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OHSU-PSU School of Public Health NTM and Bronchiectasis Research Program Overview

Nontuberculous mycobacteria (NTM) are environmental pathogens that causes chronic and progressive lung disease and disability in some, while other infected individuals remain relatively asymptomatic without progression. Pulmonary NTM disease disproportionately affects the elderly and women, and those with existing underlying lung diseases like emphysema or bronchiectasis. (1,2) Both the disease and its multi-drug treatment lasting 18-24 months can have a negative impact on health-related quality of life. The natural history of pulmonary NTM is not well understood. It is likely that the behavior of NTM infections is different depending upon many factors including the patient's type of underlying lung disease, comorbidities, and immune status. The lack of understanding of this disease complicates both the clinical care of these patients and the design of clinical trials assessing the efficacy and safety of new therapeutics.

Over the last decade Oregon Health & Science University (OHSU) in Portland, OR, has lead a variety of projects related to the natural history, burden, and treatment of NTM and bronchiectasis. OHSU is one of 13 sites in the COPD Foundation's Bronchiectasis and NTM Research Registry. In addition, the research program has a strong emphasis on the patient-centered aspects of these diseases, and has partnered with patient advocacy organizations NTM Info & Research and the COPD Foundation on several Patient-Centered Outcomes Research Institute (PCORI)-funded projects. In 2015, with a panel of patients, patient advocates, and clinical stakeholders the team identified the 14 top patient-centered NTM research priorities. (3) We also recently completed a Bronchiectasis Patient-Centered Research Priorities and Roadmap document that is publically available. (4)

Below we summarize ongoing major projects: statewide NTM surveillance, the Pacific Northwest NTM Biobank, Bronchiectasis Comparative Effectiveness Study, and NTM clinical trials. Several of these projects have been developed in collaboration with the NTM Research Consortium (NTMRC), which to date has included OHSU, National Jewish Health, Denver, CO, University of Texas Northeast, Tyler, TX, and NIH-NHLBI, Bethesda, MD.

NTM Surveillance in Oregon

In partnership with the Oregon Health Authority (state health department) several laboratory surveillance special projects have been completed. These projects established a baseline burden of disease in Oregon during 2005-6 and described outcomes in of a population-based sample of patients with pulmonary NTM. (2,5-7) Additional laboratory surveillance generated the first estimates of the incidence of pulmonary NTM during 2007-2012. (8) In 2013, Oregon made extrapulmonary NTM reportable, with most laboratories reporting electronically through the electronic laboratory reporting (ELR) system. Many laboratories also report pulmonary culture results through the ELR. While experts in Oregon agree that pulmonary NTM is important, there is not agreement on whether reporting should be mandatory or surveillance should continue using alternative methods such as used in Oregon. (9)

Ongoing efforts to identify patients with new pulmonary NTM isolation are occurring in multiple ways. First, through special project surveillance. Second, through a regional network of pulmonary and infectious disease clinics that

strengthens the surveillance network and refers patients to OHSU for clinical care and research studies. Third, patients who are seen at NTM Clinic at OHSU.

Pacific Northwest NTM Biobank and Data Repository

The Pacific Northwest (NW) NTM Biobank was established in 2013 to establish a human specimen and clinical data repository from patients identified through the surveillance network described above. Supported by an Oregon Clinical and Translational Research Institute (OCTRI) Catalyst Award, American Lung Association (ALA) DeSouza Award, and most recently an ATS Foundation/ALA of the Mountain Pacific Research Grant, enrollment is ongoing and has surpassed 300 patients with a history of respiratory NTM isolation. In addition, controls with and without underlying lung disease have been enrolled. At enrollment, we collect blood (serum, plasma, PBMCs, and RNA) and bronchiectasis- and NTM- specific health-related quality of life (HRQoL) and anxiety/depression surveys. We abstract a complete medical history into our REDCap™ database, including microbiology, radiography, comorbidities, concomitant medications, lung function, and NTM therapy. Observational clinical follow-up and chart review continue indefinitely. Blood collection and HRQoL surveys are repeated at 12-18 months. Several of the specific aims of the study are described in more detail below.

Specific Aim: Biomarkers

The reasons for disease progression in select NTM patients are unknown and largely unexplored to date. Currently clinicians cannot predict which patients will suffer disease progression or would benefit from antibiotic therapy. In collaboration with David Lewinsohn, MD, PhD, a TB immunologist at OHSU, we are conducting pilot studies using Biobank samples evaluating immune responses in patients with NTM disease. We aim to describe the phenotype and frequency of NTM-specific CD4+ and CD8+ lymphocyte responses and evaluate the predictive capacity of these T cell responses and profiles for subsequent pulmonary NTM disease progression. We will also focus on a newly described class of T cells, Mucosal Associated Invariant T (MAIT) cells that are unusual in their recognition of mycobacterial metabolites, and dependence on the highly conserved molecule MR1. We will evaluate the correlation of circulating MAIT cells with the presence of pulmonary NTM disease. In pilot evaluations we identified differences in lymphocyte response between various groups of patients, and are focusing on comparisons between COPD patients with and without NTM.

Specific Aim: Health-related quality of life

In collaboration with Alexandra Quittner, PhD, we are evaluating HRQoL in NTM patients. Patients and doctors have reported that improvement in symptoms and ability to function is an important outcome of treatment for NTM patients. In a prior project, our patient partners identified HRQoL as the most important outcome to be measured within current and future clinical trials. However, there is little data on how HRQoL corresponds with disease activity or burden as measured by culture status or other clinical measures. The QOL-B and NTM module are existing tools developed by Dr. Quittner that measure patient health-related quality of life in patients with NTM and underlying bronchiectasis. Within the Biobank, we plan to examine whether health-related quality of life can be used to measure how well NTM treatment works. Our results will provide evidence that supports the use of these patient-friendly tools in future clinical trials in addition to use in the “real-world” for patients and doctors to measure treatment success.

Comparative effectiveness research

We have partnered with patients, the COPD Foundation and NTM Info & Research, technical advisors at University of Alabama at Birmingham, and clinical co-investigators Drs. Charles Daley, David Griffith, and Timothy Aksamit in a PCORI-sponsored comparative effectiveness study. We are evaluating the benefits and harms of the most common therapies prescribed for non-CF bronchiectasis using a large cohort of bronchiectasis patients identified within Centers for

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Medicare and Medicaid Services (CMS) data. CMS data will also be linked to a national bronchiectasis registry to validate outcomes lacking prior validation. Our patient co-investigators and stakeholders have identified the two most common therapies used in this disease, inhaled corticosteroids (ICS) and suppressive macrolide antibiotics, and they have identified the potential benefits and risks of these therapies of greatest importance to them. We will compare the relative safety of ICS and macrolide therapy with regards to the acquisition of pulmonary NTM and prevention of hospitalized respiratory infections, in addition to other secondary outcomes. The patient and clinical stakeholders will work together to interpret and disseminate results from the study.

Clinical Trials

The NTMRC recently received an FDA grant for a Phase 2 double blind, randomized, placebo-controlled proof of concept trial to assess the clinical efficacy and safety of clofazimine in adults with pulmonary *Mycobacterium avium* complex (MAC) disease. Patients will be recruited at all NTMRC sites. Clofazimine is an antimicrobial drug that is approved for the treatment of *Mycobacterium leprae* infections and has been used for many years in off-label fashion against multi-drug resistant MAC and TB. Adults with stable or slowly progressing sputum culture confirmed MAC disease are eligible. Patients will be randomized to treatment with clofazimine or placebo for 24 weeks. The primary objective is to determine if clofazimine has anti-mycobacterial activity against pulmonary MAC infection (culture conversion); secondary objectives include assessment of clinical response to clofazimine treatment, monitor the safety of clofazimine when used to treat MAC infections, and drug susceptibility testing for susceptibility to clofazimine.

In collaboration with Dr. David Griffith, we recently started a pilot Phase 2 investigator initiated open-label trial of Liposomal Amikacin for Inhalation (LAI) in patients with pulmonary *M. abscessus*. Our team is also participating in Insmed's Phase 3 study to test LAI in a randomized, open-label, multicenter study in adult patients with NTM caused by MAC that are refractory to treatment (INS-212). The primary objective is to evaluate the efficacy of LAI administered once daily when added to a multi-drug regimen (MDR), for achieving culture conversation compared to MDR alone. An open-label Phase 3 extension study for non-converters (INS-312) sponsored by Insmed is currently enrolling non-converters from INS-212.

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Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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Abstract:

The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. **See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.**

The following 9 PICO questions are addressed:

PICO Question 1: Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis? (Case management is defined as patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, and incentives/enablers).

Recommendation 1: We suggest using case management interventions during treatment of patients with tuberculosis (*conditional recommendation; very low certainty in the evidence*).

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PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?

Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis (*conditional recommendation; low certainty in the evidence*).

PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

Recommendation 3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug susceptible pulmonary tuberculosis (*strong recommendation; moderate certainty in the evidence*).

Recommendation 3b: Use of thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not HIV infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) (*conditional recommendation; low certainty in the evidence*).

Recommendation 3c: In situations where daily or thrice-weekly DOT therapy is difficult to achieve, use of twice-weekly therapy after an initial 2 weeks of daily therapy may be considered for patients who are not HIV-infected and are also at low risk of relapse (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) (*conditional recommendation; very low certainty in the evidence*).

Note: If doses are missed in a regimen using twice-weekly dosing, then therapy is equivalent to once weekly, which is inferior (see PICO Question 4).

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Recommendation 4a: We recommend the use of daily or thrice weekly dosing in the continuation phase of therapy for drug susceptible pulmonary tuberculosis (*strong recommendation; moderate certainty in the evidence*).

Recommendation 4b: If intermittent therapy is to be administered in the continuation phase, then we suggest use of thrice-weekly instead of twice-weekly therapy (*conditional recommendation; low certainty in the evidence*). This recommendation allows for the possibility of some doses being missed; with twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior.

Recommendation 4c: We recommend against use of once-weekly therapy with INH 900 mg and rifapentine 600 mg in the continuation phase (*strong recommendation; high certainty in the evidence*).

In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus rifapentine 600 mg may be considered for use only in HIV uninfected persons without cavitation on chest radiography.

PICO Question 5: Does extending treatment beyond 6months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients coinfectd with HIV?

Recommendation 5a: For HIV-infected patients receiving ART, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis (*conditional recommendation; very low certainty in the evidence*).

Recommendation 5b: In uncommon situations in which HIV-infected patients do NOT receive ART during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3 months (ie, a continuation phase of 7 months in duration, corresponding to a total of 9 months of therapy) for treatment of drug susceptible pulmonary tuberculosis (*conditional recommendation; very low certainty in the evidence*).

PICO Question 6: Does initiation of ART during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients coinfectd with HIV?

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Recommendation 6: We recommend initiating ART during tuberculosis treatment. ART should ideally be initiated within the first 2 weeks of tuberculosis treatment for patients with CD4 counts <50 cells/ μ L and by 8–12 weeks of tuberculosis treatment initiation for patients with CD4 counts \geq 50 cells/ μ L (*strong recommendation; high certainty in the evidence*). Note: an exception is patients with HIV infection and tuberculous meningitis (see Immune Reconstitution Inflammatory Syndrome).

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis (*conditional recommendation; very low certainty in the evidence*).

PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis (*strong recommendation; moderate certainty in the evidence*).

PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients with paucibacillary tuberculosis (ie, smear negative, culture negative)?

Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-uninfected adult patients with AFB smear- and culture-negative pulmonary tuberculosis (*conditional recommendation; very low certainty in the evidence*).

See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

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Recent Staff Publications

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Meetings/Conferences/Lectures

The 54th Annual Denver TB Course, April 5-8, 2017, Molly Blank Conference Center at National Jewish Health Main Campus. For more information and registration: <https://www.nationaljewish.org/tbcourse2017>

Friday, May 19, 2017 at Georgetown University, Washington, DC.

Presented by: NTM Info & Research & Georgetown University School of Medicine
https://www.ntminfo.org/images/media/News/conference_flyer.pdf

Save these dates for the NTM Lecture Series:

- NTM Lecture Series for Providers, October 19-20, 2017
- NTM Lecture Series for Patients and Families, October 21, 2017

Details about these lectures will be posted at a later date. To add your name to the contact list, please call 800.844.2305 or email: proed@njhealth.org

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