteria for CAPA, Dr. Marr and her colleagues reported last year in what might be the largest U.S. cohort study (Clin Infect Dis. 2022 Jan 7. doi: 10.1093/cid/ciab223) of CAPA published to date.

“We now know definitively that people with severe influenza and with severe COVID also have high risks for both invasive and airway disease caused by airborne fungi, most commonly aspergillosis,” Dr. Marr said.

More recent unpublished analyses of patients from the start of the pandemic to June 2021 show persistent risk, said Nitipong Permpalung, MD, MPH, assistant professor in transplant and oncology infectious diseases at Johns Hopkins University and lead author of the cohort study. Among 832 patients with COVID-19 who were mechanically ventilated, almost 20% of patients with COVID-19, with influenza, and past director of the transplant and oncology infectious diseases program at Johns Hopkins University, Baltimore, who has long researched invasive fungal disease.

“**We had predicted [a rise in] aspergillosis, but we saw more than we thought we’d see. Most fungal infections became more common with COVID-19.**”

**Dr. Thompson**

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ventilated in Johns Hopkins University hospitals, 11.8% had CAPA, he said. (Also, 3.2% had invasive candidiasis, and 1.1% had other invasive fungal infections.)

Other sources said in interviews that these CAPA prevalence rates generally mirror reports from Europe, though some investigators in Europe have reported CAPA rates more toward 15%.

(The Mycoses Study Group recently collected data from its consortium of U.S. medical centers on the prevalence of CAPA, with funding support from the Center for Disease Control and Prevention, but at press time the data had not yet been released. Dr. Thompson said he suspected the prevalence will be lower than earlier papers have suggested, “but still will reflect a significant burden of disease.”)

Patients in the published Johns Hopkins University study who had CAPA were more likely than those with COVID-19 but no CAPA to have underlying pulmonary disease, liver disease, coagulopathy, solid tumors, multiple myeloma, and COVID-19–directed corticosteroids. And they had uniformly worse outcomes with regards to severity of illness and length of intubation.

How much of CAPA is driven by the SARS-CoV-2 virus itself and how much is a consequence of COVID-19 treatments is a topic of active discussion and research. Martin Hoenigl, MD, of the University of Graz (Austria), a leading researcher in medical mycology, said research shows corticosteroids and anti–IL-6 treatments, such as tocilizumab, used to treat COVID-19–driven acute respiratory failure clearly have contributed to CAPA. But he contends that “a number of other mechanisms” are involved as well.

“The immunologic mechanisms are definitely different in these patients with viral illness than in other ICU patients [who develop aspergillosis]. It’s not just the corticosteroids. The more we learn, we see the virus plays a role as well, suppressing the interferon pathway,” for example, said Dr. Hoenigl, associate professor in the division of infectious diseases and the European Confederation of Medical Mycology (ECMM) Center of Excellence at the university. The earliest reports of CAPA came “when ICUs weren’t using dexamethasone or tocilizumab,” he noted.

In a paper published recently in The Lancet Respiratory Medicine that Dr. Hoenigl and others point to, Belgian researchers reported a “three-level breach” in innate anti-fungal immunity in both IAPA and CAPA, affecting the integrity of the epithelial barrier, the capacity to phagocytose and kill Aspergillus spores, and the ability to destroy Aspergillus hyphae, which is mainly mediated by neutrophils.

**Fungal continued from previous page**

Aspergillus that has invaded the lung tissue in patients with COVID-19 appears to grow there for some time – around 8-10 days, much longer than in IAPA – before becoming angioinvasive. The researchers ran a host of genetic and protein analyses on lung samples (most collected via BAL) of 169 patients with influenza or COVID-19, with and without aspergillosis.

They found that patients with CAPA had significantly lower neutrophil cell fractions than patients with COVID-19 only, and patients with IAPA or CAPA had reduced type II IFN signaling and increased concentrations of fibrosis-associated growth factors in the lower respiratory tracts (Lancet Respir Med. 2022 Aug 24 doi: 10.1016/S2213-2600(22)00259-4).

Tom Chiller, MD, MPH, chief of the CDC’s Mycotic Disease Branch, said he’s watching such research with interest.

For now, he said, it’s important to also consider that “data on COVID show that almost all patients going into the ICUs with pneumonia and COVID are getting broad-spectrum antibiotics” in addition to corticosteroids.

By wiping out good bacteria, the antibiotics could be “creating a perfect niche for fungi to grow,” he said.

**Diagnostic challenges**

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who just aren’t moving forward and are continuing to struggle. Have a high index of suspicion, and consult with your infectious disease colleagues.”

Empiric treatment is warranted in some cases if a patient is doing poorly and suspicion for fungal infection is high based on clinical, radiographic, and/or laboratory evidence, he said.

The CDC’s Dr. Chiller said that screening and diagnostic algorithms currently vary from institution to institution, and diagnostic challenges likely dissuade clinicians from thinking about fungi. “Clinicians often don’t want to deal with fungi—they’re difficult to diagnose; the treatments are limited and can be toxic. But fungi get pushed back until it’s too late,” he said. “Fungal diagnostics is an area we all need a lot more help with,” and new diagnostics are in the pipeline, he said. In the meantime, he said, “there are tools out there, and we just need to use them more, and improve how they’re used.”

While reported CAPA thus far has typically occurred in the setting of ICU care and mechanical ventilation, it’s not always the case, Dr. Permpalung said. Lung and other solid organ transplant (SOT) recipients with COVID-19 are developing CAPA and other invasive secondary invasive fungal infections despite not being intubated, he said.

Of 276 SOT recipients with COVID-19 who required inpatient treatment at Johns Hopkins University hospitals from the beginning of the pandemic to March 2022, 23 patients developed invasive fungal infections (13 CAPA). Only a fraction—38 of the 276—had been intubated, he said.

Mucormycosis resistance

After CAPA, candidiasis and COVID-19-associated mucormycosis (CAM) – most frequently, rhino-orbital-cerebral disease or pulmonary disease – have been the leading reported fungal coinfactions in COVID-19, said Dr. Hoenigl, who described the incidence, timeline, risk factors, and pathogenesis of these infections in a review published (2022 Aug. doi: 10.1038/s41564-022-01172-2) this year in Nature Microbiology.

In India, where there has long been high exposure to Mucorales spores and a greater burden of invasive fungal disease, the rate of mucormycosis doubled in 2021, with rhino-orbital-cerebral disease reported almost exclusively, he said. Pulmonary disease has occurred almost exclusively in the ICU setting and has been present in about 50% of cases outside of India, including Europe and the United States.

A preprint meta-analysis of CAM cases posted by The Lancet in July 2022, in which investigators analyzed individual data of 556 reported cases of CAM, shows diabetes and history of corticosteroid use present in most patients, and an overall mortality rate of 44.4%, most of which stems from cases of pulmonary or disseminated disease. Thirteen of the 556 reported cases were from the United States.

An important takeaway from the analysis, Dr. Hoenigl said, is that *Aspergillus* coinfection was seen in 7% of patients and was associated with higher mortality. “It’s important to consider that coinfections [of *Aspergillus* and Mucorales] can exist,” Dr. Hoenigl said, noting that like CAPA, pulmonary CAM is likely underdiagnosed and underreported.

As with CAPA, the clinical and radiological features of pulmonary CAM largely overlap with those associated with COVID-19, and bronchoscopy plays a central role in definitive diagnosis. In the United States, a Mucorales PCR test for blood and BAL fluid is commercially available and used at some centers, Dr. Hoenigl said.

“Mucormycosis is always difficult to treat… a lot of the treatments don’t work particularly well,” said Dr. Thompson. “With aspergillosis, we have better treatment options.”

Dr. Thompson worries, however, about treatment resistance becoming widespread. Resistance to azole antifungal agents “is already pretty widespread in northern Europe, particularly in the Netherlands and part of the U.K.” because of injudicious use of antifungals in agriculture, he said. “We’ve started to see a few cases [of azole-resistant aspergillosis in the United States] and know it will be more widespread soon.”

Treatment resistance is a focus of the new WHO fungal priority pathogens list – the first such report from the organization. Of the 19 fungi on the list, four were ranked as critical: *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus*, and *Candida albicans*. Like Dr. Thompson, Dr. Hoenigl contributed to the WHO report.

Dr. Hoenigl reported grant/research support from Astellas, Merck, F2G, Gilread, Pfizer, and Scynexis. Dr. Marr disclosed employment and equity in Pearl Diagnostics and Sfunga Therapeutics. Dr. Thompson, Dr. Permpalung, and Dr. Zeki reported they have no relevant financial disclosures.

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Support lung health initiatives like these by donating to the CHEST Foundation.
Delays in diagnosing IPF. Noninvasive ventilation. BPA and CTEPH.

Diffuse Lung Disease & Transplant Network
Interstitial Lung Disease Section
Delay in diagnosis of IPF: How bad is the problem?

Idiopathic pulmonary fibrosis (IPF) is a devastating disease with a poor prognosis. Antibifrotic therapies for IPF are only capable of slowing disease progression without reversing established fibrosis. As such, the therapeutic efficacy of antifibrotic therapy may be reduced in patients whose diagnosis is delayed.

Unfortunately, diagnostic delay is common in IPF. Studies demonstrate that IPF diagnosis is delayed by more than a year after symptom onset in 43% of subjects, and more than 3 years in 19% of subjects (Cosgrove GP, et al. BMC Pulm Med. 2018;18(9)). Approximately one-third of patients with IPF have undergone chest CT imaging more than 3 years prior to diagnosis, and around the same proportion has seen a pulmonologist within the same time span (Mooney J, et al. Ann Am Thorac Soc. 2019;16(3):393). A median delay to IPF diagnosis of 2.2 years was noted in patients presenting to a tertiary academic medical center and was associated with an increased risk of death independent of age, sex, and forced vital capacity (adjusted hazard ratio per doubling of delay was 1.3) (Lamas D), et al. Am J Respir Crit Care Med. 2011;184:842).

Robust improvements are clearly required for identifying patients with IPF earlier in their disease course. The Bridging Specialties Initiative from CHEST and the Three Lakes Foundation is one resource designed to improve the timely diagnosis of ILD (ILD Clinician Toolkit available at https://www.chestnet.org).

Guidelines-and-Topic-Collections/Bridging-Specialties/Timely-Diagnosis-for-ILD-Patients/Clinician-Toolkit). This, and other initiatives will hopefully reduce delays in diagnosing IPF, allowing for optimal patient care.

Adrian Shifren, MBBSCh, FCCP
Member-at-Large
Sanjiva Khan, MD, MBBS
Member-at-Large
Robert Case Jr., MD
Pulmonary & Critical Care Fellow

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Critical Care Network
Mechanical Ventilation and Airways Section
Noninvasive ventilation

Noninvasive ventilation (NIV) is a ventilation modality that supports breathing by using mechanically assisted breaths without the need for intubation or a surgical airway. NIV is divided into two main types, negative-pressure ventilation (NPV) and noninvasive positive-pressure ventilation (NIPPV).

NPV
NPV periodically generates a negative (sub-atmospheric) pressure on the thorax wall, reflecting the natural breathing mechanism. As this negative pressure is transmitted into the thorax, normal atmospheric pressure air outside the thorax is pulled in for inhalation. Initiated by the negative pressure generator switching off, exhalation is passive due to elastic recoil of the lung and chest wall. The iron lung was a neck-to-toe horizontal cylinder used for NPV during the polio epidemic. New NPV devices are designed to fit the thorax only, using a cuirass (a torso-covering body armor molded shell).

For years, NPV use declined as NIPPV use increased. However, during the shortage of NIPPV devices during COVID and a recent recall of certain CPAP devices, NPV use has increased. NPV is an excellent alternative for those who cannot tolerate a facial mask due to facial deformity, claustrophobia, or excessive airway secretion (Corrado A, et al. European Resp J. 2002;20(1):187).

NIPPV
NIPPV is divided into several subtypes, including continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP or BiPAP), and average volume-assured pressure support (AVAPS or VAPS). CPAP is defined as a single pressure delivered in inhalation (Pi) and exhalation (Pe). The increased mean airway pressure provides improved oxygenation (O2) but not ventilation (CO2). BPAP uses dual pressures with Pi higher than Pe. The increased mean airway pressure provides improved O2 while the difference between Pi minus Pe increases ventilation and decreases CO2.

AVAPS is a form of BPAP where Pi varies in an automated range to achieve the ordered tidal volume. In AVAPS, the generator adjusts Pi based on the average delivered tidal volume. If the average delivered tidal volume is less than the set tidal volume, Pi gradually increases while not exceeding Pi Max. Patients notice improved comfort of AVAPS with a variable Pi vs BPAP with a fixed Pi (Frank, et al. Chest. 2018;154(4):1060A).

Samantha Tauscher, DO
Resident-in-Training
Herbert Patrick, MD, MSEE, FCCP
Member-at-Large

In patients with inoperable CTEPH, BPA has emerged as an attractive management option in addition to the medical therapy with riociguat.

At 26 weeks, the BPA arm showed a greater reduction in PVR but more complications, including lung injury and hemoptysis. After a 26-week crossover period, the reduction in PVR was similar in both arms. The complication rate in the BPA arm was lower when preceded by riociguat.

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In patients with inoperable CTEPH, BPA has emerged as an attractive management option in addition to the medical therapy with riociguat.
CRITICAL CARE COMMENTARY

Management strategies for patients with COVID-19 pneumonia/ARDS

BY JOHN GAILLARD, MD, FCCP, TARUN KAPOOR, MD, AND ERIN STAPLES, MD

Since the first SARS-CoV-2 (COVID-19) outbreak in Wuhan, China, in December 2019, more than 6.6 million deaths have occurred. Management strategies for patients with COVID-19 pneumonia/ARDS have continued to evolve during the pandemic. One of the strategies for those cases refractory to traditional ARDS treatments has been the use of extracorporeal membrane oxygenation (ECMO).

Before the COVID-19 pandemic, a substantial amount of data regarding the use of ECMO in ARDS was gathered during the H1N1 influenza outbreak in 2009. Mortality ranged from 8% to 65% (Zandrillo, et al. Crit Care. 2013;17[1]:R30). From these data, we learned the importance of patient selection. Young patients with few co-morbidities and less than 7 days supported by mechanical ventilation did remarkably better than elderly patients or those who had prolonged positive-pressure ventilation prior to ECMO.

To date, the mortality rate for COVID-19 patients with ARDS requiring ECMO is 48% based on data from ELSO. Interestingly though, using May 1, 2020, as a cutoff date, mortality rates for patients with COVID-19 receiving ECMO significantly increased from 37% to 52% (Barbaro, et al. Lancet. 2021;398[10307]:1230). This escalation in mortality engendered concern that ECMO may not be useful in treating patients with COVID-19 and ARDS.

Several factors can be cited for this increase in mortality. First, many new ECMO programs launched after May 1. These new programs had a higher mortality rate (59%) compared with established programs, suggesting that program and provider experience play a significant role in patient outcomes (Barbaro, et al. Lancet. 2021;398[10307]:1230). Second, patients in the latter part of 2020 experienced much longer intervals between the onset of symptoms and time of intubation. Clinicians had a tendency to delay intubation as long as possible. Subsequently, the number of days receiving high flow nasal oxygen or noninvasive ventilation (NIV) was significantly longer (Schmidt, et al. Crit Care. 2021;25[1]:355). These data suggest that prolonged NIV on high Fio2 may be a negative prognostic indicator and should be considered when assessing a patient’s candidacy for ECMO.

Early in the pandemic, clinicians realized that average ECMO run times for patients with COVID-19 and ARDS were significantly longer, 15 vs 9 days, respectively (Jacobs, et al. Ann Thorac Surg. 2022;113[5]:1452). With such long run times, beds were slow to turn over, and a shortage of ECMO beds resulted during the height of the pandemic. In a retrospective study, Gannon looked at 90 patients, all of whom were deemed medically appropriate for ECMO. Two groups were created: (1) no capacity for ECMO was available; and (2) ECMO was provided. ECMO vs (2) ECMO provided. Mortality rates were staggering at 89% and 43%, respectively (P < .001) (Gannon, et al. Am J Respir Crit Care Med. 2022;205[11]:1354). This study demonstrated a profound point: during a pandemic, when demand overcomes supply, there is a unique opportunity to see the effect of lifesaving therapies, such as ECMO, on outcomes. This study was particularly poignant, as the average age of the patients was 40 years old.

It is now widely accepted that prone positioning has survival benefit in ARDS. Prone positioning while receiving ECMO has generally been avoided due to concern for potential complications associated with the cannula(s). However, it has been shown that prone positioning while receiving veno-venous (VV) -ECMO reduces mortality rates, 37% prone vs 50% supine positioning (P = .02) (Giani, et al. Ann Am Thorac Soc. 2021;18[3]:495). In this study, no major complications occurred, and minor complications occurred in 6% of the prone events. Prone positioning improves ventilation-perfusion mismatch and reduces hypoxic vasoconstriction, which is thought to be right-sided heart-protective.

Right-sided heart dysfunction (RHD) is common in ARDS, whether COVID-19 related or not. The pathogenesis includes hypoxic vasoconstriction, pulmonary fibrosis, and ventilator-induced lung injury. Pulmonary microthrombi and patient-specific characteristics, such as obesity, are additional factors leading to RHD in patients with COVID-19. During the pandemic, several articles described using right-sided heart protective cannulation strategies for patients with COVID-19 requiring ECMO with favorable results (Mustafa, et al. JAMA Surg. 2020;155[10]:990; Cain, et al. J Surg Res. 2021;264:81-89).

This right-sided heart protective strategy involves inserting a single access dual lumen cannula into the right internal jugular vein, which is advanced into the pulmonary artery, effectively bypassing the right ventricle. This setup is more typical of right ventricle assist device (RVAD), rather than typical VV-ECMO, which returns blood to the right atrium. Unfortunately, these studies have not been translated to widespread practice.

ARDs continued on following page
COVID-19 ECMO and right ventricular failure: Lessons learned and standardization of management

BY JASON THOMAS, MD, ERIKA R. O’NEIL, MD, AND NICHOLAS VILLALOBOS, MD

T he SARS-CoV-2 pandemic changed the way intensivists approach extracorporeal membrane oxygenation (ECMO). Patients with COVID-19 acute respiratory distress syndrome (ARDS) placed on ECMO have a high prevalence of right ventricular (RV) failure, which is associated with reduced survival (Mahara V, et al. ASAIO Journal. 2022; 68 [6]: 772). In 2021, our institution supported 51 patients with COVID-19 ARDS with ECMO: 51% developed RV failure, defined as a clinical syndrome (reduced cardiac output) in the presence of RV dysfunction on transthoracic echocardiogram (TTE) (Marra A, et al. Chest. 2022;161[2]:535). Total numbers for RV dysfunction and RV dilation on TTE were 78% and 91% respectively, so many of those with RV changes on TTE did not progress to clinical failure. In essence then, TTE signs of RV dysfunction are sensitive but not specific for clinical RV failure. Rates for survival to decannulation were far lower when RV failure was present (27%) vs absent (84%). Given these numbers, we felt a reduction in RV failure would be an important target for improving outcomes for patients with COVID-19 ARDS receiving ECMO. Existing studies on RV failure in patients with ARDS receiving ECMO are plagued by scant data, small sample sizes, differences in diagnostic criteria, and heterogeneous treatment approaches. Despite these limitations, we felt the need to make changes in our approach to RV management.

Because outcomes once clinical RV-failure occurs are so poor, we focused on prevention. While we're short on data and evidence-based medicine (EBM) here, we know a lot about the physiology of COVID19, the pulmonary vasculature, and the right side of the heart. There are multiple physiologic and disease-related pathways that converge to produce RV-failure in patients with COVID-19 ARDS on ECMO (Sato R, et al. Crit Care. 2021;25:172). Ongoing relative hypoxemia, hypercapnia, acidemia, and microvascular thromboses/immunothromboses can all lead to increased pulmonary vascular resistance (PVR) and an increased workload for the RV (Zochios V, et al. ASAIO Journal. 2022; 68[4]:456). ARDS management typically involves high positive end-expiratory pressure (PEEP), which can produce RV-PA uncoupling (Wanner P, et al. J Clin Med. 2020;9:432).


Lastly, a right ventricular assist device (RVAD) can dissipate the work required by the RV and prevent decompensation. Collectively, these therapies can be considered preventive.

Knowing the RV parameters on RV are sensitive but not specific for outcomes though, when should some of these treatments be instituted? It’s clear that once RV failure has developed it’s probably too late, but it’s hard to find data to guide us on when to act. One institution used right ventricular assist devices (RVADs) at the time of ECMO initiation with protocolized care and achieved a survival to discharge rate of 73% (Mustafa AK, et al. JAMA Surgery. 2020;155[10]:990). The publication generated enthusiasm for RVAD support with ECMO, but it’s possible the protocolized care drove the high survival rate, at least in part.

At our institution, we developed our own protocol for evaluation of the RV with proactive treatment based on specific targets. We performed daily, bedside TTE and assessed the RV fractional area change (FAC) and outflow tract velocity time integral (VTI). These parameters provide a quantitative assessment of global RV function, and FAC is directly related to ability to wean from ECMO support (Mahara V, et al. ASAIO Journal. 2022). We avoided using the tricuspid annular plane systolic excursion (TAPSE) due to its poor sensitivity (Marra AM, et al. Chest. 2022;161[2]:535). Patients receiving ECMO with subjective, global mild to moderate RV dysfunction on TTE with worsening clinical data, an FAC of 20% to 35%, and a VTI of 10-14 cm were treated with aggressive diuresis, pulmonary vasodilators, and inotropy for 48 hours. If there was no improvement or deterioration, an RVAD was placed. For patients with signs of severe RV dysfunction (FAC <20% or VTI <10 cm), we proceeded directly to RVAD. We’re currently collecting data and tracking outcomes.

While data exist on various interventions in RV failure due to COVID-19 ARDS with ECMO, our understanding of this disease is still in its infancy. The optimal timing of interventions to manage and prevent RV failure is not known. We would argue that those who wait for RV failure to occur before instituting protective or supportive therapies are missing the opportunity to impact outcomes. We currently do not have the evidence to support the specific protocol we’ve outlined here and instituted at our hospital. However, we do believe there’s enough literature and experience to support the concept that close monitoring of RV function is critical for patients with COVID19 ARDS receiving ECMO. Failure to anticipate worsening function on the way to failure means reacting to it rather than staving it off. By then, it’s too late.

In conclusion, there is evidence to support the use of ECMO in patients with COVID-19 patients and ARDS failing conventional mechanical ventilation. The success of ECMO therapy is highly dependent on patient selection. Prolonged use of NIV on high Fio2 may be a negative predictor of ECMO survival and should be considered when assessing a patient for ECMO candidacy. Prone positioning with ECMO has been shown to have survival benefit and should be considered in all patients receiving ECMO.

Dr. Gaillard, Dr. Staples, and Dr. Kapoor are with the Department of Anesthesiology, Section on Critical Care, at Wake Forest School of Medicine in Winston-Salem, NC. Dr. Gaillard is also with the Department of Emergency Medicine and Department of Internal Medicine, Section on Pulmonary, Critical Care, Allergy, and Immunology at Wake Forest School of Medicine.
Here we are, 1 month into the new year, and it already feels like my time as President of the American College of Chest Physicians will pass too quickly. One of my goals is to share some thoughts on issues important to our profession by contributing quarterly to CHEST Physician. CHEST has always been like an extended family to me, and I look forward to having this regular touchpoint with all of you.

For my first written contribution, I want to focus on the future of medicine through medical education and involvement in professional associations because I am, at heart, a medical educator.

During my address at the CHEST Annual Meeting 2022, I spoke on how CHEST provided me with networking, mentoring, and volunteer opportunities that were critical in advancing my career. Those same opportunities should be extended to everyone in pulmonary, critical care, and sleep medicine – whether a current member or prospective member.

**Lighting a fire**

Attending my first CHEST Annual Meeting was possible due to my nomination for a leadership development course. The connections I made during the meeting really lit a fire within me. We need to engage with early career clinicians and provide them the same exposure and encouragement that I received.

To instill this fire in the next generation, I encourage each of our established members, years (or decades) into their careers, to pass along their expertise to someone who is just starting out, whether it be a trainee or a junior faculty member. If this applies to you: encourage a new attending who has never been to a CHEST event to attend with you; invite a fellow or resident to submit an abstract or case report to the journal CHEST® with your oversight; or simply volunteer to speak at your medical school or residency program about why you chose PCCM and the career it has given you.

Think back to when you were embarking on your journey toward where you are now – what would it have meant to be able to get career advice or even just a friendly conversation started with someone at your current level?

**CHEST offerings and accreditations**

Beyond bringing someone to a CHEST Annual Meeting – which you should definitely do – work with your learners at medical schools and residency programs to expose them to CHEST much earlier in their careers. The Trainings and Transitions Committee is an excellent resource to guide newer clinicians and can provide a vital source of encouragement and support. If your institution doesn’t have a simulation learning center or if it has limited offerings, the hands-on learning opportunities offered at CHEST headquarters may be a fit. Accredited by the Society for Simulation in Healthcare (SSH) and the Accreditation Council for Continuing Medical Education (ACCME), CHEST currently offers 24 courses with four new courses planned for 2023 in a wide variety of areas, including courses on ultrasound and bronchoscopy.

There are so many ways to introduce early career clinicians to CHEST, and it can begin with one personal outreach. If you are working on a project for CHEST right now, consider inviting an early career clinician to join you on it – this may be the opportunity that will change their career. It did for me.

As medical professionals, each of us plays an important role in the future of medicine, and the CHEST organization can bring us together to strengthen our impact.

If you are interested in brainstorming ideas for how to engage your medical students, residents, or fellows, please feel free to contact me or anyone at CHEST to help create a plan. I look forward to the next time we connect.

*Doreen J. Addrizzo-Harris, MD, FCCP
CHEST President*
Continuing our list of CHEST 2022 Winners
(see January 2023 issue)

CHEST FOUNDATION GRANT AWARDS

CHEST Foundation Research Grant in Women's Lung Health Disparities
Laura Sanapo, MD, The Miriam Hospital, Providence, RI
This grant is jointly supported by the CHEST Foundation and the Respiratory Health Association.

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
Benjamin Wu, MD, New York University Grossman School of Medicine, New York, NY
This grant is supported by AstraZeneca.

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
Richard Zou, MD, University of Pittsburgh Medical Center, Pittsburgh, PA
This grant is supported by the CHEST Foundation.

CHEST Foundation and AASM Foundation Research Grant in Sleep Medicine
Gonzalo Labarca, MD, Universidad San Sebastian, Concepcion, Chile
This grant is jointly supported by the CHEST Foundation and AASM Foundation.

CHEST Foundation and American Academy of Dental Sleep Medicine Research Grant in Sleep Apnea
Sherri Katz, MD, FCCP, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada
This grant is supported by the CHEST Foundation and American Academy of Dental Sleep Medicine.

CHEST Foundation Research Grant in Sleep Medicine
Nancy Stewart, DO, University of Kansas Medical Center, Kansas City, Kansas
This grant is supported by Jazz Pharmaceuticals.

CHEST Foundation Research Grant in Severe Asthma
Gareth Walters, MD, University Hospitals Birmingham, Birmingham, United Kingdom
This grant is supported by AstraZeneca.

CHEST Foundation Research Grant in Severe Asthma
Andréeane Côte, MD, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec, Canada
This grant is supported by AstraZeneca.

CHEST Foundation and APC-CMPD Research Grant in Medical Education
Christopher Leba, MD, MPH, University of California San Francisco, San Francisco, CA
This grant is jointly supported by the CHEST Foundation and APCMPD.

CHEST Foundation Research Grant in COVID-19
Clea Barnett, MD, New York University, New York, NY
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Critical Care
Katherine Walker, MD, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Venous Thromboembolism
Daniel Lachant, DO, University of Rochester Medical Center/Strong Memorial Hospital, Rochester, NY
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Pulmonary Hypertension
Christina Thornton, MD, PhD, University of Calgary, Calgary, AB, Canada
This grant is supported by the CHEST Foundation.

CHEST Foundation Research Grant in Pulmonary Fibrosis
Christina Eckhardt, MD, Columbia University, New York, NY
This grant is supported by an independent grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

CHEST Foundation Research Grant in Pulmonary Fibrosis
John Kim, MD, University of Virginia School of Medicine, Charlottesville, VA
This grant is supported by an independent grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

John R. Addrizzo, MD, FCCP
Research Grant in Sarcoidosis
Kerry Hena, MD, New York University Grossman School of Medicine, New York, NY
This grant is in honor of John R. Addrizzo, MD, FCCP and is jointly supported by the Addrizzo family and the CHEST Foundation.

CHEST Foundation Research Grant in Pediatric Lung Health
Ayobami Akenroye, MD, MPH, University of Rochester Medical Center/Strong Memorial Hospital, Rochester, NY
This grant is supported by the CHEST Foundation.

CHEST Foundation Young Investigator Grant
Sameer Avasarala, MD, Case Western Reserve University School of Medicine, Cleveland, OH
This grant is supported by the CHEST Foundation.

CHEST/ALA/ATS Respiratory Health Equity Research Award
Matthew Triplette, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
The Respiratory Health Equity Research Award is jointly supported by the American Lung Association, the American Thoracic Society, and the CHEST Foundation.

CHEST/ALA/ATS Respiratory Health Equity Research Award
Ayobami Akenroye, MD, MPH, Brigham and Women's Hospital, Boston, MA
The Respiratory Health Equity Research Award is jointly supported by the American Lung Association, the American Thoracic Society, and the CHEST Foundation.

CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP
Matthew Sharpe, MD, The University of Kansas Medical Center, Kansas City, KS
This grant is supported by the CHEST Foundation.

SCIENTIFIC ABSTRACT AWARDS

Alfred Soffer Research Awards
Presented abstracts will be judged by session moderators, and award recipients will be selected for their outstanding original scientific research. Finalists will be evaluated on the basis of their written abstract and the quality of their oral presentation. This award is named in honor of Alfred Soffer, MD, Master FCCP, who was Editor in Chief of the journal CHEST® from 1968 to 1993, and Executive Director of CHEST from 1969 to 1992.

Young Investigator Awards
Investigators who are enrolled in a training or fellowship program or who have completed a fellowship program within 5 years prior to CHEST 2022 are eligible for Young Investigator Awards. Presenters will be evaluated on the basis of their written abstract and presentation. Recipients will be selected by judges from the Scientific Presentations and Awards Committee for their outstanding original scientific research.

Top Rapid Fire Abstract Award
Awards are granted to two presenters from all the rapid fire sessions at the CHEST Annual Meeting for outstanding original scientific research and presentation.

Top Case Report Award
Awards are granted to one presenter in each oral case report session at the CHEST Annual Meeting for outstanding original scientific research and presentation.

Top Rapid Fire Case Report Award
Awards are granted to one presenter in each rapid fire oral case report session at the CHEST Annual Meeting for outstanding original scientific research and presentation.
**NEWS FROM CHEST**

**ALFRED SOFFER RESEARCH AWARD WINNERS**

**Palak Rath, MD**
A Sense Of Urgency: Boarding Of Critical Care Medicine Patients In The Ed

**Syed Nazeer Mahmood, MD**
Quantifying The Risk For Over-treatment And Undertreatment Of Severe Community Onset Pneumonia

**YOUNG INVESTIGATOR AWARD WINNERS**

**Anusha Devarajan, MD, MBBS**
Pneumomediastinum And Pneumothorax In Covid-19 Pneumonia: A Matched Case-Control Study

**Marjan Islam, MD**
Thoracic Ultrasound In Covid-19: Use Of Lung And Diaphragm Ultrasound In Evaluating Dyspnea In Survivors Of Critical Illness From Covid-19 Pneumonia In A Post-Icu Clinic

**Aaron St Laurent, MD**
Duchenne Muscular Dystrophy Respiratory Profiles From Real-World Registry Data: A Retrospective Longitudinal Study

**ABSTRACT RAPID FIRE WINNERS**

**Andrew J.O. Davis, MD**
Early Gas Exchange Parameters Not Associated With Survival In Covid-19-Associated Ards Patients Requiring Prolonged Venovenous Extracorporeal Membrane Oxygenation

**Benjamin Emmanuel**
Clinical Outcomes In Patients With Severe Asthma Who Had Or Had Not Initiated Biologic Therapy: Results From The Clear Study

**CASE REPORT SESSION WINNERS**

**Sathya Alekhya Bukkuri**
Smear-4-Deficient Undifferentiated Tumor: A Rare Thoracic Malignancy

**Zachary A. Banbury, MD**
Fungal Aortitis In A Patient For Whom Blood Transfusion Is Not An Option: A Rare But Potentially Fatal Complication Of Aortic Valve Replacement

**Harinivaas Shanmugavel Geetha, MD**
Respiratory Distress After Potentially Fatal Aspirin Overdose: When To Intubate?

**Lisa Hayes**
Systemic Epstein-Barr Virus-Related T-Cell Lymphoproliferative Disorder: A Rare Cause Of Dyspnea And Pulmonary Infiltrates In An Immunocompetent Adult

**Mohammed Alsagafi, MBBS**
Calcium Oxalate Deposition In Pulmonary Aspergillosis

**Cheyenne Snively**
Traffic Jam In The Vasculature: A Case Of Pulmonary Leukostasis

**Clarissa Smith, MD**
Talcoma In Lung Cancer Screening: A Rare Benign Cause Of Pet Scan Avidity

**Nitin Gupta, MD**
The Clue Is In The Blood Gas: A Rare Manifestation Of Lactic Acidosis

**Moses Hayrabedian, MD**
A Century-Old Infection Mimicking Malignancy: A Case Of Diffuse Histoplasmosis

**Gabriel R. Schroeder, MD**
A Case Of Wind-Instrument Associated Hypersensitivity Pneumonitis

**Fizza Sajid, DO**
Leaping From Lush Tropical Environments To The L-Train: A Case Of Severe Leptospirosis In New York City

**Krista R. Dollar, MD**
Looking Past The Ground Glass: It Was Only Skin Deep

**Konstantin Golubykh, MD**
Point-Of-Care Ultrasound In The Timely Diagnosis Of Colonic Necrosis

**Arsal Tharwani**
Abdominal Compression In End-Stage Fibrotic Interstitial Lung Disease (Idi) Improves Respiratory Compliance

**Ryan Kozloski**
When Asthma Isn’t: Multiplicity Approach To Fibrosing Mediatitis

**Zach S. Jarrett, DO**
Vanishing Cancer: A Case Of Smoking-Related Organizing Pneumonia

**Stephen Simeone**
Intravascular Papillary Endothelial Hyperplasia Presenting As Thoracic In Transit With Acute Pulmonary Embolism

**David Gruen, MD**
Tackling Posterior Reversible Encephalopathy Syndrome (Pres): A Rare Case Of Subtherapeutic Tacrolimus Causing Pres In Steroid-Resistant Nephropathy

**Nicholas Kunce, MD**
An Unusual Case Of Subacute Bacterial Endocarditis Presenting With Catastrophic Subarachnoid Hemorrhage

**Phillip J. Gary, MD**
Sarcoid-Like Reaction After Treatment With Pembrolizumab

**Shreya Podder, MD**
Endobronchial Valves For Treatment Of Persistent Air Leak After Secondary Spontaneous Pneumothorax In Patients With Cystic Fibrosis

**Alina Aw Wasim, MD, MBBS**
Chest-Wall Castlemann Disease Mimicking Thymoma Drop Metastasis

**Ndausung Udongwo**
The ‘Bat Bite Sign’ On Cardiac MRI: Left Dominant Arrhythmogenic Cardiomyopathy As An Atypical Etiology Of Sudden Cardiac Arrest

**Grant Senyei, MD**
Management Of Ventriculo-Subarachnoid Pleural Effusion

**Garima Singh, MD**
Covid-19-Associated Thrombotic Thrombocytopenia Purpura (Ttp)

**CASE REPORT RAPID FIRE WINNERS**

**Sandeep Patri**
Hyperammonemia Postlung Transplantation: An Uncommon But Life-Threatening Complication

**Trung Nguyen**
Dyspnea During Pregnancy Revealing Multiple Pulmonary Arteriovenous Malformations And A New Diagnosis Of Hereditary Hemorrhagic Telangiectasia

**Pedro J. Baez, MD**
Adenoid Cystic Adenocarcinoma: A Rare Esophageal Malignancy Mis-diagnosed As Copd

**Brette Guckian, DO**
Management Of Pulmonary Cement Emboli After Kyphoplasty

**Brinn Demars, DO**
Tumor Emboli In The Pulmonary Artery Secondary To Chondrosarcoma: A Rare Presentation Mimicking Pulmonary Thromboembolism

**Aakriti Arora**
A Case Of Pulmonary Hypertension As A Possible Extracranial Manifestation Of Moyamoya Disease

**Racine Elaine Reinoso**
Clot In Transit: The Role Of Point-Of-Care Ultrasound In Early Diagnosis And Improved Outcomes

**Qiraat Azeem, MD**
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Study supports banning probiotics from the ICU

BY TED BOSWORTH

FROM CHEST 2022 • NASHVILLE, TENN. – Supported by several cases series, a large cohort analysis has associated exposure to probiotics in the intensive care unit with a measurable increase in bacteremia and bacteremia-related mortality due to organisms in these preparations, according to new findings presented at the annual meeting of the American College of Chest Physicians (CHEST).

According to data presented by Scott Mayer, MD, chief resident at HealthONE Denver, which is part of the HCA Healthcare chain of hospitals, the risk is increased by any probiotic exposure. However, the risk is particularly acute for powdered formulations, presumably because powder more easily disseminates to contaminate central venous catheters.

"We think that probiotics should be eliminated entirely from the ICU. If not, we encourage eliminating the powder formulations," said Dr. Mayer, who led the study.

The data linking probiotics to ICU bacteremia were drawn from 23,533 ICU admissions over a 5-year period in the HCA hospital database. Bacteremia proven to be probiotic-related was uncommon (0.37%), but the consequences were serious.

For those with probiotic-related bacteremia, the mortality rate was 25.6% or essentially two-fold greater than the 13.5% mortality rate among those without probiotic bacteremia.

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"The evidence for benefit is weak or nonexistent, but the risks are real," Dr. Mayer said. "To confirm that probiotic-associated ICU bacteremias in the HCA hospital database were, in fact, related to probiotics being taken by patients at time of admission, Dr. Mayer evaluated the record of each of the 86 patients with probiotic bacteremia—associated mortality.

"I identified the organism that grew from the blood cultures to confirm that it was contained in the probiotic the patient was taking," explained Dr. Mayer, who said this information was available in the electronic medical records.

The risk of probiotic-associated bacteremia in ICU patients was consistent with a series of case reports that prompted the study. Dr. Mayer explained that he became interested when he encountered patients on his ICU rounds who were taking probiotics. He knew very little about these agents and explored the medical literature to see what evidence was available.

"I found several case reports of ICU patients with probiotic-associated infections, several of which were suspected of being associated with contamination of the central lines," Dr. Mayer said. In one case, the patient was not taking a probiotic, but a patient in an adjacent bed was receiving a powdered probiotic that was implicated. This prompted suspicion that the cause was central-line contamination.

This was evaluated in the HCA ICU database and also found to be a significant risk.

These deaths occur without any clear compensatory benefit from taking probiotics, according to Dr. Mayer. There is a long list of potential benefits from probiotics that might be relevant to patients in the ICU, particularly prophylaxis for Clostridioides difficile infection, but also including a variety of gastrointestinal disorders, such as irritable bowel syndrome; however, none of these are firmly established in general, and particularly for patients in the ICU.

"The American College of Gastroenterology currently recommends against probiotics for the prevention of C. diff," Dr. Mayer said. Although the American Gastroenterological Association has issued a "conditional recommendation" for prevention of C. diff. infection with probiotics, Dr. Mayer pointed out this is qualified by a "low quality of evidence" and it is not specific to the ICU setting.

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Multidrug-resistant gram-negative infections treatable with newer antibiotics, but guidance is needed

BY ERIN ARCHER, RN, BSN, CIC

Multidrug-resistant gram-negative infections (MDRGNIs) are an emerging and deadly threat worldwide. Some of these infections are now resistant to nearly all antibiotics, and very few treatment options exist. Some of the remaining antibiotics for these MDRGNIs can cause acute kidney injury and have other toxic effects and can worsen antibiotic resistance. When deciding which drugs to use, clinicians need to juggle the possible lethality of the infection with the dangers of its treatment.

Samuel Windham, MD, and Marin H. Kollef, MD, FCCP, authors of a recent article in Current Opinion in Infectious Diseases (2022. doi: 10.1097/QCO.0000000000000858), express this urgency. They offer recommendations based on current guidelines and recently published research for treating MDRGNIs with some of the newer antibiotics.

Dr. Kollef, professor of pulmonary and critical care medicine at Washington University in St. Louis, said in an email, “Our recommendations differ in that they offer an approach that is based on disease severity, local resistance prevalence in MDRGNIs, and patient risk factors for infection with MDRGNIs. For patients with severe infection and risk factors for infection with MDRGNIs, we suggest empiric coverage for MDRGNIs until susceptibility data are available or based on rapid molecular testing. Selection of antibiotic therapy would be based on which MDRGNIs predominate locally.”

In their article, the authors discuss how to best utilize the newer antibiotics of ceftazidine-avibactam (CZA), ceferodrocol, ceftolozane-tazobactam (C/T), meropenem-vaborbactam (MVB), imipenem-relebactam (I-R), aztreonam-avibactam (ATM-AVI), eravacycline, and plazomicin.

The scope of the problem

Bacterial infections are deadly and are becoming less treatable. The Centers for Disease Control and Prevention reported in 2022 that the COVID-19 pandemic has reversed years of decreases in health care–associated infections. Much of the increase has been caused by multidrug-resistant organisms.

In November 2022, authors of an article published in The Lancet (2022 Nov 21. doi: 10.1016/S0140-6736(22)02185-7) estimated worldwide deaths from 33 bacterial genera across 11 infectious syndromes. They found that these infections were the second leading cause of death worldwide in 2019 (ischemic heart disease was the first). Furthermore, they discovered that 54.9% of these deaths were attributable to just five pathogens – Staphylococcus aureus, Escherichia coli, Streptococcus pneumoniae, Klebsiella pneumoniae, and Pseudomonas aeruginosa. Three of those five bacterial species – E. coli, K. pneumoniae, and P. aeruginosa – are gram-negative and are highly prone to drug resistance.

The CDC classified each of those three pathogens as an “urgent threat” in its 2019 Antibiotic Resistance Threats in the United States report. Of particular concern are gram-negative infections that have become resistant to carbapenems, a heavy-hitting class of antibiotics. Regarding organisms that cause MDRGNIs, the major groups of concern are those that produce compounds that destroy antibiotics such as extended-spectrum beta-lactamases, AmpC beta-lactamases, and the carbapenemases known as serine-beta-lactamases (OXA, KPC, and CTX-M) and metallo-beta-lactamases (NDM, VIM, and IMP). Carbapenem-resistant Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter baumannii also produce carbapenemases, rendering them invulnerable to carbapenem antibiotics.

Traditionally, a common alternative for carbapenem-resistant infections has been colistin, an older and very toxic antibiotic. The authors cite recent research demonstrating that CZA yields significantly better outcomes with regard to patient mortality and acute kidney injury than colistin and that CZA plus aztreonam can even decrease mortality and length of hospital stay for patients who have bloodstream infections with metallo-beta-lactamase-producing Enterobacteriaceae, which are some of the hardest infections to treat.

“CZA has been demonstrated to have excellent activity against MDR Pseudomonas aeruginosa and KPC Enterobacteriaceae. It should be the preferred agent for use, compared with colistin, for the treatment of carbapenem-resistant gram-negative bacteria susceptible to CZA. Moreover, CZA combined with aztreonam has been shown to be an effective treatment for metallo-beta-lactamase MDRGNIs,” Dr. Kollef said.

Four key recommendations for treating MDRGNIs

In addition to the recent studies, the authors also based their recommendations concerning CZA, upon two major guidelines on the treatment of MDRGNIs: the European Society of Clinical Microbiology and Infectious Diseases’ Guidelines for the Treatment of Infections Caused by Multidrug-Resistant Gram-Negative Bacilli, and the Infectious Diseases Society of America’s (IDSA’s) Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections.

Dr. Windham and Dr. Kollef present a table showing the spectrum of activity of the newer antibiotics, as well as an algorithm for decision-making. They summarize their treatment recommendations, which are based upon the bacterial infection cultures or on historical risk (previous infection or colonization history). They encourage empiric treatment if there is an increased risk of death or death...
What to do when patients don’t listen

BY RACHEL REIFF ELLIS

You discuss and decide on the best course of treatment for your patients, write prescriptions, and recommend lifestyle modifications to enhance treatment outcomes and overall wellness. But once they leave your office, following through is up to the patient. What happens when they don’t listen?

The term “nonadherent” has gradually replaced “noncompliant” in the physician lexicon as a nod to the evolving doctor-patient relationship. Noncompliance implies that a patient isn’t following their doctor’s orders. Adherence, on the other hand, is a measure of how closely your patient’s behavior matches the recommendations you’ve made. It’s a subtle difference but an important distinction in approaching care.

The reasons behind a patient’s nonadherence are multifaceted, but they are often driven by social determinants of health, such as transportation, poor health literacy, finances, and lack of access to pharmacies.

Other times, patients don’t want to take medicine; they don’t prioritize their health, or they find the dietary and lifestyle modifications doctors suggest too hard to make or they struggle at losing weight, eating more healthfully, or cutting back on alcohol, for instance.

“When you come down to it, the big hindrance of it all is cost and the ability for the patient to be able to afford some of the things that we think they should be able to do,” said Teresa Lovins, MD, a physician in private practice Columbus, Ind., and a member of the board of directors of the American Academy of Family Physicians.

Another common deterrent to treatment is undesired side effects that a patient may not want to mention.

Much nonadherence is intentional and is based on experience, belief systems, and knowledge. For example, the American Medical Association finds that patients may not understand why they need a certain treatment (and therefore dismiss it), or they may be overloaded with multiple medications, fear dependency on a drug, have a mistrust of pharmaceutical companies or the medical system as a whole, or have symptoms of depression that make taking healthy actions more difficult. In addition, patients may be unable to afford their medication, or their lack of symptoms may lead them to believe they don’t really need the prescription, as occurs with disorders such as hypertension or high cholesterol.

Dr. Lovins stated that it’s crucial to establish a good rapport and build mutual trust. “If you don’t know the patient, you have a harder time asking the right questions to get to the meat of why they’re not taking their medicine or what they’re not doing to help their health.”

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Not doing so can ask, ‘Am I the right doctor to help you reach your goals? And if not, how can I help you to get to where you need to be?’ ”

SELECTED SEARCHES

• For carbapenem-resistant Enterobacteriales, clinicians should treat patients with cefiderocol, ceftazidime-avibactam, imipenem-cilastatin-relabactam, or meropenem-vaborbactam.

• For carbapenem-resistant Pseudomonas aeruginosa, clinicians should treat patients with cefiderocol, ceftazidime-avibactam, imipenem-cilastatin-relabactam, or ceftolozane-tazobactam.

• For carbapenem-resistant Acinetobacter baumannii, clinicians should treat patients with a cepiderocol backbone or without the addition of plazomicin, eravacycline, or other older antibacterials.

• For metallo-beta-lactamase-producing organisms, clinicians should treat patients with cefiderocol, ceftazidime-avibactam, aztreonam, imipenem-cilastatin-relabactam, aztreonam, or aztreonam-avibactam. The authors acknowledge that evidence is limited on treating these infections. “In general, ceftazidime-avibactam works pretty well in patients with MDRGNs, and there is no evidence that any of the other new agents is conclusively better in treatment responses. CZA and ceftolozane-tazobactam were the first of the new antibiotics active against highly MDRGN to get approved, and they have been most widely used,” Cornelius “Neil” J. Clancy, MD, chief of the Infectious Diseases Section at the VA Pittsburgh Health Care System, explained. Dr. Clancy was not involved in the Windham-Kollef review article. “As such, it is not surprising that resistance has emerged and that it has been reported more commonly than for some other agents. The issue of resistance will be considered again as IDSA puts together their update,” Dr. Clancy said. “The IDSA guidelines are regularly updated. The next updated iteration will be online in early 2023,” according to Dr. Clancy, who is also affiliated with IDSA.

“Clinical and resistance data that have appeared since the last update in 2022 will be considered as the guidance is put together.”

In general, Dr. Kollef also recommends using a facility’s antibiotic. “They are useful in determining which MDRGN’s predominate locally,” he said.

Dr. Kollef reported being a consultant for Pfizer, Merck, and Shionogi. Dr. Clancy reported receiving research funding from Merck and from the National Institutes of Health.

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presence of shock.

By pathogen, they recommend the following:

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