

RESPIRATORY EXCHANGE

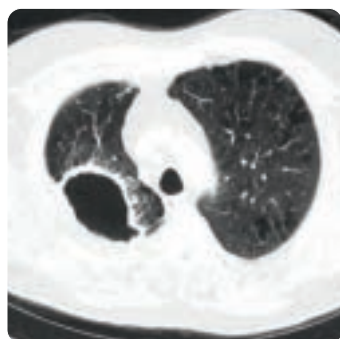
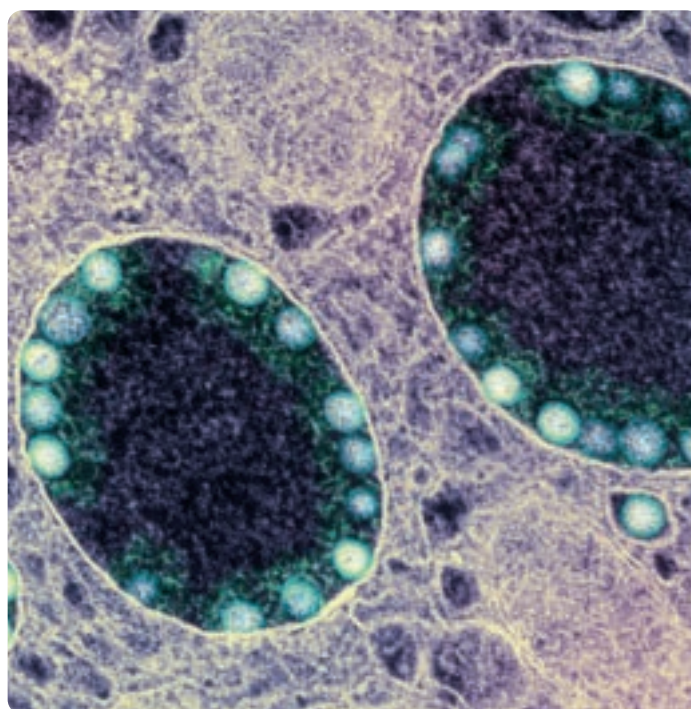
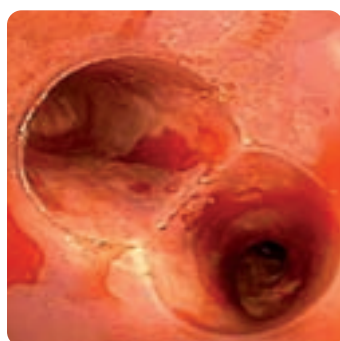
WINTER
2022

INTRANASAL CORTICOSTEROID USE AND COVID-19 OUTCOMES

— p. 16

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 institute is part of Cleveland Clinic, a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.

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ON THE COVER — Polly Barbinta, BSN, RN, cares for a patient in the COVID-19 unit.

DEAR COLLEAGUES,



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

As we pause to reflect on yet another difficult pandemic year, I am reminded that, through the collective power of our efforts and expertise, we have continued to advance clinical medicine, education and research, even in the most challenging circumstances many of us have faced in our careers. Despite these challenges, the wide range of interests and expertise in our institute's four departments of pulmonary medicine, critical care medicine, allergy/clinical immunology and infectious disease are well represented in this issue of *Respiratory Exchange*.

In the pages that follow, you'll see how our experts are:

- › Using airway stenting to solve therapeutic and palliative challenges for our lung cancer patients (p. 4).
- › Optimizing risk factor identification for patients with cystic fibrosis (CF) with electronic spirometry monitoring (p. 8).
- › Investigating the potential role for intranasal corticosteroids in the prevention of COVID-19 (p. 16).
- › Managing patients surgically with difficult-to-treat pulmonary nontuberculous mycobacterial (NTM) infections (p. 14).
- › Playing a critical role in the ongoing revision of lung cancer screening guidelines (p. 6).
- › Treating patients with NTM infections and non-CF bronchiectasis (p. 18).
- › Improving the lives of patients with peanut allergies through oral immunotherapy (p. 10).

I am excited to introduce the *Respiratory Exchange* podcast as a companion to this publication. This new podcast explores timely and timeless topics in pulmonary medicine, critical care, allergy/immunology, infectious disease and related areas.

In my 28 years at Cleveland Clinic, and especially in my recent years as Chairman of the Respiratory Institute, I have had the privilege of always putting patients first by working with and leading many high-functioning teams that have made major contributions to our core missions of clinical care, research, education and innovation. I am proud of our staff and the efforts featured in this issue of *Respiratory Exchange* that so powerfully demonstrate the Cleveland Clinic tripartite mission of caring for life, researching for health and educating those who serve. As always, we strive to provide the best care for the patients of today as we also prepare to provide the best care for the patients of tomorrow.

I look forward to sharing more with you in future publications and hearing your thoughts and feedback.

Sincerely,

A handwritten signature in black ink, appearing to read "Raed Dweik". The signature is fluid and cursive, with a long, sweeping underline that extends to the right.

RAED DWEIK, MD, MBA

Chairman, Cleveland Clinic Respiratory Institute | E. Tom and Erika Meyer Chair in Pulmonary Medicine

AIRWAY STENTING FOR LUNG CANCER: DIAGNOSTIC, THERAPEUTIC, PALLIATIVE

The role of interventional pulmonology in cancer care

KEY POINTS

This case highlights the value of multidisciplinary management of malignant central airway occlusion.

In critical airway emergencies, interventional pulmonologists can secure and palliate the airway while simultaneously obtaining diagnostic and staging tissue.

Research has demonstrated that timely interventions are associated with increased survival and measurable improvements in quality of life and lung function.

Our institute has seven American Association of Bronchoscopy and Interventional Pulmonology board-certified physicians and is the largest program in the United States.

CASE PRESENTATION — In late 2017, a patient presented to the emergency department with progressive shortness of breath with cough and wheeze. She was known to have chronic obstructive pulmonary disease (COPD), but initial treatment for this COPD exacerbation was not immediately helpful. A computed tomography (CT) scan showed evidence of lung cancer invading the trachea and main carina.

Cancer invading the main carina is defined as unresectable T4 disease in most cases. She was referred to bronchoscopy for diagnosis and palliation. A rigid bronchoscopy with biopsy was performed to prepare for a stent to palliate the airway. Francisco Almeida, MD, MS, Director of the Interventional Pulmonary Medicine Fellowship at Cleveland Clinic, placed a silicone Y stent, customized on-site to fit the patient, in the trachea. After the stent, she immediately improved and then recovered from her exacerbation. Upon completion of her evaluation, she was found to have stage IIIB (cT4N2MX) invasive squamous cell carcinoma, moderately differentiated.

She then underwent concurrent radiotherapy and chemotherapy with carboplatin and paclitaxel.

After improvement with just two months of therapy and some procedures to manage the stent, a bronchoscopy was performed to determine whether stent removal was possible. Using rigid bronchoscopy, the stent was easily removed.

In 2020, lung nodules were noted during a surveillance scan. Endobronchial ultrasound, bronchoscopy and biopsy of a peripheral lung lesion were performed. Though the airway showed some evidence of radiation injury, the lymph nodes and lung lesion were nondiagnostic for malignancy. She remains in survivorship and surveillance.

Airway stenting for lung cancer

This case highlights the value of multidisciplinary management of malignant central airway occlusion. When faced with critical airway emergencies, interventional pulmonologists can secure and palliate the airway while simultaneously obtaining diagnostic and staging tissue. “And when a patient does need a stent, we can customize it to fit properly, maintain it and then remove it when necessary,” says Thomas R. Gildea, MD, MS, Section Head of Bronchology in Cleveland Clinic’s Respiratory Institute.

Cleveland Clinic’s Respiratory Institute has seven American Association of Bronchoscopy and Interventional Pulmonology board-certified physicians, making it the largest program in the United States. “We work directly with the interventional pulmonology team on many of our lung cancer patients with airway issues,” says Nathan Pennell, MD, PhD, Director of Cleveland Clinic Cancer Center’s Lung Cancer Program. “It’s an important tool for diagnostics, therapeutics and palliation.”

Research has demonstrated that timely interventions are associated with increased survival and measurable improvements in quality of life and lung function. Recent data from a randomized, controlled trial suggest that early silicone stenting is associated with a

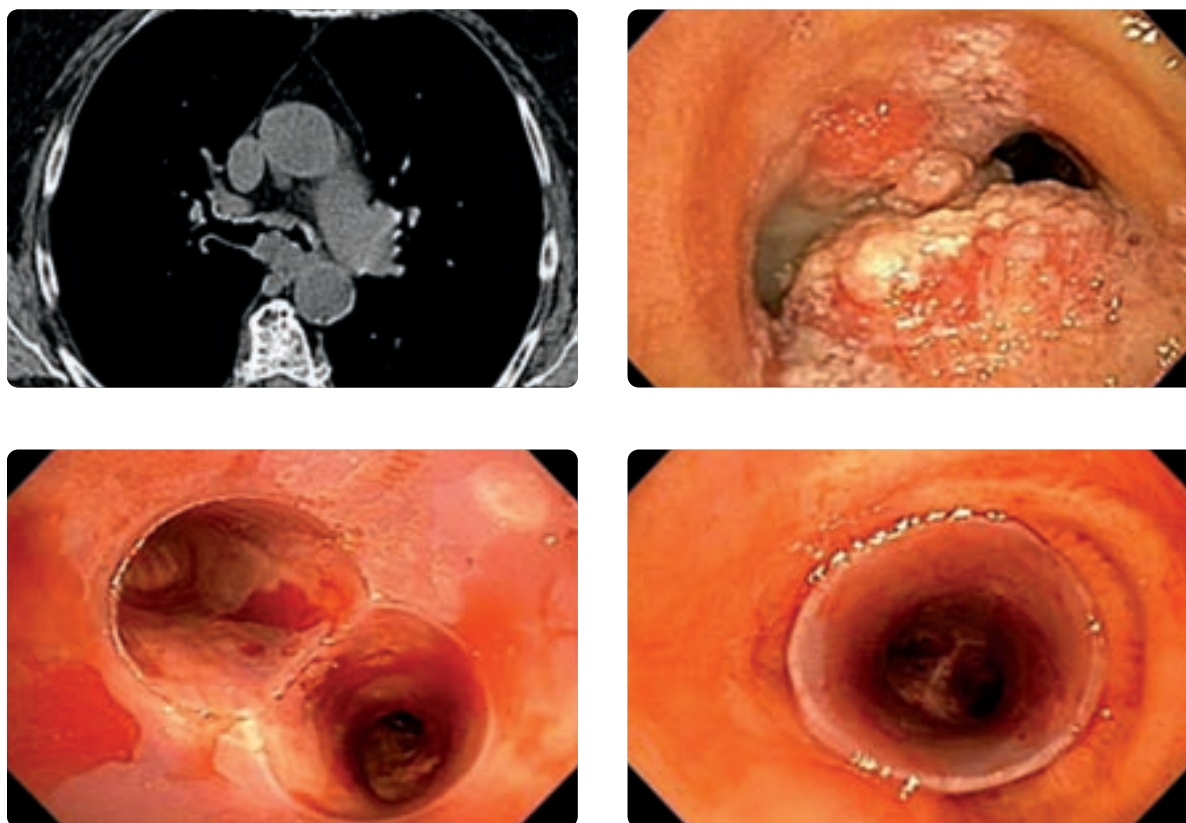


FIGURE 1. TOP LEFT. CT showing irregular mucosa at the main carina. TOP RIGHT. Bronchoscopy showing severe airway involvement (top right). After biopsy and silicone Y-stent, bottom airway is widely patent (BOTTOM).

more durable palliation of dyspnea and reduced unintended need for bronchoscopy compared with patients who did not receive stents. Further, the EVERMORE study, a multicenter retrospective analysis from Spain, noted that unadjusted Kaplan-Meier estimates showed an increase in one-year survival for patients who received therapeutic bronchoscopy with chemo/radiotherapy compared with chemo/radiotherapy alone (HR = 2.1, 95% CI, 1.1-4.8, $P = 0.003$).

“We’ve also incorporated patient-specific airway stents into our practice, a process that we developed and that received FDA approval in 2019,” says Dr. Gildea. “Overall, airway stents can play

an important role in allowing cancer patients the chance to undergo therapy and to overcome survivorship challenges.”

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EXPANDED RECOMMENDATIONS FOR LUNG CANCER SCREENING

What clinicians should know

By Peter Mazzone, MD

KEY POINTS

New USPSTF recommendations state that individuals who smoke or previously smoked (those who have quit in the past 15 years) and are age 50 to 80 with a 20 pack-year smoking history are now candidates for an annual lung cancer screening.

Some estimates suggest this expanded eligibility will increase the screening pool by 80% to 90%.

A robust screening program means developing outreach and education initiatives, thorough and collaborative diagnostic management and tracking, and smoking cessation and other support programs.

The implementation of these changes will take time and is ongoing, but many insurers are making coverage changes now.

Individuals who smoke or previously smoked (those who have quit in the past 15 years) and are age 50 to 80 with a 20 pack-year smoking history are now candidates for an annual lung cancer screening. This is according to new recommendations published by the U.S. Preventive Services Task Force (USPSTF).

This change follows new evidence that supports the benefit of screening for and better overall management of lung cancer in the identified population, given their potential risk for developing the disease. Some estimates suggest this expanded eligibility will increase the screening pool by 80% to 90%.

This new recommendation was supported by USPSTF-initiated modeling studies, in addition to findings from the NELSON trial, a large published study that included a starting age of 50 for trial participants.

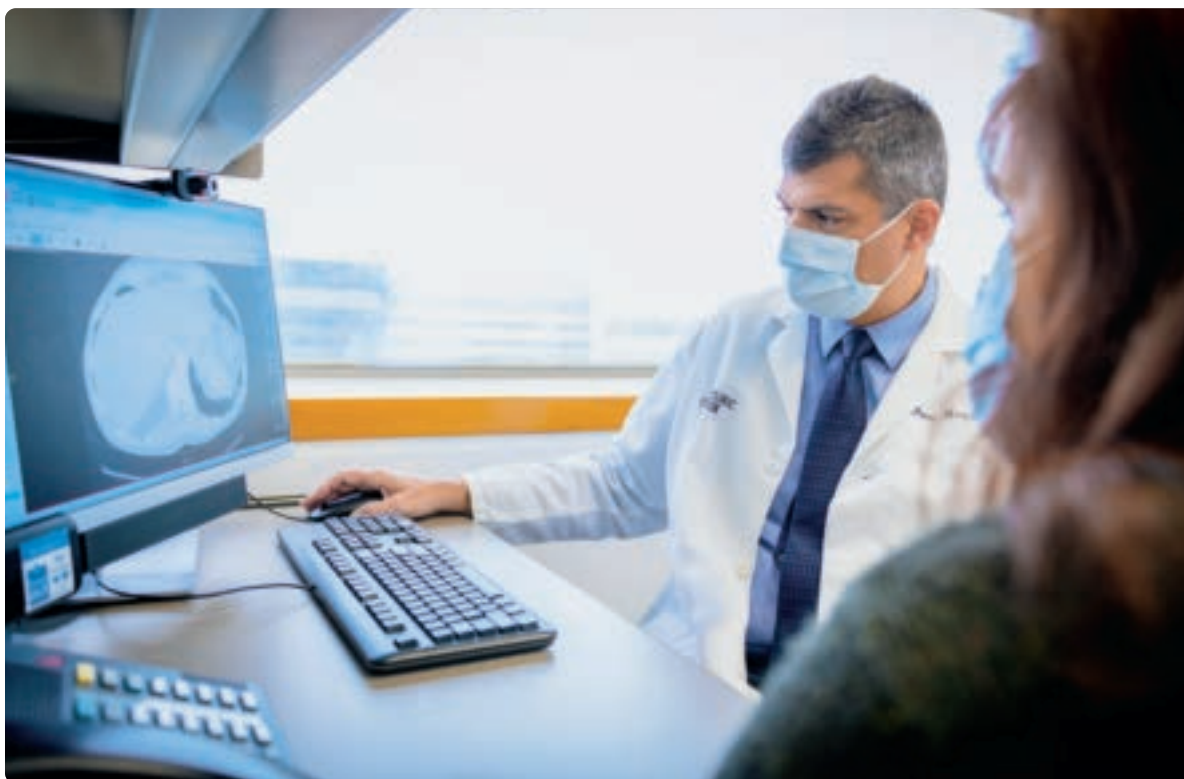
Eligibility criteria: A well-intentioned debate

However, there is still some debate as to whether the recommendations go too far — or not far enough. The camp supporting the latter argument says that individuals who previously smoked and who are ineligible for screening because of the 15-year cutoff still have a relatively high risk of developing cancer. They suggest that targeted screening tools, like risk calculators, could play a vital role in identifying those who do not meet the new recommendations but may still benefit from screening. Others argue that more restrictive criteria are beneficial, sifting out low-risk candidates and, thus, reducing screening exposures, including unnecessary biopsy of (most commonly) benign lung nodules as well as radiation exposure and undue anxiety.

What does high-quality screening mean?

It's an important and well-intentioned debate ultimately stemming from a desire to improve patient outcomes. It's also important to remember that lung cancer screening is more complex than identifying individuals who meet the selection criteria. A robust screening program means developing and implementing outreach and education initiatives, thorough and collaborative diagnostic management and tracking, and smoking cessation and other support programs. Regardless of one's views on screening parameters, there is a consensus that high-quality lung cancer screening is paramount. More specifically, this means an investment in the following:

- › Education and outreach campaigns that target eligible individuals.
- › Guidance and support to those who are referred for screening.
- › Performance of high-quality, low-radiation-dose chest CT imaging.
- › Expert interpretation of the imaging findings.
- › Expert management of the imaging findings to minimize testing in those without cancer and efficiently diagnose early-stage lung cancer when it is present.



LEFT. Dr. Mazzone reviews a scan with a patient.

- › Tracking and outreach to ensure compliance with annual screening and follow-up recommendations
- › Provision of smoking cessation guidance or connection to a smoking cessation program.

Heading in the right direction

Operationalizing these changes may still take time. Private insurers can change their coverage rules anytime between now and the end of 2022. The Centers for Medicare & Medicaid Services will take up a new net coverage determination with a decision expected in nine to 12 months. Importantly, because many insurers are making coverage changes now, clinicians need to be aware of the criteria and refer those with coverage for screening.

We look forward to a time when the majority of lung cancers are screen detected. The updated USPSTF recommendations are a step in that direction.

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NEW CLINICAL TOOL MAY BETTER DETECT DISEASE SEVERITY IN PATIENTS WITH CYSTIC FIBROSIS

Mobile app designed to improve access to lung transplant and reduce waitlist mortality

KEY POINTS

Lung transplant is a treatment option for patients with advanced lung disease due to CF, but the LAS does not include all markers of CF disease severity.

This study found that risk of waitlist mortality was higher than the LAS predicted in patients with the presence of *Burkholderia* species, massive hemoptysis, hospitalization and relative decline in FEV₁.

Incorporating these risk factors more accurately determines disease severity.

An app that monitors patient-reported symptoms and measures FEV₁ and FVC has shown early success in providing a more accurate, updated LAS for patients.

In the United States, individuals are prioritized for lung transplant by lung allocation score (LAS), which considers both the risk of mortality while awaiting transplant and the likelihood of survival after transplant. Although lung transplant is a treatment option for patients with advanced lung disease due to cystic fibrosis (CF), the LAS does not include all markers of CF disease severity.

A team of Cleveland Clinic pulmonologists has been studying ways to improve access to transplant and reduce waitlist mortality for individuals with advanced lung disease due to CF. With support from the Cystic Fibrosis Foundation's prestigious Harry Shwachman Clinical Investigator Award, Carli Lehr, MD, MS, worked with mentors Maryam Valapour, MD, MPP, and Elliot Dasenbrook, MD, to explore the impact of including markers of CF disease severity when prioritizing individuals for lung transplant.

The team found that risk of waitlist mortality was higher than predicted by LAS in patients with:

- › Presence of *Burkholderia* species.
- › Massive hemoptysis.
- › Hospitalization.
- › Relative decline in forced expiratory volume in one second (FEV₁).

They also found that considering these risk factors with the LAS helped more accurately determine disease severity.

"The addition of CF-specific risk factors led to a higher LAS in more than a third of individuals who died without a transplant, a change that may have led to a life-saving lung transplant," says Dr. Lehr, the Gregory and Maureen Church Term Chair

in Lung Transplantation Research in Cleveland Clinic's Respiratory Institute.

This work led the team to develop a new clinical tool to help identify these risk factors in patients with CF on the lung transplant waiting list.

[App combines patient survey with home spirometry](#)

Drs. Lehr, Valapour and Dasenbrook aimed to develop a clinical tool that would be easy for patients to use, contribute both clinical and patient-reported data to the transplant team, and incorporate findings from their prior analysis of factors contributing to waitlist mortality.

First, they created a 20-question patient survey, combining the previously validated and widely used Cystic Fibrosis Respiratory Symptom Diary – Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) with supplemental questions about physical functioning, appetite and hemoptysis. Next, they worked with a respiratory monitoring company to integrate the survey into a home spirometry mobile app measuring FEV₁ and forced vital capacity (FVC) — similar to the technology Cleveland Clinic uses to monitor post-transplant patients. The app provides patients with a score as soon as they answer all 20 survey questions and complete the spirometry monitoring.

Patients on the transplant waitlist use the app to complete weekly surveys and spirometry monitoring. Results are transmitted to the research team. Based on results, patients are asked to return to the clinic, repeat testing within 24 hours or repeat testing the following week. This algorithm ensures at-risk patients receive prompt medical attention to update their LAS (and potentially improve their access to lung transplant) or to detect and treat infectious causes of clinical decline.

Early successes

Since the inception of this study, researchers have enrolled four individuals, two who have undergone lung transplant. By using the tool, patients have had more frequent contact with the transplant team and more opportunities to update their LAS.

For example, one patient's survey responses revealed intermittent hemoptysis, something not captured by the LAS. Given the well-known association of hemoptysis with mortality in individuals with CF, these results led the research team to request an exception to the LAS.

"An exception can be requested when the clinical team feels that the LAS does not accurately capture an individual's risk of death without transplant," explains Dr. Valapour, Director of Lung Transplant Outcomes at Cleveland Clinic. "A new score is assigned to better approximate that risk. In this case, our exception request was granted, and the transplant for this patient was expedited."

Feedback from patients has been positive, especially regarding the increased engagement in their care and comfort with home monitoring.

"These are important qualitative successes as post-transplant engagement leads to improved compliance and connection with the transplant team," says Dr. Lehr. "Familiarity with the home monitoring device gives study patients a leg up. After the initial postoperative period, home spirometry is an important mechanism to screen for transplant rejection between clinical appointments and may help us catch rejection in its early stages."

Challenges and future direction

The landscape of end-stage lung disease in CF is changing for the better. In October 2019, a new triple-drug therapy combining elexacaftor, tezacaftor and ivacaftor was approved for patients with CF who have at least one F508del mutation in the CF transmembrane conductance regulator protein.

"Modulator therapies have important public health implications as now over 75% of individuals with CF are eligible for treatment that may slow their decline in lung function," says Dr. Dasenbrook, Director of the Adult Cystic Fibrosis Program and the Bronchiectasis Center at Cleveland Clinic.

Although follow-up has been short, individuals receiving this modulator therapy have experienced improvement in lung function. This should not change patterns of lung transplant referral for individuals with advanced lung disease, yet there has been a nationwide decline in the number of candidates awaiting transplant, including lung transplant for individuals with CF. This trend may be partly due to modulator therapy or confounded by a change in listing and transplant practices due to the COVID-19 pandemic.

Regardless, this change will require expanding the study of the disease-severity tool to more transplant centers to ensure enough patients are enrolled to produce valid conclusions.

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For more information about the tool or to refer a patient for the study, contact Dr. Lehr.



ORAL IMMUNOTHERAPY: THE ANSWER TO PEANUT ALLERGY?

Peanut-allergen powder approved by the FDA for the treatment of childhood peanut allergy

By Rachel M. Whitsel, APRN; Jaclyn A. Bjelac, MD; Ahila Subramanian, MD; and Sandra J Hong, MD

KEY POINTS

Peanut and tree-nut allergies have increased dramatically in prevalence, especially in children.

Oral immunotherapy is an emerging option offered by a limited number of allergists and immunologists.

Clinical trials show that oral immunotherapy allows patients to ingest higher doses of peanut protein without dose-limiting symptoms when compared with placebo recipients.

Patients should be cautioned that the FDA-approved oral immunotherapy product is not a cure for food allergies; instead, it is intended to reduce their reactivity.

Peanut and tree-nut allergies have increased dramatically in prevalence, especially in children. Historically, children with food allergies have been treated through strict avoidance of the allergen. Recently, an oral preparation of peanut allergen (Palforzia®) was approved for immunotherapy (i.e., desensitization) in children 4 to 17 years old. This article reviews oral immunotherapy and its role in children with peanut allergies.

Peanut allergy

Many food allergies are first diagnosed when the patient is a young child. The most common food allergy in children is peanut and tree-nut allergy, estimated to affect 1 million children, and its prevalence more than tripled between 1997 and 2008. Peanut allergy is also the most common cause of severe food-associated anaphylaxis.

Risk factors for peanut allergy include severe atopic dermatitis, egg allergy in infancy, a family history of peanut allergy and a personal or family history of atopy. The higher risk of familial peanut allergy may be in part related to delayed and reluctant introduction of peanuts to siblings of peanut-allergic children. Recent research suggests that delayed introduction of peanut into the diet is linked to higher rates of peanut allergies. The Learning Early About Peanut Allergy trial showed that introducing peanuts to children at age 4 months to 11 months decreased the risk of developing a peanut allergy in children at high risk. Once patients develop peanut allergy, only 20% to 25% develop tolerance; most maintain their allergy for life.

A new treatment option

Treatment of peanut allergy has been largely limited to educating patients and families about ingredient labeling and recommending complete avoidance of peanuts. Anaphylaxis caused by exposure to an allergen requires immediate treatment with epinephrine.

Oral immunotherapy is an emerging option offered by a limited number of allergists and immunologists. Although this therapy has shown some efficacy for food allergy desensitization, it has been criticized for lacking established protocols, having high rates of adverse reactions and using grocery store products that may contain variable amounts of the allergenic proteins.

In January 2020, the U.S. Food and Drug Administration (FDA) approved a novel peanut-derived oral immunotherapy product for treating childhood peanut allergy: Palforzia (peanut *Arachis hypogaea* allergen powder-dnfp). Containing a powder derived from roasted peanuts and packaged in capsules or sachets at varying doses, it is indicated for use in children 4 to 17 years old. The capsule or sachet is not swallowed. Instead, it is opened, and the powder is mixed with applesauce, pudding or something similar. It is given in dosing phases according to an oral immunotherapy protocol.



Patients should be cautioned that the FDA-approved oral immunotherapy product is **not a cure** for food allergies; instead, it is intended to **reduce their reactivity** to peanut.

Efficacy and safety

Safety and efficacy data for the peanut-allergen agent come from clinical trials that enrolled more than 700 patients who were allergic to peanuts.

In a phase 3 trial, 551 patients ages 4 to 55 with allergic dose-limiting symptoms at 100 mg or less of peanut protein (approximately one-third of a peanut kernel) were randomly assigned to receive the study drug or placebo in an escalating-dose protocol. Most patients (N = 496) were between ages 4 and 17, which reflects the FDA-approved age range.

Once participants reached the final study dose, they underwent a peanut challenge. The study drug recipients could ingest higher doses of peanut protein without dose-limiting symptoms than placebo recipients. The most common adverse reactions during treatment (incidence > 5%) were gastrointestinal, respiratory and skin symptoms and anaphylactic reactions.

This peanut-derived oral immunotherapy agent, like other forms of oral immunotherapy (which are not FDA approved), is not appropriate for patients with uncontrolled asthma, eosinophilic esophagitis or other eosinophilic gastrointestinal disease.

Adverse reactions are a leading reason for stopping oral immunotherapy. In the randomized controlled trial of peanut

allergen, 43 (11.6%) of the 362 patients assigned to the active treatment group withdrew because of adverse events.

Gastrointestinal disorders accounted for most of the adverse reaction-related discontinuations. Most discontinuations occurred during the escalation or up-dosing phases, with only a few patients withdrawing during the maintenance phase.

For those experiencing adverse reactions, the onset was typically rapid (median time four minutes after the dose), and symptoms resolved relatively quickly (median time 37 minutes). Thus, careful patient monitoring is crucial during the first hour after dosing. Additionally, dose escalation and up-dosing must be done in a medical setting with medical personnel experienced with oral immunotherapy and treatment of allergic reactions.

Patients should be cautioned that the FDA-approved oral immunotherapy product is not a cure for food allergies; instead, it is intended to reduce their reactivity to peanut. In the initial clinical trials, an exit challenge was included to approximate a real-life scenario of accidental ingestion.

Daily dosing important

Longitudinal studies are underway, with two-year data from an open-label follow-up study that suggest long-term efficacy of daily treatment with the peanut-derived oral immunotherapy

PHASE	DURATION	DOSAGE
Dose-escalation	Single day	5 levels: 0.5, 1, 1.5, 3 and 6 mg; increasing doses every 20-30 minutes
Up-dosing	Months	11 levels: 3, 6, 12, 20, 40, 80, 120, 160, 200, 240 and 300 mg daily; increasing doses at visits every 2 weeks
Maintenance	Months to years	300 mg daily

agent. Patients who received daily doses in the study showed greater immunomodulation and higher rates of desensitization that increased over time compared with patients given nondaily dosing. Furthermore, most patients in the daily-dosing groups had lower adverse event rates than those in the nondaily dosing groups.

All forms of oral immunotherapy carry the risk of life-threatening anaphylaxis. Oral immunotherapy has not been studied in pregnant women, and the risks to a fetus are unknown. Anaphylactic reactions could lead to hypotension and potential fetal demise.

Counseling needed

Patients and families must be carefully counseled on the signs and symptoms of anaphylaxis and carry auto-injectable epinephrine at all times. Strict avoidance of allergens, aside from daily oral immunotherapy dosing, is imperative. Illness, physical exertion around the time of dosing, and recent dental work or tooth loss may increase the risk of a reaction.

When identifying candidates for oral immunotherapy, consideration should be given to the capacity of the patient and family to adhere to the safety precautions and dosing regimens. This requires careful discussion of medication compliance, family support and ability to attend regularly scheduled appointments before initiating treatment. Patients with families who are not highly motivated to incorporate

the necessary lifestyle modifications are unlikely to be ideal candidates for therapy.

Please note: This is an abridged version of an article that originally appeared in Cleveland Clinic Journal of Medicine. To view it in its entirety, including a complete list of references, please visit ccjm.org/content/88/2/104.

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MORE PATIENTS WITH MYCOBACTERIUM AVIUM COMPLEX INFECTION COULD BENEFIT FROM LUNG SURGERY

It takes a multidisciplinary team to select candidates and optimize outcomes

KEY POINTS

The prevalence of MAC lung disease in the U.S. has increased significantly in the past 10-15 years as providers have become more aware of the disease and more likely to detect it through sputum culture or bronchoscopy as follow-up to an abnormal CT scan of the chest.

Surgery may be indicated when medical therapy fails and/or there is recurring infection, antibiotic resistance or antibiotic intolerance.

Even with the care of an expert team, only select patients with localized and refractory MAC infection are referred for surgery.

Long-term clearance rates of 95% at one year and 87% at three years after surgery have been reported.

Surgery is indeed a treatment option for select patients with *Mycobacterium avium* complex (MAC) pulmonary infection. Historically, surgical treatment was avoided, says Elliot Dasenbrook, MD, Director of Cleveland Clinic's Adult Cystic Fibrosis Program and the Bronchiectasis Center in the Respiratory Institute.

"There were a few reports of bad outcomes, which gave the impression that surgery for MAC may be ineffective or too risky," he says. "But in a multidisciplinary program — with a pulmonologist who augments the ability of the lungs to clear out infection, an infectious disease specialist who optimizes the antibiotic therapy, a dietitian to treat malnutrition and a surgeon who is highly experienced in lung resection — the outcomes are far better. It takes an expert team to select the patients most likely to benefit from surgery."

The prevalence of MAC lung disease in the U.S. has increased significantly in the past 10-15 years as providers have become more aware of the disease and more likely to detect it through sputum culture or bronchoscopy as follow-up to an abnormal CT scan of the chest, notes Dr. Dasenbrook. MAC is the most common type of nontuberculous mycobacterial infection.

"The more we see and learn about MAC, the more we can confirm that there are a number of patients who would do very well with surgery," he says.

Selecting surgical candidates

Surgery may be indicated when medical therapy fails and/or there is recurring infection, antibiotic resistance or antibiotic intolerance, explains Cyndee Miranda, MD, staff in the Department of Infectious Diseases.

"It also may be indicated to eliminate or reduce symptoms, including life-threatening hemoptysis — even if there is residual disease after resection," says Dr. Miranda. "For some patients, debulking of the most severe parenchymal damage may slow disease progression to other areas."

Even with the care of an expert team, only select patients with MAC infection are referred for surgery. In general, surgical candidates are patients with:

- › **LOCALIZED DISEASE.** If the MAC infection is in only one lobe or one lung, it is easier to treat surgically than if it is diffuse, affecting the top and bottom of both lungs.
- › **REFRACTORY DISEASE.** Because MAC infection is slow growing, antibiotic treatment can take up to 18 months. However, patients treated with airway clearance and antibiotics who still have infection after 12 months should be evaluated for surgery. The infection may be due to underlying structural lung problems, most commonly a cavity or space. Surgical removal of the structural abnormality can allow the body to eradicate residual infection more easily.

A pulmonary risk assessment, including clinical history and pulmonary function testing, is conducted for all surgical candidates. Risk of poor surgical outcomes is higher when forced expiratory volume in one second (FEV₁) is less than 70%.

Figure 1.

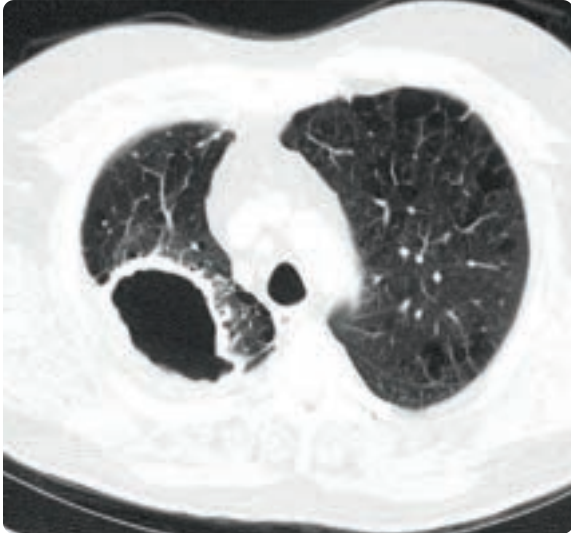


Figure 2.



LEFT. Focal bronchiectasis in the lingula (Figure 1). Nodular bronchiectatic changes of MAC lung disease (Figure 2).

Patients with low body mass index (which is common in chronic pulmonary infection, notes Dr. Dasenbrook) are likely not surgical candidates due to poor nutritional status and inability to tolerate the procedure.

Before, during and after surgery

“Patients are typically on antibiotic treatment, with oral, intravenous or inhaled antibiotics, for around eight to 12 weeks before surgery,” says Dr. Miranda. “This attempt to decrease bacterial count in the sputum helps minimize perioperative complications. Some patients with refractory disease have been on MAC treatment for several months or even years prior to surgery.”

Preoperative interventions also include pulmonary rehabilitation, as moderate to intense exercise helps improve aerobic capacity, physical fitness and quality of life in patients scheduled for lung surgery. While this rehab occurs over an average of four to six weeks in lung cancer, patients have an opportunity for months of exercise therapy before surgery for MAC due to the infection’s slow progression.

The most common types of pulmonary resection to treat MAC infection are lobectomy and segmentectomy, says thoracic surgeon Daniel Raymond, MD. Other procedures include pneumonectomy, partial resection and wedge resection.

“Limited resection is generally associated with better outcomes,” he says.

Postoperatively, antibiotics are still continued for 12 months after sputum culture conversion to negative, adds Dr. Miranda. Long-term clearance rates of 95% at one year and 87% at three years after surgery have been reported. However, there are also postoperative complications to consider, with postoperative mortality ranging from 0% to 23% and postoperative morbidity ranging from 0% to 50%.

“Pulmonary resection can be an integral part of an effective treatment regimen for MAC infection,” concludes Dr. Dasenbrook. “The key is referring patients to a medical center that is experienced in treating MAC, with a multidisciplinary approach to selecting surgical candidates and optimizing them before and after surgery.”

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Dr. Miranda is staff in the Department of Infectious Diseases and can be reached at 216.444.8845 or mirandc@ccf.org.

Dr. Raymond is staff in the Department of Thoracic and Cardiovascular Surgery in the Sydel and Arnold Miller Family Heart, Vascular & Thoracic Institute. He can be reached at 216.636.1623 or raymond3@ccf.org.

INTRANASAL CORTICOSTEROID USE AND COVID-19 OUTCOMES

Association highlights importance of the nose in infection

By Joe Zein, MD

KEY POINTS

Given the nose's critical role in the pandemic, our group studied whether intranasal corticosteroid (INCS) use suppresses viral load and receptor expression and is thus protective against hospitalization and death from COVID-19.

When compared with peers, users of INCS reported more symptoms but had lower risk for hospitalization, admission to the ICU and in-hospital death.

Our study is particularly significant because it demonstrates continued benefits after excluding patients who had used inhaled corticosteroids and with certain eosinophil counts.

INCS cannot be recommended to prevent or treat COVID-19 until we have the necessary data and approval.

The nose seems to be the major port of entry for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Nasal swabs detect higher viral loads compared with throat swabs,¹ and the highest expression of angiotensin converting enzyme 2 (ACE2), which the virus's spike protein engages as the entry receptor, is in the nose. Given the nose's critical role in the pandemic, our group recently conducted a study² in association with Ronald Strauss, MD, from the Cleveland Allergy and Asthma Center to determine whether intranasal corticosteroid (INCS) use suppresses viral load and receptor expression and is thus protective against hospitalization and death from coronavirus disease 2019 (COVID-19).

Determining the association

In a study funded by the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke, our research team used Cleveland Clinic's COVID-19 Research Registry (CCRR) to perform a propensity score matching for INCS treatment prior to infection with SARS-CoV-2 in 72,147 patients. These patients were registered from April 1, 2020, through March 31, 2021, at Cleveland Clinic. We measured endpoints of hospitalization, intensive care unit (ICU) admission and in-hospital mortality.

Just over 17% of patients were hospitalized, and about a third of those (4.1% of total) required ICU admission. A little over half of the patients admitted to the ICU died during hospitalization, 2.6% of included patients. Fourteen percent of

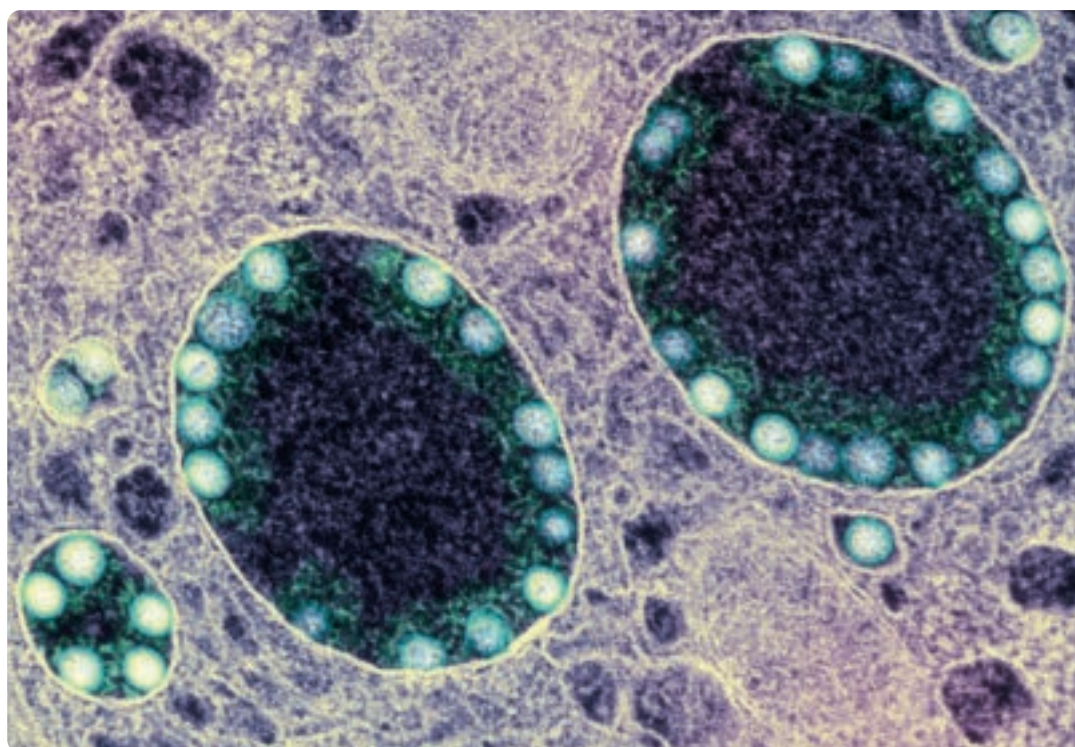
the overall cohort used INCS prior to SARS-CoV-2 infection (N = 10,187). Patients who used INCS were a bit older (52.07 vs. 50.33 years) and more likely to be female (64% vs. 53.3%) than nonusers.

When compared with peers, users of INCS reported more symptoms but had lower risk for hospitalization (adjusted OR [95% CI]: 0.78 [0.72-0.85]), admission to the ICU (adjusted OR [95% CI]: 0.77 [0.65-0.92]) and in-hospital death (adjusted OR [95% CI]: 0.76 [0.61-0.94]). In a sensitivity analysis, we were able to replicate findings after excluding patients on inhaled corticosteroids (ICS) and with allergic rhinitis. The positive impact of INCS remained significant after adjusting for pre-infection baseline blood eosinophil count in a subset of 30,289 patients.

Clinical implications

Previous studies have shown that patients with allergic rhinitis or asthma were hospitalized and ventilated less often, but those studies did not control for the use of ICS and absolute eosinophil counts. Adjusting for ICS usage is a crucial step, as it has been linked to decreased ACE2 expression in vitro. Our study is particularly significant because it demonstrates continued benefits after these adjustments.

The dominance of the B.1.617.2 variant, which has an even higher concentration of viral load in the nasal passages, brings a particular sense of urgency to corroborate our data through a



LEFT. Transmission electron micrograph of SARS-CoV-2 virus particles (teal) within endosomes of a heavily infected nasal olfactory epithelial cell. Image captured at the NIAID Integrated Research Facility in Fort Detrick, MD. Credit: NIAID.

OUTCOMES	NO INCS (N, %)	INCS	P VALUE
Hospitalization	10,932 (17.6)	1,676 (16.5)	0.003
Admission to the ICU	2,559 (4.1)	376 (3.7)	0.04
Hospital mortality	1,649 (2.7)	231 (2.3)	0.023

randomized clinical trial. If INCS use is indeed protective, we could reduce hospitalizations, mortality and healthcare resource utilization with an over-the-counter, well-tolerated and low-cost tool. However, until we have the necessary data and approval, INCS cannot be recommended to prevent or treat COVID-19 at this time.

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REFERENCES:

1. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med.* 2020;382(12):1177-1179.
2. Strauss R, Jawhari N, Attaway AH, et al. Intranasal corticosteroids are associated with better outcomes in coronavirus disease 2019 [published online ahead of print, 2021 Aug 23]. *J Allergy Clin Immunol Pract.* 2021;9(11):3934-3940.e9.

PULMONARY NONTUBERCULOUS MYCOBACTERIAL INFECTIONS AND NON-CYSTIC FIBROSIS BRONCHIECTASIS

How to diagnose and treat

By Joseph Khabbaza, MD

KEY POINTS

Patients with bronchiectasis are particularly susceptible to NTM infections because their airways have lost the ability to adequately clear secretions and the microorganisms found within the lungs.

A combination of nonspecific symptoms and a low index of clinical suspicion contributes to a significant delay in diagnosis for these patients.

Our multidisciplinary approach relies on frequent sputum cultures to develop tailored antibiotic regimens, respiratory therapy education to optimize aggressive airway clearance regimens, and adherence to the most up-to-date guidelines.

We place a very strong emphasis on designing and implementing an aggressive airway clearance regimen, even for patients with mild NTM infection.

The symptoms are nonspecific, and the treatment is often described to patients as worse than the disease. These are the realities facing patients with nontuberculous mycobacterial (NTM) pulmonary disease and the physicians who treat them.

Unfortunately, NTM pulmonary disease is underrecognized, underdiagnosed and undertreated. When a patient does receive a diagnosis, it is usually years after the onset of their symptoms. Diagnosis is challenging as symptoms tend to be attributed to underlying asthma or chronic obstructive pulmonary disease (COPD), or symptoms are those not traditionally associated with lung disease, such as fatigue, low appetite, weight loss, anxiety and night sweats.

Patients with bronchiectasis are particularly susceptible to NTM infections because their airways have lost the ability to adequately clear secretions and the microorganisms found within the lungs. Testing for and treating NTM infections in this population is particularly important because the earlier disease is recognized, the more likely treatment will result in a cure. Also, earlier treatment can slow the irreversible progression of bronchiectasis that chronic inflammation and infection are known to cause.

At Cleveland Clinic, we have a multidisciplinary approach that relies on frequent sputum cultures to develop tailored antibiotic regimens, respiratory therapy education to optimize aggressive airway clearance regimens and adherence to the most up-to-date guidelines on the treatment of NTM pulmonary diseases.

NTM lung disease

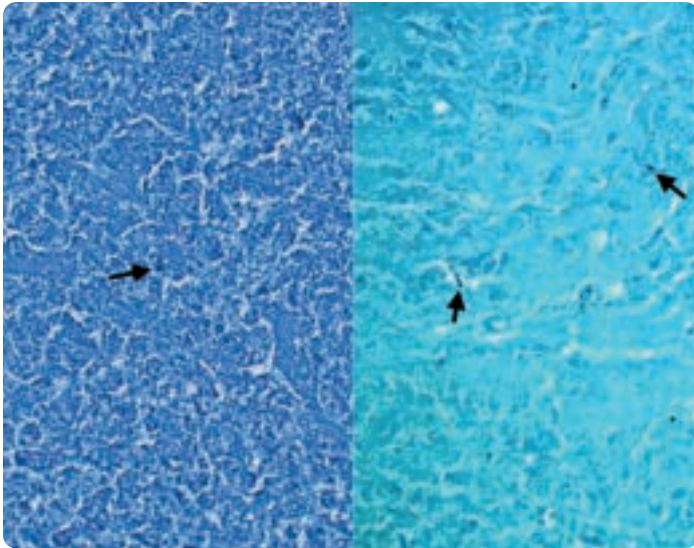
Pulmonary NTM infections due to organisms such as *Mycobacterium avium* complex

(MAC) and *Mycobacterium abscessus* are being diagnosed with increasing frequency. These organisms are commonly recovered on expectorated sputum cultures or bronchoscopic cultures obtained as part of an evaluation for an abnormal CT chest demonstrating multiple pulmonary nodules or bronchiectasis.

The diagnosis of NTM infection is often less than straightforward, and decisions regarding treatment of NTM infections can be complicated. Some patients have underlying chronic lung disease that may need to be addressed first. Often, their underlying lung disease is blamed for their symptoms, and NTM is disregarded. This approach is not ideal as NTM infection can cause flares of underlying lung disease; thus, treatment will lead to better control of their known chronic pulmonary conditions.

New guidelines published in 2020 emphasize the benefits of treatment earlier in most patients who meet criteria for lung disease as well as intensifying therapy if sputum cultures are still growing NTM despite six months of therapy. In the past, physicians steered patients away from treatment because the antibiotic regimens were felt to cause more burdensome symptoms than the NTM infection, but research has shown that earlier treatment allows patients to have a higher chance of cure and that antibiotic regimens are adequately tolerated in most.

BELOW. Mycobacteria (acid-fast bacteria, arrows) within the necrotizing granulomas [Ziehl-Neelsen stain].



Raising awareness to achieve earlier diagnosis

When I lecture on what I wish I had learned in training, I discuss the importance of recognizing and prevalence of NTM infections. A combination of nonspecific symptoms and a low index of clinical suspicion contributes to a significant delay in diagnosis for these patients. More than half have suffered one or two years, often much longer, before the diagnosis is made and treatment begins.

As clinicians, we must raise our awareness of these infections. When a patient presents with fatigue and low appetite, a slow-growing lung infection isn't usually on the radar. A patient with chronic cough and a clear X-ray often is suspicious for an indolent lung infection. If the cough does not respond to initial management, a CT chest is often beneficial to exclude NTM pulmonary disease as early nodular bronchiectatic changes often are not seen on standard radiographs.

Anyone who persistently or intermittently produces sputum who has an underlying lung disease is at risk of developing an NTM infection. Recurrent pneumonia is a big red flag for me. Since nontuberculous mycobacteria live in the alveolar macrophages, NTM lung disease will make a patient more prone to the usual types of pneumonia. If you have a patient on their second or third admission for pneumonia, add an acid-fast *bacillus* (AFB) sputum culture. Keep NTM in mind and check the cultures more than once. Know the nonspecific symptoms and know that a chest X-ray may not show mild disease.

Treatment regimen at Cleveland Clinic

Our first principle in successfully diagnosing NTM infections is doing frequent bacterial and AFB sputum cultures in those patients with both symptoms and imaging changes consistent with disease. We want to know what is growing in a patient's lungs over time. If obtaining sputum is not possible during a clinic visit, we send our patients home with a labeled sputum cup, and they drop off a sample at their convenience. For patients who don't make sputum easily, our respiratory therapists will help obtain an induced sputum sample, which can help avoid a bronchoscopy. We look for trends in the microbiology of each patient's airways and tailor antibiotic regimens to specific organisms.

We also place a very strong emphasis on designing and implementing an aggressive airway clearance regimen, even for patients with mild NTM infection. We utilize a combination of inhaled and external clearance mechanisms, from bronchodilators and hypertonic saline through a nebulizer to the Portex® acapella® Vibratory PEP and high-frequency chest wall oscillation devices. Our respiratory therapists educate patients on other modalities of airway clearance such as huff coughing. We pay special attention to patients whose COPD or asthma medications may actually impair airway clearance and optimize regimens accordingly. Pulmonary rehabilitation and patient education from respiratory therapists also play critical roles in successful long-term treatment.

As a Center of Excellence for bronchiectasis, we diagnose and treat many patients with NTM pulmonary infections. We have a multidisciplinary group of physicians and surgeons focused on both the lung disease and the infection by ensuring an optimal airway clearance regimen in addition to adherence to guideline-based antibiotic therapy. To refer a patient, call 216.445.3082.

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SELECTED CLINICAL STUDIES

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Food Allergy Center of Excellence Registry

Principal Investigator: Sandra Hong, MD

Study Coordinator: Sheffa Almahd, RRT | 216.444.3766

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COPD

Roflumilast or Azithromycin to Prevent COPD Exacerbations (RELIANCE)

Principal Investigator: Umur Hatipoglu, MD

Study Coordinator: Erica Corrao, RRT | 216.444.0843

A Sham Controlled Prospective Randomized Clinical Trial of the RejuvenAir® System for the Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease with Chronic Bronchitis (SPRAY-CB)

Principal Investigator: Thomas Gildea, MD

Study Coordinator: Yvonne Meli, RN, BC, CCRP | 216.445.4215

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CRITICAL CARE MEDICINE

A Protocol Comparing Temporary Transvenous Diaphragm Pacing to Standard of Care for Weaning from Mechanical Ventilation in ICU Patients (RESCUE 3)

Principal Investigator: Tarik Hanane, MD

Study Coordinator: Bryan Poynter | 216.445.1630

Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness: A Randomized Controlled Trial (BALANCE)

Principal Investigator: Abhijit Duggal, MD

Study Coordinator: Bryan Poynter | 216.445.1630

Cooling to Help Injured Lungs (CHILL) Phase IIb Randomized Control Trial of Therapeutic Hypothermia in Patients with ARDS

Principal Investigators: Abhijit Duggal, MD, and Rachel Scheraga, MD

Study Coordinator: Connery Brennan | 216.445.3960

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CYSTIC FIBROSIS

A Phase 4 Study to Compare US Marketed Creon® Drug Product with Drug Product Manufactured with a Modernized Process at an Alternate Manufacturing Site, in Subjects with EPI due to Cystic Fibrosis

Principal Investigator: Elliott Dasenbrook, MD

Study Coordinator: David Weaver, BSN, CCRC | 216.445.6671

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INFECTIOUS DISEASE

Prospective Observational Study of Human Immunodeficiency Virus (HIV) Positive Deceased Donor Renal Transplantation for HIV-Positive Recipients

Principal Investigator: Christine Koval, MD

Study Coordinator: Kiran Ashok | 216.445.6744

A Phase 2, Randomized, Double-Blind Placebo-Controlled Study of NPC-21 for Kidney Transplant Recipients at High-Risk of Cytomegalovirus Infection (LIONHEART21)

Principal Investigator: Aneela Majeed, MD

Study Coordinator: Kiran Ashok | 216.538.9139

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INTERSTITIAL LUNG DISEASE

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

Principal Investigator: Daniel Culver, DO

Study Coordinator: Sue Gole, RRT | 216.445.5836

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LUNG CANCER

DECAMP 1 PLUS Proposal: Prediction of Lung Cancer Using Noninvasive Biomarkers

Principal Investigator: Peter Mazzone, MD

Study Coordinator: Stuart Houltham | 216.444.1056

DNA Evaluation of Fragments for Early Interception – Lung Cancer Training Study (DELFI-L101 Study)

Principal Investigator: Peter Mazzone, MD

Study Coordinator: Brian Smith | 216.444.0679

Nodify XL2 Classifier Clinical Utility Study in Low to Moderate Risk Lung Nodules (ALTITUDE)

Principal Investigator: Peter Mazzone, MD

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)

Principal Investigator: Marie Budev, DO, MPH

Study Coordinator: Hannah Johnson | 216.444.0109

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)

Principal Investigator: Marie Budev, DO, MPH

Study Coordinator: JoAnne Baran-Smile, BSN, RN | 216.444.5023

Cleveland Clinic Lung Transplant Biorepository

Principal Investigator: Maryam Valapour, MD

Study Coordinator: Erin McNamee | 216.445.9432

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PULMONARY HYPERTENSION

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)

Principal Investigator: Joseph Parambil, MD

Study Coordinator: Mary Beukemann | 216.444.2140

SELEXipag in Inoperable or Persistent/Recurrent Chronic Thromboembolic Pulmonary Hypertension (SELECT)

Principal Investigator: Gustavo Heresi, MD

Study Coordinator: Julia Ashton | 216.445.7075

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RARE LUNG DISEASES

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alvelestat (MPH996) for the Treatment of ALpha-1 ANTITrypsin Deficiency (ATALANTa)

Principal Investigators: Umur Hatipoglu, MD, and James Stoller, MD

Study Coordinator: Erica Corrao, RRT | 216.444.0843

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BRONCHIECTASIS

Clinical Effectiveness of High Frequency Chest Wall Oscillation (HFCWO) in a Bronchiectasis Population

Principal Investigator: Elliott Dasenbrook, MD

Study Coordinator: Sheffa Almahd, RRT | 216.444.3766

ENCORE – A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Evaluate the Efficacy and Safety of an Amikacin Liposome Inhalation Suspension (ALIS)-Based Regimen in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by Mycobacterium avium Complex (MAC)

Principal Investigator: Elliott Dasenbrook, MD

Study Coordinator: Sheffa Almahd, RRT | 216.444.3766

ASPEN – A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of INS1007 Administered Once Daily for 52 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis

Principal Investigator: Elliot Dasenbrook, MD

Study Coordinator: Sheffa Almahd, RRT | 216.444.3766

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PULMONARY ALVEOLAR PROTEINOSIS

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Once-Daily Inhaled Molgramostim Nebulizer Solution in Adult Subjects with Autoimmune Pulmonary Alveolar Proteinosis (aPAP)

Principal Investigator: Leslie Tolle, MD

Study Coordinator: Sue Gole, RRT | 216.445.5836

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SARCOIDOSIS

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study in Participants with Sarcoidosis-Associated Pulmonary Hypertension (SAPH) to Assess the Efficacy and Safety of Oral Selexipag

Principal Investigator: Joseph Parambil, MD

Study Coordinators:

Mary Beukemann | 216.444.2140

Shweta Josh | 216.445.7291

ACTHAR Gel for Cutaneous Sarcoidosis

Principal Investigator: Manuel Ribeiro, MD

Study Coordinator: JoAnne Baran-Smile, BSN, RN | 216.444.5023

Routine Cardiac Screening in Sarcoidosis Patients (PAPLAND)

Principal Investigator: Daniel Culver, DO

Study Coordinator: Shweta Josh | 216.445.7291



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