

RESPIRATORY EXCHANGE

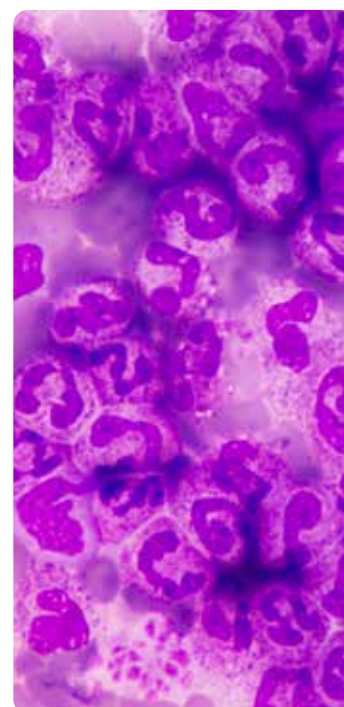
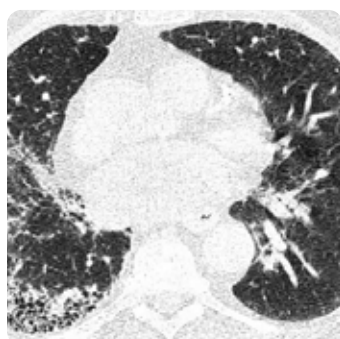
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A CLOSER LOOK AT VAPING-ASSOCIATED LUNG INJURY

— p. 18

At the Respiratory Institute, specialists in pulmonology, allergy and immunology, infectious disease, and critical care medicine work in close collaboration to diagnose and manage the full spectrum of pulmonary and allergic disorders, serving more than 200,000 patients annually. The Respiratory Institute is one of 26 clinical and special expertise institutes at Cleveland Clinic, a nonprofit academic medical center ranked as one of the nation's top hospitals by *U.S. News & World Report*, where more than 3,900 staff physicians and researchers in 180 specialties collaborate to give every patient the best outcome and experience.

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DEAR COLLEAGUES,



RAED DWEIK, MD, MBA
Chairman, Cleveland Clinic
Respiratory Institute

It is a privilege to once again share our annual issue of *Respiratory Exchange*. Cleveland Clinic's Respiratory Institute comprises nearly 200 staff physicians and 80 advanced practice providers across four interdisciplinary departments: pulmonary medicine, critical care medicine, allergy and clinical immunology, and infectious disease — a diverse and dynamic team working to provide the best care for our patients.

The articles featured in this issue are an extension of our commitment to innovation as we pursue our missions to provide exemplary care for our patients, lead basic and translational research investigations, and train the next generation of physician leaders.

In this issue — Our cover story examines the dramatic rise in vaping-related lung injury across the U.S. The article, authored by Cleveland Clinic physicians, takes a closer look at the epidemic, including a recent case study and a review of clinical management guidelines; it offers insights for clinicians as the medical community continues to investigate the etiology of this condition and work to meet the needs of this growing patient population.

We also highlight several recent studies authored by our physicians that have direct implications for patient care — one that explores mortality and cystic fibrosis, another that examines readmission rates in patients with sepsis and, finally, an analysis that calls for a reexamination of criteria involved in lung transplant prioritization with the goal to improve access to transplant for the sickest patients.

In other articles, our physicians provide commentary on new understandings in the pathobiology of systemic scleroderma and the curative role of bacteriophage therapy as an approach to bacterial infections. A clinical immunologist also shares her mission to raise awareness and provide training to prevent anaphylaxis in schools. Another article discusses strategies to better understand cardiopulmonary hemodynamics and more precisely characterize the types of pulmonary hypertension. All this, and still much more, is included in this issue of *Respiratory Exchange*. I hope you find it insightful and inspiring as we strive to provide state-of-the-art care for the patients of today as well as the patients of tomorrow.

Thank you for your interest in our program.

Sincerely,

A handwritten signature in black ink, reading "Raed Dweik". The signature is fluid and cursive, with a long, sweeping underline.

RAED DWEIK, MD, MBA | Chairman, Cleveland Clinic Respiratory Institute

MORTALITY STUDY OFFERS NEW INSIGHTS ON TREATING CYSTIC FIBROSIS

The largest study of its kind examines the survival rate of CF patients who undergo mechanical ventilation

KEY POINTS

Invasive mechanical ventilation (IMV) is a possible intervention for patients with cystic fibrosis (CF), though it's often associated with high mortality.

New research shows that the survival rate for hospitalized CF patients undergoing IMV was approximately 55%, significantly higher than expected.

Findings showed that patients undergoing IMV for more than 96 hours did not have an increased risk of mortality.

Survival in patients with CF will likely continue to improve but necessitates continued research about clinical management.

[Invasive mechanical ventilation \(IMV\), a possible intervention for cystic fibrosis \(CF\) patients with acute or chronic respiratory failure, has historically been associated with high mortality.](#)

However, in the largest study of its kind, Cleveland Clinic physicians describe new insights about survival rates for patients with CF who undergo IMV, and the role it could play in clinical decision-making.

In a retrospective study, published in the *Annals of the American Thoracic Society*, researchers examined 2002-2014 data from the U.S. Nationwide Healthcare Cost and Utilization Project database and found the survival rate for hospitalized CF patients undergoing IMV was approximately 55%, much higher than expected.

Furthermore, the mortality rate trended downward over the course of the study. Matthew Siuba, DO, Cleveland Clinic critical care physician and lead author on the study, says that the findings may upend preconceptions about IMV.

“The mortality rate was markedly lower than what people had thought in the past, and survival appears to be improving,” says Dr. Siuba.

The literature shows a wide range of mortality in patients who were intubated, from 45% to 75%, depending on the group studied and the clinical context. This range represents a gap in knowledge that the authors aimed to remedy.

As such, the study was designed to narrow selection criteria to focus on a specific patient subgroup, says Elliott Dasenbrook, MD, MHS,

pulmonologist and Director of Cleveland Clinic's Adult Cystic Fibrosis Program and the Bronchiectasis Center in the Respiratory Institute.

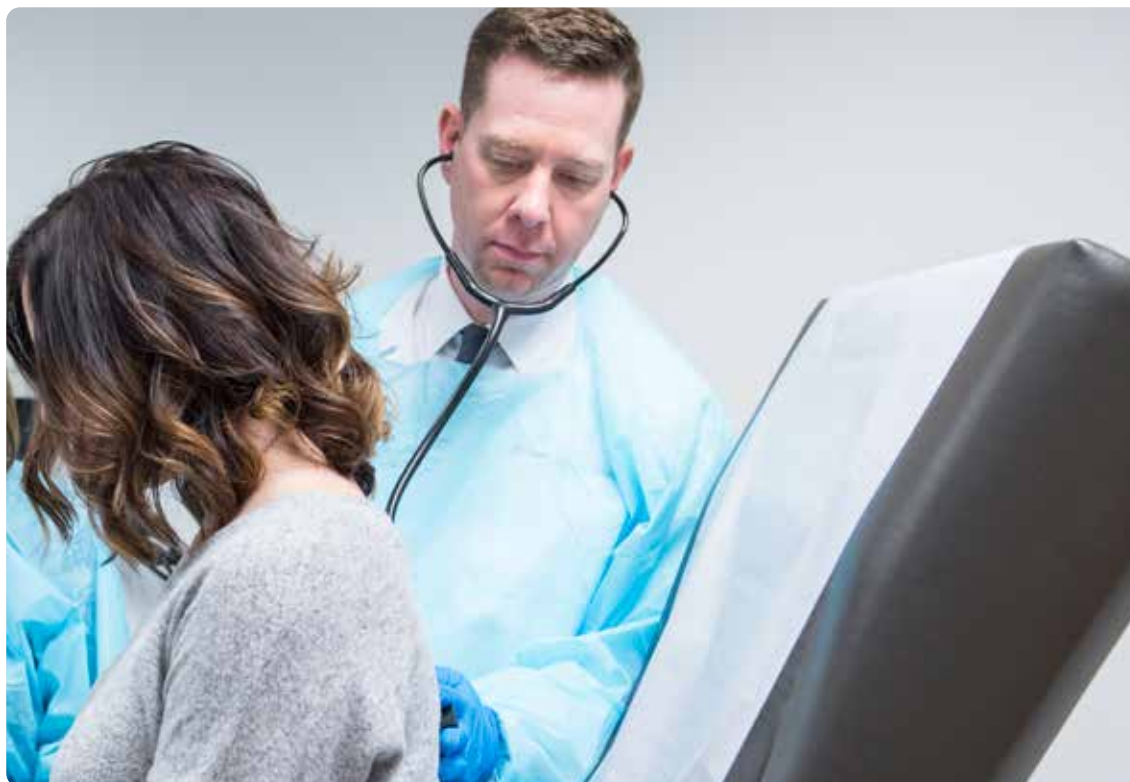
“We looked closely at patients with acute, worsening lung disease where IMV was used as a primary intervention. For example, we excluded those intubated for procedures or those who were being intubated as a bridge to lung transplant,” says Dr. Dasenbrook. “We found a 55% survival rate, which is considerably higher than previously understood.” And this finding may be conservative compared with those of other studies. Half of the study cohort received IMV for more than four days, which suggests this was a relatively sicker group of patients.

[Mortality and risk with IMV](#)

The analysis found several expected variables associated with a significant risk in mortality, which include female sex (odds ratio [OR] 1.54, 95% confidence interval [CI] 1.14-2.09), acute renal failure (OR 1.99, 95% CI 1.32-3.01) and malnutrition (OR 1.44, 95% CI 1.01-2.06).

What did surprise the team, however, was that patients undergoing IMV for more than 96 hours did not have an increased risk of mortality (OR 1.05, 95% CI 0.77-1.43).

“In other words,” Dr. Siuba says, “if a patient with cystic fibrosis gets intubated and it has been more than four days, we can't necessarily predict that outcomes will decline.”



LEFT: Elliott Dasenbrook, MD, MHS, a pulmonologist and senior author on the study, says survival in patients with cystic fibrosis is improving, but warrants continued investigation.

Implications for clinical decision-making

These findings are particularly useful for critical care providers who are managing CF patients. “When making a decision with patients, we believe this study provides the information to support IMV as a reasonable intervention with a significant likelihood of survival,” says Dr. Dasenbrook.

He also notes that a next step might be to explore the specific characteristics of modifiable variables associated with survival (such as body mass index) to better understand how interventions in the intensive care unit may improve those variables, resulting in improved outcomes in critically ill individuals living with CF.

Survival in patients with CF is improving and will likely continue to improve. This necessitates continued research into clinical management for this patient population.

“It’s a really difficult decision to decide whether you as a patient with CF, or your family member, for example, should go on a ventilator,” says Dr. Siuba. “I think this is just another piece of the puzzle that helps clinicians and families make that decision.”

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Dr. Siuba is a critical care physician. He can be reached at siubam@ccf.org or 216.978.7655.

ANAPHYLAXIS EDUCATION: PREVENTING TRAGEDY IN OUR SCHOOLS

How physicians can play a role in food allergy preparedness

KEY POINTS

IgE-mediated food allergy is the most common type of food allergy.

Prompt administration of epinephrine is critical following an allergy episode; however, many schools still struggle to adopt a policy and plan to address the treatment of anaphylaxis.

“Code Ana,” a school’s version of a “Code Blue,” addresses this need by equipping schools to prevent and prepare for anaphylactic emergencies.

Over 8,000 day care personnel have completed the Code Ana online course, and epinephrine has already been used by Code Ana trainees in three real-life emergencies to treat anaphylaxis.

“Doc, do you think it’s a food allergy?” Whether you are a pulmonologist, an infectious disease specialist or an allergist, chances are you’ve been asked this question many times and in a variety of clinical contexts.

While the term “food allergy” is often misused by the lay population to describe a food intolerance, true IgE-mediated food allergy is the immediate degranulation of mast cells upon exposure to the allergen. Other types of food allergy exist, such as eosinophilic esophagitis and food protein-induced enterocolitis syndrome, but the most common food allergy is IgE-mediated food allergy. Symptoms of IgE-mediated food allergy, which typically occur from within a few minutes to a few hours after ingestion, include urticaria, angioedema, dyspnea, possibly hypotension and, in some cases, death. Epinephrine, not antihistamines, stops this reaction. Prompt administration of epinephrine results in better outcomes than does delayed administration of epinephrine. Nonetheless, schools of all types — private and public, preschools through high schools — continue to struggle with adopting effective policies that promote prompt recognition and treatment of anaphylaxis. In fact, many schools lack a practiced medical emergency response plan.¹

[Code Ana prepares schools for swift intervention](#)

Schools today are challenged beyond educating our children. They must keep students safe and healthy throughout the school day and during after-school activities. Eight percent of children have food allergy,² so schools need to be prepared for anaphylaxis. Government and advocacy groups have developed legislation,

guidelines and tools to help schools be better prepared for medical emergencies;³⁻⁶ however, limited support is provided to schools in guiding nonmedical school personnel in the development and implementation of medical emergency protocols. Rarely do schools have a practiced medical emergency response plan and team — a school’s version of a “Code Blue.” To fill this gap, I worked with school personnel, families, students, colleagues and the Code Ana program (www.CodeAna.org). Code Ana equips schools to prevent and be prepared for medical emergencies like anaphylaxis.

[The value of epinephrine training in schools](#)

Mission-critical to anaphylaxis readiness in schools is medical education for school personnel. This need was underscored in the fall of 2017 when a young boy with food allergy and asthma accidentally ingested an allergen at his New York City preschool and subsequently died.⁷ Code Ana responded to this tragedy by developing Code Ana’s Epinephrine Training Program, which is approved by New York state as an epinephrine training course. In the fall of 2018, Code Ana donated this course to the New York City (NYC) Department of Health, specifically for NYC day care personnel. Also, I traveled to NYC to lead in-person epinephrine training workshops and answer questions about food allergy anaphylaxis. To date, over 8,000 day care personnel have successfully completed



FIGURE: Prompt administration of epinephrine is critical following a food allergy. Dr. Hoyt demonstrates where epinephrine should be administered — the middle of the outer side of the thigh.

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the online course, and epinephrine has already been used by Code Ana trainees in three real-life emergencies to treat anaphylaxis and prevent another tragedy.

Working together to keep our schools safe

In our quest to help schools, we continue to grow and share Code Ana, prescribe stock epinephrine auto-injectors through Cleveland Clinic Children's School-Based Health Care, and develop user-friendly medical emergency tracking and reporting tools.⁸ As a physician, you too have the unique opportunity to play a critical role in schools by sharing evidence-based information, thereby increasing safety and wellness for children and adults. If you are interested in participating in school-focused medical education that targets children or adults, please reach out to me. You have something invaluable to share, and it may save a life. Together, we can equip our schools to prevent and be prepared for medical emergencies. Teamwork makes the dream work!

PHAGE THERAPY FOR MULTIDRUG-RESISTANT BACTERIAL INFECTIONS

Cleveland Clinic experience with a lung transplant patient

KEY POINTS

Bacteriophage therapy (BT) has emerged as a potential strategy to treat bacterial infections.

There are advantages and disadvantages to the use of BT. While it's able to target specific bacteria, including multidrug-resistant strains, it may cause an unexpected inflammatory response in patients.

One case study reviews this treatment in a lung transplant patient with cystic fibrosis. The treatment was well tolerated and did not appear to trigger an immune response.

It's unclear how this century-old treatment will change the landscape of anti-bacterial therapy; however, there is a movement within the infectious disease community to explore its potential use.

With the emergence of extensively drug-resistant bacterial infections and the recognition of other limitations to traditional antibiotics over the past few decades, bacteriophage therapy (BT) has reemerged as a strategy for the treatment of bacterial infections.

Pharmacological anti-bacterial therapies eclipsed this century-old therapy in decades past, but now the use of lytic phages to kill infections is on the rise. In Cleveland Clinic's Respiratory Institute, we are employing this strategy with difficult-to-treat infections and are collaborating with other institutions to advance the study of this treatment.

The basics of phage therapy

Bacteriophages are viruses that infect bacteria. They are ubiquitous, present in high concentrations in environmental sources including sea, swamp and sewage waters. Present wherever bacteria reside in high concentrations, they are the next stratum of the human microbiome, infecting bacteria of the human digestive tract and other niches.

Much like viruses that infect human cells, bacteriophages are composed of RNA or DNA and viral proteins and vary in their genetic diversity and complexity. Bacteriophages can be lysogenic or lytic. Lysogenic phages integrate into the bacterial cell chromosome. Lytic phages infect the bacterial cell through attachment to specific receptors, replicate and assemble in the cellular cytoplasm, lyse the cell, and release their progeny, which are then able to infect additional targeted bacteria. Lytic phages are used almost exclusively in BT, since the intended result is destroying bacterial cells through lysis (Figure).

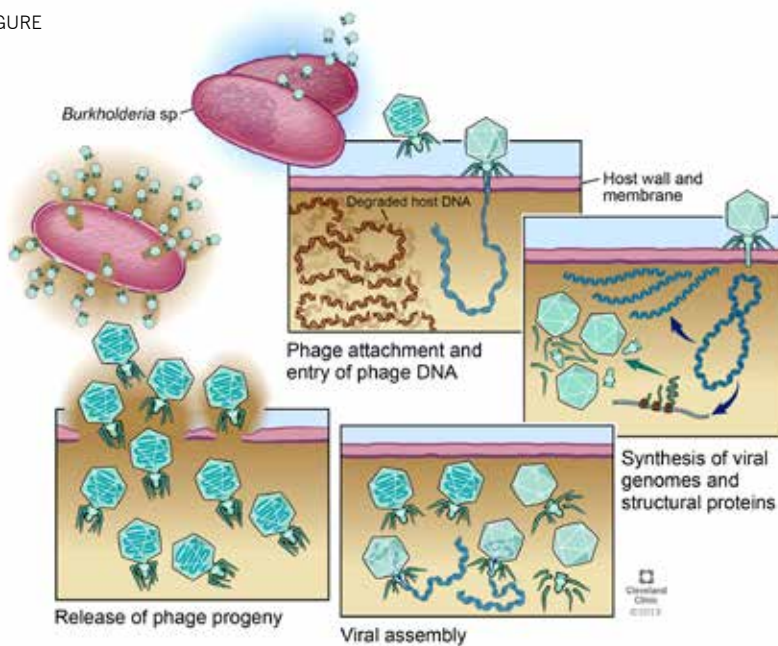
Advantages and disadvantages

Advantages of BT include its ability to target specific bacteria, including multidrug-resistant (MDR) strains, which causes minimal impact on the host microbiome. Some phage strains also penetrate bacteria within biofilm and affect slowly growing organisms. Some data suggest that phage therapy may also enhance response to traditional antibiotics, either by killing the most drug-resistant strains or by creating a defensive bacterial response that results in improved antibiotic susceptibility.

An important disadvantage of BT is the relatively rapid development of resistance to single phages. Treatment strategies thus often involve multiple phages ("phage cocktails") used in combination and in sequence. Phages can also elicit a human immunologic response. While bacteriophages do not infect human cells, they have been shown to result in complement component and antibody production in animal models and in some patients. There is thus concern that this could cause unexpected inflammatory responses that are detrimental to patients.

A major obstacle to routine BT use is the time it can take to identify an infective phage or multiple phages that will infect a patient's unique bacterial isolate. The pharmaceutical industry is aiming to create off-the-shelf cocktails likely to infect common drug-resistant bacterial species,

FIGURE



LEFT: Illustration depicts a lytic phage life cycle

most notably *Staphylococcus aureus* and *Pseudomonas aeruginosa*. However, for a specific patient isolate, the phages included in the cocktail may not be infective and must be personalized. Successful personalized BT has recently been reported for serious MDR *Acinetobacter*, *Pseudomonas* and *Staphylococcus* infections.

Phage therapy at Cleveland Clinic: a case study

As a national referral center, our lung transplantation program accepts patients with cystic fibrosis who harbor highly drug-resistant organisms. Rarely, these organisms cause serious post-transplant infection.

We recently used phage therapy in a lung transplant recipient with cystic fibrosis who developed persisting post-transplant infection with the same MDR *Burkholderia dolosa* that she harbored pretransplant, and who was unable to clear her infection with traditional antibiotic therapy. In collaboration with Adaptive Phage Therapeutics Inc. and with approval by the Food and Drug Administration for emergency investigational new drug (eIND) use, a lytic bacteriophage specific to her *Burkholderia* isolate was identified from an environmental source. It was then amplified in bacterial culture, purified and administered intravenously to our patient in combination with traditional anti-bacterial drugs. Her symptoms of infection rapidly improved with resolution of fever, improved infiltrates on CT imaging and markedly reduced bacterial counts on culture of bronchoalveolar lavage fluid. After several weeks of phage therapy, and for the first time in her

post-transplant course, she was ventilator independent and ambulatory. Despite initial improvements, the treatment response was not sustained, and she ultimately succumbed to sepsis with *B. dolosa*.

Her experience with BT was among the first reported in a lung transplant recipient. The treatment was well tolerated and did not appear to trigger an immune response directed to her donor lung. However, the use of a single phage that took several months to identify from an environmental source possibly limited the efficacy of the therapy as bacterial resistance to the phage could have evolved during this time.

Future treatment strategies

Cleveland Clinic is collaborating with the Center for Innovative Phage Applications and Therapeutics at the University of San Diego and others to plan investigative treatment strategies for cystic fibrosis patients being listed for lung transplantation and colonized with resistant *Burkholderia* strains.

It remains unclear how this century-old treatment strategy will change the landscape of anti-bacterial therapy. Several applications have been proposed. Despite its potential limitations, it is time to define the optimal use of phage therapy in our most difficult-to-treat infections.

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CLEVELAND CLINIC PULMONOLOGIST ELECTED TO LEAD PRESTIGIOUS MEDICAL JOURNAL

Dr. Peter Mazzone shares his vision as the new editor-in-chief of CHEST

KEY POINTS

Cleveland Clinic pulmonologist Peter J. Mazzone, MD, MPH, FCCP, was elected to editor-in-chief of *CHEST*®.

In this role, he plans to prioritize high-impact research by streamlining the submission process and create a new editorial strategy.

CHEST will focus on developing more engaging content, complementing traditional content with digital media.

The editorial board of *CHEST* is working closely with a statistical editor, which has already been an asset to the quality of articles published.

Peter J. Mazzone, MD, MPH, FCCP, staff and Director of the Lung Cancer Program and Lung Screening Program in Cleveland Clinic's Respiratory Institute, was recently named editor-in-chief of the prestigious pulmonary medicine journal *CHEST*.

The publication's vision, like that of the American College of Chest Physicians, is to provide clinically relevant research and patient management guidance to pulmonary medicine physicians worldwide. "It's certainly an honor and privilege to be given the opportunity to help support and guide that vision," says Dr. Mazzone.

Prioritizing high-impact research

Dr. Mazzone's goal is to provide content for readers that can be easily translated into clinical practice, and that means prioritizing the highest-quality research. "We realize that authors have a choice of where they would like to send their articles. Our goal is to foster partnership and outreach that will lead to an increased focus on competitive submissions of high-impact research."

Part of this goal is making submission to the journal a straightforward process, wherein authors receive timely, thorough feedback from journal reviewers. There will also be an emphasis on transparency. If a manuscript is rejected, efforts will be made to provide substantive guidance to authors so they may improve their work over time. One strategy to achieve this includes a new editorial format that will highlight different types of research and provide a more comprehensive framework to guide authors and reviewers.

Dr. Mazzone built an editorial team that includes nine subspecialty leaders who have recruited top clinicians and researchers across each area to serve. The board represents a geographically diverse leadership — with members from 12 countries and nearly 80 institutions around the world. "By having these teams with subspecialty expertise, we hope to be a step ahead in understanding what's going on and what we should be bringing to our audience," he remarks.

There will also be an emphasis on complementing traditional content with digital media, including video summaries, visual abstracts, discussions with authors and more. While these enhancements reflect a shift in publishing across the industry, Dr. Mazzone hopes this will also further cultivate discourse within the respiratory and critical care academic communities and encourage authors to access and create content in new ways.

Finally, the editorial board has also welcomed a statistical editor, Michael Kattan, PhD, Chair of Cleveland Clinic's Department of Qualitative Health Sciences in the Lerner Research Institute. "He's built a great team of statisticians who help with our reviews. We thought it was important to incorporate deep statistical knowledge to balance the exceptional clinical knowledge in our review process," Dr. Mazzone notes. "It has already

BELOW: Peter J. Mazzone, MD, MPH, FCCP



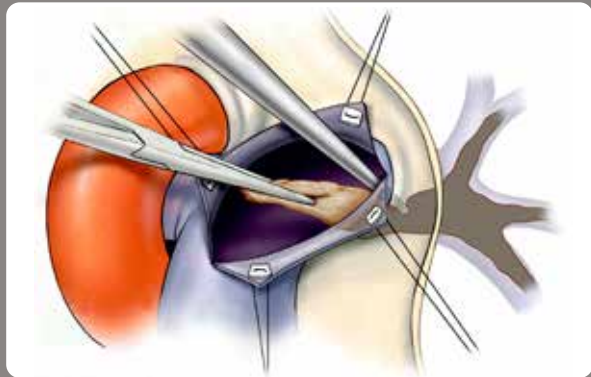
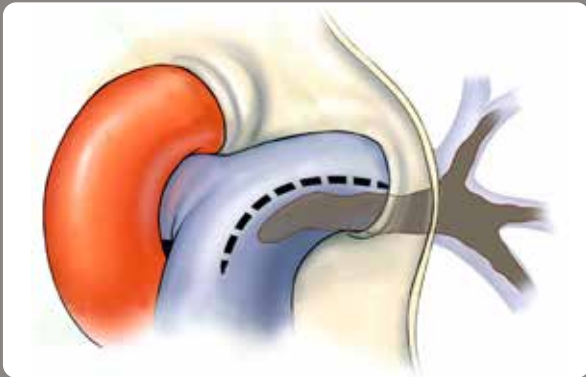
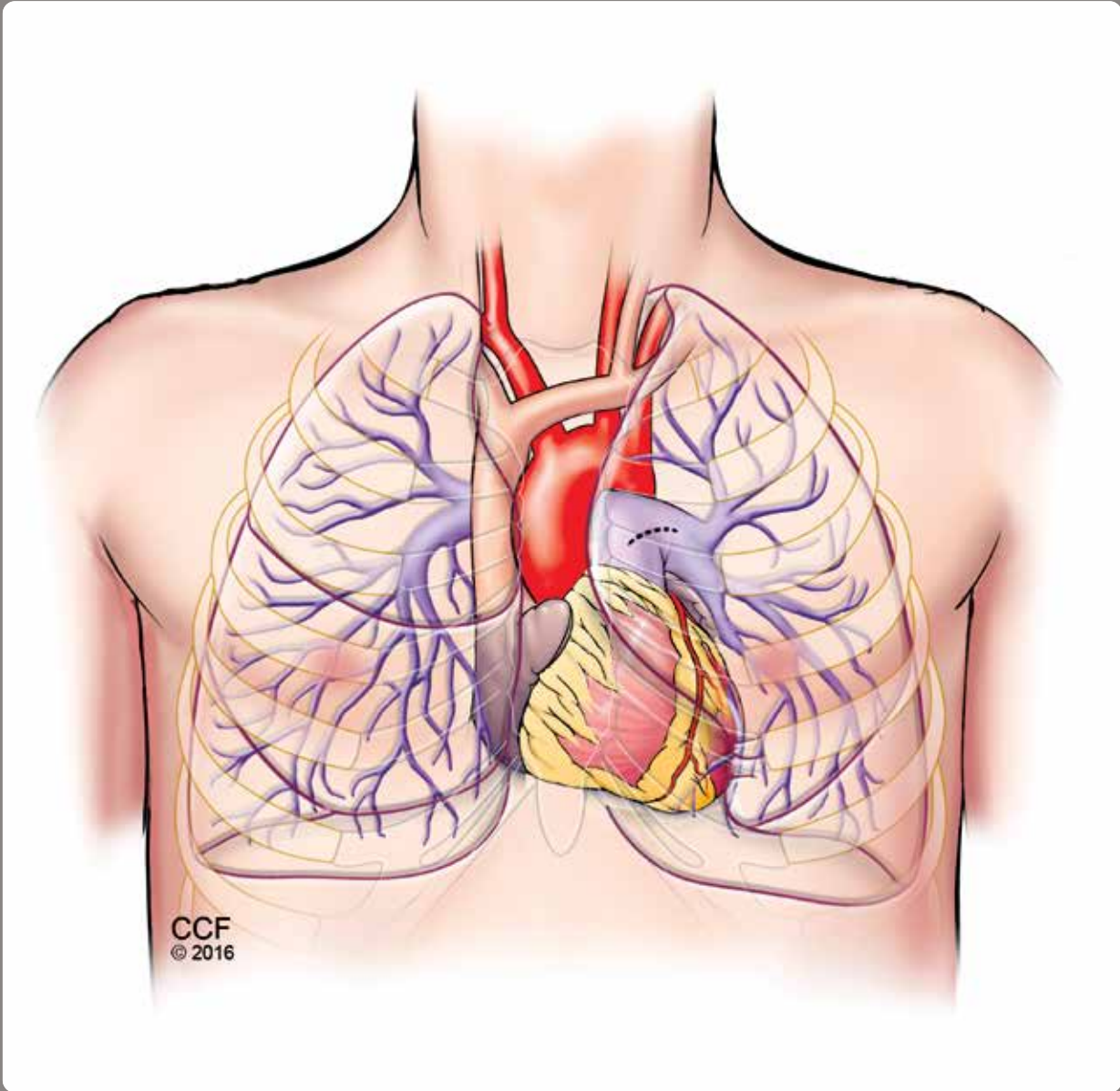
proved to be an asset to the reviews we provide and the quality of articles we publish.”

Dr. Mazzone has been a member of *CHEST* since 1999 and has served in a number of leadership positions within the organization. His inaugural issue as editor-in-chief was published in July 2019.

Dr. Mazzone is a pulmonologist and Director of the Lung Cancer Program and Lung Cancer Screening Program. He can be reached at mazon9@ccf.org or 216.445.4812.

“Our goal is to foster partnership and outreach that will lead to an increased focus on competitive submissions of high-impact research.”

— PETER J. MAZZONE, MD, MPH, FCCP



CASE STUDY: PULMONARY THROMBOENDARTERECTOMY CAN CURE EVEN THE MOST SEVERE CTEPH CASES

Greater recognition is needed that most CTEPH patients stand to benefit from this procedure

KEY POINTS

Misconceptions about which chronic thromboembolic pulmonary hypertension (CTEPH), including diagnosis and candidacy for pulmonary thromboendarterectomy, may impact patient outcomes.

Pulmonary thromboendarterectomy, the curative surgery for CTEPH, involves the removal of clot and scar tissue lining the pulmonary arteries while the patient is under deep hypothermic arrest on a heart-lung machine.

A recent case study reveals important insights, from scar tissue removal techniques and patient outcomes to longer-term clinical management.

A multidisciplinary approach is essential for good outcomes in CTEPH patients for whom pulmonary thromboendarterectomy is recommended.

Despite increasing awareness of chronic thromboembolic pulmonary hypertension (CTEPH), a large share of patients are still believed to be undiagnosed, and some who are diagnosed may not be referred for potentially curative surgery due to mistaken beliefs about patient eligibility.

The potentially deadly condition, which develops from unresorbed pulmonary emboli, is estimated to occur in about 3% of people who survive a pulmonary embolism (PE), but as many as half of patients present without that history.

Clinicians should be on the lookout for CTEPH in patients with a prior PE who exhibit shortness of breath — and in any patient with unexplained shortness of breath or pulmonary hypertension, even in the absence of prior PE, according to Gustavo Heresi-Davila, MD, MS, of Cleveland Clinic's Department of Pulmonary Medicine. "We have seen referrals for CTEPH grow over the last two or three years," he says. "But there are still many patients out there not getting the attention they need."

The great majority of patients stand to benefit

The potentially curative surgery for CTEPH is pulmonary thromboendarterectomy, which involves removal of clot and scar tissue lining the pulmonary arteries while the patient is under deep hypothermic arrest on a heart-lung machine. Cleveland Clinic is one of a handful of high-volume U.S. centers with the multidisciplinary expertise to conduct the delicate and difficult procedure, performing about 40 of the 350 to 400 cases done in the country each year.

"CTEPH is still a very underrecognized disease, and patients have a high mortality if left untreated," says Michael Tong, MD, MBA, one of the Cleveland Clinic cardiothoracic surgeons who performs pulmonary thromboendarterectomy. "But we can take someone with an otherwise limited life expectancy and completely cure them."

Moreover, contrary to some clinicians' assumptions, there are few CTEPH patients who couldn't potentially benefit from pulmonary thromboendarterectomy, including the elderly and those with high body mass index or with extremely high pulmonary pressures and severe right heart failure. Even some patients who have had previous open-heart surgery may be good surgical candidates. The following case study of a patient with extremely severe CTEPH illustrates the procedure's promise.

Case patient profile

The patient was an obese, 50-year-old male truck driver who had been treated for blood clots in his mid-30s. In May 2018, he was diagnosed with venous thrombosis and PE. He developed shortness of breath that worsened over several months.

RIGHT: The thin, scarred clot tissue was removed from the patient's pulmonary arteries during the procedure. The team removed all of the clot without complications.



When he presented to Cleveland Clinic in February 2019, he could no longer drive or climb stairs and could barely walk from the waiting room to the exam room. He had been coughing up blood, an unusual manifestation of the collateral circulation that typically occurs in CTEPH.

Assessment with ventilation/perfusion (VQ) scan demonstrated the mismatch between airflow and blood flow that characterizes both PE and CTEPH. Chest CT showed classic chronic thromboembolic lesions in the pulmonary arteries. Echocardiography showed severe right ventricular dilation and dysfunction, suggesting severe pulmonary hypertension. This was confirmed by subsequent right heart catheterization, which revealed the following:

- > Pulmonary artery pressure of 94/43 mm Hg, with a mean pressure of 64 mm Hg (vs. normal of ≤ 20 mm Hg)
- > Cardiac index of 1.7 L/min/m² (vs. normal range of 2.5-4.0)

“He was in very bad shape,” says Dr. Tong. “Without prompt treatment, his life expectancy would have been a couple of years at most.”

“Some physicians think that when the pulmonary artery pressure is as high as in this patient, surgery is too risky, so they don't send

patients for evaluation, particularly when right heart failure has also developed,” says Dr. Heresi-Davila, who serves as Medical Director of Cleveland Clinic's Pulmonary Thromboendarterectomy Program. “In fact, there is no limit beyond which surgery is contraindicated in terms of pulmonary hypertension. Sometimes patients with the most severely elevated pulmonary pressures derive the greatest benefit.”

The patient also had polycythemia, another unusual CTEPH manifestation caused by low oxygen levels.

Procedural essentials

Several days after the patient's presentation, a team led by Dr. Tong performed pulmonary thromboendarterectomy. Following median sternotomy, the patient was placed on a heart-lung machine and his body was cooled to 18 degrees Celsius. Once the patient is cold, the circulation is completely stopped. This circulatory arrest can last for 20 to 30 minutes before possible brain damage results from lack of blood flow, so surgeons must work quickly to extract the clot.

Starting on the left side, Dr. Tong quickly but carefully peeled the scar tissue from the artery wall. “It's a very delicate process,” he explains. “If you're not in the right layer just between the artery intima and the scar tissue, you won't achieve a complete extraction. But if you go too far into the artery, you risk tearing it.”

“Treating these patients who have CTEPH makes such a profound difference. They can essentially go back to a normal life.”

— MICHAEL TONG, MD, MBA

Certain clues can help. “Whereas old scar tissue typically has a whitish color and rough texture, the artery should have a smooth, pearly, slightly yellow appearance,” Dr. Tong notes. “That indicates you’re in the right layer. If it’s a bit purple, like muscle ridges, you’re too deep into the artery. If it’s white and bumpy, you’re not deep enough.”

The team was able to complete work on each side within the requisite 20 minutes, with the patient’s circulation restored between the two sessions. Overall, the team managed to remove all of the clot with no complications.

While some patients develop significant reperfusion pulmonary edema after the procedure, requiring large amounts of oxygen, this patient experienced only mild pulmonary edema.

Outcome and outlook

Within the first 48 hours after surgery, his pulmonary pressure dropped to 32/17 mm Hg, with a mean pressure of 24 mm Hg (nearly normal), and his cardiac index rose to 2.6, which was completely normal. By the end of February, the patient had improved dramatically. “He was able to carry a laundry basket up and down stairs, which he had been unable to do before, and he had no more symptoms of shortness of breath,” says Dr. Heresi-Davila.

The patient will need to take blood thinners for the rest of his life, and he has been counseled about his lifestyle. If he continues to work as a truck driver, he has been instructed to take frequent breaks, wear compression stockings, eat a healthful diet and try to lose weight. “He is certainly capable of working again,” notes Dr. Tong.

Discussion: ‘Not a one-person show’

Dr. Tong advises a high index of suspicion for CTEPH in patients with prior PE or unexplained shortness of breath. If evaluation

with a VQ scan shows a high probability of CTEPH, referral to one of the nation’s few high-volume centers for pulmonary thromboendarterectomy is recommended.

While the operation historically carried a 30-day mortality of 5% to 10%, Cleveland Clinic’s mortality is approximately 2%. Centers with lower volumes tend to have higher mortality rates, Dr. Tong notes.

He attributes Cleveland Clinic’s success to its multidisciplinary approach, which includes pulmonologists, cardiologists, vascular medicine specialists and interventional radiologists in addition to cardiothoracic surgeons. “We meet weekly to discuss patients,” he says. “This is not a one-person show. Good outcomes are a reflection of the quality of the team for these cases.”

He notes that some CTEPH patients aren’t candidates for surgery, such as those with major comorbidities or whose clot is unreachable with current instruments. For such patients, balloon angioplasty or treatment with the oral pulmonary hypertension medication riociguat may be an option.

He adds that Cleveland Clinic is nevertheless “very aggressive” in offering surgery to patients who don’t have clear contraindications. “We’ll offer this operation even to patients in their 80s,” Dr. Tong says. “Treating these patients who have CTEPH makes such a profound difference. They can essentially go back to a normal life.”

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PULMONARY ARTERY CATHETERIZATION FOR EVALUATION OF PULMONARY HYPERTENSION

Selected maneuvers during pulmonary artery catheterization may improve care for patients

KEY POINTS

Pulmonary artery catheterization (PAC) is the gold standard to diagnose pulmonary hypertension (PH) and distinguish between pre- and postcapillary PH.

Cleveland Clinic pulmonologists perform a variety of maneuvers to obtain the most accurate hemodynamic measures and best characterize the type of PH.

Established maneuvers that challenge the pulmonary circulation include vasodilatory testing, exercise testing and rapid fluid administration; other maneuvers include temporary arteriovenous dialysis access exclusion, dobutamine infusion and estimation of intrathoracic pressure using an esophageal balloon.

Selected maneuvers during PAC stand to provide critical information to improve the diagnosis, optimize treatment selection and impact prognosis.

Physicians use pulmonary artery catheterization (PAC) to diagnose pulmonary hypertension (PH) and distinguish between the two major hemodynamic types of the disease, pre- and postcapillary PH.

While PAC is the current gold standard, awareness among pulmonologists is increasing that traditional hemodynamic determinations may be insufficient to identify early stages of the disease, allocate patients to the pre- or postcapillary groups of the disease, and guide treatment decisions. Moreover, a multicenter study showed that a third of patients referred to PH centers were initially misdiagnosed and inappropriately treated.¹ In order to overcome these limitations, our laboratory performs a variety of maneuvers during PAC to better understand the cardiopulmonary hemodynamics and more precisely characterize the type of PH.

Obtaining accurate hemodynamic measures

The recent proceedings of the 6th World Symposium on PH define precapillary PH as a mean pulmonary artery pressure (mPAP) of > 20 mm Hg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg and a pulmonary vascular resistance ≥ 3 Wood units. Postcapillary PH is present when mPAP is > 20 mm Hg and PAWP is > 15 mm Hg.²

These hemodynamic definitions emphasize the critical importance of obtaining reliable hemodynamic measures, particularly PAWP and cardiac output (CO). At Cleveland Clinic, we pay particular attention to the PAWP determination³ and always confirm unexpected or abnormal CO values with direct Fick determination. Direct Fick CO requires the measurement of arterial and

mixed venous oxygen content as well as oxygen uptake (VO₂). We determine VO₂ at the time of PAC using a metabolic cart.

Established methodologies

Established maneuvers that challenge the pulmonary circulation include vasodilatory testing (commonly performed using inhaled nitric oxide),⁴ exercise testing and rapid fluid administration. The pulmonary vasodilatory test is used to identify patients with reversible vasoconstriction who could benefit from calcium channel blockers. During exercise, the CO and blood flow through the pulmonary vasculature increase; however, the pulmonary pressures marginally increase given vascular recruitment and vasodilation. A disproportionate increase in mPAP and PAWP could represent exercise PH and/or left ventricular diastolic dysfunction. Rapid fluid infusion increases the left ventricular end-diastolic volume, potentially unmasking heart failure with preserved ejection fraction.

Cardiopulmonary exercise testing can grade the severity of functional limitation and provide prognostic information in patients with PH.⁵ When combined with invasive hemodynamic determinations, the cardiopulmonary exercise test can better delineate the cardiopulmonary pathophysiology and nature of the exercise limitation, particularly in patients with dyspnea and mild PH.

Selected maneuvers during PAC stand to provide critical information to improve the diagnosis, optimize treatment selection and impact prognosis.

Other techniques

Other less frequently used methodologies that may provide valuable information include temporary arteriovenous (AV) dialysis access exclusion, dobutamine infusion and estimation of intrathoracic pressure using an esophageal balloon. The temporary AV dialysis access exclusion is important to determine the impact that an AV fistula has on CO and mPAP, which may be elevated particularly in fistulas with high flow.

A dobutamine infusion increases the CO and thus the mPAP. A disproportionate increase in mPAP for the rise in CO suggests a decrease in the right ventricular contractile and pulmonary vasodilatory reserve.

Pulmonary vascular pressures and PAWP measured during PAC reflect both true intravascular pressure and the effect of surrounding intrathoracic pressure. The intrathoracic pressure can be estimated with an esophageal balloon catheter and may be higher (positive numbers) in subjects with obesity and/or advanced chronic obstructive disease. It is important to recognize cases in which the intrathoracic pressure is elevated, because failure to recognize it can lead to the incorrect diagnosis of PH and its attribution to a postcapillary etiology.⁶ In fact, we previously showed that one-third of patients who are overweight are misdiagnosed with postcapillary PH when PAWP is unadjusted.⁶

In summary, selected maneuvers during PAC stand to provide critical information to improve the diagnosis, optimize treatment

selection and impact prognosis. These maneuvers should be particularly considered in cases of unexplained dyspnea, normal or borderline pulmonary pressures, and uncertain PH type.

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A CLOSER LOOK AT VAPING-ASSOCIATED LUNG INJURY: WHAT YOU CAN DO FOR YOUR PATIENTS

A case study, clinical guidelines and taking a multidisciplinary approach

KEY POINTS

A patient presented with a week long history of nonproductive cough, fever and malaise. After a further review of symptoms, the physicians diagnosed the patient with vaping-associated lung injury.

A total of 2,602 hospitalized cases of vaping-associated lung injury or death have been reported (as of Jan. 7, 2020) to the Centers for Disease Control and Prevention, and the onset of the epidemic remains poorly understood.

Many patients with mild disease will improve with cessation of vaping alone, but systemic corticosteroids should be considered for patients with severe symptoms. The appropriate dose and duration of treatment with corticosteroids is still unclear.

Early referral to addiction treatment is strongly recommended.

A 57-year-old Caucasian male presented with a weeklong history of nonproductive cough, fever and malaise. The patient had no significant medical history and had been in good health.

His fevers reached as high as 39.5 C (103.1 F), were cyclical in nature and accompanied by drenching night sweats. Though he did not have dyspnea, on initial assessment he was hypoxic with oxygen saturation of 85% while breathing ambient air. His physical examination was also significant for a respiratory rate of 30 to 35 breaths per minute, heart rate of 110 to 125 beats per minute and temperature of 38.7 C (101.66 F). Cardiac and pulmonary examinations were unremarkable, without audible crackles or wheezing. The patient had no skin rash or joint swelling.

He denied any recent travel or relevant occupational exposures, and had stopped smoking tobacco almost 20 years previously. However, he acknowledged having used marijuana daily. He stated that while he smoked “blunts” for 20 years, over the past year he had switched to vaping with electronic cigarettes containing tetrahydrocannabinol (THC), which he reported using three to four times daily for the past 12 months.

A CT chest scan was obtained, revealing diffuse patchy, nodular and confluent ground glass opacities with interlobular and intralobular septal thickening and dependent basilar atelectasis (Figures 1A, B). Stains and culture of sputum were negative for infectious etiologies. Bronchoscopy with bronchoalveolar lavage showed macrophage-predominant lavage fluid,

FIGURE 1A



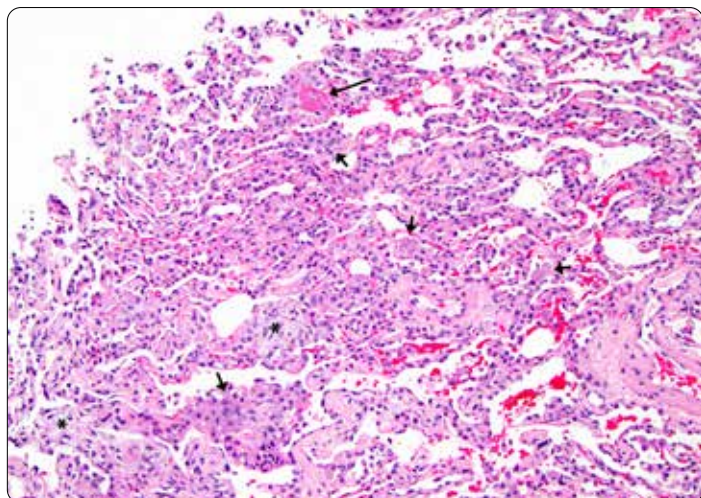
FIGURE 1B



and transbronchial biopsy revealed focal organizing pneumonia (Figures 2A, B).

Using the Centers for Disease Control and Prevention (CDC) case definition, a diagnosis of vaping-associated lung injury was made (Table).¹ With expectant management and avoidance of further vaping, the patient's symptoms improved rapidly and his hypoxia had fully resolved by day

FIGURE 2A



three after presentation. He was discharged home with referrals for substance dependence treatment and outpatient pulmonary follow-up.

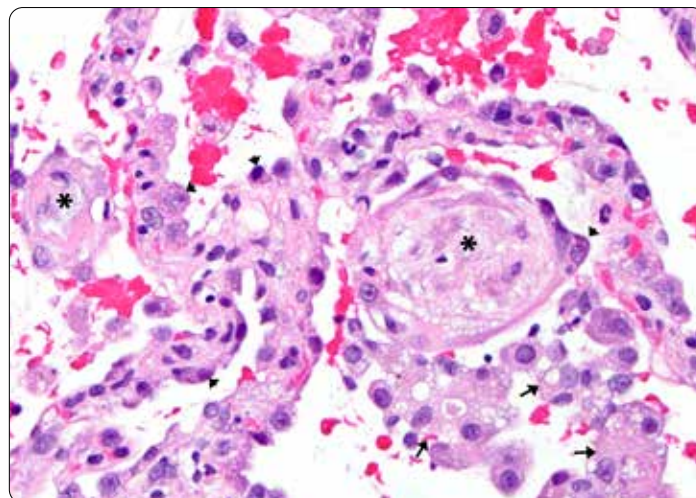
The vaping epidemic: Putting the case in context

This report illustrates a case of a patient with vaping-associated lung injury. As of Jan. 7, 2020, a total of 2,602 hospitalized cases of vaping-associated lung injury or death had been reported to the CDC.² The reason for the sudden onset of this new epidemic remains poorly understood, though increasing evidence suggests that the syndrome may be related to use of vaporizer cartridges modified with THC or other additives.

In patients for whom vaping-associated lung injury is suspected, a full vaping history should be obtained, including substances vaped, type of vaporizer used and the source of cartridges. A large number of identified cases report obtaining their vape fluid either from friends or family or from black market dealers, which has contributed to the difficulties in identifying a single cause of the outbreak.²

Initial symptoms may be nonspecific, including fever, malaise, abdominal pain and diarrhea.³ The majority of patients will also develop respiratory symptoms, though these may not present until later in the disease course. The spectrum of severity is variable, ranging from mild symptoms to acute respiratory failure requiring mechanical ventilation. To date, 57 deaths due to

FIGURE 2B



vaping-associated lung injury have been documented, likely an underestimate of the true burden of disease, since recognition may be difficult and there has been no standard for reporting the diagnosis to public health agencies.

Clinical management guidelines

Evaluation of suspected vaping-associated lung injury should include a complete blood count with differential, toxicology screening and chest imaging early in the disease course. Testing for infectious etiologies should be performed in keeping with initial clinical presentation. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsies may be considered in cases where the diagnosis is uncertain or where infection is not fully excluded.

The lung histopathology in our case demonstrated organizing pneumonia. The main histopathologic findings that have been described in association with vaping-associated lung injury are those of organizing acute lung injury, including organizing pneumonia, diffuse alveolar damage, acute fibrinous pneumonitis and eosinophilic pneumonia.⁴ Foamy macrophages were described in a subset of cases; however, features of exogenous lipid pneumonia have not been documented.⁵ Peribronchial inflammation and, rarely, features similar to hypersensitivity pneumonitis have also been reported.

Many patients with mild disease will improve with cessation of vaping alone. For those whose symptoms are severe or who have

Confirmed vaping-associated lung injury	Probable vaping-associated lung injury
E-cigarette use (vaping) or “dabbing” within 90 days of symptom onset	E-cigarette use (vaping) or “dabbing” within 90 days of symptom onset
Pulmonary infiltrate on chest X-ray or CT chest scan	Pulmonary infiltrate on chest X-ray or CT chest scan
Absence of pulmonary infection on initial workup ¹	Infection identified via culture or polymerase chain reaction, not thought to be the sole cause of underlying respiratory disease process, or minimum criteria to rule out pulmonary infection not met ¹
No evidence in medical record of alternative plausible diagnoses	No evidence in medical record of alternative plausible diagnoses

TABLE: Minimum criteria include negative respiratory viral panel, influenza polymerase chain reaction or rapid test if local epidemiology supports testing. All other clinically indicated respiratory infectious disease testing (e.g., urine antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, human immunodeficiency virus-related opportunistic respiratory infections if appropriate) must be negative.

significant hypoxia, treatment with systemic corticosteroids may be considered. The appropriate dose and duration of treatment with corticosteroids are still unclear.

Taking a multidisciplinary approach

A multidisciplinary team within Cleveland Clinic’s Respiratory Institute has developed an internal guideline for early recognition and management of patients with vaping-associated lung injury. Early input from a radiologist and a pathologist is recommended in cases where vaping-associated lung injury is suspected, given the variety of imaging findings and pathologic patterns identified to date.

It is important to note that many of these patients, in addition to their severe acute lung disease, may also be addicted to nicotine or to other substances, placing them at increased risk of vaping relapse. Early referral to addiction treatment is strongly recommended. Cleveland Clinic’s Smoking Cessation Program offers resources and support for patients interested in overcoming vaping-related nicotine dependence. For those patients interested in accessing these services, further information can be found at <http://www.clevelandclinic.org/stopsmoking>.

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STUDY FINDS STRIKINGLY HIGH 30-DAY READMISSION RATES IN PATIENTS WITH SEPSIS

Diabetes, kidney disease and congestive heart failure emerge as significant predictors of readmission

KEY POINTS

A new study finds that 1 in 5 patients, a significant portion of the study cohort, was readmitted within 30 days of sepsis discharge.

The study also identified several predictors associated with increased 30-day readmission, such as diabetes, chronic kidney disease and congestive heart failure.

Findings demonstrate the most common cause of readmission in the study was infectious disease, reinforcing the importance of antibiotic stewardship.

Some of the comorbidities and reasons for readmission, such as heart failure or acute kidney injury, could be addressed in an outpatient setting, necessitating a closer look at post-ICU discharge clinics as a way to reduce the potential for readmission.

A study conducted by a team of Cleveland Clinic investigators has found readmissions after sepsis hospitalizations to be common and costly, and most often associated with infectious etiologies. Study findings, published in the March 2019 issue of *Chest*, have shed new light on the epidemiology and predictors of 30-day readmission in patients with sepsis.

“There are a limited number of studies specifically looking at the causes behind sepsis-related readmission, although sepsis is one of the most common reasons for admission to the intensive care unit (ICU),” says Shruti K. Gadre, MD, Cleveland Clinic critical care physician and lead author of the study. “This study aimed to assess the healthcare burden attributable to sepsis and sepsis-related readmissions.”

One in 5 patients readmitted within 30 days of sepsis discharge

The study cohort included a total of 898,257 patients admitted with sepsis in 2013-2014 who survived to discharge and whose information was included in the Healthcare Cost and Utilization Project’s Nationwide Readmission Data. Mean patient age was 66.8 ± 17.4 years, with 60% of the study cohort ≥ 65 years. The primary outcome was 30-day readmission, and the causes for readmission were identified using the codes outlined in the International Classification of Diseases, Ninth Revision, Clinical Modification.

Of the cohort, a total of 157,235 (17.5%) had a 30-day readmission, with a median time to readmission of 11 days. The most common cause for readmission was infectious etiology (42.16%, of which 22.86% was due to sepsis), followed by gastrointestinal (9.6%),

cardiovascular (8.73%), pulmonary (7.82%) and renal problems (4.99%).

“One of the most striking findings was that readmissions within the 30 days after a sepsis discharge were quite common and affected approximately 1 in 5 patients, which is a significant portion of the study cohort,” says Dr. Gadre.

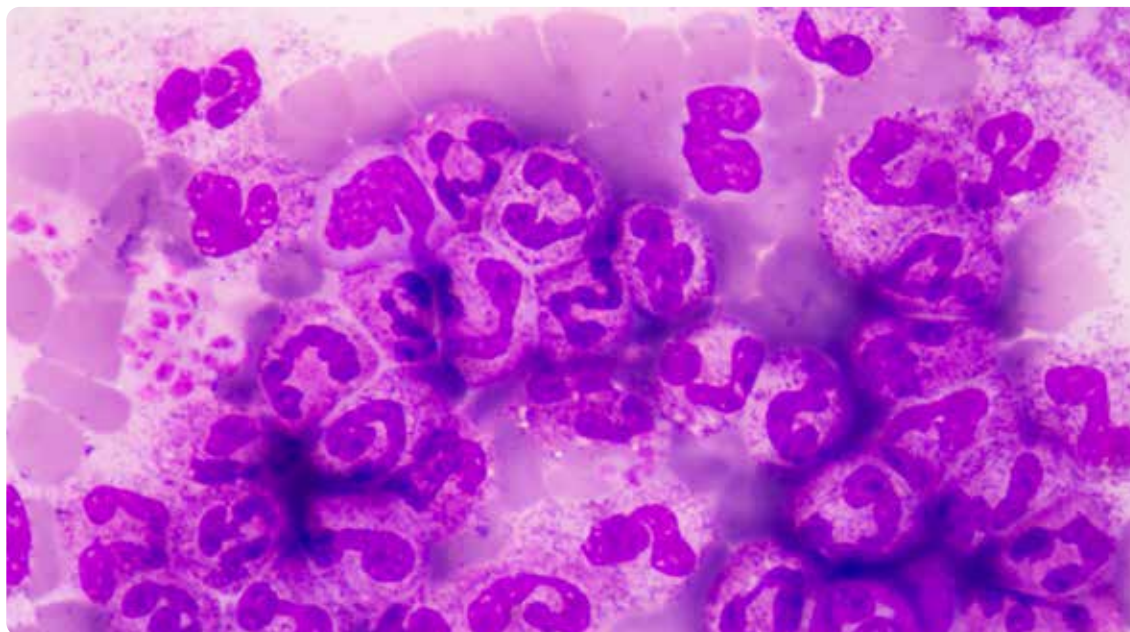
Predictors of readmission

The other interesting aspect was that patients who had a lot of comorbidities at the index admission were at an increased risk for 30-day readmission.

“We found that a lot of the patients were readmitted for comorbid conditions, such as heart failure or acute kidney injury, that could potentially be addressed in the outpatient setting,” she says.

The study also identified several predictors associated with increased 30-day readmission, such as diabetes, chronic kidney disease and congestive heart failure.

“Longer lengths of hospital stay at index admission were also associated with a higher risk for readmission, as was the discharge to either a long-term or short-term care facility and a Charlson comorbidity index ≥ 2 ,” notes Dr. Gadre.



LEFT: Abnormal neutrophil in pleural fluid smear.

The cost of readmission

In assessing readmission costs, the study found the mean cost per readmission to be \$16,852, which amounts to approximately \$3.5 billion in annual costs within the United States. Putting things into context, Dr. Gadre says that the annual economic burden due to conditions for which the Hospital Readmissions Reduction Program monitors readmissions is close to \$7 billion. These conditions include heart failure, chronic obstructive pulmonary disease, pneumonia and acute myocardial infarction.

“So, sepsis readmissions account for half of that amount on an annual basis, which is a significant cost to the healthcare system,” says Dr. Gadre, adding that several approaches could be explored as potential solutions to this problem.

Areas for improvement

“The most common cause of readmission was infectious disease, so thinking about antibiotic stewardship is really important,” she says. “This means using the right antibiotics for the right duration for the right patient, as well as completing the courses of antibiotics and not just stopping them at discharge.”

The other potential area of improvement, Dr. Gadre notes, is in facilitating a smooth transition of care from the ICU to the regular nursing floor to a skilled nursing facility.

“Lastly, some of these comorbidities and reasons for readmission are potential factors that we can address in the outpatient setting. We should think about post-ICU discharge clinics where we could look at these conditions and treat them earlier rather than their leading to readmission,” she says.

In continuation of their research, Dr. Gadre and her collaborators are planning to look at the epidemiology of readmission for patients with acute respiratory distress syndrome.

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A photograph of two medical professionals in white lab coats standing in a hospital hallway. The man on the left is wearing glasses and has a goatee. The woman on the right has blonde hair. Both lab coats have the Cleveland Clinic logo. A blue semi-transparent banner is overlaid on the bottom half of the image, containing white text.

THE MEDICAL INTENSIVE LIVER UNIT:

A Multidisciplinary Approach
to a Common Problem

LEFT TO RIGHT: Eduardo Mireles-Cabodevila, MD; Christina Lindenmeyer, MD;
Hassan Khouli, MD; and Aanchal Kapoor, MD



THE MEDICAL INTENSIVE LIVER UNIT: A MULTIDISCIPLINARY APPROACH TO A COMMON PROBLEM

Cleveland Clinic opens liver-specific intensive care unit, one of few in the U.S.

KEY POINTS

To optimize the management of critically ill patients with liver disease, Cleveland Clinic developed the medical intensive liver unit (MILU), a subunit model, to address the specific needs of this patient population.

Physicians compared the outcomes of patients with cirrhosis to a historical control of 772 patients with liver cirrhosis admitted to Cleveland Clinic's medical intensive care unit (MICU) between 2007 and 2017 (non-MILU cohort).

Outcomes data demonstrate that patients in the MILU group had a significantly higher transplant-free survival rate (79.5%) compared with patients in the non-MILU group (70.8%).

There was no significant difference in length of stay between the two groups. Continued investigation is warranted to realize how this model can further optimize outcomes.

Decompensated cirrhosis, acute liver failure and acute-on-chronic liver failure usually require management in the intensive care unit. Although the overall survival rate of critically ill patients with liver disease has increased over time due to improved management of these patients, the mortality rate of patients with liver cirrhosis admitted to the ICU is high (32% to 69%) and leads to high resource utilization and prolonged hospital stay.

A novel model for care

The medical intensive care unit (MICU) at Cleveland Clinic cares for a large number of critically ill patients with liver disease. To optimize management, we assembled a multidisciplinary team of medical intensivists, hepatologists, nurses, pharmacists, social workers, advanced practice providers, nutritionists, physical therapists and hospital operators. The goal was to develop a novel care model focused on addressing the specific needs of this patient population. The objectives were to improve patient care by developing standardized approaches, with the goals of improving survival, decreasing ICU length of stay, expediting transplant evaluation and optimizing patient clinical status before liver transplantation. To achieve this, we started an iterative process to understand workflows, recognize priorities of the different disciplines and organize approaches. The result was a new reorganization of the MICU to create an area designated to the care of critically ill patients with liver disease. Our group developed institutional guidelines, nursing protocols and order sets based on current evidence.

The final product of this collaborative effort was Cleveland Clinic's medical intensive liver unit

(MILU), which opened in the summer of 2018. One of few liver-specific intensive care units in the U.S., the MILU offers multidisciplinary care for critically ill patients with liver failure — including acute liver failure, acute-on-chronic liver failure, cirrhosis and its complications — as well as patients waiting or being evaluated for liver transplant. The MILU is unique in bringing special expertise, in the form of a multidisciplinary team, to daily rounds. The combination of professions at the bedside, along with standardized approaches, improves alignment among teams, the patient and the family. It has also generated fertile ground for continuous improvement and research.

Outcomes: A closer look at transplant-free survival rates

From August 2018 to February 2019, 273 patients were cared for by the MILU team; of these, 185 had liver cirrhosis. The remaining patients (88) had acute liver failure or acute alcoholic hepatitis. We compared the outcomes of patients with cirrhosis to a historical control of 772 patients with liver cirrhosis admitted to Cleveland Clinic's MICU between 2007 and 2017 (non-MILU cohort). We did not have data on acute liver failure patients in the historical group. Patients in the MILU group had a significantly

TABLE 1:
Length of Stay
(LOS)

	[ALL] N = 987	ICU N = 772	MILU N = 215	P overall
Hospital LOS (Days)	10.400 [5.070;19.515]	9.930 [4.950;19.553]	11.000 [6.000;19.000]	0.154
	[ALL] N = 1015	ICU N = 772	MILU N = 243	P overall
ICU LOS (Days)	3.01 [1.70;6.26]	3.02 [1.62;6.27]	3 [2.6]	0.233

TABLE 2:
Transplant-Free
Survival

	[ALL] N = 987	ICU N = 772	MILU N = 215	P overall
Hospital Mortality	270 (27.383%)	226 (29.275%)	44 (20.561%)	0.015

higher transplant-free survival rate (79.5%) compared with patients in the non-MILU group (70.8%) ($P = 0.015$). After adjusting for age, gender and liver disease severity (using the model for end-stage liver disease-sodium score), transplant-free survival was significantly higher in MILU group patients than in the non-MILU group ($P = 0.028$). There was no significant difference in length of stay between the two groups. Of the 67 total liver transplants performed at our institution during August 2018 and February 2019, 25 of these patients (37.3%) were cared for in the MILU at some point prior to their transplant.

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IMPROVING ACCESS TO TRANSPLANT FOR THE SICKEST CYSTIC FIBROSIS AND COPD PATIENTS

Changes to criteria would bring some patients closer to receiving a lung transplant

KEY POINTS

The Lung Allocation Score (LAS) is a standardized system in the U.S. for clinicians to prioritize the sickest candidates for a lung transplant. The variables used to derive this score are collected by the Scientific Registry of Transplant Recipients.

Clinical variables relating to patients with cystic fibrosis (CF) and chronic obstructive pulmonary disease, including infection caused by *Burkholderia* species, hospitalization 29-42 days before the transplant, massive hemoptysis and a drop in FEV1, are not reflected in the LAS calculation.

The addition of these variables improved the ability of the LAS to identify the sickest CF candidates, giving them better access to a transplant.

This highlights the value of maintaining longitudinal patient registries.

In 2018, over 2,500 patients with end-stage lung disease received a lifesaving lung transplant. Clinicians in the U.S. use a standardized system to prioritize the sickest candidates for lung transplant. However, our analysis reveals that patients with cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) experience barriers to access based on the exclusion of critical data points, which may impact their candidacy for transplant. CF affects more than 30,000 people in the U.S., and almost all CF patients eventually die of respiratory failure, making transplant a critical intervention strategy.

What is the Lung Allocation Score?

In the U.S., patients gain access to lung transplant through the Lung Allocation Score (LAS) system. The LAS, first implemented in 2005, generates a composite score that ranks patients based on (1) their risk of death without a transplant and (2) their chance of survival with a transplant. The model has undergone relatively few changes since its inception. Patients are categorized into one of the following diagnosis groups:

- › Chronic obstructive pulmonary disease
- › Pulmonary arterial hypertension
- › Cystic fibrosis
- › Idiopathic pulmonary fibrosis

The variables used to derive this score are collected by the Scientific Registry of Transplant Recipients (SRTR), which provides comprehensive data on transplant donors, candidates and recipients in the U.S. However, some important variables relating to patients with CF are not included in this registry.

Our analysis

Our team merged the SRTR with the Cystic Fibrosis Foundation Patient Registry to evaluate transplant candidates and recipients from 2011 to 2014. This included 9,043 patients on the lung transplant waiting list and 6,110 lung transplant recipients. Of these, 1,020 and 677, respectively, had CF.

Individuals with CF who are sick enough to need a lung transplant have significant heterogeneity in survival. In this work, we identified new clinical variables using the merged registry that were found to best predict their risk of mortality as they awaited a transplant.

Their LAS was recalculated using these variables. Additionally, the forced expiratory volume in one second (FEV1) is known to be an important predictor of survival not only in CF patients, but also in patients with other chronic lung diseases. The impact of change in FEV1 was reassessed for patients in all diagnosis groups awaiting a lung transplant.

The goal of the LAS is to allocate organs to those at the highest risk of death who are more likely to experience a survival benefit with transplant.

Risk factors for CF and COPD patients

The risk of death on the waiting list was increased for CF candidates with the following clinical variables: infection caused by *Burkholderia* species (hazard ratio [HR] 2.8, 95% confidence interval [CI] 1.2-6.6), hospitalization 29-42 days prior to the transplant (2.8, 1.3-5.9), massive hemoptysis (2.1, 1.1-3.9) and a relative drop in FEV1 \geq 30% over 12 months (1.7, 1.0-2.8). Their post-transplant mortality risk was increased for those with pulmonary exacerbation time of 15-28 days (1.8, 1.1-2.9). The inclusion of the FEV1 variable also predicted mortality for COPD candidates with a relative drop in FEV1 of \geq 10% while they awaited a transplant (2.6, 1.2-5.4).

A change in LAS: Why it matters

The addition of CF-specific variables improved the ability of the LAS to identify the sickest CF candidates, which gave them better access to a transplant. Importantly, in the population studied, more patients who died awaiting transplant would have experienced an increase in their score. For candidates with COPD, the addition of the FEV1 variable increased their access to transplant.

The LAS is scored from 0 to 100, with the majority of candidates having a score of 35-57 points at the time of transplant. For illustrative purposes, the score of an "average" CF candidate awaiting transplant, with the addition of the *Burkholderia* variable, would increase about 6 points. The addition of the hospitalization variable would increase their score by 6 points, 3.75 points for hemoptysis and 2.5 points for a relative decrease in FEV1 of \geq 30%. Candidates with COPD would experience an increase in score of 2-4 points with the inclusion of the variable indicating

a relative drop in FEV1 of \geq 10%. Currently, candidates with CF and COPD have the lowest average LAS at the time of transplant, and the increases in scores may also significantly increase their likelihood of receiving a transplant.

What are the clinical implications?

The goal of the LAS is to allocate organs to those at the highest risk of death who are more likely to experience a survival benefit with transplant. This work shows that the addition of new clinical variables can help improve the ability of the LAS model to provide more accurate predictions of those most at risk for mortality on the transplant waiting list. It also highlights the importance of longitudinal patient registries to help identify the patients who may benefit the most from medical intervention to improve survival.

This study was made possible with the support of the U.S. Department of Health and Human Services.

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Maryam Valapour, MD, MPP, is a lung transplant pulmonologist and the Director of Lung Transplant Outcomes. She is the Senior Lung Transplant Investigator for the Scientific Registry of Transplant Recipients. She can be reached at valapom@ccf.org or 216.445.4071.

A PARADIGM SHIFT IN THE TREATMENT OF SCLERODERMA-ASSOCIATED INTERSTITIAL LUNG DISEASE

New pathways to consider in the treatment of SSc-ILD

KEY POINTS

Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in systemic sclerosis (scleroderma, SSc). Mycophenolate mofetil has become the standard of care for SSc-ILD in the U.S.

Based on data from the SENSICIS study, a multinational, phase 3 randomized, double-blind, placebo-controlled trial that investigated the efficacy and safety of nintedanib in 580 patients with SSc-ILD, nintedanib became the first drug approved by the Food and Drug Administration for SSc-ILD.

Substantial evidence supports a “vascular hypothesis” for the pathogenesis of SSc-associated ILD. Thrombin is elevated in the bronchoalveolar lavage fluid of patients with SSc-ILD and can induce the myofibroblast phenotype.

Targeting thrombin with a direct thrombin inhibitor could prove to be a novel and effective treatment strategy.

Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in systemic sclerosis (scleroderma, SSc). It is a consequence of the interplay of disordered immunologic, fibrotic and vascular pathways that culminates in nonreversible scarring of the lungs (Figure). Although the traditional approach to the treatment of SSc-ILD has focused on immunosuppression, there is a rationale for targeting the other two pathways.

The first Scleroderma Lung Study (SLS I)¹ studied oral cyclophosphamide versus placebo. In this study, there was a significant but modest improvement in forced vital capacity (FVC), dyspnea, skin thickening and health-related quality of life. Unfortunately, these effects were no longer apparent one year after discontinuation of therapy,² and the toxicity of cyclophosphamide precludes its long-term use. These findings prompted the SLS II,³ which compared two years of mycophenolate mofetil (MMF) to one year of oral cyclophosphamide followed by one year of placebo. In this study, both drugs resulted in significant improvements in FVC, and MMF was associated with less toxicity. The hypothesis that two years of MMF would have greater efficacy than one year of cyclophosphamide at 24 months was not confirmed. Nevertheless, MMF has become the standard of care for SSc-ILD in the United States.

Promising clinical trials for SSc-ILD

Tocilizumab, targeting IL-6, looks promising for SSc-ILD based on subgroup analysis of the focuSSced (A Study of the Efficacy and Safety of Tocilizumab in Participants With Systemic Sclerosis) and faSSciate (Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis:

results from the open-label period of a phase II randomized controlled trial) clinical trials, which were designed to examine the effects of tocilizumab on skin fibrosis.^{4,5} Finally, autologous stem cell transplantation is emerging as a novel treatment option for refractory disease based on the outcomes of three randomized controlled trials (ASSIST, SCOT and ASTIS), which included patients with SSc-ILD, that showed improved event-free survival and modest improvement in pulmonary function.⁶⁻⁸

Based on the observation that the anti-fibrotics nintedanib and pirfenidone slowed the rate of FVC decline in idiopathic pulmonary fibrosis, these drugs have also been studied in SSc-ILD. In the phase 2 LOTUSS trial, pirfenidone was found to be safe and well tolerated in patients with SSc-ILD.⁹ With regard to efficacy, we await the results from SLS III, which compares initial combination pirfenidone plus mycophenolate versus placebo plus mycophenolate over 18 months in patients with newly diagnosed SSc-ILD (clinicaltrials.gov: NCT03221257). The SENSICIS study⁹ was a multinational, phase 3 randomized, double-blind, placebo-controlled trial that investigated the efficacy and safety of nintedanib in 580 patients with SSc-ILD. Patients

were randomly assigned to receive 150 mg of nintedanib twice daily or placebo. Approximately 50% of patients were on stable background mycophenolate. There was a significant reduction in the adjusted rate of change in FVC (-52.4 mL/year in the nintedanib group versus -93.3 mL/year in the placebo group [difference, -41.0 mL/year; $P = 0.04$]). Based on these data, nintedanib became the first drug approved by the Food and Drug Administration for SSc-ILD on Sept. 6, 2019, changing the treatment paradigm for SSc-ILD.

Examining a ‘vascular hypothesis’

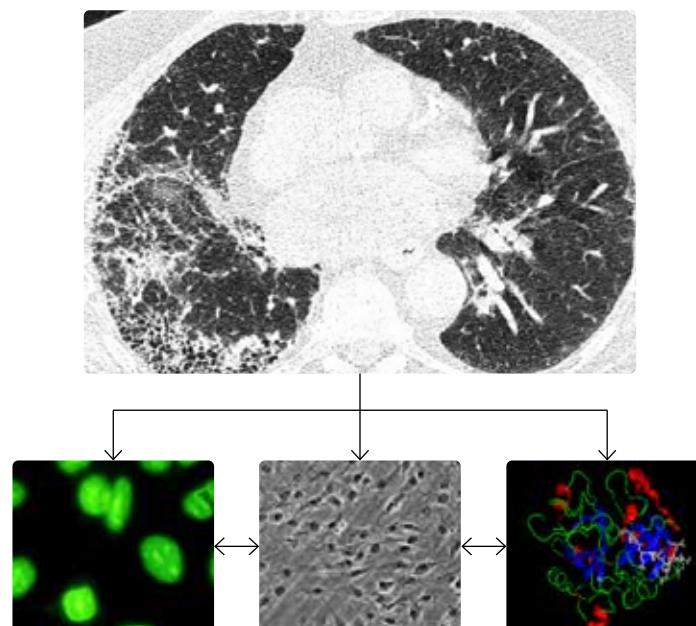
Substantial evidence supports a “vascular hypothesis” for the pathogenesis of SSc-associated ILD. Not only is thrombin elevated in the bronchoalveolar lavage fluid of patients with SSc-ILD, but thrombin can induce the myofibroblast phenotype. Therefore, targeting thrombin with a direct thrombin inhibitor could prove to be a novel and effective treatment strategy based on preclinical data. As a first step toward designing a clinical trial to test the efficacy of thrombin inhibition in SSc-ILD, a single-center, open-label treatment trial with the direct thrombin inhibitor dabigatran was performed in patients with SSc-ILD.¹⁰ Dabigatran appeared to be safe and well tolerated. In addition, thrombin activity in bronchoalveolar lavage fluid decreased or remained stable in 92.8% of the subjects.

Max Hirsch, MD, the father of modern rheumatology, once said that “no drug has truly failed until it has been tried in scleroderma.” As a result of a better understanding of the pathobiology of SSc-ILD and its multiple pathways, the future of SSc-ILD is much brighter.

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FIGURE 1



ABOVE: SSc-ILD is a consequence of the interplay of disordered immunologic, fibrotic and vascular pathways. The figure shows a SSc-ILD on a chest computed tomography, the Scl-70 auto-antibody, lung fibroblasts and the thrombin molecule.

Kristin Highland, MD, is a pulmonologist and critical care physician and a rheumatologist. She is Director of the Rheumatic Lung Disease Program. She was an investigator in the SLS II and dabigatran studies and the co-global lead of the SENSICIS trial. She can be reached at highlak@ccf.org or 216.445.5429.

SELECTED CLINICAL STUDIES

Consider offering your patients enrollment in a leading-edge clinical research trial at our Respiratory Institute. Obtain further information by contacting the study coordinator or principal investigator.

ASTHMA

A Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study to evaluate the efficacy and safety of GBO01 as maintenance therapy in adult subjects with moderate-to-severe asthma (LEDA)

The purpose of this Phase 2b study is to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of GBO01 in subjects with moderate-to-severe asthma and an eosinophilic phenotype.

Principal Investigator
Emily Pennington, MD

Study Coordinator
Valerie Shaner, RRT | 216.444.3766

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COPD

Roflumilast or Azithromycin to Prevent COPD Exacerbations (RELIANCE)

To conduct a pragmatic, non-inferiority trial in a high-risk population of patients with COPD and chronic bronchitis to compare azithromycin to roflumilast for prevention of all-cause exacerbations.

Principal Investigator
Umur Hatipoglu, MD

Study Coordinator
Rick Rice, RRT | 216.444.1150

Economic and Humanistic Impact of Low Peak Inspiratory Flow Rate (PIFR) in COPD Patients: An Observational Analysis

This is an observational study to explore the relationship between PIFR and the patient-reported outcomes (PROs) and COPD-related exacerbations among COPD patients.

Principal Investigator
Umur Hatipoglu, MD

Study Coordinator
Rick Rice, RRT | 216.444.1150

A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) – (BOREAS)

The objective of this study is to evaluate the efficacy of dupilumab in patients with moderate or severe COPD.

Principal Investigator
Umur Hatipoglu, MD

Study Coordinator
Rick Rice, RRT | 216.444.1150

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CRITICAL CARE MEDICINE

Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)

The objective of this NIH-sponsored trial is to determine the impact of a restrictive fluids strategy (vasopressors first followed by rescue fluids) as compared to a liberal fluid strategy (fluids first followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

Principal Investigator
Abhijit Duggal, MD

Study Coordinators
Andrei Hastings, MD | 216.445.3960
Omar Mehkri, MD | 216.445.1939

A Prospective, Multicenter, Randomized, Controlled, Pivotal Trial to Validate the Safety and Efficacy of the Hemolung® Respiratory Assist System for COPD Patients Experiencing an Acute Exacerbation Requiring Ventilatory Support (VENT-AVOID)

The primary objective of this study is to demonstrate the safety and efficacy of using the Hemolung RAS to provide low-flow ECCO2R as an alternative or adjunct to invasive mechanical ventilation versus standard of care invasive mechanical ventilation alone to increase ventilator-free days for COPD patients who require respiratory support due to an acute exacerbation of their COPD.

*Principal Investigator**Abhijit Duggal, MD**Study Coordinators**Andrei Hastings, MD | 216.445.3960**Omar Mehkri, MD | 216.445.1939*[A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning from Mechanical Ventilation in ICU Patients \(RESCUE 3\)](#)

The goal of this study is to investigate the safe and effective performance of the Lungpacer DPT System™ in patients who have failed to wean from mechanical ventilation.

*Principal Investigator**Tarik Hanane, MD**Study Coordinators**Andrei Hastings, MD | 216.445.3960**Omar Mehkri, MD | 216.445.1939*[Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: A Randomized Controlled Trial \(BALANCE\)](#)

This is a non-inferiority, concealed allocation trial of shorter duration (7 days) versus longer duration (14 days) antibiotic treatment for critically ill patients with bloodstream infections.

*Principal Investigator**Abhijit Duggal, MD**Study Coordinators**Andrei Hastings, MD | 216.445.3960**Omar Mehkri, MD | 216.445.1939*

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CYSTIC FIBROSIS[Cystic Fibrosis \(CF\) Foundation Patient Registry](#)

The CF Patient Registry collects information on the health status of people with cystic fibrosis who receive care in CF Foundation-accredited care centers and agree to participate in the registry. This information is used to create CF care guidelines, assist care teams providing care to individuals with CF and guide quality improvement initiatives at care centers. Researchers also use the patient registry to study CF treatments and outcomes and to design CF clinical trials.

*Principal Investigator**Elliott Dasenbrook, MD**Study Coordinator**David Weaver, BSN, CCRC | 216.445.6671*[Cystic Fibrosis Lung Transplant Consortium](#)

The objective of this proposal is the establishment of a clinical and translational research network of CF lung transplant centers to facilitate the study of lung transplant for CF and other lung diseases to improve access, clinical care and long term outcomes of individuals with CF who undergo lung transplant.

*Principal Investigator**Maryam Valapour, MD**Study Coordinator**David Weaver, BSN, CCRC | 216.445.6671*[Impact of Pre-and Post- Transplant T Cell Alloreactivity on Lung Transplant Injury](#)

While many patients experience benefits from lung transplant, complications such as infections and lung rejection may affect long-term survival and quality of life. In this study, we are looking at a complication called chronic lung allograft dysfunction (CLAD). CLAD is thought to be chronic rejection of the lung by the immune system and is the leading cause of death after lung transplant.

*Principal Investigator**Maryam Valapour, MD**Study Coordinator**David Weaver, BSN, CCRC | 216.445.6671*[Prospective study of peripherally inserted venous catheters in CF patients — The PICC-CF study](#)

The goal of this study is to evaluate associations between patient- and catheter-level factors and risk of subsequent PICC and midline complications and evaluate the strength of any associations.

*Principal Investigator**Elliott Dasenbrook, MD**Study Coordinator**David Weaver, BSN, CCRC | 216.445.6671*

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INTERSTITIAL LUNG DISEASE[A Phase 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of GLPG1690 in addition to local standard of care for minimum 52 weeks in subjects with idiopathic pulmonary fibrosis. \(ISABELA\)](#)

The objective of this study is to evaluate the efficacy of GLPG1690 in subjects with idiopathic pulmonary fibrosis as evaluated by the rate of decline of forced vital capacity.

*Principal Investigator**Leslie Tolle, MD**Study Coordinator**Ron Wehrmann, RRT | 216.445.0574*

[A randomized, double-blind, multicenter, parallel, placebo-controlled Phase 2b study in subjects with idiopathic pulmonary fibrosis \(IPF\) investigating the efficacy and safety of TD139, an inhaled galectin-3 inhibitor administered via a dry powder inhaler over 52 weeks \(GALACTIC-1\)](#)

The study is designed to evaluate the efficacy and safety of TD139, a galectin-3 blocker, administered by dry powder inhalation over 52 weeks of dosing in addition to the subject's current SoC (including treatment with either pirfenidone or nintedanib), which will be maintained throughout the study.

*Principal Investigator**Aman Pande, MD**Study Coordinator**Ron Wehrmann, RRT | 216.445.0574*

[Chronic Fibrosing Interstitial Lung Disease with Progressive Phenotype Prospective Outcomes \(ILD-PRO\) Registry](#)

This registry is a prospective registry that will collect information regarding treatment of participants with a diagnosis of a chronic fibrosing interstitial lung disease with progressive phenotype.

*Principal Investigator**Daniel Culver, DO**Study Coordinator**Ron Wehrmann, RRT | 216.445.0574*

[Study of Pulmonary Rehabilitation in Nintedanib-Treated Patients with IPF: Improvements in Activity, Exercise Endurance Time and QoL](#)

This is a Phase IV open label clinical trial to investigate the effect of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis currently taking nintedanib.

*Principal Investigator**Aman Pande, MD**Study Coordinator**Valerie Shaner, RRT | 216.444.3766*

[A Phase I, Double-Blind, Placebo-Controlled, Single and Multiple Inhaled Dose, Safety, Tolerability, and Pharmacokinetic Study of TRK-250 in Subjects with Idiopathic Pulmonary Fibrosis \(IPF\)](#)

The principal aim of this study is to obtain safety and tolerability data when TRK-250 is administered by inhalation as single and multiple doses to subjects with IPF.

*Principal Investigator**Daniel Culver, DO**Study Coordinator**Ron Wehrmann, RRT | 216.445.0574*

[Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Efficacy and Safety Study with Inhaled RVT-1601 for the Treatment of Persistent Cough in Patients with Idiopathic Pulmonary Fibrosis \(IPF\): SCENIC Trial](#)

The primary objective of this study is to assess the efficacy of inhaled RVT-1601 in patients with IPF and a persistent cough.

*Principal Investigator**Daniel Culver, DO**Study Coordinator**JoAnne Baran-Smiley, BSN, RN | 216.444.5023*

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LUNG CANCER

[Pragmatic Trial of More versus Less Intensive Strategies for Active Surveillance of Patients with Small Pulmonary Nodules](#)

In conjunction with the Patient Centered Outcomes Research Institute (PCORI) and Kaiser Permanente of California, the main objective of this study is to compare two protocols for lung nodule evaluation, with cluster randomized assignment to treatment groups at the level of the hospital or health system. The design of the trial is a hospital-based cluster randomized trial of more frequent surveillance versus less frequent surveillance of pulmonary nodules, and immediate or delayed participation in quality improvement collaboratives.

*Principal Investigator**Peter Mazzone, MD, MPH**Study Coordinator**Stuart Houltham | 216.445.1056*

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LUNG TRANSPLANT

[Improving Frailty with a Rigorous Ambulation Intervention in Lung Transplant Patients \(iFRAIL\)](#)

The objective of this study is to evaluate frailty pre- and post-

transplant to determine the effect of dedicated ambulator-assisted physical activity in lung transplant inpatients.

Principal Investigator

Marie Budev, DO, MPH

Study Coordinator

Bryan Poynter | 216.445.1630

[A Phase III, Prospective, Multicenter, Randomized, Controlled Clinical Trial to Demonstrate the Effectiveness and Safety of Liposomal Cyclosporine A \(L-CsA\) Inhalation Solution Delivered via the PARI Investigational eFlow® Device plus Standard of Care versus Standard of Care Alone in the Treatment of Bronchiolitis Obliterans Syndrome in Patients Post Lung Transplantation \(BOSTON-1 and BOSTON-2\)](#)

The objective of the trial is to assess the efficacy and safety of add-on aerosolized L-CsA to standard-of-care therapy as compared to standard-of-care therapy alone in the treatment of BOS in lung transplant recipients.

Principal Investigator

Marie Budev, DO, MPH

Study Coordinator

Valerie Shaner, RRT | 216.444.3766

[An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Itacitinib in Participants with Bronchiolitis Obliterans Syndrome Following Lung Transplantation](#)

The purpose of this study is to test itacitinib, a JAK inhibitor, to identify an appropriate dose as a treatment for patients with BOS following lung transplantation.

Principal Investigator

Marie Budev, DO, MPH

Study Coordinator

JoAnne Baran-Smiley, BSN, RN | 216.444.5023

[Cleveland Clinic Lung Transplant Biorepository](#)

The aim of this program is to establish a patient-linked biological sample repository for use in future research studies related to metabolic, inflammatory and immunologic markers related to organ transplantation in general and in lung transplantation in particular.

Principal Investigator

Maryam Valapour, MD

Study Coordinator

David Weaver, BSN, CCRC | 216.445.6671

PULMONARY HYPERTENSION

[Pulmonary Hypertension Research Registry](#)

The Pulmonary Hypertension Research Registry is a collection of patients' clinical and demographic data to be used for future research. The purpose of this registry is to develop a list of prospective participants with pulmonary hypertension who are interested in learning about future research opportunities. In addition to being part of the registry, participants will receive quarterly newsletters including information about recent research findings in pulmonary hypertension, currently enrolling and upcoming studies, and more.

Principal Investigator

Kristin Highland, MD

Study Coordinator

Mary Beukemann | 216.444.2140

[SPHERE; Uptravi® \(Selexipag\): The Users Drug Registry](#)

This registry describes the demographics, disease characteristics, dosing regimens and titration schemes, and the clinical course of patients treated with Uptravi, including any transition processes from other PAH-specific therapies to Uptravi and from Uptravi to other prostanoids.

Principal Investigator

Neal Chaisson, MD

Study Coordinator

Mary Beukemann | 216.444.2140

[Study evaluating the efficacy and safety of ralinepag to improve treatment outcomes in PAH Patients \(ADVANCE\)](#)

The primary objective of this Arena-sponsored study is to compare the effect of ralinepag versus placebo in subjects with standard-of-care or PAH-specific background therapy on disease progression and achievement of a satisfactory clinical response in subjects with WHO Group 1 PAH.

Principal Investigator

Alice Goyanes, MD

Study Coordinator

Mary Beukemann | 216.444.2140

[Phase 2 Multicenter, Double-Blind, Placebo Controlled, Efficacy, Safety, and Pharmacokinetic Study of 2 Doses of CXA-10 on Stable Background Therapy in Subjects with Pulmonary Arterial Hypertension \(PAH\)](#)

Sponsored by Complexa, the objective of this study is to evaluate the safety and efficacy of CXA-10 for the treatment of PAH.

*Principal Investigator**Gustavo Heresi, MD**Study Coordinator**Amy Pritchard-Matia | 216.444.8347***Pulmonary Arterial Hypertension Improvement with Nutrition and Exercise (PHINE) – A Randomized Controlled Trial**

The National Institutes of Health is funding this study to assess the effect of diet and exercise on metabolism and its role in pulmonary hypertension. This is a 12-week diet and exercise study that has 5 days a week of exercise training and 1 day a week of diet counseling.

*Principal Investigator**Gustavo Heresi, MD**Study Coordinators**Chazity Bush | 216.444.3702**Celia Melillo | 216.445.3763***A Phase 3, Randomized, Placebo-controlled, Double-blind, Adaptive Study to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Chronic Obstructive Pulmonary Disease (PH-COPD) – (PERFECT)**

The objective of this study is to demonstrate the efficacy of inhaled treprostinil in improving exercise ability as measured by change from baseline in 6-Minute Walk Distance (6MWD) in subjects with PH-COPD.

*Principal Investigator**Joseph Parambil, MD**Study Coordinator**Mary Beukemann | 216.444.2140***SELEXipag in inoperable or persistent/recurrent Chronic Thromboembolic pulmonary hypertension (SELECT)**

This Phase 3 study will assess the efficacy and safety of selexipag as an add-on to standard-of-care therapy in subjects with inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical and/or interventional treatment.

*Principal Investigator**Gustavo Heresi, MD**Study Coordinator**Amy Pritchard-Matia | 216.444.8347***A Phase 1b, Randomized, Subject- and Investigator-Blinded, Placebo-Controlled, Multi-Center Clinical Trial to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Biomarkers of Inhaled GB002 in Subjects with WHO Group 1 Pulmonary Arterial Hypertension (PAH)**

The primary objective of this study is to evaluate the safety and tolerability of inhaled GB002, a small-molecule PDGFR kinase inhibitor, in patients with PAH.

*Principal Investigator**Kristin Highland, MD**Study Coordinator**Mary Beukemann | 216.444.2140*

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RARE LUNG DISEASES**ALPHA-1 ANTITRYPSIN DEFICIENCY: Alvelestat (MPH996) for the Treatment of ALpha-1 ANTITrypsin Deficiency (ATALANTa)**

This National Center for Advancing Translational Sciences-sponsored, Phase 2, multicenter, double-blind, randomized (1:1), placebo-controlled, proof-of-concept study is designed to evaluate the safety and tolerability as well as the mechanistic effect of oral administration of alvelestat (MPH996) in subjects with confirmed alpha-1 antitrypsin deficiency (AATD)-related emphysema.

*Principal Investigators**Umur Hatipoglu, MD, and James Stoller, MD**Study Coordinator**Rick Rice, RRT | 216.444.1150*

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SARCOIDOSIS**Ocular Sarcoidosis: Open Label Trial of ACTHAR Gel**

Sponsored by Mallinckrodt ARD, this study will investigate whether treatment with ACTHAR gel will result in a reduction of ocular inflammation in patients with active ocular sarcoidosis that requires systemic immunosuppressant therapy.

*Principal Investigator**Daniel Culver, DO**Study Coordinator**David Weaver, BSN, CCRC | 216.445.6671***ACTHAR gel for cutaneous sarcoidosis**

Supported by Mallinckrodt ARD and Albany Medical College, this

study aims to provide evidence that ACTHAR gel may serve as a therapeutic immune-modulating alternative to glucocorticoids in patients with active cutaneous sarcoidosis.

Principal Investigator

Daniel Culver, DO

Study Coordinator

David Weaver, BSN, CCRC | 216.445.6671

[A Phase 4 Multicenter, Randomized, Double Blind, Placebo Controlled Pilot Study to Assess the Efficacy and Safety of H.P. ACTHAR Gel in Subjects with Pulmonary Sarcoidosis](#)

Sponsored by Mallinckrodt Pharmaceuticals, this is a Phase IV trial investigating the effect of ACTHAR gel versus placebo on the clinical disease activity of pulmonary sarcoidosis patients. There is an open label phase to this trial.

Principal Investigator

Debasis Sahoo, MD

Study Coordinator

Allison Wimer, RRT | 216.445.9557

[Routine Cardiac Screening in Sarcoidosis Patients \(PAPLAND\)](#)

This is an unblinded randomized screening trial for cardiac

sarcoidosis in patients seen during routine clinical care who have not been clinically suspected to have cardiac sarcoidosis according to conventional criteria, comparing the addition of echocardiogram and ambulatory ECG to usual clinical follow-up.

Principal Investigator

Daniel Culver, DO

Study Coordinator

Allison Wimer, RRT | 216.445.9557

[A Randomized, Double-Blind, Placebo-Controlled Multiple Ascending Dose Study of Intravenous ATYR1923, novel molecular entity that acts as an extracellular immunomodulator, in patients with pulmonary sarcoidosis](#)

This study is evaluating the safety and tolerability of multiple ascending intravenous doses of ATYR1923 in patients with pulmonary sarcoidosis.

Principal Investigator

Daniel Culver, DO

Study Coordinator

Allison Wimer, RRT | 216.445.9557

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BY THE NUMBERS

WHO WE ARE*

Number of physicians

194

Number of locations

28

Number of advanced
practice providers

82

Number of federal grants

42

Number of fellows

48

Allergy and Immunology – 4

Critical Care Medicine – 12

Infectious Disease – 7

Pulmonary & Critical Care – 24

Interventional Pulmonology – 1

* Data from 2019

HOW WE PERFORM**

Outpatient visits

234,705

Pulmonary function test visits

71,564

Bronchoscopies

4,758

Daily enterprise ICU and floor census

335

Number of lung transplants

113

Advanced diagnostic
bronchoscopy procedures

1,468

Therapeutic bronchoscopy
procedures

1,034

** Data from 2018

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ABOUT CLEVELAND CLINIC

Cleveland Clinic is a nonprofit, multispecialty academic medical center integrating clinical and hospital care with research and education for better patient outcomes and experience. More than 3,900 staff physicians and researchers in 180 medical specialties provide services through 26 clinical and special expertise institutes. Cleveland Clinic comprises a main campus, 11 regional hospitals and more than 150 outpatient locations, with 19 family health centers and three health and wellness centers in northern Ohio, as well as medical facilities in Florida, Nevada, Toronto and Abu Dhabi. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.

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