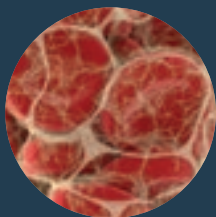


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RespiratoryExchange

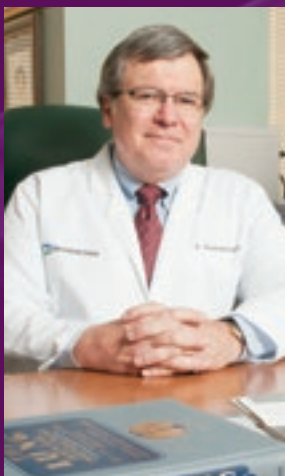
Research and News for Physicians from Cleveland Clinic's Respiratory Institute

Winter | 2018

FEATURE

Lung Transplantation in High-Risk Patients

p. 3



Dear Colleagues:

Welcome to this issue of *Respiratory Exchange*, which highlights the latest discoveries and innovations of our pulmonary, critical care medicine, allergy and clinical immunology staff within Cleveland Clinic's Respiratory Institute. We recently welcomed the Department of Infectious Diseases into our institute as well.

This issue is particularly representative of the wide range of interests and expertise of the staff in our institute. In these pages you'll find:

- The unique patient cohorts we see in our leading lung transplantation program (p. 3)
- Insights into the relationship between asthma and sepsis-related mortality (p. 5)
- Research that brings us closer to comprehensive screening guidelines for lung cancer (p. 6)
- Collaboration with our cardiovascular medicine colleagues on the diagnosis and treatment of cardiac sarcoidosis (p. 9)
- An exploration of chronic beryllium disease and Cleveland Clinic's role in its discovery (p. 12)
- Discussion of the LOTT trial results from one of its principal investigators (p. 14)
- A reflection on the importance of physician leadership from one of our foremost experts (p. 16)
- A glimpse into the design, operations and outcomes of our pulmonary embolism response team (p. 17)
- Studies of the role of the extracellular matrix in asthma severity (p. 20)

We hope you enjoy the articles in this issue of *Respiratory Exchange* and find something useful for your patients, practice, trainees or research. Inside, you'll also find a listing of our actively enrolling clinical trials (p. 26). Visit clevelandclinic.org/pulmonary to learn more about our clinical research activities.

Finally, we mourn the passing of Dr. Muzaffar Ahmad (p. 25), a past chair of our department. He was dear to many and is greatly missed.

If you have questions or would like to refer a patient, call our toll-free number for physicians, 855.REFER.123. We welcome your thoughts, feedback and questions.

Sincerely,

Herbert P. Wiedemann, MD, MBA

CHAIRMAN | CLEVELAND CLINIC RESPIRATORY INSTITUTE

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17-PUL-3665



Lung Transplantation in High-Risk Patients

Advanced age, coronary artery disease and multi-organ transplant

By Marie Budev, DO, MPH

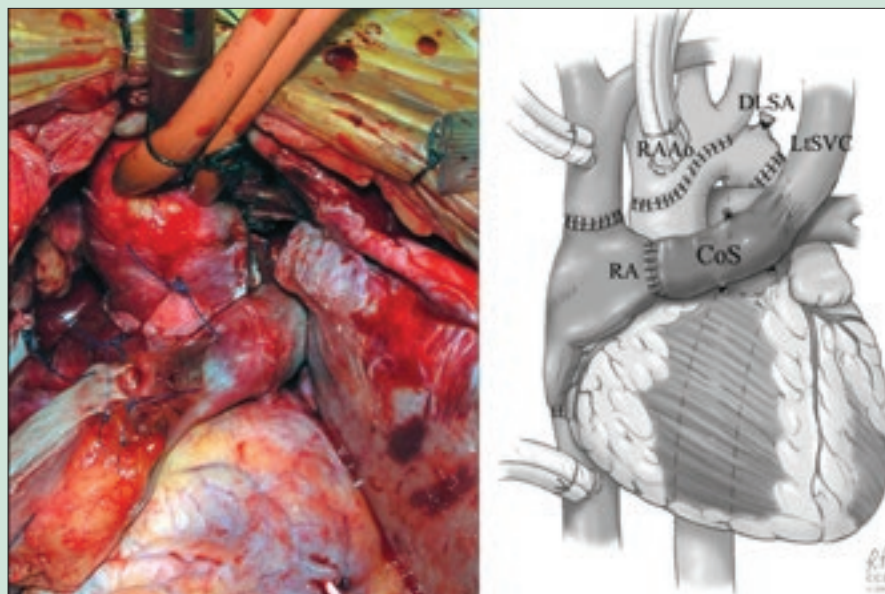
Lung transplantation (LT) has evolved to represent the therapy of choice for a growing number of patients with end-stage lung diseases. In selected patients, LT may significantly prolong survival and improve quality of life. Careful candidate selection is an important part of the effort to increase the likelihood of successful outcomes.

The most recent edition of International Society for Heart and Lung Transplantation (ISHLT) guidelines for the selection of lung transplant candidates is an excellent guide to help physicians identify patients who are most likely to benefit from LT.¹ However, transplant centers are now being faced with unconventional candidates, and the ISHLT guidelines are limited regarding management of these higher-risk patients who may be older than 65, need multi-organ transplant or have concomitant coronary artery disease (CAD).

Cleveland Clinic's Lung and Heart-Lung Transplant Program has gained significant expertise in the management and successful transplantation of recipients who are older than 65, have concomitant CAD or may need liver-lung or heart-lung transplantation. Here we share some recent experiences with these unconventional recipient cohorts.

THE OLDER RECIPIENT

As life expectancy increases, the proportion of the population over the age of 65 is also growing. As a result, the number of potential LT candidates over the age of 65 is increasing, yet many transplant centers in the U.S. set the cutoff age at 65. Published data regarding outcomes among older LT recipients have been conflicting, precluding firm recommendations. At this time, the decision to transplant candidates older than the arbitrary cutoff age of 65 is center-specific.



► Heart-lung transplant in a patient with congenital heart disease and Eisenmenger's syndrome.

Cleveland Clinic's Lung Transplant Program has amassed a significant amount of experience in transplanting candidates over the age of 65 and does not view advanced age alone as a contraindication to transplantation. Our current philosophy is that the numerical value assigned to a person's age provides an incomplete assessment of the patient's overall status and suitability for transplant.

Utilizing a multidimensional assessment of a patient's neurocognitive status, frailty, medical comorbidities and social support, we try to create a composite evaluation that provides more meaningful information than the patient's chronological age alone. In general, patients of advanced age must be free of any other nonpulmonary complications and be physically, nutritionally and cognitively capable of undergoing rigorous surgery and postsurgical rehabilitation.

Since our program's inception in 1990, we have performed 274 LTs in recipients older than 65, including several patients over

the age of 75. We have achieved excellent one- and three-year survival in this high-risk group (Figure 1).

CONCOMITANT CAD

The 2014 ISHLT candidate selection consensus document cites CAD as a relative contraindication. Research from Sudish Murthy, MD, PhD, Section Head of Thoracic Surgery, and colleagues from Cleveland Clinic's surgical transplant team, however, found that LT recipients who were found to have CAD that could be adequately addressed with either percutaneous coronary intervention or coronary artery bypass grafting (CABG) performed prior to or concurrent with LT do not have poorer outcomes.² These findings demonstrate that the potential risks posed by the presence of CAD can be mitigated by effective interventions. They highlight the need for an experienced team of interventional cardiologists as well as transplant surgeons skilled in managing the technical complexities of performing LT in patients with prior or concurrent CABG.

With this level of experience and expertise at Cleveland Clinic, we have been able to offer transplantation to patients whom other centers deemed unsuitable.

MULTI-ORGAN TRANSPLANTATION

Currently, Cleveland Clinic is one of only a few transplant centers in the U.S. to offer heart-lung transplantation (HLT). The leading indication for HLT is adult congenital heart disease, which accounts for almost 35 percent of all HLT worldwide.

Gosta Pettersson, MD, PhD, Vice Chairman of the Department of Thoracic and Cardiovascular Surgery, and colleagues reported Cleveland Clinic's experience with 34 HLT procedures performed from 1992 to 2014.³ Congenital heart disease was the indication for HLT in approximately 50 percent of cases, and idiopathic pulmonary arterial hypertension accounted for an additional 25 percent of cases. Fifteen percent of the patients who underwent HLT required extracorporeal membrane oxygenation support (ECMO) as a bridge to transplant. Overall survival for the entire group at one, five, 10 and 15 years was 82, 62, 54 and 54 percent, respectively.³

Cleveland Clinic is also one of a limited number of centers offering combined liver-lung transplantation (LLT) as a therapeutic option for selected patients with coexisting

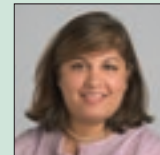
cirrhotic liver and end-stage lung disease. The main indications for LLT are cystic fibrosis and alpha-1 proteinase inhibitor deficiency, diseases that are prone to both pulmonary and hepatic complications in which the impairment of the liver may jeopardize LT outcomes if the transplants are performed separately.

Jamak Modaresi Esfeh, MD, staff gastroenterologist, and colleagues recently presented Cleveland Clinic's experience with five LLT transplants performed between 2000 to 2015. They found that one-year survival for these five combined-organ transplant recipients was significantly better than the survival of patients with advanced lung disease and cirrhosis with portal hypertension who underwent LT alone (80 versus 33 percent, $P > 0.001$).⁴ Thus, for select patients with advanced lung and liver disease, combined transplantation affords an opportunity for extended survival.

MULTISPECIALTY CENTERS TAKE ON TOUGH PATIENTS

Cleveland Clinic's position as a multispecialty tertiary care center allows us to perform LT, HLT and LLT on complex, challenging patients. Further, emerging technologies such as ex vivo perfusion and our research on alternative lung allocation models are helping us bring transplants to more patients. In 2016, we performed 110 LTs,

including LLTs. Since our program began in 1990, our long-term survival rates have remained above the national average. As we continue to push the boundaries of LT, we remain centered on our tripartite mission of better care of the sick, investigation of their problems and further education of those who serve.

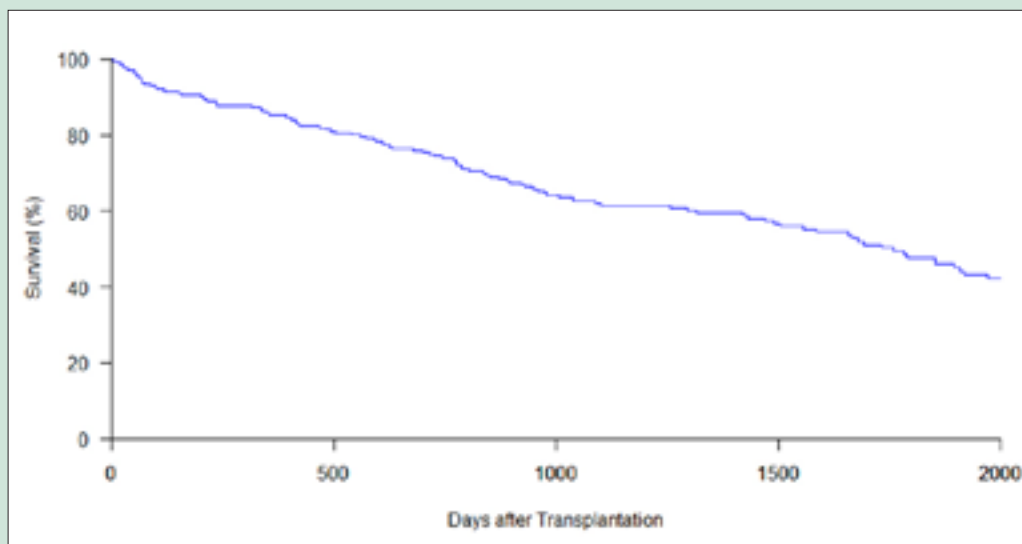


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► **Figure 1:** Survival curve for patients over 65 years of age (N = 274).

Asthma Associated with Decreased Sepsis-Related Mortality

Are chronically activated pro-inflammatory pathways key?

By Joe Zein, MD, and Serpil Erzurum, MD

Asthma's complex immunopathology involves several major mechanisms, including classic type 2 helper cell (Th2) immune responses, activation of interleukin-17-mediated neutrophilic inflammation, and innate toll-like receptor (TLR) responses to pathogens. These mechanisms are all important to normal host response to pathogens.

Asthma also involves enhanced mast cell degranulation and release of mediators, such as tumor necrosis factor alpha (TNF- α) and interleukin 6 (IL-6), that may counter the impact of infections through enhanced neutrophil influx and killing of bacteria. Heightened innate responses in non-Th2 pathways in patients with asthma would also enable faster pathogen clearance.

Given this heightened activation of pro-inflammatory pathways and the potential enhancement of host defenses in patients with asthma, we hypothesized that the incidence and severity of sepsis would be lower in this patient population.

To test this hypothesis, we designed a study analyzing the 2012 Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS).¹ We validated this data with additional sources: 2007, 2008 and 2011 NIS and Cleveland Clinic health system admissions between 2010 and 2014. We sought to assess the impact of asthma on septicemia, sepsis, severe sepsis, septic shock and mortality in patients hospitalized for pneumonia, urinary tract infection (UTI), or skin and soft tissue infection (SSTI). Diagnoses were defined using ICD-9-CM codes. Unlike in previous studies, we excluded patients with remote or current smoking history to minimize bias of smoking-related airways disease.

Studies using a large database can take advantage of big data to detect more accurate effect-size estimates using large, real-life data. They provide a valuable tool to predict epidemiological associations relevant to population health.

ASTHMA = LOWER SEPSIS-RELATED MORTALITY

In this analysis we found that asthma is associated with lower sepsis-related mortality. From the NIS 2012 sample, which includes 20 percent of all U.S. hospital discharges, 23,386 patients with asthma and 203,603 without asthma were hospitalized across the U.S. with pneumonia, UTI or SSTI. Asthma patients had decreased risk for:

- hospital mortality (aOR [95% CI]: 0.41 [0.37; 0.45])
- septicemia (aOR [95% CI]: 0.60 [0.58; 0.61])
- sepsis (aOR [95% CI]: 0.59 [0.56; 0.62])
- severe sepsis (aOR [95% CI]: 0.60 [0.58; 0.63])
- septic shock (aOR [95% CI]: 0.74 [0.71; 0.78])

Risk reductions were also consistently significant within each type of infection (pneumonia, UTI, SSTI). Asthma was associated with lower risk for acute kidney injury (adjOR [95% CI]: 0.65 [0.63; 0.68]) and intensive care unit admission (adjOR [95% CI]: 0.80 [0.64; 0.99]). Hospital lengths of stay were shorter, and costs were lower. Analyses of other NIS years and Cleveland Clinic health system data sets confirmed the NIS 2012 results.

This protective effect of asthma against sepsis challenges findings in prior case-controlled studies, which suggested asthma was associated with higher risk for invasive pneumococcal and nonrespiratory infections. The results in this study, adjusted for gender, age, income, race and comorbidities across four different years, are consistent across five independent, large data sets that include a total of 99,257 patients with asthma among nearly 1 million hospitalized individuals.

Future work focusing on further defining the types of immune responses associated with asthma that confer this protective effect may translate into therapeutic approaches to improving sepsis-related outcomes in nonasthmatic individuals.

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Cleveland Clinic's Lung Cancer Screening Program

Centralized management, patient education and incidental findings

Humberto Choi, MD, and Peter Mazzone, MD, MPH

The Center for Medicare & Medicaid Services (CMS) and the U.S. Preventive Services Task Force recommend lung cancer screening with a low-dose chest CT scan (LDCT) for a well-defined cohort at high risk of having lung cancer based on age and smoking history. Our years of experience in designing, implementing, testing and improving Cleveland Clinic's lung cancer screening program have conferred valuable insights from which other programs may benefit.

Lung cancer screening reduces lung cancer mortality, but this benefit is realized in only a small fraction of screened patients. Risks of screening include the performance of the test (radiation exposure) and the evaluation of screen-detected findings (anxiety, morbidity and mortality from procedures). Most stakeholder societies feel the balance of benefits and risks favors lung cancer screening while recognizing that this favorable balance depends on screening in high-quality programs.

Important aspects of screening capable of altering this balance include the selection of screen-eligible patients, appropriate management of screen-detected findings, and smoking cessation. Given the potential for harm, it is also important that patients are educated in a manner that allows them to make value-based decisions about participation.

CENTRALIZED MANAGEMENT YIELDS FAVORABLE RESULTS

We implemented Cleveland Clinic's lung cancer screening program in 2012. Our multidisciplinary program is structured to meet the core components of a high-quality screening program as outlined by the American Thoracic Society and American

College of Chest Physicians. Our program uses clinical care paths that guide the management of common incidental findings such as coronary artery calcification and thyroid nodules. These care paths are based on specialist expertise and national guidelines.

Initially, a clinician ordering an LDCT was responsible for communicating with the patient and managing the screening results. Based on a review of screening performance and mandates for both the provision of a shared decision-making visit and data reporting to a national registry, we centralized communication and management within the lung cancer screening program in April 2015. Now, rather than ordering the screening itself, clinicians instead order a consult to the screening program.

Following centralization, the number of patients screened who were outside the CMS criteria decreased (Figure 1), and the percentage of screen-detected stage 1 cancers increased (Figure 2). These findings suggest the value of the centralized approach to screening in our health system.

PATIENT EDUCATION KEY TO QUALITY PROGRAM

The quality of implementation has a significant impact on the overall balance of benefit versus risk in lung cancer screening. The mandate from CMS for a counseling and shared decision-making visit for patients referred for screening recognizes the importance of patient education to permit value-based decision-making.

Our group recently published the first study detailing the impact of this mandated visit on patient understanding and interest in participating.¹ We showed that a single counseling and shared decision-making

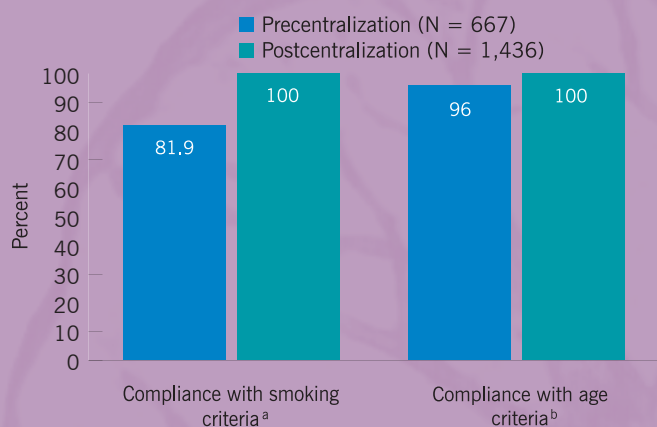
visit with a physician or advanced practice provider increases patient understanding of the potential harms and benefits of lung cancer screening.

These visits are a crucial part of our program. To measure their impact, we surveyed patients immediately before their visit, immediately afterwards and at one month post-visit. Our pre-visit in-person and one-month post-visit phone surveys included questions about lung cancer screening benefits and risks, and age and smoking eligibility for screening. The immediate post-visit survey asked additional questions about how the information was presented and whether it was helpful.

Our results indicated a substantial increase in knowledge about lung cancer screening eligibility and about the benefits and risks of screening (Figure 3). Knowledge levels waned by the one-month follow-up survey; however, they remained significantly higher than at the initial visit. Patients also stated that the individualized presentation of risks and benefits made them more comfortable about their decision. These results highlight the potential value of a shared decision-making visit and suggest that an annual visit may be beneficial.

HOW TO MANAGE COMMON INCIDENTAL FINDINGS

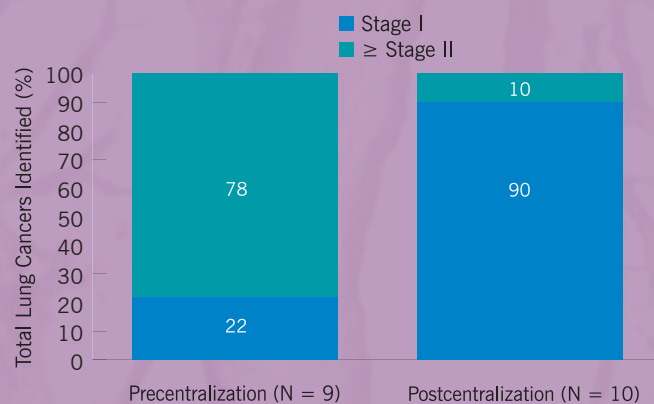
Finally, we set out to define the frequency of incidental findings found on LDCT for lung cancer screening and determine their clinical and financial downstream effects. Our recently published findings show that almost every patient had at least one abnormality other than a lung nodule described on the radiology report (Figure 4), with 15 percent of patients undergoing further evaluation of an incidental finding.²



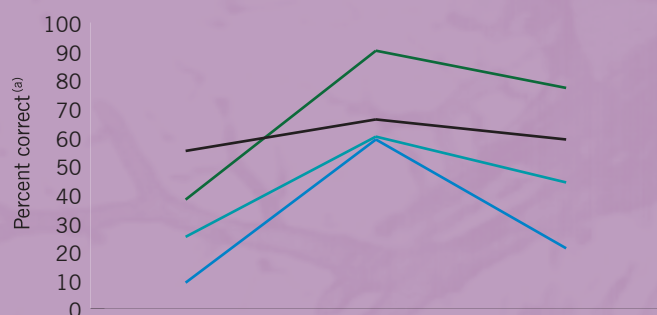
► **Figure 1.** Improvement in compliance with screening guidelines following centralization, 2012–2017 (N = 2,103).

^aEligible smoking criteria are ≥ 30 pack years and either is a current smoker or has quit smoking in last 15 years.

^bEligible age range for LDCT screening is 55–77.



► **Figure 2.** Early-stage cancers diagnosed as a percentage of total lung cancers identified, 2012–2017 (N = 19).



	Pretest (N = 125)	After Visit (N = 123)	1-Month Follow-Up
Age Criteria	9	59	21
Smoking Criteria ^b	25	60	44
Benefits	55	66	59
Harm ^c	38	90	77

► **Figure 3.** Change in knowledge of lung cancer screening following shared decision-making visit, 2012–2017.

^aPercentages rounded to the nearest whole number.

^bPercentage of those surveyed who gave partially correct or correct answers.

^cPercentage of those surveyed who were able to identify at least one potential harm of lung cancer screening.

One in seven patients required a referral to a specialist, and one in eight had additional testing performed. These results suggest programs should engage other specialists to develop well-defined care paths to help with the appropriate management of these incidental findings.

FUTURE DIRECTIONS AND RESEARCH

Based on our experience at Cleveland Clinic, we favor centralized management of screening decisions in our health system, detailed and thorough shared decision-making visits with one-year follow-up, and concrete plans for managing incidental findings.

We continue to conduct research to provide evidence-based support for the elements of a quality program. Currently, we are reviewing why some eligible patients choose not to enter our screening program, why others are noncompliant with their annual visit, and whether the shared decision-making visit impacts rates of smoking cessation. We hope these results will translate into further improvements to our program.



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Following centralization, the number of patients screened who were outside the CMS criteria decreased, and the percentage of screen-detected stage 1 cancers increased.

Figure 4. Incidental findings on low-dose CT screening for lung cancer.

PULMONARY	<ul style="list-style-type: none"> • Emphysema (47%, N = 115) • Bronchial wall thickening (36%, N = 87) • Atelectasis (14%, N = 34)
CARDIOVASCULAR	<ul style="list-style-type: none"> • Coronary artery calcifications (51%, N = 126) • Aortic calcification (21%, N = 52) • Thoracic aortic ectasia (8%, N = 20)
BONE	<ul style="list-style-type: none"> • Degenerative joint disease (17%, N = 42)
GASTROINTESTINAL	<ul style="list-style-type: none"> • Hiatal hernia (10%, N = 25) • Hepatic cyst (6%, N = 14)

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Cardiac Sarcoidosis: What Do We Know?

An overview from our multidisciplinary team

By Manuel Ribeiro Neto, MD, Emer Joyce, MD, PhD, Christine Jellis, MD, PhD, Rory Hachamovitch, MD, and Daniel Culver, DO

Sarcoidosis is a systemic disease of unknown etiology, characterized by non-necrotizing granulomas. Symptomatic cardiac involvement occurs in only 2 to 5 percent of patients, but screening with MRI or autopsy studies reveals a prevalence closer to 25 percent. The relevance of those subclinical cases is unknown, but many are unlikely to develop clinically significant disease.

The most common manifestations of cardiac sarcoidosis are atrio-ventricular block, ventricular arrhythmia and heart failure. Less common are bundle branch blocks, atrial arrhythmias, valvular abnormalities, pericardial effusion and sudden cardiac death. Although nonspecific chest pain is extremely common in sarcoidosis, it is not usually a manifestation of cardiac sarcoidosis.

SCREENING AND DIAGNOSIS

Patients with sarcoidosis should be screened with history (significant palpitations, presyncope or syncope, unexplained dyspnea) and electrocardiogram. Echocardiogram and Holter monitor testing are useful when initial screening is suggestive. If any abnormality is encountered, advanced cardiac imaging should be performed.

There is no reference standard in cardiac sarcoidosis. The sensitivity of endomyocardial biopsy is low (30 percent). Three sets of clinical criteria have been proposed by the following organizations: Japanese Ministry of Health and Welfare (JMHV) (Table), Heart Rhythm Society (HRS) and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG).

Cardiac PET has been compared to the JMHV criteria in at least seven studies (sensitivity 79 to 96 percent, specificity 68 to 86 percent). Based on perfusion and inflammation (the latter with fluorodeoxyglucose [FDG]) imaging, there are four possible results (Figure 1).

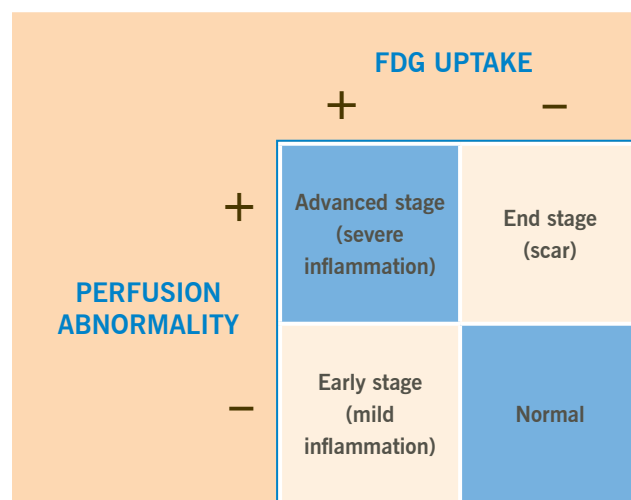
Cardiac MRI also performed well (sensitivity 76 to 100 percent, specificity 78 to 92 percent) in two studies utilizing the JMHV criteria and endomyocardial biopsy, respectively, as the gold standard. Findings included regional wall motion abnormalities with or without wall thinning in a noncoronary artery distribution, increased signal on T2-weighted imaging suggestive of inflammation, and late gadolinium enhancement (LGE). The pattern of LGE is typically

patchy, midmyocardial or epicardial, and in a noncoronary distribution. LGE can be seen in both active disease (due to inflammation) and in scar (Figure 2).

The results of cardiac PET and MRI must be interpreted with caution. Although typical imaging findings are observed as described above, cardiac sarcoidosis can always masquerade with patterns suggestive of other disease etiologies. As such, there is still uncertainty around important aspects of these tests and no consensus on which test is preferable. A multidisciplinary approach involving pulmonologists, cardiologists and advanced cardiac imaging specialists is recommended and available at reference centers to integrate clinical and imaging findings.

The differential diagnosis should include:

- Hypertensive and other forms of nonischemic cardiomyopathy
- Ischemic cardiomyopathy
- Giant cell myocarditis
- Arrhythmogenic right ventricular cardiomyopathy
- Cardiomyopathy
- Left ventricle noncompaction
- End-stage hypertrophic cardiomyopathy
- Cardiac iron overload (hemochromatosis, β -thalassemia)
- Infectious causes (viruses, Chagas disease, toxoplasmosis, Lyme disease)



► **Figure 1.** Interpretation of cardiac PET scan based on perfusion abnormalities and FDG uptake.

TREATMENT

A multidisciplinary approach to therapy is critical. Depending on the clinical manifestations, specialists in sarcoidosis, advanced cardiac imaging, heart failure and cardiac electrophysiology should be involved. Those specialists are readily available at our institution, allowing us to offer integrated care to our patients.

Medical therapy

Corticosteroids (CS) are the first-line agent to treat active inflammation. The dosing needs to be individualized; in a meta-analysis, dosing ranged from 20 mg of prednisone daily to pulse therapy in more severe cases.¹ Depending on the severity of the disease and the complications caused by CS, it is reasonable not to use CS in selected cases.

Second-line agents are methotrexate, leflunomide, azathioprine, mycophenolate and hydroxychloroquine. There are no head-to-head comparisons between these agents, so which agent to use depends on expert opinion. In our Sarcoidosis Center, we favor methotrexate and leflunomide.² We also favor starting a second agent early in the process, ideally at the same time CS are started. This approach decreases the patient's exposure to CS and their undesirable side effects.

Third-line agents are the tumor necrosis factor-alpha (TNFα) antagonists infliximab and adalimumab. A randomized controlled trial of infliximab in patients with pulmonary sarcoidosis showed a reduction in extrapulmonary organ involvement severity.³ Based on this study and others, TNFα antagonists are recommended as third-line therapy by sarcoidosis experts.

Nonimmunosuppressive medications targeting specific cardiac manifestations of sarcoidosis should also be used. They include heart failure medications and anti-arrhythmic medications.

Device/ablation therapy

The use of the electrophysiology armamentarium should follow HRS guidelines. A permanent pacemaker should be placed in high-degree atrioventricular block even if it reverses transiently. An implantable cardiac defibrillator (ICD) should be placed in patients who have spontaneous sustained ventricular arrhythmias, prior cardiac arrest, ejection fraction (EF) ≤ 35 percent despite optimal medical therapy, or are receiving a pacemaker. In patients with EF between 36 and 49 percent despite optimal medical therapy, ICD implantation may be considered (an electrophysiology study could help stratify the sudden-death risk). Ablation therapy is an option in patients with refractory ventricular arrhythmias.

PROGNOSIS

The prognosis of patients with clinically overt cardiac sarcoidosis was demonstrated in a recent study from Finland.⁴ One-, five- and 10-year transplant-free cardiac survival rates were 99.1, 93.5 and

JAPANESE MINISTRY OF HEALTH AND WELFARE CRITERIA (REVISED 2006)

HISTOLOGICAL DIAGNOSIS GROUP

Endomyocardial biopsy showing non-caseating granulomas with histological or clinical diagnosis of extracardiac sarcoidosis

CLINICAL DIAGNOSIS GROUP

Extracardiac sarcoidosis is diagnosed histologically or clinically and when the following conditions are met: (1) two or more major criteria, or (2) one major criteria and two minor criteria.

• MAJOR CRITERIA

- Advanced atrioventricular block
- Basal thinning of the interventricular septum
- Positive gallium-67 uptake in the heart
- Depressed left ventricular ejection fraction < 50%

• MINOR CRITERIA

- Abnormal EKG findings: ventricular arrhythmias (ventricular tachycardia or multifocal or frequent premature ventricular contractions), complete right bundle branch block, axis deviation or abnormal Q waves
- Abnormal echocardiogram: wall motion abnormality or morphological abnormality (aneurysm or wall thickening or ventricular dilation)
- Perfusion defects on nuclear imaging: thallium-201/technetium-99m SPECT
- Delayed gadolinium enhancement on cardiac MRI
- Interstitial fibrosis or monocyte infiltration on cardiac biopsy

Table: Japanese Ministry of Health and Welfare Criteria.

89.3 percent, respectively. Heart failure/low EF predicted worse survival. Other predictors are age ≥ 46 years, extent of mismatch defect in cardiac PET and extent of LGE in cardiac MRI. The prognosis of patients with subclinical cardiac sarcoidosis is controversial.

As a WASOG Sarcoidosis Clinic, we provide a multidisciplinary approach to patients with cardiac sarcoidosis and continue to research treatment approaches to better serve these patients.





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► **Figure 2.** Cardiac MRI four-chamber view demonstrating regions of midmyocardial delayed enhancement (blue arrows) representative of scar/inflammation in a patient with known cardiac sarcoidosis.

Providing Specialized Expertise for Chronic Beryllium Disease

Cleveland Clinic continues its leadership role

By Raed Dweik, MD, MBA

Inhalation of beryllium (Be) has been associated with acute and chronic lung disease. Due to improved industrial hygiene measures, acute beryllium disease has essentially disappeared, but chronic beryllium disease (CBD) continues to affect workers in industries where beryllium is manufactured and processed.

CBD represents a delayed-type hypersensitivity reaction to beryllium and is clinically similar to other granulomatous diseases, such as sarcoidosis. While most beryllium exposure occurs through inhalation and the lung is the primary organ involved in CBD, exposure can also occur through the skin or mucous membranes. Developing beryllium immune sensitization and overt disease depends on several factors including genetics and type of exposure. Generally, about 10 percent of exposed individuals develop beryllium sensitization, and about 50 percent of sensitized individuals (5 percent of all exposed) develop CBD.

ACQUISITION AND DIAGNOSIS OF THE DISEASE

Occupations with the highest potential for exposure are those involved with the primary production, metal machining and reclaiming of scrap alloys. Other high exposure areas are in the nuclear power, aerospace and electronics industries. The disease has been reported in individuals with very low exposure (e.g., administrative assistants) who are not involved in the manufacturing process. This may be a reflection of genetic predisposition, which seems to have a major role in the development of CBD. A variant of the major histocompatibility complex (HLA-DP1Glu⁶⁹) was found in 97 percent of patients with CBD and only in 30 percent of controls.

The very first case of beryllium-induced lung disease in English-language literature was reported in Cleveland Clinic Quarterly in 1943 by Howard S. Van Ordstrand, MD, the first Chairman of Pulmonary Disease at Cleveland Clinic.

The clinical history (other than the occupational history) and physical examination are usually nonspecific. The blood beryllium lymphocyte proliferation test is currently the screening test of choice to identify workers who develop beryllium sensitization or CBD. This test is also currently an integral part of the diagnosis of CBD. The test involves exposing peripheral blood mononuclear cells in vitro to beryllium salts at varying concentrations for variable time intervals. Cell proliferation in the presence of beryllium indicates a positive test. Cleveland Clinic has one of the few laboratories in the country that can run this highly specialized test.

On pulmonary function testing, spirometry may show evidence of obstruction, restriction or both. The diffusing lung capacity usually declines over the course of the disease. A chest radiograph is normal in more than half of the patients who are eventually confirmed to have CBD based on lung pathology. High-resolution chest CT is more sensitive than chest radiograph but can still be normal in more than 25 percent of patients with CBD. Typical findings on high-resolution CT are ground-glass opacities or interstitial changes.

Flexible fiber-optic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies are usually necessary to confirm a suspected diagnosis of CBD. Typical findings on bronchoscopy include BAL lymphocytosis (more than 20 percent lymphocytes). The beryllium lymphocyte proliferation test can also be performed on BAL cells.

To diagnose CBD, the following two criteria must be satisfied: a positive blood or BAL beryllium lymphocyte proliferation test, and the presence of non-necrotizing granulomas (or other compatible pathology) on lung biopsy. Patients who have a positive blood beryllium lymphocyte proliferation test but normal lung pathology are considered to be sensitized to beryllium but do not have CBD. Sensitized individuals have a lifelong risk for developing the disease and require periodic monitoring.

NATURAL HISTORY AND TREATMENT

Due to the use of the beryllium lymphocyte proliferation test to screen workers exposed to beryllium, many cases are now diagnosed very early, before radiographic or physiologic changes are seen and symptoms develop. The natural history of the disease is not

clear in patients who have granulomas on transbronchial biopsy but are asymptomatic with no physiologic or radiographic abnormalities. For many individuals, the disease may not progress beyond asymptomatic granulomas in the lungs. For some, the granulomas become organized and eventually cause fibrosis, resulting in progressive impairment of pulmonary function.

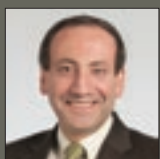
No controlled studies for CBD therapy are available. Based on the pathogenesis of the disease (immune-mediated) and given the similarities to sarcoidosis, CBD is treated with corticosteroids. In end-stage cases, lung transplantation may be considered.

ADVANCES FROM CLEVELAND CLINIC

Cleveland Clinic has been and continues to be on the forefront of evaluating and caring for patients with beryllium-induced lung disease, investigating their problems and educating healthcare professionals about beryllium disease-related issues. Some program highlights include:

- The very first case of beryllium-induced lung disease in English-language literature was reported in *Cleveland Clinic Quarterly* in 1943 by Howard S. Van Ordstrand, MD, the first Chairman of Pulmonary Disease at Cleveland Clinic.
- The early work on the development of the lymphocyte proliferation test was pioneered by Cleveland Clinic researchers Sharad D. Deodhar, MD, PhD, and Barbara P. Barna, PhD.
- The first lung transplant for a patient with CBD was performed at Cleveland Clinic.
- The Clinic participated in several international studies that helped define the role of genetics in the development of beryllium sensitization and CBD.
- Cleveland Clinic hosted the International Beryllium Summit in 2011, which drew participants from 16 states and four countries to hear presentations by Cleveland Clinic and visiting national and international speakers.

Cleveland Clinic remains one of only a few referral centers in the United States to offer comprehensive evaluation for individuals with beryllium exposure, beryllium sensitization and CBD, including full-service, on-site beryllium lymphocyte proliferation testing on blood and BAL.



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► Howard S. Van Ordstrand, MD, Cleveland Clinic's first Chairman of Pulmonary Disease and author of the first report in English-language medical literature of beryllium-induced lung disease.

Suggested reading

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Prescribing Supplemental Oxygen for Patients with COPD

Implications from the Long-Term Oxygen Treatment Trial (LOTT)

By James K. Stoller, MD, MS

For patients with chronic obstructive pulmonary disease (COPD) and severe resting room air hypoxemia, supplemental oxygen has been shown to be life-prolonging. Specifically, the time-honored Nocturnal Oxygen Therapy Trial (NOTT) and the Medical Research Council study showed that supplemental oxygen used continuously (i.e., as close to 24 hours per day as possible) was significantly associated with enhanced survival for individuals whose resting room air PaO_2 was ≤ 55 mm Hg or 56-59 mm Hg with accompanying polycythemia or cor pulmonale. On the basis of these studies, the Centers for Medicare & Medicaid Services (CMS) currently supports and funds prescribing supplemental oxygen for individuals with COPD who satisfy the following indications:

1. Resting room air $\text{PaO}_2 < 55$ mm Hg or $\text{SaO}_2 < 88\%$
2. Resting room air PaO_2 56-59 mm Hg with "P" pulmonale on electrocardiogram, polycythemia $> 55\%$
3. Exercise desaturation to $\text{SaO}_2 < 88\%$ or sleep desaturation not corrected by CPAP

In this context, supplemental oxygen currently accounts for a \$2 billion expenditure in the United States.

ADDRESSING THE QUESTION

In contrast to the clarity that supplemental oxygen benefits COPD patients with severe resting hypoxemia, the role of supplemental oxygen in COPD patients with moderate resting hypoxemia or with isolated exercise desaturation remains unclear. Indeed, small studies in the late 1990s failed to demonstrate that supplemental oxygen confers benefit for COPD patients whose resting room air PaO_2 levels were 56-65 mm Hg and 56-69 mm Hg, respectively.

To address this common and naggingly unclear issue for clinicians, the National Heart, Lung, and Blood Institute and CMS sponsored the Long-Term Oxygen Treatment Trial (LOTT), which was an unblinded, randomized controlled trial of supplemental oxygen for COPD patients with moderate resting hypoxemia and/or exercise desaturation. LOTT was conducted in 42 centers throughout the United States, including Cleveland Clinic.

LOTT recruited 738 COPD patients whose resting SpO_2 was 89 to 93 percent and/or who desaturated with activity (defined as desaturating to $\text{SpO}_2 < 90\%$ for > 10 seconds but remaining $> 80\%$ SpO_2 for > 5 minutes on a six-minute walk test). Participants were randomized to a control group (which received no supplemental oxygen)

versus an intervention group, which received either supplemental oxygen at rest and during sleep for patients with resting moderate hypoxemia, or supplemental oxygen with activity and sleep alone for those patients whose resting room air SpO_2 values exceeded 93 percent but who satisfied desaturation criteria as outlined above.

RESULTS

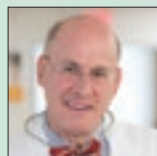
The primary outcome measure of LOTT was time to death or first hospitalization, with patient follow-up for one to six years (median follow-up 18.4 months). In a time-to-event analysis, no significant difference between the supplemental oxygen group and the control group was observed in time to death or first hospitalization. Similarly, no difference between groups was observed in rates of all hospitalizations, COPD exacerbations or COPD-related hospitalizations. A variety of other measures of quality of life, lung function and distance walked in six minutes were also assessed (e.g., the St. George's Respiratory Questionnaire, the Quality of Well-Being Scale, SF36, the Hospital Anxiety and Depression Scale, the Pittsburgh Sleep Quality Index) (Table). Notably, in secondary analysis of pre-specified groups, the only groups who demonstrated a benefit from using supplemental oxygen were those who experienced a COPD exacerbation between one and three months before enrollment into LOTT and patients > 71 years old at the time of study enrollment.

LOTT is among the landmark studies in COPD because it addresses a critically important everyday clinical question that had remained unanswered for many years. To the extent that LOTT showed no benefit from supplemental oxygen in most of the COPD patients studied, we expect that the results of this trial will change prescribing patterns for patients with COPD and moderate resting hypoxemia or isolated exercise desaturation; specifically, clinicians may no longer prescribe supplemental oxygen for stable COPD patients who desaturate to the level studied in LOTT.

Several important caveats must be considered in interpreting the results of this landmark trial. First, the results do not reliably apply to COPD patient groups who were not included in the study, such as those who severely desaturate with activity (i.e., to $< 80\%$ SpO_2 on exercise for > 1 minute). Similarly, as all LOTT patients were stable for at least one month, the results do not apply to COPD patients who desaturate on being discharged from the hospital after a COPD exacerbation.

As with so many other important NIH-sponsored clinical trials or observational studies in which Cleveland Clinic Respiratory Institute has participated (e.g., Registry of Patients with Severe Deficiency of Alpha-1 Antitrypsin, the Lymphangioleiomyomatosis Registry, Severe Asthma Research Network and the ARDSNet trial), LOTT presents another powerful example of how Cleveland Clinic Respiratory Institute is fulfilling its tripartite mission of better care of the sick, investigation of their problems, and further education of those who serve.

Figure and legend adapted from: Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med.* 2016;375(17):1617-1627.



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TABLE. PRIMARY COMPOSITE OUTCOME OF DEATH OR FIRST HOSPITALIZATION FOR ANY-CAUSE AND COMPOSITE EVENTS IN THE INTENTION-TO-TREAT POPULATION

OUTCOME	NO SUPPLEMENTAL OXYGEN (N = 370)	SUPPLEMENTAL OXYGEN (N = 368)	HAZARD RATIO (95% CI)	P VALUE
PRIMARY OUTCOME				
• DATE OF FIRST HOSPITALIZATION FOR ANY CAUSE			0.94 (0.79-1.12)	0.52
• Number of events	250	248		
• Composite rate per 100 person-years	36.4	34.2		
PRIMARY-OUTCOME COMPONENT EVENTS				
• DEATH			0.90 (0.64-1.25)	0.53
• Number of deaths	73	66		
• Rate per 100 person-years	5.7	5.2		
• FIRST HOSPITALIZATION FOR ANY CAUSE			0.92 (0.77-1.10)	0.37
• Number of first hospitalizations	237	229		
• Rate per 100 person-years	34.5	31.6		

From the Bedside to the Boardroom: Developing Physician Leaders

By James K. Stoller, MD, MS

Leadership matters in healthcare. Importantly, physician leadership matters both in the boardroom and at the bedside. Many lines of evidence support this observation:

- Healthcare faces the challenge of the “triple threat” (quality, access, affordability/value).
- Physicians are traditionally trained as “heroic lone healers”¹ and may be “collaboratively challenged.”²
- Leadership competencies differ from clinical skills and are traditionally taught neither in medical school nor in graduate medical training.
- Observational data³ suggest that top-tier hospital ranking in *U.S. News & World Report* is associated with having a physician as the hospital CEO.

Though leadership development is offered only in a minority of healthcare organizations,⁴ the pulmonary/critical care/sleep community has recognized the importance of developing leadership competencies among physicians. Indeed, physician leadership development programs are becoming more widely available and are being offered by some medical centers for their caregivers, by business schools (sometimes in concert with academic medical centers) and by medical societies. For example, both the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP) have recently added leadership development courses to their educational portfolios.

ATS ELP BUILDING CLINICIAN LEADERS

For the past several years, I have directed a full-day postgraduate leadership development course through the ACCP at CHEST.

I am also directing a new ATS-funded course called the ATS Emerging Leaders Program (ATS ELP).⁵ Aimed at high-potential emerging leaders within the pulmonary/critical care/sleep communities, the ATS ELP invited ATS leadership to nominate both physician and nurse emerging leaders.

The ATS ELP consists of five full-day sessions that focus on key leadership competencies, including emotional intelligence, team building, change management, conflict resolution and situational leadership. The course meetings are both face to face and virtual and are taught by faculty dyads — business school content experts coupled with physician subject matter “context experts.”

Current ATS ELP participants are physicians (N = 17) and a nurse (N = 1), adult (N = 14) and pediatric (N = 4) clinicians, and have strong track records of academic achievement and service to the ATS. Consistent with the course focus on emerging leaders, the mean age of participants is approximately 40; most are assistant (N = 10) or associate professors (N = 5), and two-thirds are women. The program is also an innovation incubator, and participants work in small teams to develop business plans for executing group-determined innovative projects.

OUR MODEL OF PHYSICIAN LEADERSHIP DEVELOPMENT

The design of the ATS ELP is based on a long-standing leadership development course offered to emerging leaders within Cleveland Clinic, called Leading in Healthcare. Over the 13 years of that course, more than 530 Cleveland Clinic physicians, nurses and administrators have attended. As a measure of Leading in Healthcare's impact, a follow-up study regarding leadership promotion after the course indicated that 43 percent of course alumni were promoted to Cleveland Clinic leadership positions over the decade following their participation.⁶

Finally, to address the growing appetite for leadership development among healthcare leaders nationally and internationally, Cleveland Clinic offers the Samson Global Leadership Academy. In its 12 offerings to date, the academy has attracted emerging and established healthcare leaders from outside Cleveland Clinic who desire an immersive, small-group, highly personalized experience within a leading healthcare organization. The curriculum is offered by leadership experts in dyads and, like Leading in Healthcare, focuses on leadership competencies framed through the lens of “system” and “self” development. Offered twice a year since 2011 and now in both one- and two-week versions, the Samson Global Leadership Academy has attracted 125 nurses, physicians, dentists and administrators from 25 countries to date.

Overall, the growth of these programs and others reflects the growing appetite of physicians to develop their leadership competencies. Just as with physicians' pursuit of clinical excellence, this demand reflects physicians' desire to achieve mastery and to have an impact on the important matter of improving healthcare.



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See p. 31 for references.

Cleveland Clinic's Pulmonary Embolism Response Team

Design, typical case, current outcomes

By Gustavo A. Heresi, MD, MS

Each year 300,000 to 600,000 cases of pulmonary embolism (PE) occur in the U.S. Ten to 30 percent of the time, the patient dies within one month.¹ Lack of a standardized approach to treating PE — especially submassive PE — may influence this high mortality rate.

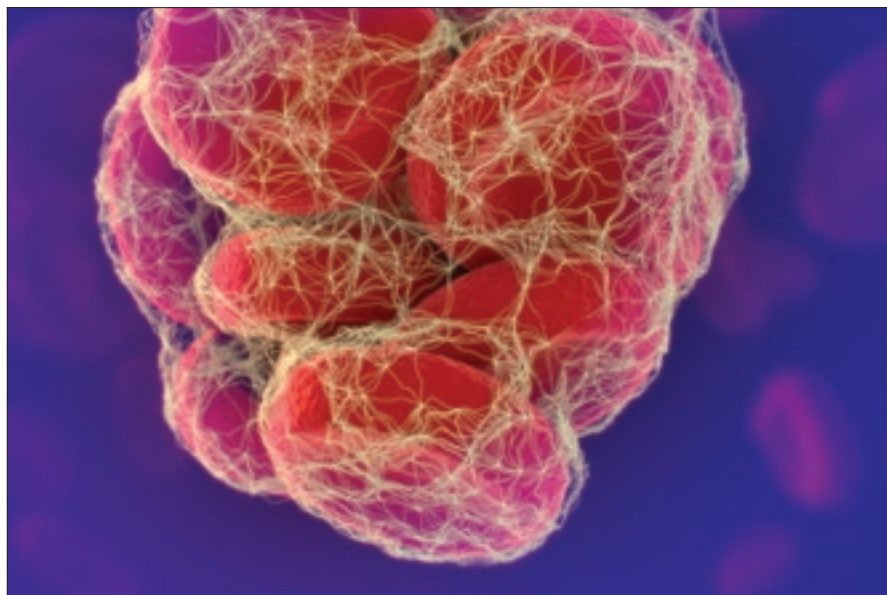
Current guidelines do not clearly outline treatment for acute PE, particularly massive and submassive. Decision-making lacks consistency, and procedures performed vary significantly by medical service and clot location and size.²

To address this problem, we assembled a multidisciplinary pulmonary embolism response team (PERT) to provide rapid evaluation, risk stratification and management recommendations for PE patients.

Our team, created in 2014, consists of caregivers representing pulmonary and critical care medicine, vascular medicine, interventional radiology and cardiology, cardiothoracic surgery, hematology and pharmacy. This multidisciplinary group, available around the clock, allows for a diversity of viewpoints when evaluating patients and their particular situation with an eye toward rapid initiation of optimal treatment.

ACTIVATING THE PERT

When a patient is admitted with PE, we follow an algorithm to assess their risk and determine whether to activate the team. Patients judged as low risk — small clots, normal blood pressure and no evidence of right ventricular strain — are started on anticoagulants. Those deemed high risk — hypotension, massive PE — are treated with systemic lysis or embolectomy with or without inferior vena cava (IVC) filter. Those



with submassive PE present the biggest treatment dilemma (Figure). Massive and especially submassive PE benefit the most from PERT activation.

A dedicated pager number notifies team members of an online meeting (via email or instant messaging platform) followed by a bedside meeting with PERT members joining in person or virtually. The team devises a recommended management plan within 180 minutes of PERT activation. The team draws on resources in the OR, the cardiac and interventional radiology labs, and the vascular ultrasonography suite for targeted implementation. If any of these resources is deemed necessary, the PERT is able to mobilize the appropriate staff to facilitate expedited intervention.

TYPICAL CASE HIGHLIGHTS PERT IMPACT

To understand the complexity of cases the PERT confronts, consider this case study

that my colleagues and I described in a 2017 paper published in the *Journal of Thrombosis and Thrombolysis*.³

A 56-year-old man presents with deep vein thrombosis (DVT) and PE 10 days after having undergone microdecompression for degenerative lumbar disease. He is treated with subcutaneous low-molecular-weight heparin, but anticoagulation is complicated by a lumbar spine hematoma. Attending physicians stop the anticoagulant until neurosurgeons can evaluate the patient, and an IVC filter is inserted.

Six days later, the patient suddenly feels lightheaded and is found to be hypotensive, tachycardic and hypoxic. Transthoracic echocardiogram shows a thrombus in the right atrium extending through the tricuspid leaflets. The PERT is activated.

The patient's cardiac biomarkers are normal, but a repeat chest CT reveals evidence

of new PE with right heart strain. His IVC filter has migrated to the intrahepatic vena cava, and a thrombus is noted within the suprahepatic vena cava. A visceral ultrasound shows no flow in the common iliac veins, with thrombus extension into the IVC. Duplex ultrasound of both legs is positive for extension of thrombus.

The PERT recommends anticoagulation and aspiration thrombectomy. The patient is taken to the OR, placed on venovenous extracorporeal bypass, and undergoes catheter aspiration thrombectomy.

A large amount of thrombus within the right atrium and IVC is removed, and the IVC filter is retrieved. During the procedure, however, the patient becomes acutely hypotensive, requiring vasopressor support. A transesophageal echocardiogram shows a moderate to large thrombus in the right pulmonary artery too distal for further catheter aspiration.

Given the patient's deterioration, the cardiothoracic surgeon who was initially involved in the PERT call rapidly performs a pulmonary embolectomy. The patient does well after surgery and is bridged to warfarin. A postoperative echocardiogram shows no evidence of residual intracardiac thrombus, and right ventricular function is normal. His thrombophilia testing is also normal.

OUTCOMES THROUGH 2016

Based on a retrospective chart review from October 2014 through August 2016 presented at the CHEST 2016 annual meeting,⁴ our PERT has been activated for 134 patients, 112 of whom were found to have PEs. The number of low-risk, submassive

and massive PEs were 14 (12 percent), 76 (68 percent) and 22 (20 percent), respectively. Just over half, 55 percent (60 patients), were treated with anticoagulation therapy alone. IVC filters were placed in 32 patients (29 percent). Twenty-one patients received systemic thrombolysis, 14 received catheter-directed thrombolysis, three received a suction thrombectomy and four received a surgical embolectomy.

For this time period, the 30-day all-cause mortality rate was 9 percent; deaths occurred in six patients with massive PEs, three patients with submassive PEs and one patient with a low-risk PE. Six of the patients who died had been treated with anticoagulation, two had received catheter-directed thrombolysis and one had received a full dose of systemic thrombolysis. Only four deaths (3.6 percent) were related to PE. The remaining six patients died under terminal hospice care.

Bleeding complications occurred in 14 patients (12.5 percent), 11 of whom were treated with anticoagulation alone and three of whom underwent catheter-directed thrombolysis. There were no major bleeding complications in patients treated with systemic thrombolysis. Before PERT, the major bleeding rate in patients treated with systemic thrombolysis for PE in our institution was 45 percent.

We expect the number of PERTs around the country to grow in the next five years. This will give patients with PE access to advanced beneficial therapies such as systemic thrombolysis, catheter-directed interventions and surgical embolectomies. We are already seeing evidence that the number

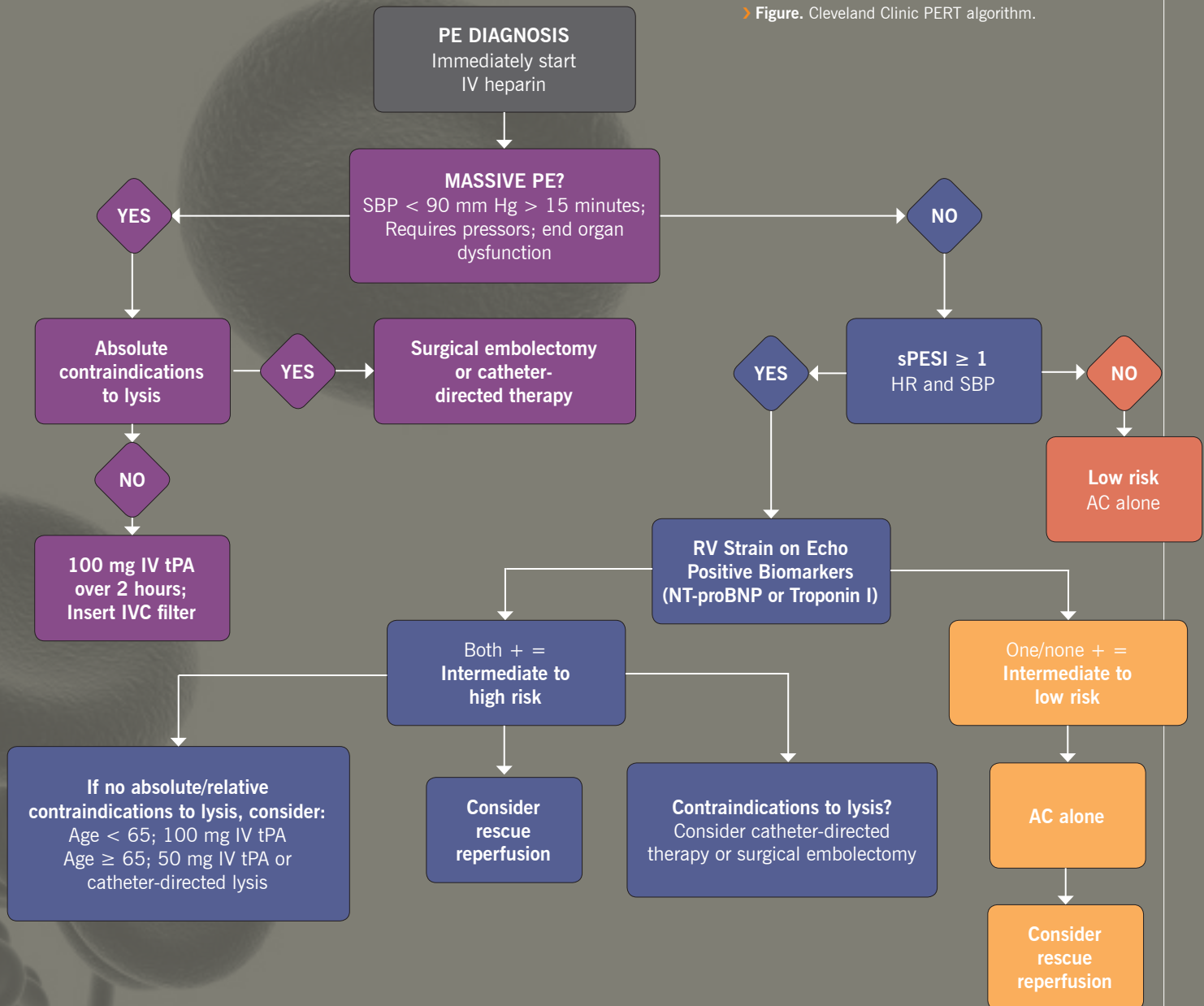
of these procedures is rising and that safety is improved. Effective PERTs reduce mortality, and the growth of these teams is a good example of how multidisciplinary, coordinated, team-based care can work in a complex setting.



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Effective PERTs reduce mortality, and the growth of these teams is a good example of how multidisciplinary, coordinated, team-based care can work in a complex setting.

Figure. Cleveland Clinic PERT algorithm.



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The Role of the Extracellular Matrix in Asthma Severity

Hyaluronan and heavy chains

By Mark Aronica, MD



Despite our increased understanding of the pathobiology of airway inflammation and the development of biologics as a therapeutic tool in the treatment of severe asthma, we still have much to learn regarding the movement of inflammatory cells within the lung and the long-term consequences of chronic inflammation within the lung. Part of the answer may lie in the extracellular matrix.

Much of our understanding of inflammatory cell movement is based on the established roles of selectins, integrins and chemokines in trafficking cells from blood vessels to sites of inflammation. Though we know how these cells move, we don't fully understand what happens when they do.

HYALURONAN: MORE THAN JUST GOO

Hyaluronan (HA) is a glycosaminoglycan in which the disaccharide (glucuronic acid-beta-1,3-N-acetylglucosamine-beta-1,4-) is repeated several thousand times. HA is a major constituent of the extracellular matrix. Due to its very simple composition, physical properties and nearly ubiquitous distribution, for many years HA was considered to be inert scaffolding, having only a mechanical role in supporting and maintaining tissue structure — essentially a goo. However, findings over the past decade indicate that the role of HA is much broader than previously thought.

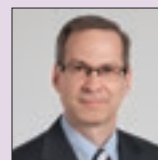
HA was first noted in the secretions of asthmatics in 1978, and HA levels in the bronchoalveolar lavage (BAL) of asthmatics have since been associated with severity of disease. Additionally, HA can be covalently modified during inflammation with the heavy chains (HCs) of inter-alpha-inhibitor (I α I) to form an HC-HA complex. We and others have shown that HC substitution of HA significantly increases leukocyte adhesion to HA, thereby potentially defining a mechanism through which HC-HA could direct inflammatory events in the asthmatic lung.

Our group's research has revealed the importance of HA in inflammation and has provided strong evidence for HA's major role in providing the preliminary matrix necessary for collagen synthesis and fibrosis noted in asthmatic airways.¹⁻³ We have shown that HA deposition is an early event in the lung, with detectable levels within 12 hours of the first antigen exposure.^{1,2} Our data also reveal that inflammatory cells co-localize in areas of HA deposition, suggesting a role for HA in maintaining and localizing inflammatory cells to sites of danger.^{1,2}

TRANSLATING THE DATA TO HUMAN ASTHMA

Although we completed much of this work in murine models of asthma, we also wanted to confirm that these findings and pathways are present in human asthma.⁴ We used immunofluorescent microscopy to examine the distribution of leukocytes within HC-HA matrices in lung tissue from three patients with acute severe asthma (Figure). The airways of these patients displayed significant smooth muscle proliferation, epithelial metaplasia, mucus gland hypertrophy and airway obstruction due to mucus plugging (Figure E,F). HA was distributed throughout the submucosa region and distributed around, but not within, serous mucous glands (Figure A). Furthermore, HA was largely absent within the mucus of the airway lumen. I α I (i.e., HC) distribution was almost exclusively present in the submucosa region, displaying a striking co-localization with HA indicative of pathological HC-HA matrices (Figure B). Using the common leukocyte antigen CD45 as a generic marker of inflammatory cells, we found large numbers of leukocytes in the submucosa region of these lungs co-localizing with and embedded within pathological HC-HA matrices.

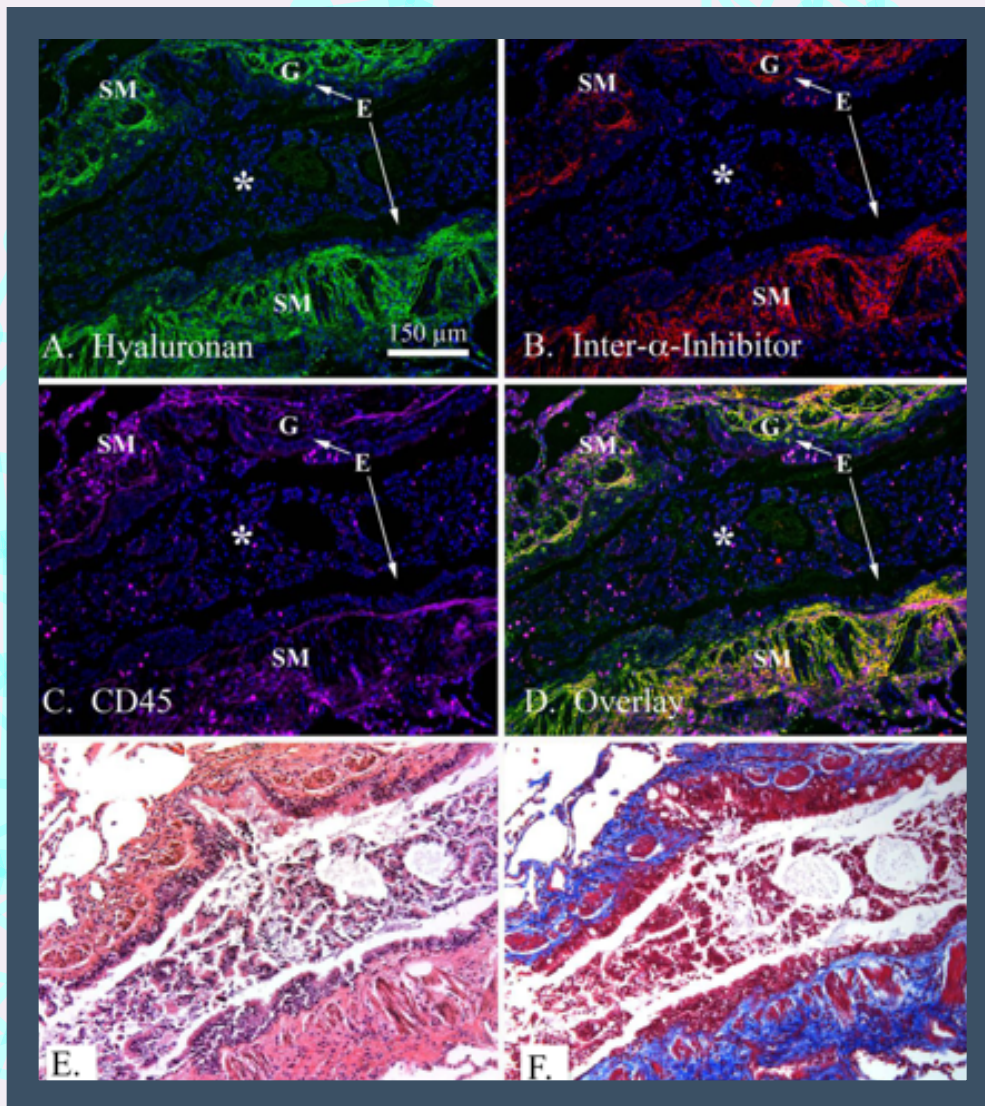
In summary, we believe that the extracellular matrix, an often ignored component in many diseases, is an active and direct participant in inflammatory processes including asthma, and a better understanding of these mechanisms may lead not only to insights into these processes but also to novel treatment pathways.



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► **Figure.** Co-localization of leukocytes within HA matrices modified with heavy chains in asthmatic airways. A paraffin lung section of a patient with acute severe asthma was probed with a hyaluronan binding protein (green; panel A), an antibody against IαI (red; panel B) and the common leukocyte antigen CD45 (magenta; panel C). DAPI-stained nuclei are shown in blue. Overlay is shown in panel D. H&E and trichrome staining from the same region shown in panels A-D are shown in panels E and F, respectively. Magnification is 10x. A magnification bar is portrayed as a white line in panel A (150 μ m). The airway epithelium is identified by an E, airway smooth muscle by SM, submucosal glands by G and a mucus plug by an asterisk in panels A-D. These images were representative of three asthmatic replicates. Figure and legend originally appeared in *J Biol Chem.* 2015;290(38):23124-23134.

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Respiratory Institute by the numbers

WHO WE ARE*

154

PHYSICIANS

26

LOCATIONS

64

ADVANCED PRACTICE PROVIDERS

61

FEDERAL GRANTS

49

FELLOWS



13 CRITICAL CARE MEDICINE

23 PULMONARY & CRITICAL
CARE MEDICINE

08 INFECTIOUS DISEASE

04 ALLERGY AND IMMUNOLOGY

01 INTERVENTIONAL
PULMONOLOGY

HOW WE PERFORMED**

54,966

OUTPATIENT VISITS

53,399

PFT VISITS

4,492

BRONCHOSCOPIES

364

AIRWAY STENTS

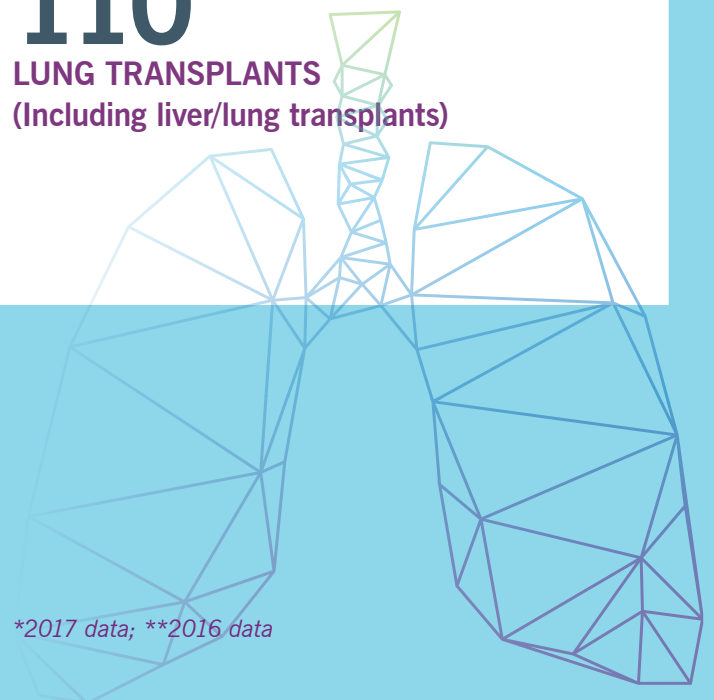
151

ICU CENSUS DAILY

110

LUNG TRANSPLANTS
(Including liver/lung transplants)

*2017 data; **2016 data



Cystic Fibrosis Program Gains Accreditation from U.S. Cystic Fibrosis Foundation

Adult program a leader in CF lung transplants

Cleveland Clinic has obtained accreditation as a Cystic Fibrosis (CF) Care Center from the U.S. Cystic Fibrosis Foundation. Cleveland Clinic's Adult Cystic Fibrosis Program joins a network of more than 100 care centers across the U.S. specializing in the diagnosis, management and treatment of individuals with CF.

"We're excited that our efforts to provide world-class care to all patients with cystic fibrosis have been recognized by the Foundation," says Elliott Dasenbrook, MD, Director of the program and a member of the Department of Pulmonary Medicine.

Cleveland Clinic's Adult CF Program provides multidisciplinary patient- and family-centered care for patients living with CF, from maintaining health for those with early-stage lung disease to supporting patients through and after lung transplant. The program partners with patients and their families to deliver high-quality care that respects patient preferences, needs and values. Members of the Adult CF team work closely with Nathan Kraynack, MD, and his team at Cleveland Clinic Children's CF Program to transition patients who are ready for adult care. The adult program cares for more than 100 patients.

SPECIALIZING IN TOUGH INFECTIONS, TRANSPLANTS

The multidisciplinary team treats local patients as well as CF patients from all over the world with difficult-to-treat infections. The program includes physicians from pulmonary medicine, infectious disease, transplant surgery, gastroenterology, endocrinology and hepatology. With a robust infection control protocol and clinical and research expertise¹ in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with CF, the team aims to reduce morbidity and mortality from this disease.

The CF team works closely with the Cleveland Clinic Lung Transplant program, one of the busiest and most experienced in the world. This close collaboration allows evaluation of CF patients with advanced lung disease who require lung transplantation and provides comprehensive care to those awaiting transplantation in order to optimize their suitability for this procedure. In recognition of its expertise in both CF care and transplantation, Cleveland Clinic is a member of the CF Lung Transplant Consortium, comprised of leading centers around the country and charged with the task of improving post-transplant outcomes for the CF population.

"We are leaders in lung transplant for patients with cystic fibrosis, including those with difficult-to-treat infections² such as *Burkholderia cepacia* complex, patients requiring combined liver-lung transplant, and patients with acute decompensation needing urgent evaluation for transplant," says Dr. Dasenbrook. Research shows that the more transplants a center performs on patients with CF, the better the patients' chances of long-term survival.³ "We're very focused on providing patients with the best possible outcomes," he says.

References

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2. Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, et al. Antibiotic management of lung infections in cystic fibrosis. II. Nontuberculous mycobacteria, anaerobic bacteria, and fungi. *Ann Am Thorac Soc*. 2014;11(8):1298-1306.
3. Hayes D, Sweet SC, Benden C, et al. Transplant center volume and outcomes in lung transplantation for cystic fibrosis. *Transpl Int*. 2017;30(4):371-377.



To refer a patient, contact Dr. Dasenbrook at dasenbe@ccf.org or 216.445.3082.

NewsBriefs



Ashton Becomes President of APCCMPD

Rendell Ashton, MD, was inaugurated as President of the Association of Pulmonary and Critical Care Medicine Program Directors (APCCMPD) at the

American Thoracic Society 2017 International Conference. The APCCMPD provides leadership for training programs and their directors. Dr. Ashton is staff in the departments of Pulmonary and Critical Care Medicine at Cleveland Clinic and has led the combined fellowship program since 2010.



Mireles-Cabodevila Named Director of Simulation Center

Eduardo Mireles-Cabodevila, MD, has been selected as the Medical Director for Cleveland Clinic's Simulation and Advanced Skills Center. A pulmonologist

and critical care specialist, Dr. Mireles-Cabodevila is staff in the departments of Pulmonary and Critical Care Medicine and serves as the Program Director for the Critical Care Medicine Fellowship for the Respiratory Institute. His clinical practice involves caring for patients with neuromuscular disorders, and his research interests include education, mechanical ventilation, acute respiratory failure, critical care medicine and neuromuscular diseases affecting the respiratory system.



Highlights from CHEST 2017

Peter Mazzone, MD, MPH, FCCP, served as Chair, Program Committee for the CHEST 2017 Annual Meeting. Dr. Mazzone is staff and Director of the Lung Cancer Program and Lung Cancer Screening Program for the Respiratory Institute.



Atul Mehta, MBBS, FCCP, delivered the Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture. Dr. Mehta is staff in the Department of Pulmonary Medicine in Cleveland Clinic's Respiratory Institute.



Remembering Muzaffar Ahmad, MD

Muzaffar Ahmad, MD, retired staff in the Respiratory Institute, died on Sept. 25, 2017, at the age of 74. Dr.

Ahmad was appointed to Cleveland Clinic's professional staff in

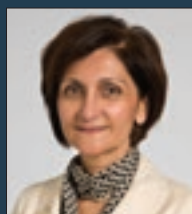
the Department of Pulmonary Disease in 1973. He later served as Director of the Pulmonary Fellowship Program from 1979 to 1991. Dr. Ahmad served as Chair of the Department of Pulmonary Medicine from 1983 to 1991, and as Chair of the Division of Medicine from 1991 to 2003. Dr. Ahmad was a Fellow of the American College of Physicians and the American College of Chest Physicians. He also held leadership positions in the American Thoracic Society and the Association of Pulmonary Program Directors, where he served on the board of directors.

Researchers Awarded NIH Funds



Several Respiratory Institute clinician researchers were awarded NIH grants in 2017.

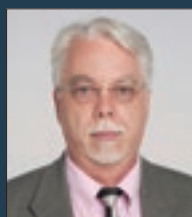
- **Joe Zein, MD** (*above left*), was awarded a five-year K08 from the NHLBI to investigate the interaction between sex, sex hormones and genetic variants in the risk for severe asthma across the life span.
- **Rachel Scheraga, MD** (*above center*), was awarded a K08 grant for her project "Transient Receptor Potential Vanilloid 4 (TRPV4) Mediates the Host Defense and Lung Injury Response to Bacterial Pneumonia."
- **Brian Southern, MD** (*above right*), was awarded a K08 grant for his proposal "Matrix-Myosin II Interactions Drive Fibrosis in Idiopathic Pulmonary Fibrosis." Dr. Southern also received the Parker B. Francis Fellowship Award, but was ineligible for funding because of the K08 grant. He was instead granted the Parker B. Francis Research Opportunity Award for this work.



Erzurum Elected to National Academy of Medicine

Serpil Erzurum, MD, Chair of the Lerner Research Institute and the Alfred Lerner Memorial Chair in Innovative Biomedical Research, has been elected to the National

Academy of Medicine (NAM), one of the highest honors in the fields of health and medicine. "Serpil is the rare 'triple threat' physician scientist, excelling as a researcher, clinician and educator," said Herbert Wiedemann, MD, Chairman of Cleveland Clinic Respiratory Institute. "Over the past three decades as a leader in respiratory medicine, she achieved her vision of accelerating research to impact patient care, more rapidly bringing scientific discoveries from the lab to the bedside." Dr. Erzurum is founding chair of the Department of Pathobiology, a professor at the Cleveland Clinic Lerner College of Medicine and a staff physician in the Respiratory Institute.



Chatburn Receives Top Honor in Field

Robert Chatburn, MHHS, RRT-NPS, FAARC, Research Program Manager of Cleveland Clinic's Respiratory Therapy Program, received the American Association

for Respiratory Care's highest honor, the Jimmy A. Young Medal, for his lifetime of service to patients and advancement of the respiratory care profession. Chatburn is a professor in Cleveland Clinic's Lerner College of Medicine and on the editorial board of *Respiratory Care Journal*.

Respiratory Institute

Selected Clinical Trials

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

ASTHMA

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 additional Functional Medicine management approach.

ELIGIBILITY: Women and men ages > 18 and < 65; nonsmokers or former smokers, with 15 pack-years or less history of smoking; clinical history consistent with moderate to severe asthma; measures of airflow obstruction and reactivity consistent with asthma (12 percent BD response and/or positive methacholine challenge test) historically or at initial/screening visit; FEV1 between 40 and 100 percent predicted post bronchodilator; uncontrolled asthma categorized (ACT ≤ 19); willing to be seen in Asthma Center and willing to consider Functional Medicine approach as an add-on to Asthma Center care.

EXCLUSION: Life-threatening asthma; any disorder, including but not limited to gastrointestinal, renal, neurological, infectious, endocrine, metabolic or other physical impairment, that is not stable in the opinion of the investigator; clinically important pulmonary disease other than asthma; controlled asthma defined by stability and by ACT > 19; current asthma exacerbations; stable lung function.

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 (βLOCK-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.

ELIGIBILITY: 40-84 years of age, a clinical diagnosis of at least moderate COPD and a history of cigarette consumption of 10 pack-years or more and not active smokers. Patients must meet one or more of the following four conditions: (1) a history of receiving a course of systemic corticosteroids or antibiotics for respiratory problems in the past year, (2) an emergency department visit for a COPD exacerbation within the past year, (3) hospitalization for a COPD exacerbation within the past year, or (4) use or prescribed use of supplemental oxygen for > 12 hours per day.

PRINCIPAL INVESTIGATOR
Umur Hatipoğlu, MD

STUDY COORDINATOR
Rick Rice | 216.444.1150

CRITICAL CARE MEDICINE

Re-Evaluation of Systemic Early Neuromuscular Blockade (ROSE)

The primary objective of this NIH-supported study (PETAL Network) is to assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate to severe ARDS in comparison with a control group with no routine early neuromuscular blockade.

ELIGIBILITY: 18 years or older; endotracheal ventilation for < five days (120 hours). Presence of all of the following conditions for < 48 hours: PaO₂/FiO₂ < 150 with PEEP > 8 cm H₂O or SpO₂/FiO₂ ratio that is equivalent to a PaO₂/FiO₂ < 150 with PEEP > 8 cm, and a confirmatory SpO₂/FiO₂ ratio one to six hours after initial SpO₂/FiO₂ ratio determination; bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules; respiratory failure not fully explained by cardiac failure or fluid overload.

PRINCIPAL INVESTIGATOR
R. Duncan Hite, MD

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

Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)

The primary objective of this NIH-supported study (PETAL Network) is to assess the efficacy and safety of early administration of vitamin D3 (cholecalciferol) in reducing mortality and morbidity for vitamin D-deficient patients at high risk for ARDS and mortality.

ELIGIBILITY: 18 years or older; intention to admit to ICU from emergency department, hospital ward, operating room or outside facility. One or more of the following acute risk factors for ARDS and mortality contributing directly to the need for ICU admission: pulmonary causes such as pneumonia, aspiration, smoke inhalation, lung contusion; mechanical ventilation for acute hypoxemic or hypercarbic respiratory failure; extra-pulmonary causes such as shock, sepsis, pancreatitis; vitamin D deficiency (screening 25OHD level < 20 ng/mL).

PRINCIPAL INVESTIGATOR
R. Duncan Hite, MD

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

The NGAL Test™ as an Aid in the Risk Assessment for AKI Stage II and III in an Intensive Care Population (NGAL)

The primary objectives of this study are as follows: to demonstrate that the sum of sensitivity and specificity is greater than one using a cutoff of 140 ng/mL when compared to the primary clinical endpoint AKI as adjudicated KDIGO stage 2/3 AKI; to demonstrate that the lower limit of the 95% CI for sensitivity is greater than 0.60 using a cutoff of 140 ng/mL when compared to the primary clinical endpoint AKI (KDIGO stage 2/3 AKI); to demonstrate that the lower limit of the 95% CI for specificity is greater than 0.40 using a cutoff of 140 ng/mL when compared to the primary clinical endpoint AKI (KDIGO stage 2/3 AKI).

ELIGIBILITY: 18 years or older; subjects should be enrolled within 24 hours of ICU admission, from ED or floor; or if the subject is from another ICU, no more than 24 hours from presentation; within 24 hours prior to enrollment a cardiovascular SOFA score of ≥ 1 MAP < 70 mm Hg and/or receiving any vasopressor support.

PRINCIPAL INVESTIGATOR
R. Duncan Hite, MD

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

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.

ELIGIBILITY: Patients must be Caucasian. Biopsy-proven sarcoidosis or Lofgren's syndrome and at least one of the following documenting pulmonary disease involvement due to sarcoidosis: a biopsy from the lung (either via bronchoscopy or otherwise) or chest lymph nodes demonstrating granulomas; pulmonary parenchymal involvement with Scadding chest X-ray stage I, II, III, IV, in the past or present; abnormal spirometry and/or DLCO (< 80% predicted). **EXCLUSION:** Positive lung washing or biopsy cultures for fungi or mycobacterial disease or the inability to undergo venipuncture.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
Christopher Estling | 216.445.8951

A Double Blind, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Nintedanib Over 52 Weeks in Patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

Sponsored by Boehringer Ingelheim Pharmaceuticals, this is a phase 3 trial investigating the efficacy and safety of twice-daily 150 mg nintedanib (versus placebo) in patients with PF-ILD. The primary endpoint is the annual rate of decline in FVC in mL over 52 weeks.

ELIGIBILITY: ≥ 18 years of age; features of diffuse fibrosing lung disease of ≥ 10 percent extent on HRCT; lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice

to treat ILD; FVC ≥ 40 percent predicted; DLCO 30-80 percent predicted (corrected for Hb). **EXCLUSION:** Current use of immunosuppressants.

PRINCIPAL INVESTIGATOR
Leslie Tolle, MD

STUDY COORDINATOR
Ron Wehrmann, RRT | 216.445.0574

IP-PRO Registry

Sponsored by Boehringer Ingelheim, this is a registry with the overall goal to collect data and biological samples that will support future research studies, as well as to obtain for future research studies biological samples at serial time points that are matched to the well-characterized IPF participants enrolled in this registry.

ELIGIBILITY: > 40 years old; new diagnosis of IPF by the enrolling subspecialty center (as defined by ATS/ERS/JRS/ALAT criteria).

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

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 (PCORI) and Kaiser Permanente of California, the main objective of the trial, also known as the Lung Nodule Surveillance Trial (LNST), is to compare two protocols for lung nodule evaluation, with cluster-randomized assignment to treatment groups at the level of the hospital or health system. The design of the trial is a hospital-based cluster randomized trial of more frequent surveillance versus less frequent surveillance of pulmonary nodules, and immediate or delayed participation in quality improvement collaboratives. Existing medical information systems at each facility will be used to passively enroll patients in the trial.

Patients will be enrolled at the time they undergo chest CT and are found to have a pulmonary nodule of the appropriate size range that meets our inclusion criteria, and who otherwise do not have exclusion criteria (such as no known lung cancer).

PRINCIPAL INVESTIGATOR

Peter Mazzone, MD, MPH

STUDY COORDINATOR

Christopher Estling | 216.445.8951

LUNG TRANSPLANT

A Prospective Multicenter Observational Cohort Study to Define the Risk Factors, Mechanisms and Manifestations of Chronic Lung Allograft Dysfunction (CLAD) Phenotypes (CTOT 20)

The primary aim of this NIAID-sponsored, noninterventive, prospective, observational study is to define the risk factors and biological mechanisms that lead to the development of the CLAD phenotypes, BOS and RCLAD, after lung transplantation in order to guide future approaches to prevent or treat CLAD.

ELIGIBILITY: ≥ 18 years of age; within 45 days of having received a single or bilateral lung transplant; must be first lung transplant operation.

PRINCIPAL INVESTIGATOR

Marie Budev, DO, MPH

STUDY COORDINATORS

Bette Maieron, BA, RRT | 216.444.2901
Stuart Houltham | 216.445.1056

Prospective Multicenter Cytomegalovirus (CMV) Specific Immune Monitoring to Predict Patient Risk After Lung Transplantation (CTOT 22)

The primary aim of this NIAID-sponsored noninterventive, prospective, observational study is to determine whether a blood test can predict development of active CMV infection in lung transplant recipients.

ELIGIBILITY: ≥ 18 years of age; within 45 days of having received a single or bilateral

lung transplant; first lung transplant operation; enrolled in the CTOT 20 study; CMV recipient positive.

PRINCIPAL INVESTIGATOR

Marie Budev, DO, MPH

STUDY COORDINATORS

Bette Maieron, BA, RRT | 216.444.2901
Stuart Houltham | 216.445.1056

LYMPHANGIOLEIOMYOMATOSIS

Registry: Multicenter International Durability and Safety of Sirolimus in Lymphangioleiomyomatosis Trial (MIDAS Trial)

Sponsored by the NIH via Cincinnati Children's Hospital Medical Center, this study is a real-world, long-term, prospective, observational drug registry of LAM patients taking or considering taking mTOR inhibitor therapy (sirolimus or everolimus) based on clinical indications. Patients will be diagnosed, treated and followed by their physician according to routine clinical practice.

ELIGIBILITY: The study will enroll LAM patients taking or considering taking mTOR inhibitors from participating clinics in academic health centers and community hospitals. All LAM patients who are chronically treated, newly treated or who may be considered for treatment with mTOR inhibitors are eligible to enroll in the study. Patients who have failed or have been intolerant to mTOR inhibitors will also be recruited. Inclusion criteria include: female LAM patients, age 18 or over; signed, dated informed consent form; diagnosis of TSC or LAM; currently on mTOR inhibitors, and previously intolerant of or have failed mTOR inhibitors, or may be considered for mTOR therapy. **EXCLUSION:** Inability to attend clinic visit for LAM evaluation at least once per year; inability to give informed consent; and inability or unwillingness to perform pulmonary function testing.

PRINCIPAL INVESTIGATOR

Robert Kotloff, MD

STUDY COORDINATOR

JoAnne Baran-Smiley, BSN, RN
216.444.5023

PULMONARY HYPERTENSION

A Phase 3, Placebo Controlled, Double-Blind, Randomized, Clinical Study to Determine Efficacy, Safety and Tolerability of Pulsed, Inhaled Nitric Oxide (iNO) Versus Placebo in Symptomatic Subjects with Pulmonary Arterial Hypertension (PAH): iNOvation-1 (Part 1 and Part 2)

This study will evaluate the efficacy of iNO on exercise using 6MWD in subjects with PAH currently receiving background PAH medication and LTOT.

ELIGIBILITY: 18-85 years old with confirmed WHO Group 1 PAH functional class II-IV diagnosis receiving at least one stable PAH specific therapy and using oxygen therapy by nasal cannula for at least four weeks prior to screening; PVR ≥ 5 WU; mPAP ≥ 25 mm Hg; PCWP or LVEDP ≤ 15 mm Hg; 6MWD 100-450 meters. **EXCLUSION:** HIV and history of opportunistic pulmonary disease within three months of screening; PAH associated with hematologic or metabolic disorders; subjects of WHO Groups 2-5; receiving riociguat or oral prostanoids as monotherapy; significant cardiac abnormalities; severe obstructive lung disease or moderate to severe restrictive lung disease; Child-Pugh Class B or C; systemic hypotension; on dialysis; acute or chronic physical impairment; concurrent use of BiPAP or CPAP device; any subject previously administered iNO through clinical trials.

Subjects who meet Part 2 eligibility and consent will be able to receive open-label iNO following the 18 weeks of blinded therapy.

PRINCIPAL INVESTIGATOR

Gustavo Heresi, MD

STUDY COORDINATOR

Bryan Poynter | 216.445.1630



SPHERE; Uptravi® (Selexipag): the usErs dRug rEgistry

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

ELIGIBILITY: 18 years and older with stable PAH Group 1 disease who either initiate Uptravi at the time of enrollment or have been receiving treatment with Uptravi and have a documented titration regimen. **EXCLUSION:** Previous exposure to Uptravi treatment during a clinical trial; previous discontinuation of Uptravi for any reason; enrollment in a blinded trial or a clinical trial of an unapproved drug.

PRINCIPAL INVESTIGATOR
Neal Chaisson, MD

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

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

For patients with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) enrolled in this study, the objectives are to assess the efficacy and safety of bardoxolone methyl relative to placebo.

ELIGIBILITY: 18-75 years old with confirmed WHO Group 1 PAH associated with connective tissue disease; PH WHO/NYHA functional class II-III; PVR ≥ 5 WU; mPAP ≥ 25 mm Hg; PCWP or LVEDP ≤ 15 mm Hg; 6MWD ≥ 150 m; receiving no more than two approved PAH therapies; TLC ≥ 65 percent; imaging showing no evidence of thromboembolic disease. **EXCLUSION:** Receiving IV or SC prostacyclin/prostacyclin analogues, with history of clinically significant left-sided heart disease and/or cardiac disease; more than two risk factors for left ventricle diastolic dysfunction; uncontrolled

sleep apnea; history of portal hypertension or chronic liver disease; Hgb concentration < 10.5 g/dL.

PRINCIPAL INVESTIGATOR
Kristin Highland, 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 (RIN-PH-201)

This study will evaluate the safety and efficacy of inhaled treprostinil in subjects with pulmonary hypertension associated with interstitial lung diseases including combined pulmonary fibrosis and emphysema (CPFE).

ELIGIBILITY: 18 years or older, with WHO Group 3 PH based on CT imaging, which demonstrates evidence of diffuse parenchymal lung disease; any form of ILD or CPFE; PVR > 3 WU; mPAP ≥ 25 mm Hg; PCWP ≤ 15 mm Hg; 6MWD ≥ 100 meters. **EXCLUSION:** Diagnosis of PAH or PH for reasons other than WHO Group 3 PH-ILD; shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue; currently receiving any PAH approved therapy (prostacyclin, ERA, PDE5-I, sGC); clinically significant left-sided heart disease; current use of inhaled tobacco/marijuana products; significant history of drug abuse; exacerbation of underlying lung disease or upper respiratory infection; initiation of pulmonary rehabilitation within 12 weeks of randomization.

PRINCIPAL INVESTIGATOR
Joseph Parambil, MD

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

A Prospective, Randomized, International, Multicenter, Double-Arm, Controlled, Open Label Study of Riociguat in Patients with Pulmonary Arterial Hypertension

(PAH) Who Are on a Stable Dose of Phosphodiesterase-5 Inhibitors (PDE-5i) with or without Endothelin Receptor Antagonist (ERA), but Not a Treatment Goal (REPLACE)

This study will assess the proportion of patients in each treatment arm with a satisfactory clinical response as defined by a composite primary endpoint at week 24.

ELIGIBILITY: Aged 18-75 years with symptomatic PAH; PVR > 3 WU; mPAP ≥ 25 mm Hg; PCWP ≤ 15 mm Hg; stable dose of PDE5i and ERA combination therapy or PDE5i monotherapy; 6MWD ≥ 165 m and ≤ 440 m; WHO functional class III. **EXCLUSION:** Previous treatment with riociguat; treatment with prostacyclin analogues and prostacyclin-receptor agonists; TLC < 60 percent; FEV1/FVC < 50 percent; severe diffusion impairment; uncontrolled arterial hypertension; permanent atrial fibrillation; left ventricular disease/dysfunction; disorders in organ function.

PRINCIPAL INVESTIGATOR
Kristin Highland, MD

STUDY COORDINATOR
Mary Beukemann | 216.444.2140

A Multicenter, Open-Label, Single-Sequence Cross-Over Study to Assess Safety, Tolerability, and Pharmacokinetics of Intravenous Selexipag in Subjects with Stable Pulmonary Arterial Hypertension Switching from an Oral Stable Dose of Selexipag

The primary objective of this study is to assess whether temporary switching from a stable oral dose of selexipag to an IV dose of selexipag providing comparable exposure to active metabolite ACT-333679 and switching back to the initial oral dose of selexipag is safe and well-tolerated in subjects with stable PAH.

ELIGIBILITY: 18-75 years old with stable PAH Group 1 disease WHO functional class I-III; prescribed Uptravi in compliance with local prescribing information with no dose

changes for at least 28 days prior to visit two. Women of childbearing potential must have negative urine pregnancy tests at visits one and two. **EXCLUSION:** Moderate to severe hepatic impairment; administration of gemfibrozil while taking Uptravi; treatment with any prostacyclin or prostacyclin analogue within 28 days of visit one; systolic BP < 90 mm Hg; uncontrolled hyperthyroidism; severe renal failure or ongoing/ planned dialysis.

PRINCIPAL INVESTIGATOR
Joseph Parambil, MD

STUDY COORDINATOR
Bryan Poynter | 216.445.1630

SARCOIDOSIS

A Multiple-Dose, Subject- and Investigator-Blinded, Placebo-Controlled, Parallel Design Study to Assess the Efficacy, Safety and Tolerability of ACZ885 (Canakinumab) in Patients with Pulmonary Sarcoidosis

Sponsored by Novartis, this is a phase 2 trial investigating the effect of ACZ885, a monoclonal antibody targeting interleukin-1 beta versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in percent predicted FVC at week 24.

ELIGIBILITY: Ages 18-80 with biopsy-proven clinically active disease having all of the following criteria: MMRC dyspnea scale > 1, 2; threshold FVC 50-80 percent of predicted; evidence of parenchymal lung involvement by HRCT. Subjects must weigh at least 50 kg. Subjects must be able to communicate well with the investigator and to understand and comply with the requirements of the study. Disease duration of > 1 year. **EXCLUSION:** Selected criteria include current inhaled use of tobacco products; known hypersensitivity to canakinumab; prior treatment with any biologic drug targeting the immune system within 180 days of randomization or history of any previous use of rituximab; FVC < 50 percent of predicted; diagnosis of pulmonary hypertension requiring treatment.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
Christopher Estling | 216.445.8951

Nicotine Treatment for Pulmonary Sarcoidosis: A Clinical Trial Pilot Study

The primary objective of this NIH-sponsored trial is to provide preliminary data required to design subsequent phase 2/3 trials to evaluate nicotine as a novel, low-cost, highly effective and safe treatment option for patients with active pulmonary sarcoidosis.

ELIGIBILITY: Adult male and female subjects 18-75 years of age; histologically proven sarcoidosis, diagnosed at least two months before screening, with evidence of parenchymal disease on a recent chest radiograph (within three months or at the time of screening); a Medical Research Council dyspnea score of at least grade 1; confirmation of active pulmonary sarcoidosis as the cause of worsening pulmonary disease manifestations will be established by the sarcoidosis experts; patients must be on no treatment or on a stable treatment regimen for sarcoidosis.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
JoAnne Baran-Smiley, BSN, RN
216.444.5023

Acthar®-Eye (Ocular Sarcoidosis Open Label Trial of Acthar Gel)

Sponsored by Questcor, 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.

ELIGIBILITY: Selected criteria include patients with sarcoidosis as defined by ATS/ERS/WASOG; posterior, intermediate or panuveitis of sufficient severity to warrant

therapy, in the opinion of the treating physician OR anterior uveitis requiring four or more daily applications of topical corticosteroids to maintain control of inflammation, or uncontrolled with topical therapy; persistent disease activity (active uveitis) at the time of screening. **EXCLUSION:** Selected criteria include other causes for ocular inflammation; recent intra-ocular or intra-orbital steroid injection within the last four weeks; history of any malignancy within the last five years; severe other organ disease felt to be likely to lead to death within the next six months.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
JoAnne Baran-Smiley, BSN, RN
216.444.5023

Investigation of the Efficacy of Antimycobacterial Therapy on Pulmonary Sarcoidosis Phase II Randomized, Double-Blind, Placebo-Controlled Trial (CLEAR)

The objective of this NIH-supported study is to assess the efficacy and safety of oral CLEAR therapy in patients with confirmed progressive pulmonary sarcoidosis.

ELIGIBILITY: Selected criteria include patients with sarcoidosis as defined by the ATS/ERS/WASOG statement on sarcoidosis; biopsy demonstrating granulomas, and no alternative for the cause of the granulomas; evidence of disease progression; positive peripheral immune responses to ESAT-6 as a biomarker of response to the CLEAR regimen; evidence of parenchymal or nodal disease on chest radiograph.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
Allison Wimer, RRT | 216.444.9975

Development of an Online Sarcoidosis Assessment Platform (OSAP) to Validate Sarcoidosis Phenotypes and Monitor Disease Burden Longitudinally

Sponsored by the Foundation for Sarcoidosis Research, this study looks to establish an online sarcoidosis assessment platform (OSAP) that can evaluate health-related quality of life and psychosocial issues of sarcoidosis in real time in a prospective fashion.

ELIGIBILITY: Diagnosis of sarcoidosis by established criteria; completed pulmonary function tests (spirometry) as per standard of care; access to a computer, iPad, smartphone or another electronic device that will support the online sarcoidosis assessment platform; willing to wear a daily activity and sleep tracker wristband (Fitbit™ wristband) for six months.

PRINCIPAL INVESTIGATOR
Daniel Culver, DO

STUDY COORDINATOR
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