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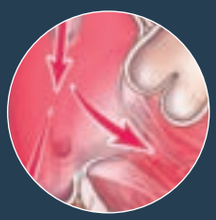

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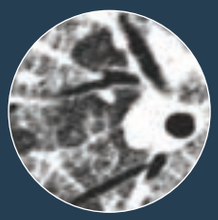

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Cleveland Clinic

Respiratory Exchange

Research and News for Physicians from Cleveland Clinic's Respiratory Institute

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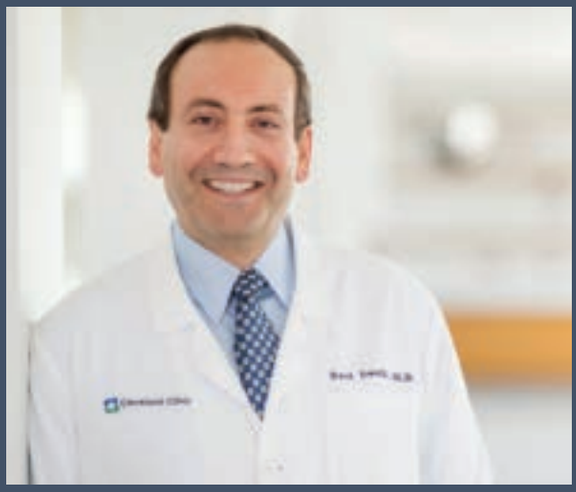
Dear Colleagues:

The vast array of clinical, research and education activities that occur daily in our large respiratory practice aren't always easy to convey in a single issue of *Respiratory Exchange*. However, this issue is particularly representative of the wide range of interests and expertise in our institute's four departments of pulmonary medicine, critical care medicine, allergy and clinical immunology and infectious diseases.

In this issue, you'll find how our experts are:

- Using venovenous extracorporeal membrane oxygenation in patients with lung failure (p. 3).
- Optimizing the care of patients with COPD by using electronic inhaler monitoring (p. 6).
- Addressing airway complications after lung transplantation (p. 8).
- Managing patients with difficult-to-treat pulmonary nontuberculous mycobacterial infections (p. 10).
- Treating patients with the rare disorder pulmonary alveolar proteinosis (p. 12).
- Participating in three major multicenter trials to expand therapeutic approaches for pulmonary complications of rheumatic disease (p. 15).
- Studying how omalizumab can block aspirin-provoked respiratory reaction during aspirin desensitization (p. 18).
- Investigating how beta blockers may help treat pulmonary arterial hypertension (p. 20).
- Using simulations to improve the training for pulmonary artery catheter placement and management (p. 22).
- Preparing the next generation of medical educators with a new master's in health professions education program (p. 24).



I am as excited about assuming my new role as Chairman of Cleveland Clinic's Respiratory Institute as I am humbled to follow in the footsteps of Herbert P. Wiedemann, MD, MBA, who masterfully led the institute for more than a decade.

In my 25 years at Cleveland Clinic, 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. These experiences helped me understand and appreciate the inherent value of each one of these missions and the importance of teamwork to seamlessly integrate them in a synergistic way that amplifies their combined value. This synergy allows us to provide the best care not only for the patient of today, but also the patient of tomorrow.

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

Sincerely,

Raed Dweik, MD, MBA
CHAIRMAN | CLEVELAND CLINIC RESPIRATORY INSTITUTE

Extracorporeal Membrane Oxygenation for Lung Failure

VV ECMO AT CLEVELAND CLINIC

By Sudhir Krishnan, MD

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is a temporary mechanical assistance device that allows for prolonged cardiopulmonary support. A modification of the cardiopulmonary bypass machine, it is instituted in patients with life-threatening respiratory failure (predicted mortality 80 percent). ECMO is considered for patients with potentially reversible forms of respiratory failure and as a bridge to lung transplantation for suitable candidates with irreversible disease. The respiratory ECMO service at Cleveland Clinic was recently established as a 24/7 on-call service that facilitates the use of VV ECMO to manage ventilatory failure (refractory hypoxemia or hypercarbia) that is not amenable to conventional ventilatory support and adjunctive therapy (e.g., neuromuscular paralysis and prone ventilation).

ECMO CIRCUIT

The VV ECMO circuit (in its rudimentary form) consists of specialized cannulae attached to a conduit tubing connected to a centrifugal pump. Venous blood is siphoned into an extracorporeal artificial membrane oxygenator, and oxygenated blood is returned to the systemic venous circulation (Figure 1). The oxygenator consists of numerous low-resistance, hollow, nonmicroporous fibers that allow for oxygen transfer across a semipermeable membrane from gas to blood interphase (Figure 2). VV ECMO improves systemic oxygenation and provides for a reduction in ventilatory inflation pressures, thereby decreasing ventilator-induced lung injury and facilitating lung recovery. VV ECMO does not support systemic circulation or alter hemodynamics, in contrast to venoarterial ECMO.

PATIENT SELECTION

ECMO is a resource-intensive endeavor associated with a high mortality rate (approximately 50 percent). In order to maximize the utility of this modality, its application should be restricted to those patients with a reasonable likelihood of survival either with supportive care (bridge to recovery) or lung transplantation (bridge to transplant). Initiation of ECMO as a desperation measure should be avoided when factors suggesting futility are present. However, identifying patients with a reversible underlying condition is often a contentious and challenging task. Cleveland Clinic's respiratory ECMO program uses a selection process that identifies patients with an overall favorable prognosis who are likely to return to a highly independent functional status. Appropriate timing, stringent selection criteria and the use of clinical prediction models to estimate the likelihood of survival are integral to the process. Decisions about initiation of ECMO are made within the framework of active communication between the MICU team, medical and surgical ECMO staff, and the patient's surrogate decision makers.

ECMO MULTIDISCIPLINARY ROUNDS

Our medical ECMO team is staffed by members of our pulmonary and critical care departments who have expertise in a wide range of pulmonary disorders, management of respiratory failure and lung transplantation. Bedside rounds are conducted in conjunction with members of the surgical ECMO team and anesthesia critical care team as well as respiratory therapists, perfusionists and pharmacists. This multidisciplinary

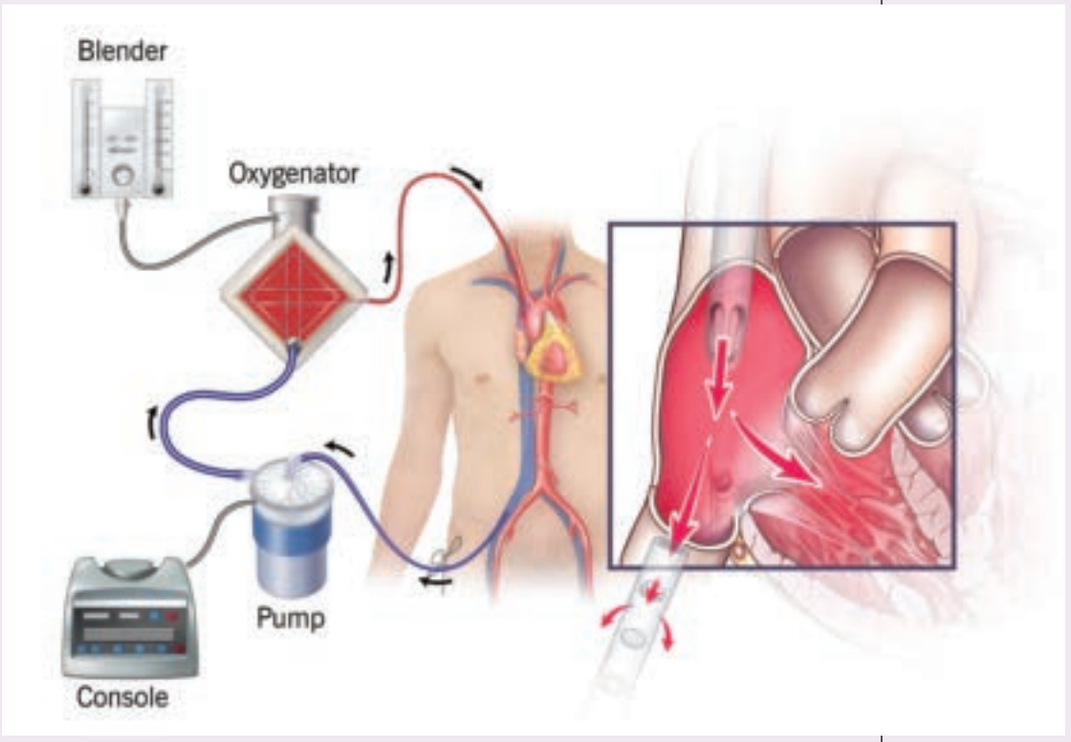


Figure 1. Venous blood is siphoned into the ECMO, and oxygenated blood is returned to the systemic venous circulation.

medical/surgical ECMO team is involved in decisions about initiation of ECMO, management of the patient while on the device, and decisions to decannulate and transition to conventional ventilatory support or palliative care.

Recognizing that ECMO survivors face a long and often arduous road to full recovery, staff from our Department of Critical Care Medicine have initiated a post-ECMO care program. This involves a team that follows these patients after transfer out of the ICU until hospital discharge as well as the establishment of a post-ICU outpatient clinic to transition their care to the ambulatory setting and to address residual pulmonary, neuromuscular, cognitive and psychological dysfunction.

NEXT STEPS FOR VV ECMO AT CLEVELAND CLINIC

While awaiting the outcome of large clinical trials aimed at defining the group of patients most likely to benefit from ECMO, we will continue our judicious application of the modality to critically ill patients who are failing conventional support measures and whose disease is either deemed potentially reversible or amenable to transplant.

With our extensive experience with ECMO at Cleveland Clinic, we are poised to expand the role of this intervention as warranted by demonstration of efficacy. We believe that our dedicated ECMO team, multidisciplinary approach and commitment to provide longitudinal inpatient and outpatient care maximize the chances of successful outcome, minimize practice variation and avoid the indiscriminate use of this evolving technology.

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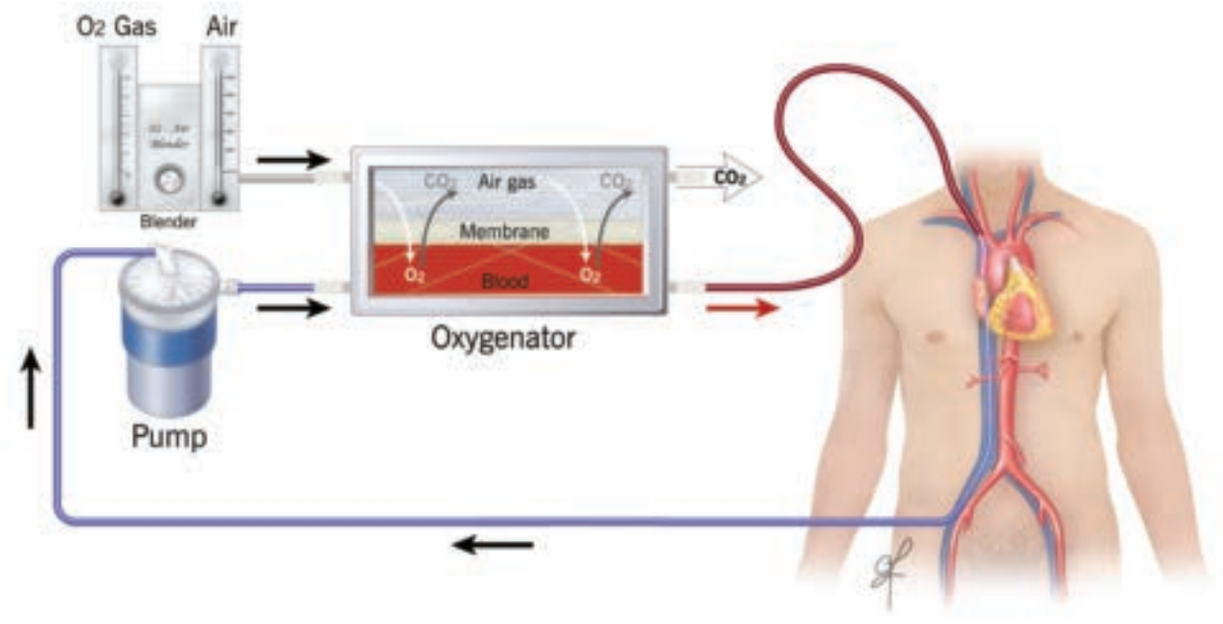

Figure 2. The oxygenator consists of numerous low-resistance, hollow, nonmicroporous fibers that allow for oxygen transfer across a semipermeable membrane from gas to blood interphase.

CASE STUDY: REFRACTORY HYPOXEMIA SECONDARY TO ILD EXACERBATION

A 37-year-old female with obesity and a history of unspecified interstitial lung disease (ILD) on long-term oxygen therapy and empiric steroids and mycophenolate is transferred to the MICU for monitoring following an uncomplicated surgical lung biopsy. Over the next 48 hours, she develops worsening hypoxemic respiratory failure necessitating mechanical ventilation. The lung biopsy reveals acute fibrinous organizing pneumonia. Despite high-dose steroid therapy, her situation deteriorates over the following week, resulting in severe hypoxemia (P/F < 60) refractory to low tidal volume and high PEEP strategy, neuromuscular blockade, prone ventilation and inhaled prostacyclin therapy. The multidisciplinary ECMO team convenes, reviews the available data and commits the patient to VV ECMO as a bridge to recovery. Her clinical course is further complicated by septic shock, ICU delirium, acute kidney injury and alveolar hemorrhage. Despite this, she eventually improves and is successfully removed from ECMO after 33 days and from mechanical ventilation four weeks thereafter. Three months following discharge from the hospital, she is seen in the outpatient clinic, where she is noted to have returned to her baseline functional status.

TABLE 1. Patient Selections for VV ECMO — Clinical Scenarios in Which Use of ECMO Should Be Considered

A	Respiratory failure secondary to potentially reversible etiology (hypoxemia/hypercapnia/combination)
1	ARDS with primary lung injury secondary to infection, aspiration or direct trauma
2	Primary graft dysfunction following lung transplantation
3	Pulmonary parenchymal or vascular disease exacerbation (COPD, ILD, vasculitis)
4	Traumatic lung injury
5	Massive pulmonary embolus
6	Inability to ventilate due to temporary airway compromise (traumatic, surgical, pathologic)
B	Respiratory failure secondary to irreversible etiology (hypoxemia/hypercapnia/combination)
1	ECMO as a bridge to lung transplantation

TABLE 2. Clinical Triggers for VV ECMO

	Acute severe respiratory failure with refractory hypoxemia and hypercarbia despite maximal conventional therapy
1	P/F < 60 with FiO_2 > 0.8 with conventional mechanical ventilation with/without use of rescue therapies
2	Murray score ≥ 3 (mortality risk > 80% with conventional management)
3	Ph ≤ 7.25 despite optimal mechanical ventilator setting
4	Uncorrectable hypercarbia with pH < 7 and peak inspiratory pressure > 45, or $PaCO_2$ > 45 despite minute ventilation > 200 ml/kg/min

Electronic Inhaler Monitoring at the Respiratory Institute

By Amy Attaway, MD, and Umur Hatipoğlu, MD

Electronic inhaler monitoring (EIM) is a novel modality that enables real-time assessment of adherence to inhaled therapy. EIM systems generally consist of sensors placed on inhalers that record the time of administration for inhaled medications coupled with cloud-based data analytics and mobile and computer-based user interfaces. They may include reminders to patients when doses are missed. Through interactive user interfaces accessible via computers or cellphones, providers and patients can track medication utilization patterns.

Adherence data, shared with the provider and available at the point of care, facilitate discussions between the provider and patient. Methods proven effective in fostering adherence, such as shared decision-making and educational interventions, can be implemented with more confidence. EIM also can inform the assessment of treatment effectiveness. For instance, a patient whose disease is poorly controlled and whose adherence to medications is poor should benefit from interventions that foster adherence. On the other hand, patients whose disease is not adequately controlled in the face of satisfactory adherence should be considered for augmentation of their treatment regimen.

Most of the EIM studies performed in the clinical arena have involved asthma patients. In an elegant study by Foster and colleagues,[1] 143 subjects with asthma were randomized into four groups involving:

1. Usual care only.
2. Reminders for inhaler usage.
3. Personalized adherence discussions.
4. Reminders for inhaler usage and personalized adherence discussions.

All groups were given an EIM, and their adherence was tracked via the device for the study's six-month period. The investigators found that adherence was higher in the groups that had access to inhaler reminders compared with the groups for whom reminders were not offered (73 +/- 26 percent of prescribed doses versus 46 +/- 28 percent; $P < 0.0001$). Although all groups experienced similar improvement in overall asthma control, a smaller proportion of patients in the inhaler reminder groups experienced severe exacerbations compared with nonreminder groups.

Sulaiman and colleagues combined EIM with inhaler technique feedback, using previously validated digital audio recordings of flow pattern to assess technique.[2] Adult subjects (N = 218) with severe uncontrolled asthma were block randomized to intensive education versus biofeedback. Both groups received EIM. In the intensive education group, patients received instruction for optimal inhaler technique based on a checklist. The biofeedback group received training and instruction based on EIM-collected data to reinforce regular dosing intervals and improve inhaler technique. At the three-month point in the study, adherence among the subjects in the biofeedback group was significantly higher than that of the intensive education group (74 and 64 percent, respectively; $P < 0.007$). Errors in inhaler technique were common in both groups and included low peak inspiratory flow (50 percent of errors) and exhalation into the Diskus® inhaler before inhalation (39 percent of errors).

In this study, EIM also allowed the clinicians to combine adherence data with disease control status to fine-tune treatment. For instance, nonadherent patients who had poor disease control would receive interventions that target better adherence. On the other hand, patients with good adherence and poor disease control would need escalation of treatment.

The Respiratory Institute's Center for Comprehensive Care in COPD has piloted an EIM program that enrolled COPD patients who had a hospital admission or ED visit due to COPD exacerbation during the prior year. Our experience suggests good acceptance of EIM by patients and higher medication adherence rates than what has been reported in the literature for patients with COPD. We recently reported the preliminary healthcare utilization data from this cohort at the 2018 American Thoracic Society Annual Meeting. Among the 20 patients who completed at least six months of monitoring, annualized all-cause hospitalizations and ED visits were reduced (5.2 + 3.5 visits pre-implementation versus 3.2 + 2.3 post-implementation; $P = 0.034$). Annualized COPD-related hospitalizations and ED visits were lower as well although this did not achieve statistical significance (3.9 + 3.2 visits pre-implementation versus 2.3 + 2.2 post-implementation; $P = 0.07$).[3]

Studies published to date suggest benefit from EIM in poorly controlled asthma patients. It is highly plausible that this benefit would extend to patients with COPD who have poor adherence and high healthcare utilization. Additionally, EIM-guided protocols could provide a practical, in-office approach to objectively assessing adherence and inhaler technique.

While EIM appears promising, further studies are necessary to understand how best to implement the technique and

which populations to target with the intervention. The Center for Comprehensive Care in COPD will continue to investigate the utility of EIM in optimizing the care of our patients.

To refer a patient to the Center for Comprehensive Care in COPD, call 855.REFER.123.

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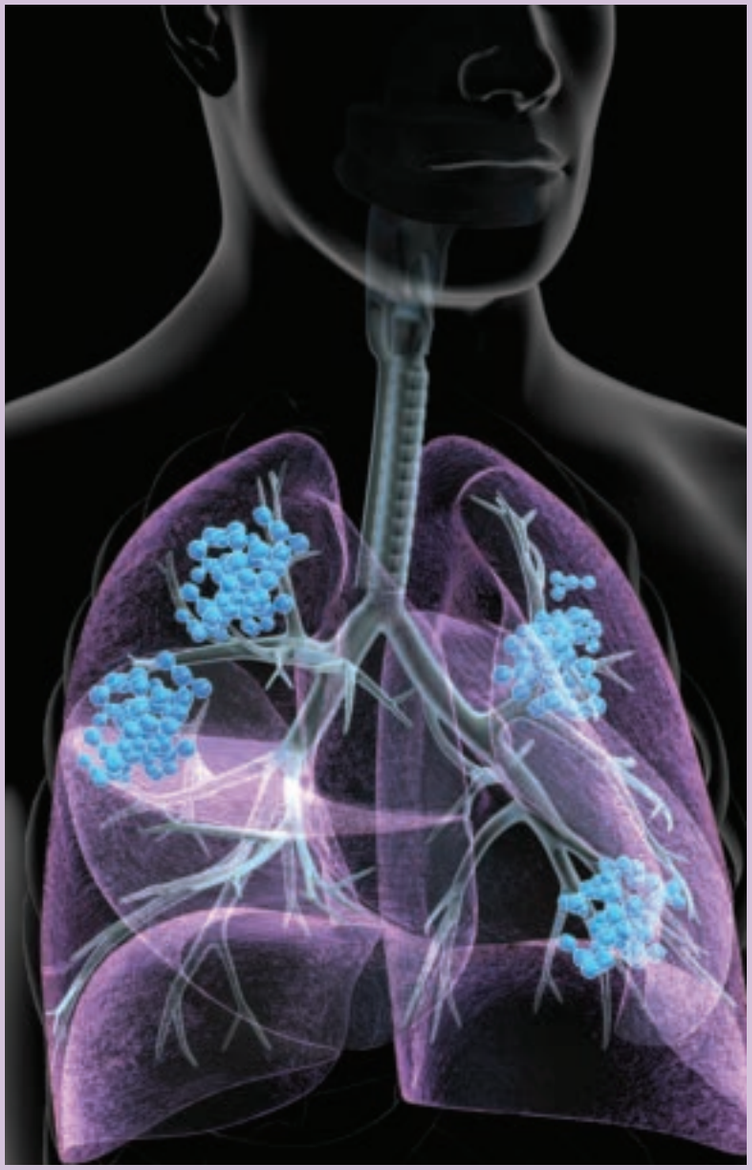

Airway Complications After Lung Transplantation

TAKING STEPS TOWARD STANDARDIZING PREVENTION AND MANAGEMENT

By Marie Budev, DO, MPH, and Michael Machuzak, MD

Early in the history of lung transplantation, airway complications were recognized as a major contributor to morbidity and mortality. Improvements in lung preservation, surgical techniques and perioperative management have led to a decrease in the incidence of airway complications, but they continue to adversely impact outcomes following transplantation.[1] The incidence of airway complications has been reported to be in the range of 2 to 18 percent, with this marked variability attributed to lack of standardized definitions for diagnosis.[2,3]

Airway complications, in the form of dehiscence, stenosis or malacia, most commonly involve the bronchial anastomosis, but the latter two complications also can involve the bronchial tree distal to the anastomosis. While initially encountered in the early post-transplant period, airway complications can persist as a chronic problem throughout the post-transplant course.

Recently, we were invited by the International Society for Heart and Lung Transplantation to join the Airway Complications Workgroup, composed of experts in lung transplantation and interventional pulmonology from around the world. The Airway Complications Workgroup developed and published the first consensus statement on airway complications after lung transplantation.[3] This consensus statement provides clear definitions of the common airway complications and also proposes a new adult and pediatric grading system based on the location and extent of ischemic injury, dehiscence and stenosis.

In addition to standardizing definitions and grading of complications, the intent of the consensus statement is to facilitate dialogue between pulmonologists and interventional bronchoscopy teams in developing standardized approaches to prevention and management of these complications. With extensive experience in both lung transplantation and interventional pulmonology, Cleveland Clinic physicians and surgeons have been at the forefront of developing strategies to address airway complications.

Our surgeons pioneered and investigated the impact of bronchial artery revascularization in reducing the risk of airway complications. Our interventional pulmonologists perform more than 250 procedures annually for airway complications after transplantation and also benefit from extensive experience in treating other benign and malignant airway disorders. This experience has allowed our team to introduce novel approaches, including use of uncovered metallic stents[4] and amniotic membrane grafts[5] in treating bronchial dehiscence after transplantation. Additionally, technical innovations such as in vivo modification of stents and custom 3D-printed stents developed by our team for airway complications in other patient populations now can be applied to management of post-transplant airway complications (Figure).

The combination of a successful, high-volume lung transplant program and an experienced interventional pulmonology team has positioned Cleveland Clinic to be a leader in the management of post-transplant airway complications. Through experience and innovation, we hope not only to develop effective treatment strategies but also techniques to mitigate the risk of developing these complications.

Dr. Budev (budevm@ccf.org; 216.444.3194) is the Medical Director of Lung Transplantation and holds the Macon and Joan Brock Endowed Chair for Lung Transplantation.

Dr. Machuzak (machuzm@ccf.org; 216.444.2718) is staff in the Department of Pulmonary Medicine.

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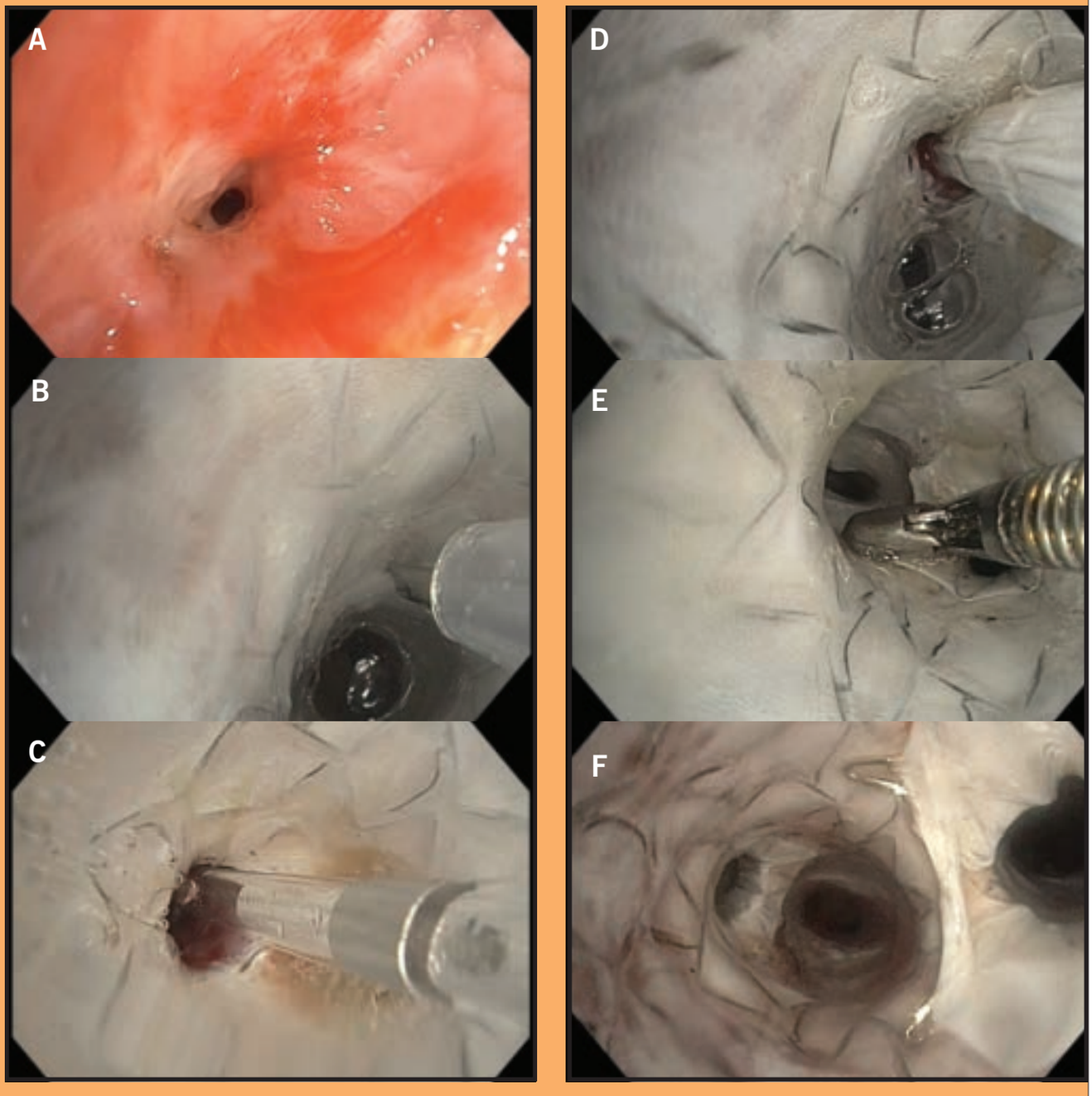

Figure. Severe refractory bronchial stenosis status post bilateral lung transplant. Patient suffered from severe stenosis refractory to standard techniques. Stenosis involved right bronchus intermedius, right middle lobe (RML) and right lower lobe superior segment. Multiple attempts were made to preserve segments. In vivo stenting allowed for two additional years of airway patency with reduced procedures until patient unfortunately died in a motor vehicle accident almost eight years after transplant.

A. Severe bronchial stenosis status post transplant, refractory to standard techniques.

B. Primary stent is placed, and needle is used to poke hole in location of RML.

C. Balloon dilation of newly created "airway" to RML.

D. Stent-in-stent placement.

E. Minor adjustments made to stent allowing for ideal fit.

F. Final result.

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Pulmonary Nontuberculous Mycobacterial Infections

A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

By Elliott Dasenbrook, MD, and Cyndee Miranda, MD

Pulmonary nontuberculous mycobacterial (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 sputum or bronchoscopic cultures obtained as part of an evaluation for an abnormal CT scan of the chest demonstrating multiple pulmonary nodules or bronchiectasis (Figure).

The diagnosis of NTM infection is often less than straightforward, and decisions regarding treatment can be complicated. Sometimes patients have underlying chronic lung disease that may need to be addressed first. Expert consultation is often warranted.

DIAGNOSIS OF NTM LUNG DISEASE

Both clinical and microbiologic criteria must be met for a diagnosis of NTM lung disease. Diagnostic benchmarks from the American Thoracic Society and Infectious Diseases Society of America help differentiate true infection from a transient infection or colonization (Table 1).

It is important to note that since patients with NTM infections frequently have underlying chronic pulmonary conditions, these should be treated first. For example, patients with bronchiectasis may be coinfected with *Pseudomonas aeruginosa*. Clinicians should consider treating the *P. aeruginosa* first, then re-evaluate the symptoms and imaging.

DIAGNOSIS DOES NOT IMPLY TREATMENT

Discovery of NTM lung disease does not necessarily mean physicians should immediately begin treatment. Lung disease from these infections progresses slowly, so there is time to evaluate whether an NTM infection or a transient infection or colonization is responsible for the patient's clinical symptoms and/or radiographic abnormalities.

If clinical and microbiologic criteria are met, then clinicians can discuss with the patient the risks and benefits of therapy. The length of drug therapy is typically at least 12 months from the time cultures have turned negative. The medication regimen requires monthly monitoring, and patients often report difficulty managing the gastrointestinal side effects.

IMPORTANCE OF AIRWAY CLEARANCE

The majority of patients with pulmonary NTM infections have underlying lung disease such as bronchiectasis, chronic obstructive pulmonary disease and cystic fibrosis. In addition to treatment of the airway infection, it is important to address airway clearance. A frequently used, twice-daily regimen for airway clearance consists of nebulized albuterol followed by nebulized hypertonic saline (3 or 7 percent), and then use of a positive expiratory pressure device with airway vibration, such as the acapella® Vibratory PEP Therapy System (Table 2).

In addition, many patients will mobilize secretions with exercise. If a patient qualifies for pulmonary rehabilitation, this is an excellent option. If they do not qualify, then clinicians can suggest a program consisting of cardiovascular and core strengthening with a goal of 150 minutes per week.

TREATMENT: WHEN TO CONSIDER EXPERT CONSULTATION

Medical regimens for NTM infections are complex. They can consist of oral, intravenous and inhaled antibiotics that are not routinely encountered in clinical practice, and monitoring for side effects and toxicities should occur at least monthly. Thus, outside expertise may be needed.

The following situations may warrant referral:

- Patients with macrolide-resistant MAC, who may require additional second-line agents.
- Refractory MAC patients — Individuals, for instance, who are treated for at least six months with appropriate therapy (most commonly ethambutol, rifampin and azithromycin) for MAC lung disease and remain culture positive.
- Patients who are culture positive for *M. abscessus* or other less common NTM infections.
- Patients for whom surgery is being considered as an adjunct to medical therapy.
- Patients who are immunocompromised.

At Cleveland Clinic, our NTM program brings together experts from infectious disease, pulmonary medicine and respiratory therapy who collaborate with patients in the diagnosis and treatment of these difficult-to-treat pulmonary NTM infections.

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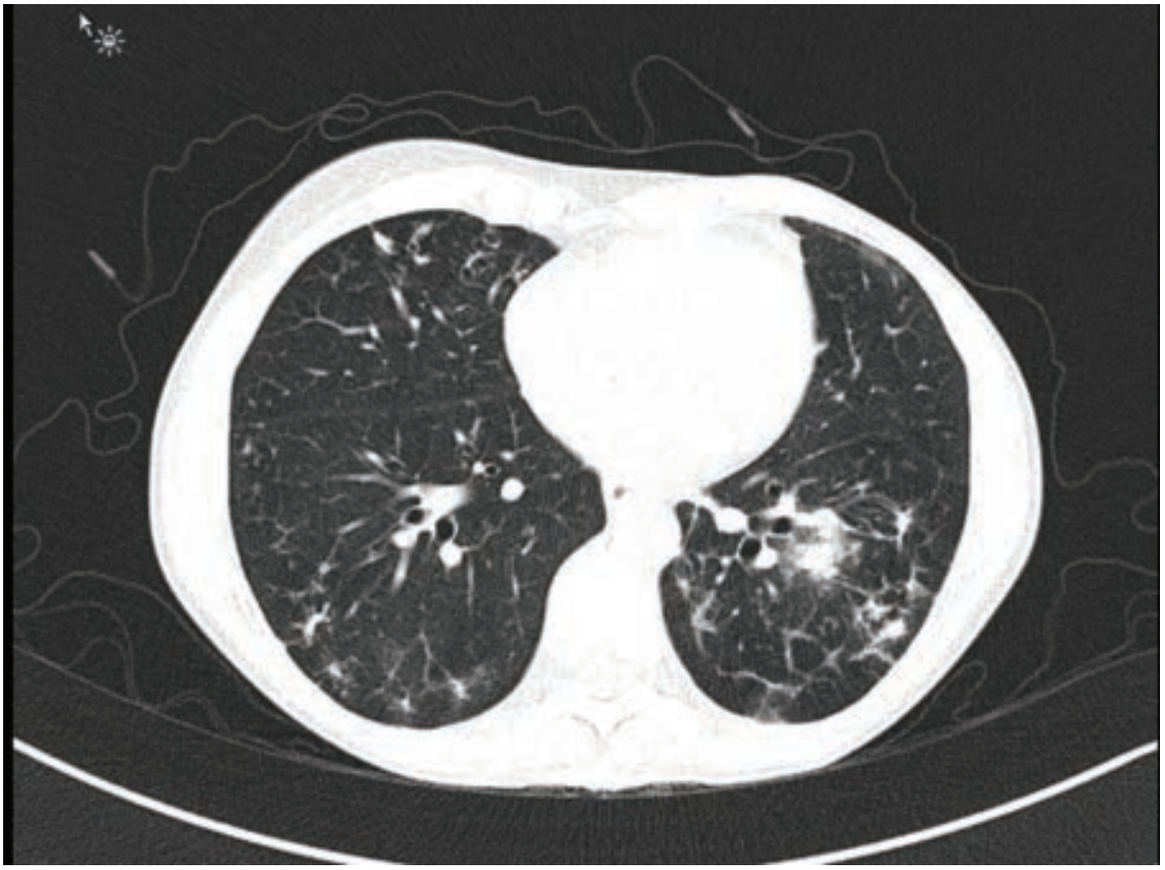

Figure. Thoracic computed tomography of a patient with MAC lung disease and characteristic radiologic findings of centrilobular nodules and bronchiectatic disease in the right middle lobe and lingula.

Table 1. Diagnosis of Nontuberculous Mycobacterial Lung Disease
CLINICAL
1. Pulmonary symptoms (cough, mucus production, fevers, night sweats, fatigue) OR
Imaging (nodular or cavitary opacities) OR
High-resolution CT scan (multifocal bronchiectasis with multiple small nodules) and
2. Exclusion of other diagnoses
MICROBIOLOGIC
1. At least two separate expectorated sputum samples OR
A single bronchial wash or lavage OR
Positive lung biopsy

Table 2. Order of Twice-Daily Airway Clearance
1. Nebulized albuterol
2. Nebulized 3% or 7% hypertonic saline
3. Device (such as acapella Vibratory PEP Therapy System)
4. Inhaled antibiotics (if indicated)
5. Inhaled corticosteroids (if indicated)

Table 1. Diagnostic benchmarks for NTM infection from the American Thoracic Society and Infectious Diseases Society of America.

Table 2. Twice-daily regimen for airway clearance.

Pulmonary Alveolar Proteinosis: A Rare Lung Disease

AN OVERVIEW OF PAP AND OUR TREATMENT APPROACH

By Daniel Culver, DO, and Basem Abdelmalak, MD

Pulmonary alveolar proteinosis (PAP) is a lung disease in which the failure of alveolar macrophages to clear surfactant causes its accumulation in the alveoli, leading to impaired gas exchange and hypoxemia. PAP is rare, more common in men and typically presents at 30 to 60 years of age. The clinical course is variable, ranging from spontaneous resolution to death due to progressive respiratory failure or infections. We recently reviewed the pathophysiology of and clinical approach to PAP in *The Lancet Respiratory Medicine*, summarized below.

PATHOPHYSIOLOGY OF PAP

The underlying pathophysiology of all forms of adult PAP is abnormal alveolar macrophage capacity to catabolize surfactant (Figure 1). Elucidation of the role of granulocyte-macrophage colony-stimulating factor (GM-CSF) in mediating macrophage maturation and surfactant catabolism greatly advanced our understanding of PAP. In autoimmune PAP, anti-GM-CSF antibodies lead to impaired bioavailability of GM-CSF, which disrupts the GM-CSF signaling pathways that regulate alveolar macrophage maturation and function. Autoimmune PAP is the most common form of the disease and accounts for approximately 90 to 95 percent of cases of adult PAP.

A number of hematological or environmental factors including hematological malignancies, primary immunodeficiency diseases, infections and drugs cause abnormal alveolar macrophage function that leads to secondary PAP, characterized by the absence of anti-GM-CSF antibodies. Congenital (or hereditary) PAP is attributed to genetic mutations in GM-CSF receptor proteins or surfactant proteins.

DIAGNOSIS OF PAP

Clinical findings and pulmonary function tests

Symptoms of autoimmune PAP include dyspnea, chest discomfort and constitutional symptoms. Cough is a common symptom, but up to a third of patients may be asymptomatic. Physical examination is usually nonspecific, although inspiratory crackles and clubbing may be observed. Pulmonary function tests usually demonstrate a restrictive impairment and reduced single-breath diffusing capacity for carbon monoxide. Arterial blood gas measurements may reveal hypoxemia and elevation of the alveolar-arterial oxygen gradient. Secondary polycythemia is a commonly encountered laboratory abnormality.

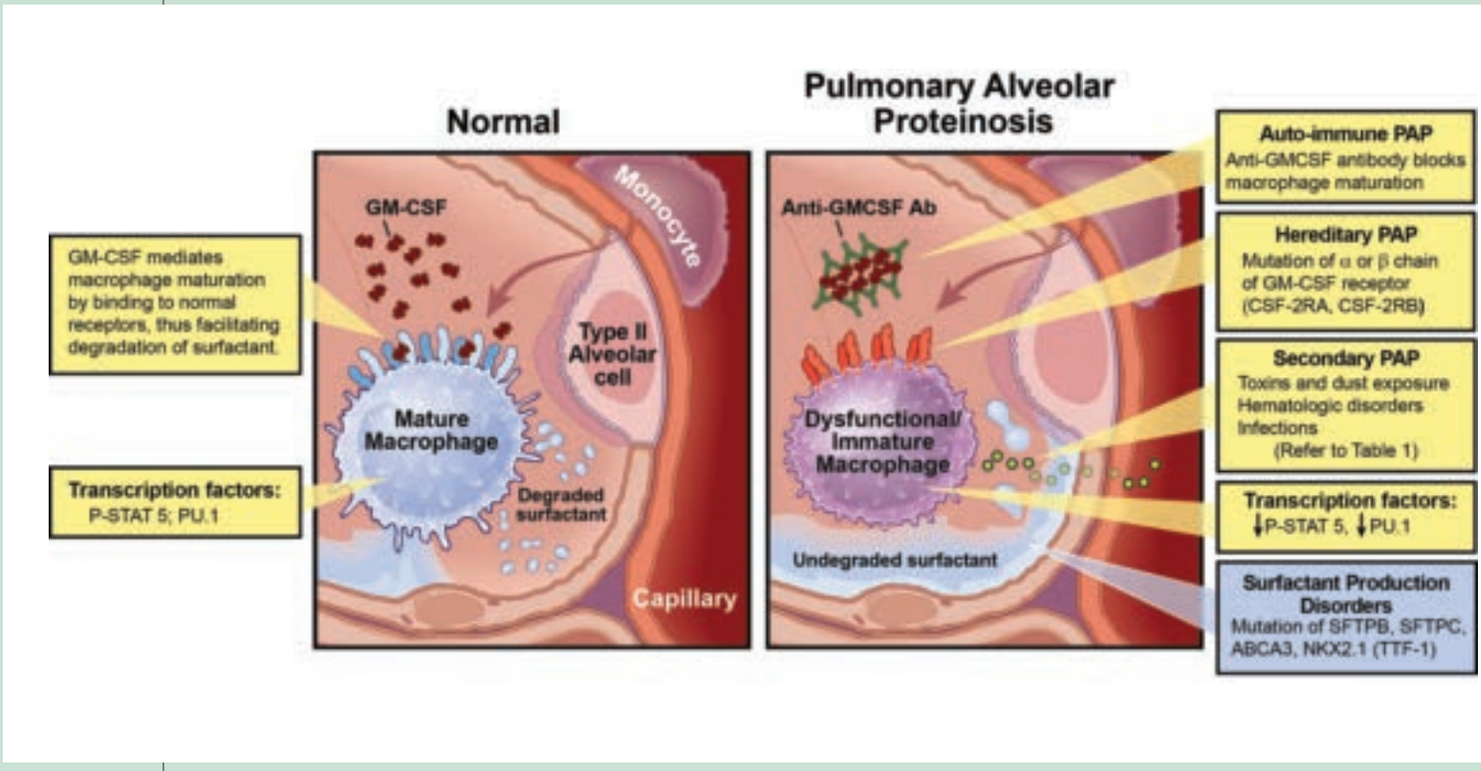

Figure 1. PAP pathophysiology.

Imaging studies

Chest radiographs typically show bilateral symmetric alveolar opacities located centrally in the mid and lower lung zones, often in a "bat wing" distribution. Distinctive features on high-resolution computed tomography (HRCT) include patchy ground glass opacities and smooth thickening of interlobular septal lines. The septal thickening commonly observed with PAP has been referred to as "crazy paving" because of the polygonal appearance of the secondary pulmonary lobules with interspersed ground glass attenuation (Figure 2).

Bronchoscopy

Bronchoscopy can confirm a diagnosis of PAP in most patients. Bronchoalveolar lavage (BAL) usually yields opalescent or milky-appearing fluid due to the high lipoproteinaceous content of the amorphous material in the alveolar spaces (Figure 3). Transbronchial lung biopsy (TBLB) can be considered if the BAL is not characteristic of PAP. The high yield of TBLB eliminates the need for a surgical lung biopsy in most patients; surgical biopsy to confirm PAP is required in only 10-20 percent of cases.

Serologic tests and biomarkers

Antibodies to GM-CSF in serum and BAL fluid are detected in nearly all patients with autoimmune PAP but not in patients with secondary or congenital PAP. Although the presence of anti-GM-CSF antibodies is an extremely useful diagnostic test, the serum concentration of GM-CSF antibodies does not appear to correlate with severity of autoimmune PAP. In the future, testing for antibodies in an appropriate clinical context may be sufficient for establishing a diagnosis, but no clinical test is currently available outside of a research setting.

Elevated serum concentrations of lactic dehydrogenase (LDH) have been reported in up to 80 percent of patients with PAP. High concentration of LDH has been shown to correlate with a high alveolar-arterial gradient and reduced partial pressure of arterial oxygen (PaO_2), but is considered nonspecific.

Many other biomarkers have been investigated, but none are widely accepted in clinical practice to determine severity of PAP or to monitor disease progression.

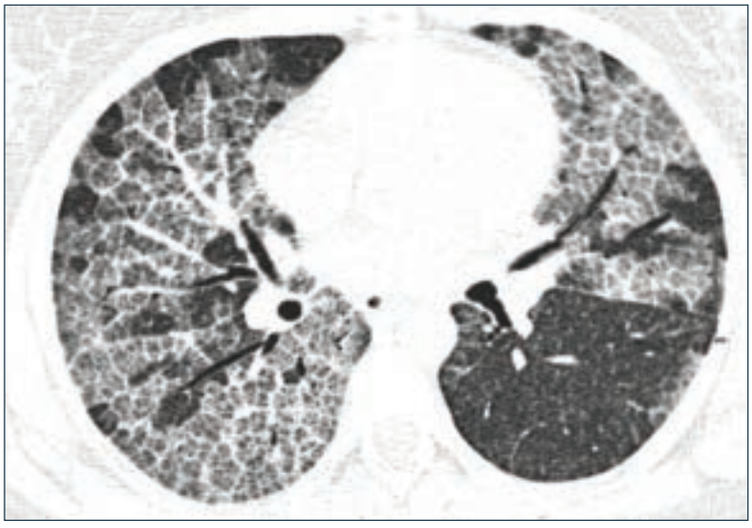

Figure 2. HRCT images show diffuse ground-glass opacification and the "crazy paving" pattern.

Figure 3. Characteristic milky or opalescent appearance of fluid return from whole-lung lavage in a patient with PAP. L1 and R1 show the drained fluid after the first lavage cycle in the respective left and right lung; L2 and R2 bottles were collected after 9 L of lavage; and L3 and R3 show the clear drained fluid at the last lavage cycle, in this case after a total of 30 L per lung.

TREATMENT OPTIONS

Patients whose disease is asymptomatic and who do not have substantial physiological impairment (e.g., hypoxemia) can be monitored by pulmonary function tests, symptom assessments and chest radiography. A more aggressive treatment approach is warranted for patients with moderate-to-severe PAP. Patients with secondary PAP should be treated for the underlying conditions.

Therapeutic whole-lung lavage

Therapeutic whole-lung lavage (WLL) has been the cornerstone of treatment of PAP for decades, and approximately 80 percent of patients experience improvement with an initial WLL (Figure 3). Our Interstitial Lung Disease Program at Cleveland Clinic has long served as a referral center for PAP and was among the first to develop same-day bilateral WLL and more recently, to offer a large volume lavage option where volumes as high as 55L per lung are used to achieve a thorough removal of the accumulated surfactant with very good clinical results. Patients are usually able to return to their homes the day after the procedure. WLL has dramatically improved the natural history of PAP and continues to be the standard initial treatment in patients with clinically significant lung disease.

Therapeutic bronchoalveolar lavage (BAL)

Segmental lobar lavage performed with fiberoptic bronchoscopy, while inferior to WLL, may be considered for patients who are unable to tolerate WLL under general anesthesia.

ADDITIONAL TREATMENT MODALITIES

Other therapeutic approaches to PAP have been considered, including aerosolized GM-CSF and rituximab infusions. Subcutaneous and inhaled recombinant GM-CSF preparations are being explored as initial treatment or following WLL as a treatment for autoimmune PAP; however, large-scale studies directly comparing the efficacy of GM-CSF therapy to WLL are currently lacking.

Rituximab, a monoclonal antibody directed against the CD20 antigen, has shown variable promise in treatment of autoimmune PAP in a limited number of reported cases. Additional studies are needed to determine the efficacy of rituximab as well as the patients most likely to benefit from therapy. Given that WLL is effective for a large proportion of patients, the use of these therapies must be carefully considered and tailored to each individual. Lung transplantation is a consideration for patients with refractory PAP, but underlying genetic PAP should be ruled out based on concern for disease recurrence in the lung allograft.

AN INTEGRATED APPROACH

The management of PAP at Cleveland Clinic is collaborative, individualized and innovative. Our bronchoscopy team and thoracic surgeons are able to perform both standard and advanced procedures when a biopsy is required for diagnosis. Our multidisciplinary team is comprised of pulmonologists, intensivists, anesthesiologists, lung pathologists, nurses and respiratory therapists. This team is thoroughly trained and highly specialized in caring for PAP patients and performing WLL. The dedication of this team, combined with our substantial experience performing several dozen WLL procedures annually, allows us to perform WLL in a highly organized and aggressive fashion. We have had numerous experiences in which repeat WLL performed by our group for reportedly recalcitrant cases has resulted in very satisfactory outcomes that at times have obviated the need to consider lung transplantation. We also have the capacity to perform these procedures in patients with frank respiratory failure with the support of extracorporeal membrane oxygenation. We continue to pursue advances in the diagnosis and treatment of this rare disease.

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Dr. Abdelmalak (abdelmb@ccf.org; 216.444.3746) directs the anesthesia service for Advanced Bronchoscopy and performs WLL in the Department of General Anesthesiology.

Cleveland Clinic's Rheumatic Lung Disease Program

INVESTIGATING NOVEL TREATMENTS FOR INTERSTITIAL LUNG DISEASE AND PULMONARY HYPERTENSION

By Kristin Highland, MD, MS

Pulmonary hypertension (PH) and interstitial lung disease (ILD) are leading causes of morbidity and mortality in rheumatic disease. Both PH and ILD may occur in patients with well-defined rheumatologic disorders (Figure 1), but they may also precede the extrapulmonary manifestations by years, or may have a forme fruste presentation limited to the lungs as seen in systemic sclerosis sine scleroderma. There is also a heterogeneous group of patients with PH and/or ILD that have a clinical flavor of an underlying autoimmune disease. Recently the terminology "interstitial pneumonia with autoimmune features" has been proposed for patients with ILD and autoimmune features who do not meet American College of Rheumatology criteria for a defined connective tissue disease (CTD).[1]

Early identification and treatment of these pulmonary complications is essential in order to improve outcomes in rheumatic diseases. Cleveland Clinic's Rheumatic Lung Disease Program offers a comprehensive multidisciplinary approach to the care of these complex patients that includes close collaboration with physicians from our rheumatology department as well as from the ILD, PH and transplantation programs within the Respiratory Institute.

The pathogenesis of rheumatic disease is complex and is characterized by systemic, immunological, vascular and fibrotic abnormalities. At Cleveland Clinic, we are involved in multiple research studies that are shifting treatment paradigms toward the targeting of these multiple pathways by repurposing drugs approved for other indications and by the exploration of novel therapies. Detailed below are three of the major multicenter trials in which the Rheumatic Lung Disease Program is participating. We hope that one or more of these trials will ultimately expand the therapeutic approach to treating the devastating pulmonary complications of rheumatic disease.

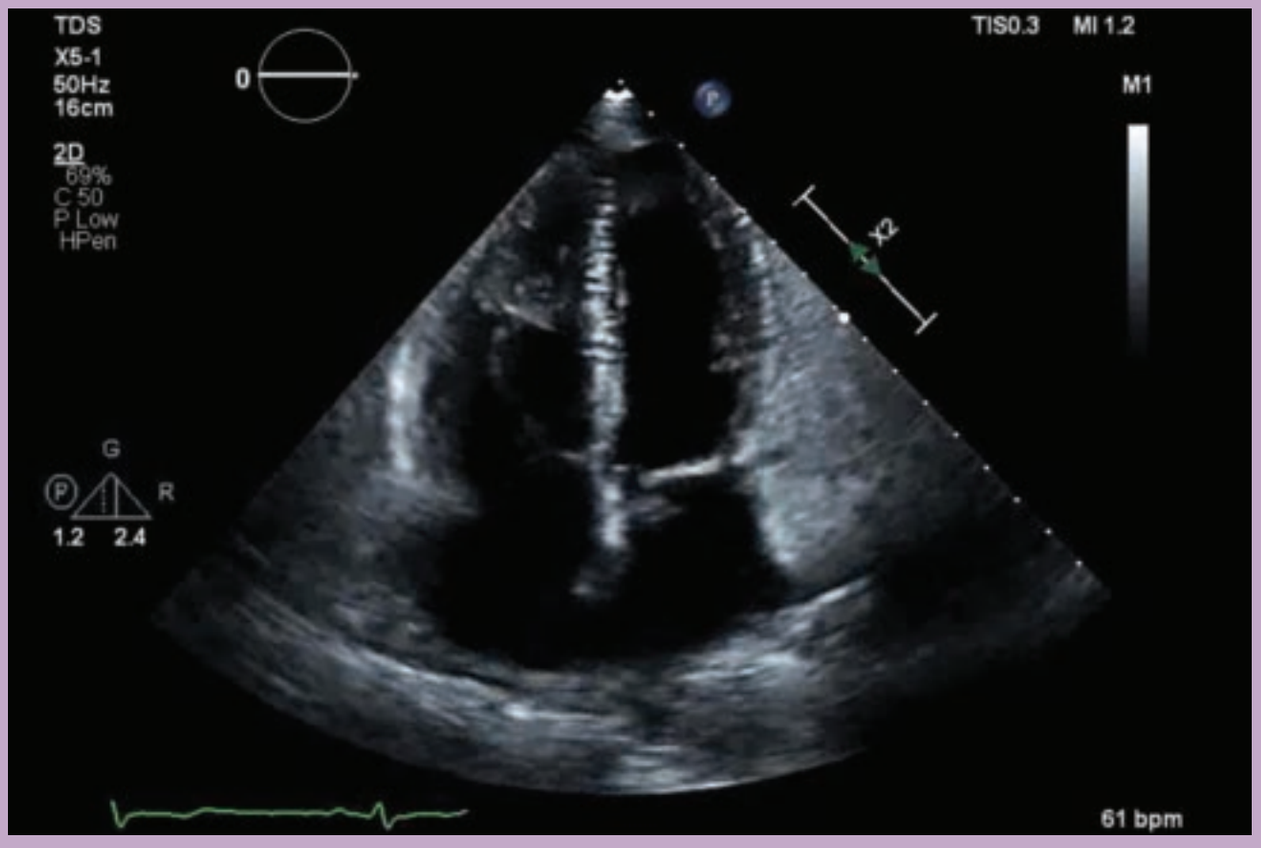

Figure 1. Echocardiogram that reveals a dilated right atrium and ventricle with intraventricular septal flattening in a patient with scleroderma-associated PH.

SCLERODERMA-ASSOCIATED INTERSTITIAL LUNG DISEASE

Systemic sclerosis (SSc) is a debilitating disease of unknown etiology (Figure 2). Patients suffer from fibrosis of multiple organs, leading to chronic morbidity and premature death. Second only to skin involvement, lung involvement is common and portends a poor prognosis, with a median survival of five to eight years in SSc-ILD.

Historically, cyclophosphamide was considered the treatment of choice for SSc-ILD, based on a modest effect on forced vital capacity (FVC), but treatment duration is limited due to its toxicity. Mycophenolate mofetil (MMF) is widely used for SSc-ILD based on results of the Scleroderma Lung Study II, which showed that MMF had a similarly modest effect on FVC, but better tolerability than cyclophosphamide.[2]

Nintedanib is an antifibrotic agent that is approved for the treatment of idiopathic pulmonary fibrosis (IPF) based on its ability to slow the rate of decline in FVC. In animal models of SSc, nintedanib effectively attenuated skin and lung fibrosis by reducing extracellular matrix deposition and myofibroblast accumulation. Nintedanib also attenuated pulmonary vascular remodeling by reducing the number of vascular smooth muscle cells and occluded pulmonary vessels.[3] Lastly, nintedanib has been demonstrated to inhibit T-cell and B-cell activity. These pleiotropic effects of nintedanib on the fibrotic, vascular and inflammatory pathways support its further investigation in rheumatic lung disease.

The SENSCIS® study, which I co-lead with Dr. Oliver Distler of the University Hospital in Zurich, Switzerland, is a multinational, randomized, placebo-controlled trial of nintedanib versus placebo in 580 subjects with SSc-ILD, making it the largest trial in scleroderma to date. Patients may be on baseline MMF or methotrexate. The primary outcome measure of the trial is the annual rate of decline in FVC over 52 weeks, while secondary measures are skin fibrosis score and quality of life as measured by the Saint George's Respiratory Questionnaire.

RHEUMATOID ARTHRITIS-ASSOCIATED ILD

Rheumatoid arthritis (RA) is a chronic inflammatory disease occurring in 1 to 2 percent of the general population. ILD is a common comorbidity that increases risk for premature death by nearly threefold and is responsible for approximately 10 percent of deaths in RA. Although most patients develop articular symptoms before lung manifestations, these may occur simultaneously, or ILD may precede joint manifestations.

There is evidence on high-resolution chest computed tomography of ILD in approximately 20 percent of unselected patients with RA and in up to 80 percent of those with respiratory symptoms, and of these about 60 percent will have evidence of radiographic progression over the next 18 months.[4] Among RA patients biopsied for a diagnosis of ILD, usual interstitial pneumonia is the most common histopathologic pattern seen, which may account for the poorer prognosis associated with RA-ILD in comparison with other CTD-ILDs for which nonspecific interstitial pneumonia is the prevailing pattern.[5]

Available treatment for RA has resulted in marked improvement in the control of articular disease, but these benefits have not extended to RA-associated lung disease.

Pirfenidone is another antifibrotic agent approved for IPF based on its ability to reduce the rate of decline in FVC. The mechanism of action of pirfenidone in ILD is thought to be both anti-inflammatory and antifibrotic, making it an ideal candidate for investigation in RA-ILD.

The TRAIL-1 study is a multicenter, randomized, placebo-controlled study to test the safety and tolerability of pirfenidone versus placebo for the treatment of RA-ILD. The primary composite endpoint is incidence of decline from baseline in predicted FVC of 10 percent or greater or death during the 52-week treatment period.

CTD-ASSOCIATED PULMONARY HYPERTENSION (CTD-PH)

Despite available therapies, the prognosis for PH remains poor, especially for patients with CTD, and approved vasodilation therapies generally do not yield significant functional improvements in CTD-PH patients.

Bardoxolone methyl and its analogs are potent inhibitors of the NF-αB inflammatory pathway. The established pharmacologic effects of bardoxolone, including suppression of inflammation, mitochondrial dysfunction and autoimmune processes, are directly applicable to the treatment of WHO Group I CTD-PH. Preliminary efficacy data from a phase 2 study in PH patients showed that bardoxolone methyl improves six-minute walk distance (6MWD) on top of optimal vasodilation background therapies in CTD-PH patients.[6]

The Catalyst study is a phase 3,multinational, placebo-controlled study of bardoxolone versus placebo for CTD-PH. The primary endpoint is change from baseline in 6MWD relative to placebo at week 24. The secondary endpoint is time to first clinical improvement consisting of a persistent change in functional class, increase from baseline in 6MWD by at least 10 percent, and decrease from baseline in creatinine kinase, as a surrogate biomarker for muscle injury and inflammation, by at least 10 percent.

THE RESPIRATORY INSTITUTE'S RHEUMATIC LUNG DISEASE PROGRAM

With unique expertise in the intersection of rheumatic and lung diseases and involvement in multiple national clinical trials, Cleveland Clinic's Rheumatic Lung Disease Program serves as a resource for clinicians and patients. To refer a patient or learn more, please contact me or call 855.REFER.123.

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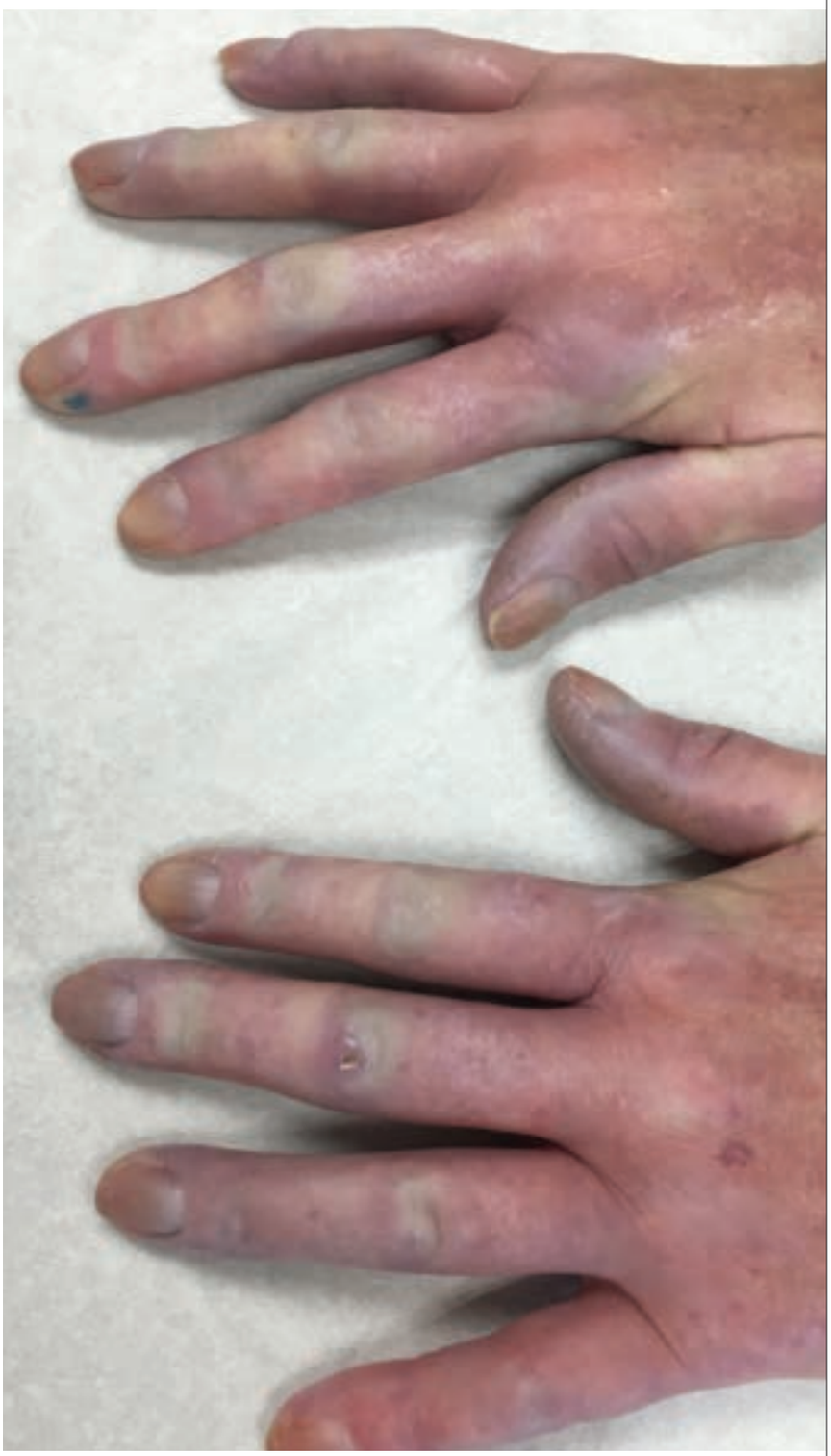

Figure 2. A scleroderma patient with Raynaud phenomenon, sclerodactyly and a digital ulcer.

Omalizumab Can Block Aspirin-Provoked Respiratory Reaction During Aspirin Desensitization

MECHANISM LIKELY RELATED TO REDUCED CAPACITY FOR RELEASE OF LEUKOTRIENES

By David Lang, MD

In 1968, Samter and Beers described a clinical syndrome currently known as aspirin-exacerbated respiratory disease (AERD), characterized by a triad of nasal polyposis, bronchial asthma and "life-threatening reactions to acetylsalicylic acid."[1] Despite avoidance of aspirin and cross-reacting nonsteroidal anti-inflammatory drugs, patients with AERD frequently experience refractory rhinosinusitis and asthma — in some cases requiring numerous sinus surgery procedures.[2] As many as 50 percent of AERD patients have severe asthma and are steroid-dependent.

In the Department of Allergy and Clinical Immunology at Cleveland Clinic's Respiratory Institute, aspirin desensitization is commonly performed as a therapeutic intervention to improve the clinical course of AERD. Aspirin desensitization is cost-effective[3] and has been associated with statistically significant benefit in patients with AERD, including improved quality of life and reductions in hospitalization and emergency department utilization, annual numbers of outpatient visits, medication reliance, respiratory symptoms, episodes of sinusitis, and need for polypectomy and sinus surgery procedures.[2] In this procedure, tolerance is induced via administration of aspirin in a graded-dose fashion, until the patient can tolerate 325 mg without respiratory reaction. Despite use of combination controller therapy including antileukotrienes, and ensuring that asthma is well-controlled at the time of the desensitization procedure, aspirin-provoked reactions during this procedure can be volatile and entail serious bronchospasm.

We hypothesized that administration of omalizumab would foster a significant reduction in the capacity for mediator release provoked by aspirin in patients with AERD, and attenuate respiratory reaction during aspirin desensitization. Our results were published in *Annals of Allergy and Immunology*.[4]

STUDY DESIGN

Subjects fulfilling criteria for both AERD[2] and label criteria for omalizumab[5] were randomized to either omalizumab or identical placebo (2 to 1) for 16 weeks. Within four weeks after receiving the study drug, aspirin desensitization was performed. Subjects then took aspirin daily to perpetuate the desensitized state.

Aspirin desensitization was carried out according to recommended protocol, beginning at 30 mg and advancing with serial dosing to 650 mg (Table 1).

Subjects were classified into five groups based on the observed respiratory reaction to aspirin:

(1) Combined upper and lower respiratory reaction (decline in forced expiratory volume in one second [FEV1] > 20 percent).

(2) Upper airway reaction with partial lower respiratory reaction (subthreshold decline in FEV1 = 15 to 20 percent).

(3) Isolated upper respiratory reaction.

(4) Isolated lower respiratory reaction (FEV1 decline > 20 percent).

(5) No respiratory reaction.

Urine samples were obtained for measurements of leukotriene E4 (LTE4).

RESULTS

Eleven subjects completed aspirin desensitization. Seven were randomized to omalizumab and four to placebo. Each of the 11 subjects had moderate to severe persistent asthma and was taking combination controller therapy. We found no statistically significant differences at baseline in age, body mass index, number of sinus surgeries or FEV1; however, all four subjects randomized to receive placebo were women, while four women and three men were randomized to the omalizumab arm. We observed a statistically significant difference in mean IgE level, which was higher in those randomized to omalizumab.

Four of the 11 subjects who underwent aspirin desensitization had isolated upper airway reactions, two had combined upper and lower airway reactions with declines in FEV1 > 20 percent of baseline, and five subjects completed aspirin desensitization without respiratory reaction. We observed four reactions at the 100 mg challenge dose. One combined reaction and one upper airway reaction occurred at 60 mg and 150 mg, respectively.

When the blind was removed after study completion, we found that two subjects in each group had upper airway reactions. The two subjects with combined reactions had received placebo. The five subjects who completed aspirin desensitization with no respiratory reaction had all been randomized to omalizumab (Table 2).

The patterns of respiratory reaction during aspirin desensitization were significantly different ($P = 0.04$, Fisher exact test), indicating that compared with placebo, randomization to omalizumab was associated with a statistically significant increase in the likelihood that subjects would exhibit no respiratory reaction during aspirin desensitization.

Mean urinary LTE4 levels remained relatively low during aspirin desensitization in the five nonreactors. We observed a statistically significant overall difference between LTE4 levels in subjects receiving omalizumab who did not exhibit respiratory reactions compared with subjects randomized to

placebo (P = 0.035, mixed model with interaction). Compared with levels obtained after the 100 mg dose in nonreactors, urinary LTE4 levels were significantly higher with reaction in placebo subjects.

The strengths of this study include its randomized, double-blind, placebo-controlled design and inclusion of a 650 mg aspirin challenge dose to confirm that "silent desensitization" had occurred. Several case reports in which omalizumab was associated with induction of aspirin tolerance in patients with AERD support our observations.[6-8]

Our findings imply that the protective effect of omalizumab is related to a diminished capacity for leukotriene release with exposure to a provocative dose of aspirin. Clinicians should be aware that false-negative aspirin challenges may be observed in AERD patients receiving omalizumab. These findings cannot be generalized to patients with AERD who have received omalizumab for less than 16 weeks or to patients with AERD not fulfilling label criteria for omalizumab.[5] Further studies to explore the therapeutic utility of omalizumab in AERD patients undergoing aspirin desensitization are warranted.

Dr. Lang (langd@ccf.org; 216.445.5810) is Chair of the Department of Allergy and Clinical Immunology as well as Co-Director of the Asthma Center and Director of the Allergy/Immunology fellowship program.

[This protocol was approved by the Cleveland Clinic Institutional Review Board, and for an IND by the United States Food and Drug Administration. Genentech/Novartis provided financial support, but had no role in the design of this study, data tabulation, analysis or interpretation.]

	Day 1	Day 2	Day 3
8 a.m.	Placebo	60 mg	325 mg
11 a.m.	Placebo	100 mg	650 mg
2 p.m.	30 mg	150 mg	

Table 1. Aspirin desensitization was performed according to the oral desensitization protocol established for this procedure, with the first day including two placebos in order to confirm stability of asthma and rhinosinusitis symptoms prior to proceeding with aspirin dosing.

	Lower Airway Reaction (Decline in FEV1 ≥ 20%)	Upper Airway Reaction	No Respiratory Reaction
Placebo	2	2	0
Omalizumab	0	2	5

Table 2. Patterns of respiratory reaction observed during aspirin desensitization are displayed. Randomization to omalizumab was associated with a statistically significant increase in the likelihood for no respiratory reaction to aspirin during desensitization compared with placebo (P = 0.04).

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Beta Blockers Have Positive Effect in Pulmonary Arterial Hypertension

TURNING ATTENTION TO THE RIGHT VENTRICLE

A team of Cleveland Clinic researchers has determined that beta blockers may help treat pulmonary arterial hypertension (PAH).

Right-sided heart failure is the leading cause of death in PAH patients. Right ventricular dysfunction occurs independently of increased blood pressure, yet all currently approved PAH treatments target the pulmonary vessels rather than address the more likely cause of death in these patients.

In contrast, targeting left ventricular dysfunction has been the foundation of left-sided heart failure therapy for nearly 40 years; beta blockers are the cornerstone of therapy in left-sided heart failure.

"There is a critical need for new therapies to support right ventricular function in pulmonary hypertension," says lead author Serpil Erzurum, MD, practicing pulmonologist and Chair of Cleveland Clinic Lerner Research Institute. "While treatments with beta blockers such as carvedilol are standard therapy in patients with left-sided heart failure, successful therapies in right-sided heart failure and PAH have lagged behind. Longer-term studies are needed, but our initial analysis shows that carvedilol may also benefit patients with PAH, who currently have few available treatment options."

The Cleveland Clinic team assessed carvedilol use in a group of 30 patients with PAH in a double-blind, randomized study. The participants received either placebo, low fixed dose or escalating doses of carvedilol over a six-month period. Results showed that the drug lowered heart rate in correlation with carvedilol dose, improved heart rate recovery from exercise, and did not worsen heart failure or lead to airflow deterioration (Figure). The findings suggest carvedilol is safe to use in PAH patients for six months with evidence of improved outcomes that could prevent right-sided heart failure.

DECREASED FUNCTIONAL LUNG CAPACITY A MYTH

Previously, the use of beta blockers in PAH patients had not been widely studied due mostly to anecdotal concerns about decreased functional lung capacity.

"There is good reason to consider beta blockers for the right ventricular failure in PAH," says W.H. Wilson Tang, MD, study co-author and staff cardiologist in the Section of Heart Failure and Cardiac Transplantation Medicine in the Sydell and Arnold Miller Family Heart & Vascular Institute at Cleveland Clinic. "The fact that beta blockers were well-tolerated and effective in lowering heart rates, thereby improving heart efficiency, is unto itself a key observation, since doctors have been cautioned against using them in this setting for safety concerns. This study provides important new data that advances our knowledge of using this class of drugs in this chronic and life-threatening lung-associated vascular disease."

Samar Farha, MD, associate staff in the Respiratory Institute, is first author on the study, which was published in *JCI Insight*.[1] This work was supported by National Institutes of Health (NIH) grants R01HL115008 and R01HL60917 and in part by the National Center for Advancing Translational Sciences, UL1TR000439.

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Dr. Farha (farhas@ccf.org) is associate staff in the Respiratory Institute.

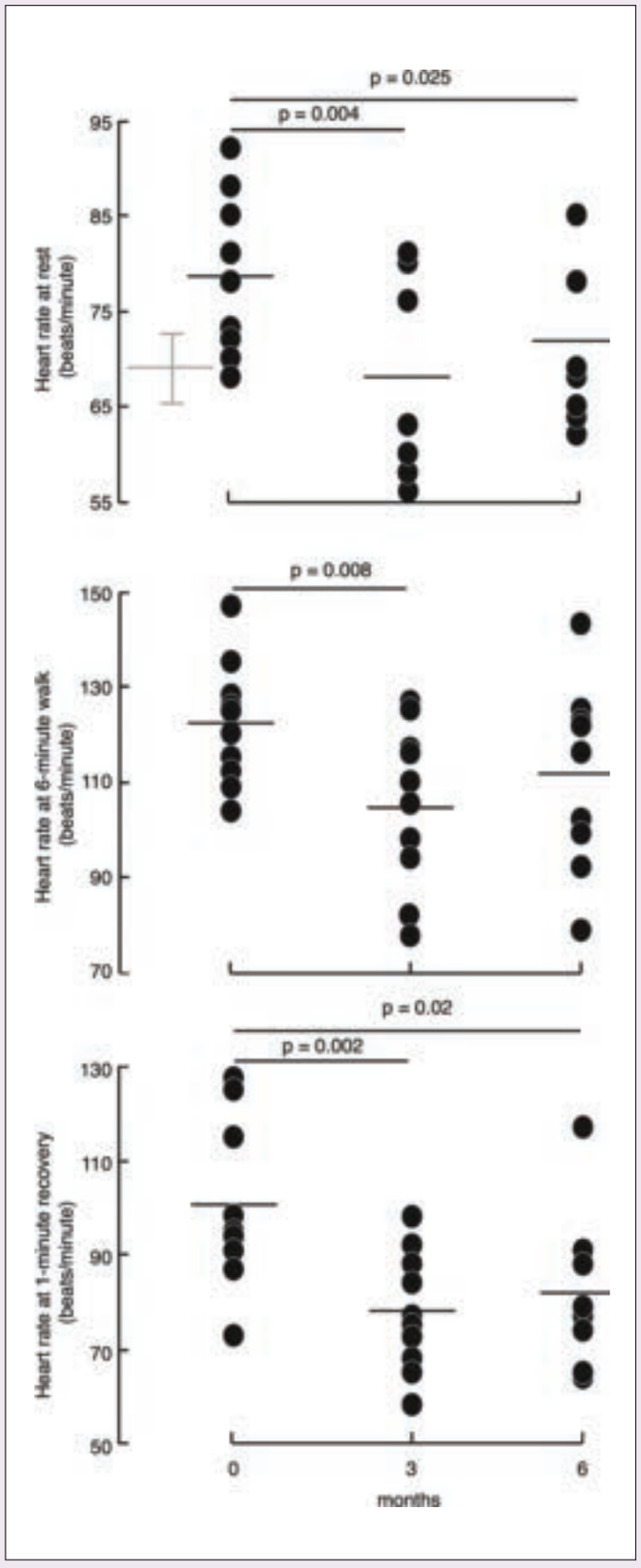

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Figure. Carvedilol therapy reduced heart rate over the six-month period in the dose-escalating group (N = 10 at each time point). The effect was more pronounced at rest and during recovery at one minute after a six-minute walk test. The drop in heart rate was not accompanied by a worsening of functional capacity as measured by six-minute walk distance (not shown in figure). Horizontal lines represent the mean. The gray lines represent control heart rate mean and SEM. Paired t test with Bonferroni-adjusted significance level 0.025 used to adjust for comparisons to each of three and six months. Figure and caption republished with permission from the American Society for Clinical Investigation.

Simulation to Teach PA Catheter Placement and Management

NEW TOOLS TO TEACH AN OLD PROCEDURE

By Neal F. Chaisson, MD; Eduardo Mireles-Cabodevila, MD; Rendell Ashton, MD; Aanchal Kapoor, MD; Abhijit Duggal, MD; Anirban Bhattacharyya, MD, MPH; Siddharth Dugar, MD

In 2014, the Accreditation Council for Graduate Medical Education (ACGME) published recommendations for entrustable professional activities (EPAs), which are areas of procedural and cognitive proficiency expected of trainees who completed specialty or subspecialty training. For critical care and pulmonary/critical care trainees, the current EPAs include proficiency in placing and interpreting data from a pulmonary artery catheter (PAC).

Historically, PAC placement was a common procedure in intensive care units. A series of studies demonstrating that routine use of PACs does not improve clinical outcomes led to a significant decline in their use. Nonetheless, in select patients, such as those with pulmonary hypertension, use of a PAC to guide management is still recommended.

In a 2013 survey of pulmonary and critical care program directors, several concerns were raised with regard to the state of training in PAC placement and use. Fifty-four percent of respondents estimated that current fellows place fewer than 10 PACs during fellowship, and 57 percent suggested that PAC training was inadequate. Eighty-one percent of respondents agreed that proficiency in PAC data interpretation should be an ACGME requirement.

When we reviewed our program's training methods for PAC placement and management in 2014, we realized we were no different. Teaching was sporadic and did not follow a well-formed curriculum. Experience with PAC use among fellows was low, and less than 40 percent of our fellows felt confident in using PACs.

To address this issue, we devised an educational curriculum to provide didactic and hands-on training in the proper use and interpretation of PACs, arterial catheters and echocardiograms for shock assessment.

Our curriculum included three components:

1. A series of online modules reviewing heart-lung physiology and hemodynamic waveform interpretation.
2. Four lectures on the physiology of shock.
3. A one-day simulation course to integrate principles learned in the modules and lectures with hands-on procedural training.

As part of the course, our team developed a right heart catheter insertion simulator from moldable plastic, a clear plastic bottle and Foley catheter tubing (Figure 1). Although the product was rudimentary, trainees felt it offered valuable instruction on how to correctly place a PAC.

In subsequent years, we have made major improvements and now have two PAC task trainers. The first, which includes a 3D-printed model of the right atrium and ventricle and pulmonary arteries, represents a more sophisticated version of our first simulator and allows learners to visualize the concept of PAC insertion, flotation and wedging (Figure 2). The second, a PAC waveform simulator, helps learners review waveforms associated with PAC placement and visualize wedging technique and thermodilution cardiac output.

As a result of these simulation improvements, 89 percent of our trainees now

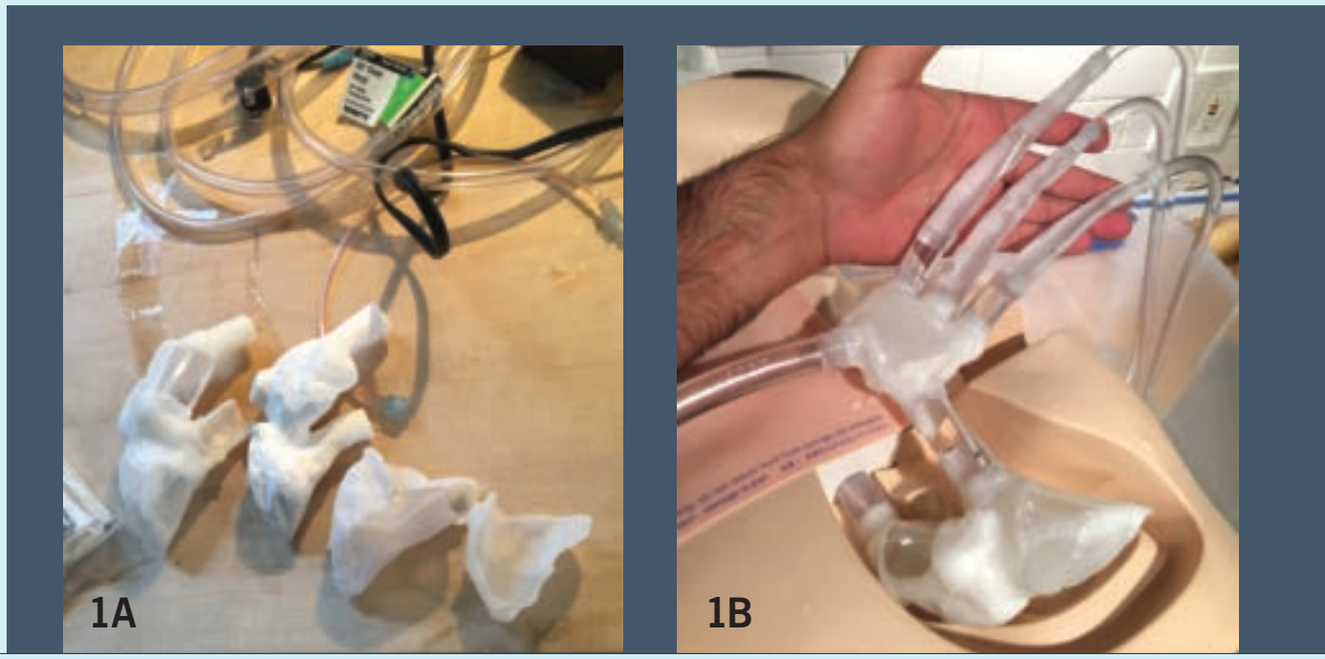

Figure 1. Initial models of the right ventricle (1A) were attached to a pulmonary circuit (1B). Vessels within the pulmonary circuit were tapered to allow wedging of the PA catheter during insertion.

Figure 2. Learners insert a Swan-Ganz catheter through an introducer sheath in the neck of the simulator (2A). The current right ventricle was developed using reconstructed CT scan images and a 3D printer (2B).

agree or strongly agree that they can safely insert a PAC and interpret data for assessment of shock. Eighty-two percent of fellows agree or strongly agree that they can safely troubleshoot a PAC without assistance.

Beyond the use of these simulators to train our fellows, we have had opportunities to use these tools in other educational settings. We added PAC simulation training to our medical student hemodynamics curriculum in 2018, and it was heralded as a best-practice model in medical school education by the Dean's Office. We have collaborated with industry to provide a workshop on hemodynamics for medical science liaisons and pharmaceutical representatives involved in the area of pulmonary hypertension. Feedback from these sessions has been uniformly positive, and these workshops are now a major educational component of our pulmonary hypertension program.

Although our PAC simulators have improved the educational experience well beyond our initial goals, the future holds additional opportunities. The next generation of PAC simulator — to be completed by late 2018 — will combine the two prior models and will allow learners to interpret both normal and abnormal PAC waveforms. It will also provide a simulation-based mechanism to enable ICU nurses to review proper PAC insertion, maintenance and data collection.

Continued enhancements to the modules within our hemodynamics curriculum will be rolled out in 2019. We look forward to those opportunities as we work to further the education of those who serve, one of the founding tenets of Cleveland Clinic.

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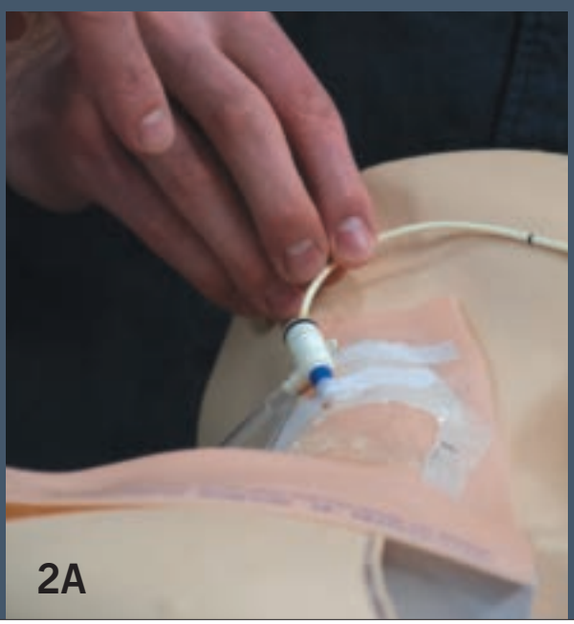
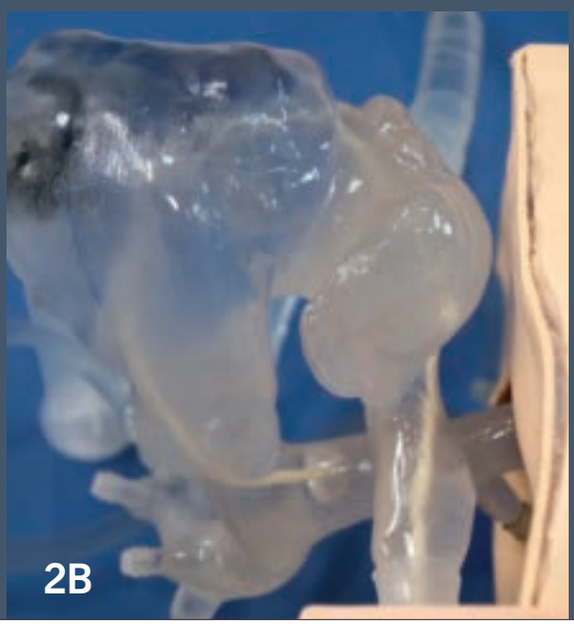


2A



2B

The Cleveland Clinic-Cleveland State University Master of Education in Health Professions Education

TRAINING THE NEXT GENERATION OF MEDICAL EDUCATORS

By James K. Stoller, MD, MS

The tripartite mission of Cleveland Clinic is "better care of the sick, investigation of their problems and more teaching of those who serve." In the context of its long-standing commitment to teaching, Cleveland Clinic has addressed the needs of many educational audiences, e.g. — medical students, allied health students, graduate medical trainees, nurses, colleagues engaging in continuing medical education, healthcare visitors from around the world and international healthcare executives seeking executive education. Indeed, Cleveland Clinic's Education Institute has been shaped over time and organized around these needs, with 10 centers currently addressing each of these audiences. For example, the Cleveland Clinic Lerner College of Medicine (CCLCM) offers a novel, problem-based learning-based curriculum to a highly selected group of collaborative, mindful, research-oriented students. The Center for International Medical Education organizes observerships and preceptorships for international visiting medical professionals and offers courses that Cleveland Clinic faculty deliver abroad. The Center for Educational Resources (CER) comprises talented PhD medical educators who provide instruction and guidance in the design and assessment of curricula (e.g., in CCLCM and in graduate medical education) and educator development and who help optimize teaching for all educational audiences.

One of the benchmarks of a successful organization is the extent to which it provides growth and pipeline development for its members in order to develop them and sustain and propel organizational success. In the context of its educational mission, Cleveland Clinic's Education Institute serves this benchmark by providing educational growth opportunities through various pipeline programs. Two such programs are the Cleveland Clinic-Weatherhead School of Management Executive Master of Business Administration and the Master of Education in Health Professions Education (MEHPE), the latter a collaboration between the Cleveland Clinic CER and Cleveland State University.

The MEHPE program was first conceived in 2012 and graduated its first cohort in 2015. The purpose of the program — a collaboration with the Cleveland State University College of Education and Human Services — is to provide a rigorous, healthcare-oriented curriculum to emerging medical educators who see acquiring educational skills as critical to their professional growth. Cultivating educational skills among caregivers aligns closely with Cleveland Clinic's desire and need to develop a pipeline of interdisciplinary, skilled medical educators who can design and assess optimal pedagogy for its many educational audiences.

The two-year curriculum focuses on the skills needed to be a medical educator. Specifically, courses address adult learning theory, curriculum design and instruction, assessing learners, evaluating educational programs, healthcare educational research, and technology in health professions education. The pedagogy is blended between live and online courses, with live courses delivered at Cleveland Clinic main campus during the evening to accommodate working health professionals. The program occupies six semesters of instruction and 30 credit hours for degree attainment.

First offered in 2013, the program has graduated two cohorts (20 individuals), with the third cohort (of nine individuals) currently underway. Alumni and current matriculants include physicians in various specialties, nurses, respiratory therapists, radiation technologists and administrators. Examples of roles played by alumni include service as Cleveland Clinic's Designated Institutional Officer for Graduate Medical Education, director of physician advisors in CCLCM, continuing medical education director and education managers in radiology and respiratory therapy. Further description of the program can be found at clevelandclinic.org/mehpe.

Healthcare providers at any institution with an interest in developing their educational knowledge and skills are invited to apply. Applications can be submitted to allin1@csu.edu or to:

Office of Graduate Admissions Processing
Cleveland State University
2121 Euclid Ave., UN 301
Cleveland, OH 44115

Dr. Stoller (stollej@ccf.org; 216.444.1960) is a practicing pulmonologist and Chair of the Education Institute and holds the Jean Wall Bennett Professorship in Emphysema Research at Cleveland Clinic Lerner College of Medicine as well as the Samson Global Leadership Academy Endowed Chair.

PERSPECTIVE: THE MASTER OF HEALTH PROFESSIONS EDUCATION PROGRAM

By Amit Diwakar, MD

I have always enjoyed learning and teaching and have wanted to incorporate medical education into my career. When I joined the pulmonary and critical care group at Cleveland Clinic Akron General a few years ago, I quickly found my way to the conference rooms to participate in ongoing educational activities. I became progressively more involved with resident education, which culminated in my appointment as Associate Program Director for the Internal Medicine Residency Program and more recently as Vice Chair for Education and Research at Cleveland Clinic Akron General.

I decided to enroll in the Cleveland Clinic/Cleveland State University's Master of Education in Health Professions Education (MEHPE) program for three main reasons: (1) to learn about adult education theories and educational assessment methods; (2) to improve my teaching skills; and (3) to provide me with the knowledge and tools necessary to succeed as a program director and medical educator. The MEHPE program is tailored specifically for health professions education and thus suited my needs. The use of an online curriculum in addition to face-to-face classes made it possible for me to participate while maintaining my full-time clinical job.

I am now midway through the two-year course, and so far the experience has been a highly satisfying and enjoyable one. The program places major emphasis on adult learning theories and their applications. This initially challenging material became increasingly familiar and understandable through class discussions, debates, use of multimedia and literature review and, most effectively, by creating and implementing educational projects. Emphasis is also placed on incorporating technology into education, a growing and essential component of the contemporary classroom.

This entire experience has added a whole new dimension to my philosophy and approach to teaching and learning. My teacher-centric style has evolved into a learner-centric one. I have learned several new teaching techniques: debate, gaming, snowballing, brainstorming and simulation, to name a few. I am learning to use technology for teaching as well as for keeping up with current information.

Creativity is embedded in the culture of the MEHPE program and has prompted me to develop and implement several novel programs for the medical residents at Akron General. One example is the housestaff orientation program for taking night calls in the cardiovascular intensive care unit, which employs the social constructivism theory. Based on the assumption that learning is the construction of meaning from experience, the program draws heavily on the residents' on-call experiences to create a preparatory program, thereby making it more meaningful. I am also in the process of making our didactic sessions more interactive with the help of electronic devices (e.g., mobile phones and laptops). Using an online platform will enable active participation for our learners, who will provide real-time responses to questions embedded in the lecture slides. This will help meet the learning goals for the session, and the data thus generated will allow for program improvement measures.

In sum, I have found the MEHPE program to be an invaluable experience and one that will prepare me for what is shaping up to be a rewarding career as a medical educator.

Dr. Diwakar (diwakaa@ccf.org; 330.344.6676) is staff in the Department of Critical Care Medicine.

News Briefs

Hassan Khouli, MD, Appointed Chair of the Department of Critical Care Medicine

Hassan Khouli, MD, has been appointed Chair of the Department of Critical Care Medicine. He was previously Chief, Critical Care Section of Mount Sinai St. Luke's and Mount Sinai West Hospitals in New York City and Professor of Medicine at the Icahn School of Medicine at Mount Sinai.

Dr. Khouli's accomplishments as a clinician, educator, administrator and innovator include leadership in the development of simulation training, founding both the Center for Advanced Medical Simulation and a one-year simulation fellowship at St. Luke's and Roosevelt Hospitals. He was voted Teacher of the Year at St. Luke's-Roosevelt Hospital Center four times and received the Dr. Nathan Kase Innovations in Medical Education Award from the Icahn School of Medicine.

He received his medical degree from Damascus University School of Medicine in Syria and trained in internal medicine at Atlantic City Medical Center in Atlantic City, New Jersey. He completed a two-year critical care medicine fellowship at Cooper Hospital-University Medical Center, Robert Wood Johnson Medical School, and a two-year pulmonary medicine fellowship at St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons. He trained in interventional pulmonary medicine at Johns Hopkins University and completed a fellowship in clinical quality from the Greater New York Health Association.

David Lang, MD, Elected to AAAAI Board of Directors

David Lang, MD, Chair, Department of Allergy and Clinical Immunology, was elected to the board of directors of the American Academy of Allergy, Asthma & Immunology (AAAAI). In this four-year leadership pathway, Dr. Lang served as Secretary-Treasurer in 2017-2018, is currently Vice President (2018-2019), and will be named President in 2019 and Immediate-Past President in 2020. His 30-year legacy of leadership in AAAAI includes positions as past-Chair of the Health Outcomes, Education, Delivery and Quality Interest Section and as a member of the Practice Parameters Task Force since 2001.

Dr. Lang is Professor of Medicine at Cleveland Clinic Lerner College of Medicine as well as Asthma Center Co-Director in Cleveland Clinic's Respiratory Institute. He received his medical degree from the University of Michigan and completed internal medicine training at Henry Ford Hospital, an allergy/immunology fellowship at Scripps Clinic and a medical education fellowship at Cleveland Clinic. He studies drug allergy, asthma and urticaria.

Rachel Scheraga, MD, Named ATS Rising Star

Rachel G. Scheraga, MD, was awarded the American Thoracic Society's Rising Star Award at the 2018 ATS International Conference. Rising Stars are basic and translational science researchers at the assistant or early associate professor level making waves in their fields. Dr. Scheraga is a member of the Olman lab and studies how immune cells interact with the biophysical properties of the lung. She is staff in the Respiratory Institute and holds a secondary appointment in the Lerner Research Institute.

Herbert Wiedemann, MD, MBA, Appointed Cleveland Clinic Chief of Staff

Herbert Wiedemann, MD, MBA, has been appointed Chief of Staff of Cleveland Clinic. He joined Cleveland Clinic in 1984 and has served as Chairman of the Department of Pulmonary and Critical Care Medicine since 1990. Dr. Wiedemann served as the inaugural Respiratory Institute Chair from 2007 to 2018.

Dr. Wiedemann's leadership grew a six-member Department of Pulmonary and Critical Care Medicine into one of the largest respiratory institutes in the country, with over 550 employees including 172 faculty members, 72 advanced practice providers and 49 fellows in four departments: Pulmonary Medicine, Critical Care Medicine, Infectious Disease, and Allergy and Immunology.

Dr. Wiedemann has served on many committees and in several leadership roles, including as President of the Staff (1995-1996), an elected member to the Board of Governors (2002-2006) and a physician representative on Cleveland Clinic's Board of Trustees (2005-2006) and Board of Directors (2006).

Dr. Wiedemann has clinical interests in intensive care medicine and the evaluation of dyspnea. He has participated in several large multicenter trials of new therapies for acute respiratory distress syndrome and sepsis, and he served as principal investigator for three of these trials. He is a member or fellow of the American College of Chest Physicians, the American College of Critical Care Medicine and the American College of Physicians.

After receiving his medical degree from Cornell University College of Medicine, Dr. Wiedemann completed training in internal medicine and a chief year at University of Washington Medical Center in Seattle. He completed his fellowship in pulmonary and critical care medicine at Yale University. Dr. Wiedemann earned an MBA from the Yale University School of Management.

Mitchell Olman, MD, MA, Receives ATS Scientific Accomplishment Award

Mitchell Olman, MD, MA, was awarded the Assembly on Allergy, Immunology & Inflammation Scientific Accomplishment Award at the 2018 American Thoracic Society Annual Meeting. This award is intended for an established, internationally recognized investigator with a record of sustained exemplary achievement in the scientific areas of the Assembly, and is given once annually. Dr. Olman holds joint appointments in the Department of Pulmonary Medicine and Lerner Research Institute. He is the recipient of an R01 grant from the National Heart, Lung, and Blood Institute for "Myofibroblast Differentiation and Fibrosis Are Mediated by TRPV4 Mechano-Sensing."

Cleveland Clinic Joins Pulmonary Fibrosis Foundation's Care Center Network

Cleveland Clinic has been named a designated Care Center of the Pulmonary Fibrosis Foundation. Cleveland Clinic's Interstitial Lung Disease (ILD) Program, directed by Daniel Culver, DO, joins a network of more than 60 Care Centers across the U.S. specializing in the diagnosis, management and treatment of individuals with pulmonary fibrosis. The program provides care for patients living with conditions including idiopathic pulmonary fibrosis, other idiopathic interstitial pneumonias, sarcoidosis, pulmonary alveolar proteinosis, chronic beryllium disease, lymphangioleiomyomatosis and other ILDs.

The program offers invasive and noninvasive diagnostic procedures, pulmonary rehabilitation, pulmonary function testing, transtracheal oxygen catheter placement and a wide range of clinical trials. ILD staff are familiar with and able to supervise the administration of a wide range of therapeutic agents, including conventional anti-inflammatory drugs, newer biologic agents and antifibrotic drugs. For patients with advanced disease, the program works closely with Cleveland Clinic's Lung Transplant Program, one of the busiest and most experienced in the world.

NewsBriefs

Introducing the Medical Intensive Liver Unit

Cleveland Clinic's Medical Intensive Liver Unit (MILU), a collaboration between the departments of Critical Care Medicine (Respiratory Institute) and Gastroenterology, Hepatology and Nutrition (Digestive Disease & Surgery Institute), opened in summer 2018. One of only a few liver-specific intensive care units in the U.S., it promises to offer the best in multidisciplinary care for critically ill patients with liver failure — including acute liver failure, acute-on-chronic liver failure and cirrhosis and its complications — as well as patients waiting or being evaluated for liver transplant.

The MILU is unique in bringing talent in the form of a multidisciplinary team to rounds on a daily basis. The team includes specialists in critical care, hepatology, pathology, transplant, social work, pharmacology, nursing, nutrition and physical therapy.

"Our goal is to implement best practices and provide standardized and innovative care for critically ill patients with liver disease and multiple organ failure," says critical care specialist Aanchal Kapoor, MD, Director of the MILU. "We aim to improve morbidity and mortality, expedite transplant evaluations, increase transplant referrals and reduce wait-list mortality."

The MILU also will be a hub of education and research in advanced liver disease, adds hepatologist and MILU Co-Director Christina Lindenmeyer, MD.

To arrange a patient transfer, call 216.444.8302 or 800.553.5056.

Peter Mazzone, MD, MPH, Named *CHEST* Editor-in-Chief

CHEST's Board of Regents appointed **Peter J. Mazzone, MD, MPH**, as the journal's next Editor-in-Chief. Dr. Mazzone directs the Respiratory Institute's Lung Cancer Program and Lung Cancer Screening Program. He served as Program Chair of CHEST 2017 and chaired the *CHEST* guideline panel on screening for lung cancer. His tenure begins in July 2019.

Respiratory Institute Outcomes

Now Available Online

Quality counts now more than ever as healthcare transforms from a volume-based to a value-based system.

That's why we're made our outcomes — including clinical data, volumes and overviews of patient experience, quality and satisfaction — easily accessible online.

Visit clevelandclinic.org/outcomes

Respiratory Institute by the numbers

WHO WE ARE*

172
PHYSICIANS

26
LOCATIONS

72
ADVANCED PRACTICE PROVIDERS

50
FEDERAL GRANTS

49
FELLOWS

- **24** PULMONARY & CRITICAL CARE
- **13** CRITICAL CARE MEDICINE
- **07** INFECTIOUS DISEASE
- **04** ALLERGY AND IMMUNOLOGY
- **01** INTERVENTIONAL PULMONOLOGY

HOW WE PERFORM**

208,069
OUTPATIENT VISITS

61,725
PFT VISITS

5,122
BRONCHOSCOPIES

1,607
ADVANCED DIAGNOSTIC BRONCHOSCOPIES

957
THERAPEUTIC BRONCHOSCOPY PROCEDURES

164
DAILY ENTERPRISE ICU CENSUS

129
LUNG TRANSPLANTS
(Including liver/lung transplants)

** 2018 data; **2017 data*

Respiratory Institute | Selected Clinical Trials

Consider offering your patients enrollment in a leading-edge clinical research trial at our Respiratory Institute. For more information, contact the study coordinator or principal investigator.

ASTHMA

Functional Medicine in Asthma (FAst) Study

The objective of this study, sponsored by executive administration, is to determine if standardized guideline-based specialist asthma treatment with respect to asthma control (as measured by ACQ/AQLQ) is equivalent to guideline-based specialist treatment plus an additional functional medicine management approach.

PRINCIPAL INVESTIGATOR
Sumita Khatri, MD, MS

STUDY COORDINATOR
JoAnne Baran-Smiley, BSN, RN
216.444.5023

COPD

Beta-Blockers for the Prevention of Acute Exacerbations of COPD (βBLOCK-COPD)

Sponsored by the Department of Defense Office of Congressionally Directed Medical Research Programs, the primary objective of this study is to determine the effect of once-daily metoprolol succinate compared with placebo on the time to first exacerbation in moderate to severe COPD patients who are prone to exacerbations and who do not have absolute indications for beta-blocker therapy.

PRINCIPAL INVESTIGATOR
Umur Hatipoğlu, MD

STUDY COORDINATOR
Rick Rice, RRT | 216.444.1150

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 with a liberal fluid strategy (fluids first, followed by rescue vasopressors) on 90-day in-hospital mortality in patients with sepsis-induced hypotension.

PRINCIPAL INVESTIGATOR
R. Duncan Hite, MD

STUDY COORDINATORS
Andrei Hastings, MD | 216.445.3960
Omar Mehkri, MD | 216.445.1939

A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Adaptive Clinical Trial of Vitamin C, Thiamine and Steroids as Combination Therapy in Patients with Sepsis (VICTAS)

This study is supported by the Marcus Foundation in collaboration with Johns Hopkins University and Emory University. The primary goal of the study is to demonstrate the efficacy of combination therapy using vitamin C, thiamine and corticosteroids in reducing mortality and improving organ function in critically ill patients with sepsis.

PRINCIPAL INVESTIGATOR
R. Duncan Hite, MD

STUDY COORDINATORS
Andrei Hastings, MD | 216.445.3960
Omar Mehkri, MD | 216.445.1939

A Prospective, Multi-Center, Randomized, Controlled, Pivotal Trial to Validate the Safety and Efficacy of the Hemolung® Respiratory Assist System (RAS) 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 extracorporeal carbon dioxide removal as an alternative or adjunct to invasive mechanical ventilation versus standard-of-care invasive mechanical ventilation alone to increase ventilator-free days for patients who require respiratory support due to an acute exacerbation of their COPD.

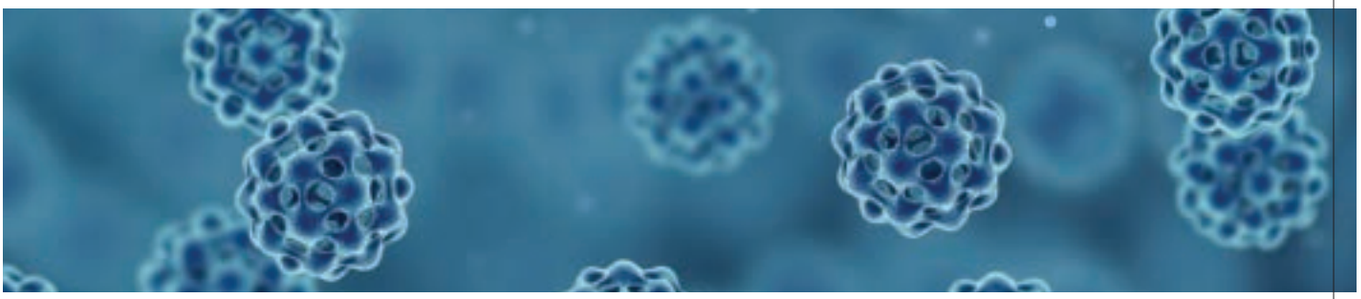
PRINCIPAL INVESTIGATOR
Abhijit Duggal, MD

STUDY COORDINATORS
Andrei Hastings, MD | 216.445.3960
Omar Mehkri, MD | 216.445.1939

CYSTIC FIBROSIS

Cystic Fibrosis Foundation Patient Registry

The Cystic Fibrosis (CF) Foundation 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
Elliot 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

INTERSTITIAL LUNG DISEASE

Genetic Risk for Granulomatous Interstitial Lung Disease

The objective of this NIH-supported study is to identify genetic risk factors for sarcoidosis and granulomatous lung disease.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
Allison Wimer, RRT | 216.444.9975

Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP-IPF)

This is a randomized, unblinded, phase 3, multicenter clinical trial of an antimicrobial therapy strategy in idiopathic pulmonary fibrosis (that is funded by an NIH subaward through the University of Pittsburgh. This study will randomize patients 1-to-1 to either oral antibiotic (co-trimoxazole or doxycycline) in addition to standard of care or standard of care alone to compare the impact of an antimicrobial therapy strategy on clinical outcomes.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
Jenna Brinker | 216.445.5836

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients with Idiopathic Pulmonary Fibrosis (SPIRIT)

Sponsored by Biogen MA Inc., this phase 2b study for subjects with mild to moderate idiopathic pulmonary fibrosis, who may or may not be receiving background therapies (pirfenidone or nintedanib), is designed to evaluate the change in forced vital capacity after 56 mg of BG00011 administered subcutaneously once weekly for 52 weeks.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
Ron Wehrmann, RRT | 216.445.0574

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Safety, Tolerability and Efficacy of Pirfenidone in Patients with Rheumatoid Arthritis Interstitial Lung Disease (TRAIL1)

Sponsored by Brigham and Women's Hospital, through a grant from Genentech Inc., this is a phase 2 trial investigating the efficacy, tolerability and safety of three-times-daily 801 mg pirfenidone (versus placebo) in patients with rheumatoid arthritis and interstitial lung disease.

PRINCIPAL INVESTIGATOR
Kristin Highland, MD | 216.445.5429

STUDY COORDINATOR
Ron Wehrmann, RRT | 216.445.0574

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 and Kaiser Permanente of California, the main objective of the trial 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 trial compares more frequent with less frequent surveillance of pulmonary nodules, and immediate or delayed participation in quality improvement collaboratives.

PRINCIPAL INVESTIGATOR
Peter Mazzone, MD, MPH

STUDY COORDINATOR
Amy Pritchard-Matia | 216.444.8347

A Study to Evaluate a Panel of Blood Biomarkers for Use in Patients Undergoing Evaluation for Lung Cancer (ONC-LN-04)

The primary objective of this study, sponsored by Oncocyte, is to develop a blood-based gene expression signature to be used in the detection of lung cancer in patients who underwent radiologic screening for lung cancer and had lung nodules detected.

PRINCIPAL INVESTIGATOR
Joseph Cicenia, MD

STUDY COORDINATOR
Stuart Houltham | 216.445.1056

Blood Sample Collection in Subjects with Pulmonary Nodules or CT Suspicion of Lung Cancer

The primary objective of this study, sponsored by Exact Sciences, is to assess new biomarkers for the detection of neoplasms of the lung.

PRINCIPAL INVESTIGATOR
Peter Mazzone, MD, MPH

STUDY COORDINATOR
Stuart Houltham | 216.445.1056

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

PULMONARY HYPERTENSION

A Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension (CATALYST)

Sponsored by Reata Pharmaceuticals, the study's main objective is to assess the efficacy and safety of bardoxolone methyl relative to placebo in patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH).

PRINCIPAL INVESTIGATOR
Kristin Highland, MD, MS

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

A 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 assess the efficacy and safety of ralinepag when added to pulmonary arterial hypertension (PAH) standard of care or PAH-specific background therapy in subjects with World Health Organization (WHO) Group 1 PAH.

PRINCIPAL INVESTIGATOR
Kristin Highland, MD, MS

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

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 on recent research findings in pulmonary hypertension and currently enrolling or upcoming studies.

PRINCIPAL INVESTIGATOR
Kristin Highland, MD

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

Uptravi® (SelexiPag): tHe usErs dRug rEgistry (SPHERE)

This registry describes the demographics, disease characteristics, dosing regimens and titration schemes, and 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

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension Due to Parenchymal Lung Disease (INCREASE)

The purpose of this study is to evaluate the safety and efficacy of inhaled treprostinil in subjects with precapillary pulmonary hypertension associated with interstitial lung disease including combined pulmonary fibrosis and emphysema.

PRINCIPAL INVESTIGATOR
Joseph Parambil, MD

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) in Heart Failure with Preserved Ejection Fraction (HFpEF) (SOUTHPAW)

United Therapeutics is sponsoring this study to assess the effect of oral treprostinil compared with placebo on change in exercise capacity as measured by change in 6-minute walk distance from baseline to week 24 in subjects with PH associated with HFpEF.

PRINCIPAL INVESTIGATOR
Miriam Jacob, MD

STUDY COORDINATORS
Mary Beukemann | 216.444.2140
Bryan Poynter | 216.445.1630

Phase 3 Open-Label, Multicenter Study to Evaluate the Long-Term Safety and Tolerability of Inhaled LIQ861 (Treprostinil) in Pulmonary Arterial Hypertension (WHO Group 1) Patients (INSPIRE)

Liquidia is the sponsor of this study that will evaluate the long-term safety and tolerability of LIQ861 in patients with PAH. This study will also evaluate the comparative bioavailability of treprostinil between two formulations of inhaled therapy.

PRINCIPAL INVESTIGATOR
Adriano Tonelli, MD

STUDY COORDINATORS
Mary Beukemann | 216.444.2140
Bryan Poynter | 216.445.1630

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 five days a week of exercise training and one day a week of diet counseling.

PRINCIPAL INVESTIGATOR
Gustavo Heresi, MD

STUDY COORDINATORS
Chazity Bush | 216.444.3702
Celia Melillo | 216.445.3763

RARE LUNG DISEASES

ALPHA-1 ANTITRYPSIN DEFICIENCY

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

This NCATS-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-related emphysema.

PRINCIPAL INVESTIGATORS
Umur Hatipoğlu, MD, and
James Stoller, MD

STUDY COORDINATOR
Rick Rice, RRT | 216.444.1150

BRONCHIECTASIS

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Assess the Efficacy, Safety and Tolerability and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis (WILLOW)

This is a phase 2 study sponsored by Insmed to evaluate if INS1007 can reduce pulmonary exacerbations over a 24-week treatment period in patients with non-cystic fibrosis bronchiectasis.

PRINCIPAL INVESTIGATOR
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STUDY COORDINATOR
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LYMPHANGIO-LEIOMYOMATOSIS

Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS)

This NIH-funded study through the University of Cincinnati is a real-world, long-term, prospective, observational drug registry of LAM patients taking or considering taking mTOR inhibitor therapy (sirolimus or everolimus).

PRINCIPAL INVESTIGATOR
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SARCOIDOSIS

Acthar® Therapy for Central Nervous System Sarcoidosis

Supported by Mallinckrodt ARD, this study aims to provide evidence that Acthar gel may serve as a therapeutic immune-modulating alternative to glucocorticoids in patients with moderate to severe neurosarcoidosis.

PRINCIPAL INVESTIGATOR
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STUDY COORDINATOR
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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
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STUDY COORDINATOR
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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
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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 ARD, this is a phase 4 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
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A Multicenter, Open-Label Study to Estimate the Effect Sizes of HRCT Endpoints in Response to Glucocorticoid Induction Therapy in Subjects with Pulmonary Sarcoidosis

Sponsored by Celgene Corp., this is an open-label trial to estimate the effect size of change from baseline in high-resolution computed tomography (HRCT)-based measurements of lobar volumes at functional residual capacity (FRC), total lung capacity (TLC) and airway wall thickness in response to glucocorticoid induction therapy (e.g., prednisone or prednisolone) in subjects with pulmonary sarcoidosis.

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