

# FisherFocus

Winter 2020

NEWS FROM THE SHERRILYN AND KEN FISHER CENTER FOR ENVIRONMENTAL INFECTIOUS DISEASES



X-ray of bronchiectasis caused by NTM in the lungs

## Meeting the Challenge of Nontuberculous Mycobacteria

Dedicated to the clinical research of environmental pathogens which improves the diagnosis and treatment of these infections.

Imagine you have a cough that won't quit for months, that doesn't respond to treatments such as allergy medications or a course of antibiotics. The cough might not be initially troublesome to you, but in this era of COVID-19, the frequent coughing despite wearing a mask likely makes you a pariah. Such coughing could represent several problems including recalcitrant post-nasal drip or gastroesophageal reflux. However, for a growing number of people, the cause of chronic cough can be traced to infection with a cousin of the bacteria responsible for tuberculosis. These non-tubercular mycobacteria (NTM) are hardy, ubiquitous in water and soil. These pathogens are increasingly afflicting many Americans, at last count > 100,000 people, far outpacing the more widely known tuberculosis (TB), which only affects approximately 10,000 Americans annually. NTM infection often affects the lungs of women and older age groups, and in addition to chronic cough, these infections can cause fatigue and weight loss.

**THE NUMBER OF PEOPLE IN THE US WITH NTM LUNG DISEASE IS RAPIDLY INCREASING AND OUTNUMBERS THOSE INFECTED WITH TB.**

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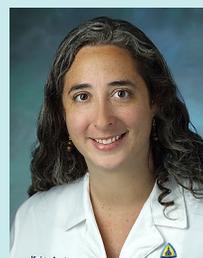
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### Fisher Center Grant

Despite being among the most challenging infections to eradicate with antibiotics, these nontubercular mycobacteria have not received nearly as much research focus as other lung infections. Progressive NTM infection is more likely to occur in individuals with a type of chronic scarring of the lungs known as bronchiectasis, as well as in chronic obstructive pulmonary disease (COPD) and in the setting of lung cavities. The Fisher Center Discovery Program (FCDP) has sponsored research of **Keira A Cohen, MD**, who was awarded a 2020



FCDP grant for a pilot study seeking to improve *Mycobacterium avium complex* (MAC) treatment, the most common NTM worldwide. MAC is found in soil, dust, and water. They most frequently cause a chronic lung infection, which at times may be mistaken for TB. In past years before the era of modern diagnostics, people may have been held in sanitariums for TB inappropriately due to this non-contagious infection. Details about MAC and other Nontuberculous Mycobacteria (NTM) may be found in the article on page 4.

# MESSAGE FROM THE DIRECTOR



More than ever, we might consider, “**now is the winter of our discontent.**” This well-known phrase opens Shakespeare’s Richard III. Considered a tragedy, it depicted the short reign of the sovereign following his Machiavellian rise to power. Some could look at our modern affairs for parallels about feared rather than loved rulers. Despite the pandemic coronavirus’s human costs mounting these dark months, recent news about highly efficacious vaccines stokes hopes that the worst may be passed by spring.

Success must be attributed to two key factors. First, scientific research into new methods for treating cancers has directly led to the novel message RNA (mRNA) vaccines for a novel coronavirus infection. Two vaccines by BioNTech/Pfizer and Moderna, as of this writing, have won emergency approvals in the United States in record time. As is often the case, research in unrelated areas have fostered breakthroughs elsewhere. Also, the pharmaceutical and biotechnology industries have embraced considerable risk and have produced winners that have left many of us pinching ourselves at this good fortune. Second, with President Trump’s direction, the United States has taken considerable risks in funding research and buying unproven vaccines. Nearly five different vaccines have been purchased for every person in the United States, betting on all horses as it were, hoping one might pay off. Rather than waiting to see which vaccines work after clinical trials results are concluded, many months have been shaved off original projections that were realistically looking at fall 2021 for first dose approvals.

These gambles need to be thoroughly recognized and applauded. Despite many disputes among citizens, politicians, business people, public health officials, healthcare providers and researchers on how to best address the worst pandemic in more than 100 years, vaccines will be our way out. Medicines, social distancing, mask wear and so on help but have not blunted the tremendous human and economic suffering in most countries.

With sufficient immunizations, the virus will be corralled. Until then, I wish you and your families the best of health and safety as we close 2020 and enter 2021.

## Fisher Center Grant

cont'd from page 1

Lung infections caused by MAC constitute a significant challenge for physicians to treat. Current therapy relies on the use of antibiotics that were not explicitly developed for NTM. Unfortunately, despite recognition since the 1950s, we do not yet know how best to test for antibiotic effectiveness when treating MAC lung disease. Dr. Cohen outlined the significant challenges, “It would be hard to find a person who has not been exposed to NTM in the environment. NTM cases far outnumber TB disease in the US, the reason for which is poorly understood. NTM lung disease is even more difficult to treat than TB, with most patients treated with multiple antibiotics for 1-2 years. Also, the increasing number of cases has heightened the need for innovations in NTM clinical care. We thank the Fisher Center for recognizing and supporting this need.”

For the Fisher award, Dr. Cohen assembled a multidisciplinary team of researchers, including infectious disease physicians Dr. Kelley Dooley and Dr. Elisa Ignatius, and Dr. Nicole Parish, who directs the Johns Hopkins Clinical Mycobacteriology Laboratory. Dr. Cohen and her colleagues seek to repurpose earlier TB study designs, which examined how well drugs killed TB bacteria during the first few weeks of treatment, known as early bactericidal activity (EBA). Some antibiotics kill TB bacteria early on in treatment, while other antibiotics kill bacteria only months thereafter, thereby reaching dormant bacteria. To treat appropriately and prevent relapse of TB, antibiotics are used for at least six months. Since MAC treatment has not been sufficiently studied to understand which antibiotics and which combinations work best, treatment is often 12 to 18 months of duration using multiple drugs that are often tough for patients to tolerate.

To expand on the important EBA concept, Dr. Cohen and her colleagues ask study participants to have their MAC drugs introduced in a standardized, stepwise fashion. Sputum collections will occur periodically throughout the first two months of treatment. MAC bacterial counts can be followed over time to determine how quickly the antibiotics in the regimen are effectively killing MAC. In addition, the drug levels of these antibiotics in the blood will also be analyzed. This trial design may ultimately provide a reliable method to determine which drugs or drug combinations are most effective at the early killing of these bacteria in humans. A similar well-validated model has been used in TB; however, this is the first time it will be used in the study of NTM. By gaining these fundamental data regarding the EBA of antibiotics for MAC, treatment regimens for MAC may be designed to be more effective for these challenging bacteria. Moreover, the findings may encourage pharmaceutical companies to develop medications specifically for NTM.

## PANDEMIC IMPACT ON NTM RESEARCH



**Cohen NTM Research Team, photo taken December 2019**

First row, L to R: Jonathan Grant, Erin D'Achino, Angie Muse, Renee Vaughnley, Meghan Ramsay  
 Second row, L to R: Mary Rykiel, Jonathan Zenilman, Jan Nguyen, Mark Jennings, Asli-Bahadirli-Talbott, Keira Cohen, Sera-Kim Huenergard, Fin Mears  
 Not pictured: Chris Lippincott, Tony Lin, Elisa Ignatius, Sara Carson, Andrew Wu, Aaron Ong

The team was ready to begin their research in March 2020, when the COVID-19 pandemic forced the closure of most clinical research services. The NTM team quickly pivoted to a nearly 100% telemedicine model, conducting clinical visits over video or telephone.

Most in-person clinical research was put on hold, including Cohen's Fisher funded MAC study. The

pandemic prompted innovation, moving the detailed study from the research clinic to the patients' homes. Since an EBA study has never been done remotely by mail, the team had to refine study procedures and materials for self-collected sputum samples and processing. Jan Nguyen, the Senior Research Program Coordinator, was "absolutely instrumental" in developing mailing procedures, while lab manager Asli Bahadirli-Talbott, MSC, perfected laboratory techniques for analysis of mailed in sputum specimens.

### COLLABORATION WITH OTHER CLINICIANS

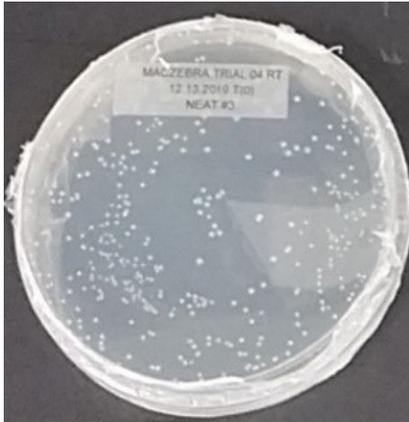
A team-based approach is the best recipe for success, essential for clinical care and studies of NTM patients. Dr. Cohen stresses the collaborative efforts needed across disciplines. In particular, Christopher Lippincott, MD and Kelly Dooley, MD, PhD have joined the group. According to Dr. Lippincott, "A multidisciplinary care team is essential for the treatment of NTM infections. By combining the expertise of pulmonology, infectious diseases and respiratory therapy, the Center for NTM and Bronchiectasis is uniquely situated to provide the individualized multidisciplinary care that our patients need." Marrying both clinical and research resources, the new Center has assembled a program ready to diagnose and treat NTM.

infections, contributing to improved quality of life for NTM patients. The Fisher Center is pleased to support innovative NTM research.

### ADDITIONAL FISHER CENTER SUPPORT

The Fisher Center has supported the burgeoning NTM scientific community at Johns Hopkins. While an Infectious Diseases fellow, Elisa Ignatius, MD, with the assistance of Fisher Center staff, organized the NTM Interest Group in 2018, using the Fisher Center as meeting space. With the onset of the pandemic, the meeting has moved to an online teleconference. NTM Interest Group members include former Fisher Center Discovery Program grant recipients Nicole Parrish, PhD (2014), Petros Karakousis, MD (2016), and Gyanu Lamichhane, PhD (2020).

# A Primer on Nontuberculous Mycobacteria



MAC on a laboratory plate

Though not widely known, nontuberculous mycobacteria (NTM) are environmental bacteria found most everywhere including soil, dust, and water (both natural and municipal water sources). These bacteria can cause human disease, most frequently in a chronic lung infection similar to pulmonary tuberculosis (TB). Unlike TB, NTMs are generally not contagious from person-to-person. The most common NTMs in the US are *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus* complex and *Mycobacterium kansasii*.

## Prevalence

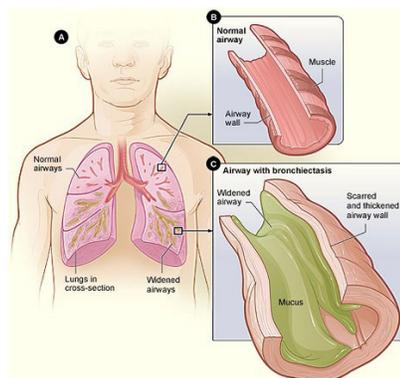
Since public health reporting of NTM is not mandatory in many states, it is difficult to obtain an accurate caseload. It is estimated there are 100,000 cases per year in the US, and prevalence is rapidly increasing, likely due to our growing, aging population. In contrast, there were 8,900 reported TB cases in 2019. Because the bacteria are not contagious and are less virulent than TB, NTMs have mostly been ignored in the research and drug development arenas.

## Transmission

NTM can clump together to create lasting biofilms on plumbing surfaces resistant to disinfectants (including chlorine) and are difficult to remove. As water passes through these surfaces (such as showerheads, sink faucets, therapy baths, hot tubs, ice machines, and decorative fountains), the bacteria are aerosolized, then inhaled by persons nearby. How precisely some people acquire the infection as opposed to others remains incompletely understood. Transmission may also occur rarely during invasive medical procedures using contaminated equipment, such as respiratory machines, bronchoscopes, and heater-cooler devices used during open-heart surgery.

## Human Infections

Only a tiny number of people exposed to NTM develop infections. NTM is an opportunistic infection, meaning it occurs more frequently in people who have some predisposition for it or who have significantly weakened immune systems. NTM is primarily a lung infection, which can occur in individuals with a type of lung scarring in which there are inflammation and widening of the airways (bronchiectasis). Inflammation in bronchiectasis triggers airway scarring and loss of ability to clear mucus. This then invites recurring respiratory infections like pneumonia. NTM can also form cavities in the lung, leading to damaged lung architecture and subsequent respiratory decline.



Bronchiectasis is the condition where the bronchi become widened, leading to mucus build-up, which breeds bacteria causing infections.

NTM infections can also occur outside the lung, where they can cause skin and soft tissue infections, device-related infections (central line sites, pacemaker sites), and blood infections.

## Who is at risk?

Many NTM infections are in persons with pre-existing conditions such as:

- ▶ Underlying severe lung disease (bronchiectasis, emphysema)
- ▶ Gastroesophageal reflux (heartburn)
- ▶ Cystic fibrosis
- ▶ Weakened immune systems (immunosuppressing medications, HIV, cancer, transplant, autoimmune disorders)

Oddly, post-menopausal, slender women with no significant medical history are also at increased risk for NTM. Why some older women are prone is unknown but may be due to age-related changes in the immune system or lung architecture.

## Symptoms

Typically, a person with NTM infection develops a cough, fatigue, and weight loss. This may continue for months or years.

Symptoms depend on the infection site and the underlying immune status of the patient. Symptoms may include chronic cough (may produce mucus or blood), fever, chills, fatigue, shortness of breath, bloody sputum, night sweats, decreased appetite, weight loss, muscle aches, rash and skin lesions. Since these symptoms are vague, they are often subtle and can imitate other diseases. Clinicians often need a high index of suspicion to order the right tests, such as CT scans or special mycobacterial cultures to diagnose NTM infections. Patients who have plastic surgery especially on the torso appear prone to NTMs such as *Mycobacterium abscessus* or *Mycobacterium fortuitum*. A hint can be gleaned with infections arising after surgery which do not yield standard bacterial growth and fail to respond to usual antibiotic therapy.

# BreakOut

## Diagnosis

Diagnosis is determined by first assessing that NTMs could be at play and then order the correct microbiology and imaging tests (chest CT scan). NTMs are notoriously difficult to culture, complicating the diagnosis. For their species, some may be fast-growing for the species (7-10 days, such as *Mycobacterium abscessus* or slow-growing (> 14 days), such as *Mycobacterium avium* complex (MAC). Sometimes the first sign of infection may be that special acid-fast bacilli (AFB) stains reveal organisms under the microscope. For slow-growing NTM, cultures require up to six weeks of incubation for detection. In an even further sign of the difficulty diagnosing these bugs, not all hospitals can identify species, so samples must be sent to a reference lab (government or academic center, such as Johns Hopkins) for definitive diagnosis. These labs may use special equipment such as mass spectrometry and DNA sequencing to identify a species.

## Prevention for individuals

There is little data regarding prevention. People not at risk for NTM do not necessarily need to change their habits. For those with NTM infection presently or in the past, clinicians recommend no smoking and vaccination for flu and pneumonia to prevent further complications. For people who may be at risk, there are no known prevention approaches at this time.

## Treatment

Treatment overseen by clinicians who have experience in the diagnosis and treatment of NTMs is recommended. As one patient states, "It was the best and most thorough medical experience I have ever had. It was a huge relief to be cared for in a center where my rare infection isn't rare for the medical team, but instead treated commonly."

Chest physiotherapy plays a pivotal role in airway clearance to reduce mucus build-up in the lungs. Correction of gastric reflux (heartburn) can be a component of clinical treatment.

MAC must be treated with a combination of antibiotic therapy for many months or a year or more. Patients often have difficulty tolerating the necessary, multiple antibiotics. Even with prolonged multidrug treatment, MAC lung disease is sometimes fatal or severely debilitating. Early treatment may stave off such dire complications. Surgery could help some patients with localized lung disease or if to staunch bleeding.

## When to see your doctor

Persons living with chronic lung disease, whose symptoms are getting worse or their treatment is not working and used to, are encouraged to visit their pulmonologist and consider an NTM evaluation. Evaluation is warranted for otherwise healthy people who develop a chronic cough that does not improve. If you cough up blood or have severe shortness of breath, seek help immediately.

## COVID-19 Proposals Under Consideration

The 2021 Fisher Center Discovery Program (FCDP) grant cycle is well underway. From across Johns Hopkins University, faculty submitted 17 proposals for funding consideration. The FCDP will continue its focus on environmental infectious diseases. However, in response to the COVID-19 pandemic, we also offer the funding opportunity for clinical and translational research related to COVID-19 and SARS-CoV-2. Submissions with both a COVID-19/SARS-CoV-2 and environmental focus will receive special funding consideration. Our Advisory Board will announce funding decisions in late December 2020.

## Advisory Board Changes



**Richard Moore, MD** has announced he is stepping down from the Fisher Center Advisory Board. Since 2013, the Board has leveraged his extensive clinical trial research expertise to assist with the selection of FCDP grant awardees from many excellent proposals. We sincerely thank Dr. Moore for his thoughtful proposal

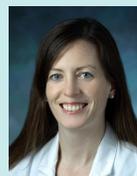
reviews and wise counsel that were helpful over the years. As a well-regarded HIV researcher, mentor, and Institutional Review Board committee chair, Dr. Moore continues his work within the Department of Medicine and Johns Hopkins.



Succeeding Dr. Moore on the Board is **Yukari Manabe, MD**. Dr. Manabe's extensive research and clinical experience in point-of care diagnostics and chronic infections in low resource settings are valuable resources for the FCDP to draw upon for proposal reviews. Welcome to the Board, Dr. Manabe.



Lending his wide-ranging expertise in clinical trials, **Mark Sulkowski, MD** will review 2021 FCDP grant proposals. Dr. Sulkowski is the Medical Director of the Johns Hopkins Viral Hepatitis Center, Associate Dean for Research in the Capital Region (CAPRES), and is the Director of the Division of Infectious Diseases at Johns Hopkins Bayview Medical Center.



Also reviewing 2021 FCDP grant proposals is **Eileen Scully, MD, PhD**. Dr. Scully sits on the Johns Hopkins University (JHU) Baltimore Washington India Clinical Trials Committee. She is the recipient of a JHU Center for AIDS Research (CFAR) grant for her work on HIV immune activation and metabolism. Her extensive

knowledge of the human immune system will greatly assist in the evaluation of scientific proposals.

# FUNDING OUR FUTURE

Thanks so much to the generous donors who support the research efforts in the Fisher Center. We are grateful. If you would like to make a donation, please give online at <https://secure.jhu.edu/form/infdis>.

WE THANK THE GENEROUS CONTRIBUTORS THAT HELP SUPPORT THE FISHER CENTER PROGRAM

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IF YOU HAVE ANY QUESTIONS ABOUT GIVING, PLEASE CONTACT DONNA BOLIN AT 410-336-5761 OR BY EMAIL AT [DBOLIN1@JHMI.EDU](mailto:DBOLIN1@JHMI.EDU).

## + RECENT PRESENTATIONS

COVID-19 Vaccine: Which Country Should Get It First? Arthur L. Caplan, PhD; Paul G. Auwaerter, MD; Ronald J. Waldman, MD, MPH; Helen Rees, MD, MRCGP. <https://www.medscape.com/viewarticle/936107>. August 27, 2020

This 'Slowly Evolving Crisis' Needs Attention. Paul G. Auwaerter, MD. Medscape Infectious Diseases. <https://www.medscape.com/viewarticle/935740>. August 28, 2020

'No One Is Protected' From COVID-19, Not Even the President. Paul G. Auwaerter, MD. Medscape Infectious Diseases. <https://www.medscape.com/viewarticle/938537>. October 5, 2020

What's Hot in Clinical Infectious Diseases. Paul G. Auwaerter, MD. Infectious Diseases Society of America (IDSA), IDWeek 2020, online. October 24, 2020.

Highlights From IDWeek 2020: Fauci on COVID-19. Paul G. Auwaerter, MD. Medscape Infectious Diseases. <https://www.medscape.com/viewarticle/939671>. October 27, 2020

'Warning Lights' Ahead: Insights From COVID Epidemiology. Paul G. Auwaerter, MD. Medscape Infectious Diseases. <https://www.medscape.com/viewarticle/939806>. October 29, 2020

SARS-CoV-2 Diagnostics, From Serology to Spit. Paul G. Auwaerter, MD. Medscape Infectious Diseases. <https://www.medscape.com/viewarticle/940204>. November 16, 2020

## + RECENT PUBLICATIONS

Deployment of convalescent plasma for the prevention and treatment of COVID-19.

Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JP, Pekosz A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski LA, Bailey JA, Tobian AA. *J Clin Invest*. 2020 Jun 1;130(6):2757-2765. doi: 10.1172/JCI138745. PMID: 32254064

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Pathways to Leadership: Reflections of Recent Infectious Diseases Society of America (IDSA) Leaders During Conception and Launch of the Inclusion, Diversity, Access, and Equity Movement Within the IDSA. Sears CL, Powderly WG, Auwaerter PG, Alexander BD, File TM. *J Infect Dis*. 2020 Sep 14;222(Supplement\_6):S554-S559. doi: 10.1093/infdis/jiaa297. PMID: 32926740

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease. Lantos PM, Rumbaugh J, Bockenstedt LK, Falck-Ytter YT, Aguero-Rosenfeld ME, Auwaerter PG, Baldwin K, Bannuru RR, Belani KK, Bowie WR, Branda JA, Clifford DB, DiMario FJ Jr, Halperin JJ, Krause PJ, Lavergne V, Liang MH, Cody Meissner H, Nigrovic LE, Nocton JJJ, Osani MC, Pruitt AA, Rips J, Rosenfeld LE, Savoy ML, Sood SK, Steere AC, Strle F, Sundel R, Tsao J, Vaysbrot EE, Wormser GP, Zemel LS. *Arthritis Rheumatol*. 2020 Nov 29. doi: 10.1002/art.41562. Online ahead of print. PMID: 33251716.

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. Krause PJ, Auwaerter PG, Bannuru RR, Branda JA, Falck-Ytter YT, Lantos PM, Lavergne V, Meissner HC, Osani MC, Rips JG, Sood SK, Vannier E, Vaysbrot EE, Wormser GP. *Clin Infect Dis*. 2020 Nov 30;ciaa1216. doi: 10.1093/cid/ciaa1216. Epub ahead of print. PMID: 33252652.

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