Launching a New Online Newsletter

Increasing morbidities of nontuberculous mycobacterial (NTM) lung disease, a never ending number of newly described mycobacteria species, and multidrug-resistant tuberculosis (TB) that continues to be a public health threat have lead National Jewish Health to develop the NTM-TB INSIGHTS newsletter. It provides the latest information for patients, advocates, educators, health care providers, laboratory scientists, researchers, public health officials and all who want to learn more about NTM disease and TB. NTM-TB INSIGHTS will be published 4 to 6 times a year. We hope you enjoy the publication.

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World TB Day

On March 24th 1882, Dr. Robert Koch announced that he had found the cause of tuberculosis. Eventually, effective medications were discovered and we learned that TB is a preventable, treatable and curable disease. So why hasn’t TB been eliminated? Unfortunately the advent of effective treatment led to complacency as the public’s attention shifted to other diseases. One hundred years later, in 1982, World TB Day was established to raise awareness about TB that continued to cause disease and death in millions of people each year. These efforts went largely unnoticed until active TB and drug-resistant disease suddenly increased in the mid and late 1980s causing a public health crisis.

So, how far have we come since the first World TB Day thirty-three years ago? The medications to treat TB today are the same as they were in 1982. The World Health Organization estimates that billions of people are infected with TB, over 9 million get sick from it each year, 3 million receive inadequate treatment, and 1.5 million die. In the U.S., an estimated 11 million people are infected and 9,412 were diagnosed with active TB in 2014. This represented a 2.2% decline from 2013, the smallest decrease in over a decade. As for awareness, ask the average American about TB and they will likely think that it has been eliminated.

The U.S. and other countries with resources have achieved TB control despite inadequate diagnostic tests and poorly tolerated treatment. Globally, TB control is improving but remains fragile. Unstable funding and increasing drug resistance threaten to reverse the progress both domestically and globally. Still, TB elimination remains a goal that is theoretically achievable. Attaining it will require a willingness by our society to dedicate the money and support needed to succeed. Until then, World TB Day is our opportunity to raise awareness about the potential for TB elimination and the devastating consequences of complacency.

Robert Belknap M.D., Director, Denver Metro TB Program

njhealth.org/MycobacterialConsultation
Co-editors: Charles Daley, MD and Max Salfinger, MD, FIDSA, FAAM
Welcome Dr. Drummond!

The Division of Mycobacterial and Respiratory Infections welcomes Wendi Drummond, DO, MPH, as a new member of the faculty. Dr. Drummond, who is originally from Pueblo, Colorado, attended Boston University and the University of Utah for her undergraduate training and eventually earned a Master’s degree in public health. Following a position as epidemiologist in the Los Angeles County Tuberculosis Control Program she attended Kansas City University of Medicine and Biosciences followed by a residency in Phoenix, Arizona where she received training in both internal medicine and pediatrics. She then performed a fellowship in Infectious Diseases at the University of Oregon. During her fellowship, she was able to work in the nontuberculous mycobacterial clinic with Kevin Winthrop, MD, MPH, a close colleague and collaborator with our Division. Wendi moved back to Colorado in 2010 and was in private practice in pediatric infectious diseases at Presbyterian St. Luke’s and Rocky Mountain Hospital for Children before joining National Jewish in January of this year. Dr. Drummond will be seeing adult patients with mycobacterial infections and other infectious diseases in addition to leading our Infection Prevention Program as the Infection Prevention Officer for National Jewish Health. Welcome Wendi!

Charles L. Daley, MD, Chief, Division of Mycobacterial and Respiratory Infections, National Jewish Health

Interesting Recent NTM Publication


Intermittent, three times weekly therapy is recommended for the initial treatment of noncavitary nodular bronchiectatic Mycobacterium avium complex (MAC) disease although the evidence to support this recommendation is limited. Jeong and colleagues recently reported the results of a retrospective cohort study comparing treatment outcomes of 217 patients with treatment-naïve noncavitary nodular bronchiectatic MAC lung disease. All patients received either daily (n = 99) or intermittent therapy (n = 118) that included clarithromycin or azithromycin, rifampin, and ethambutol. Patients treated before January 2011 were given daily regimens whereas those treated afterwards were treated with intermittent therapy. Sputum conversion was slightly lower in the intermittent group (67%) than in the daily group (76%) although the difference was not statistically significant. Additionally, the rates of symptomatic improvement and radiographic improvement were not different between the two groups. However, modification of the initial antibiotic therapy occurred more frequently in the daily therapy group than in the intermittent therapy group (46 vs. 21%, p < 0.001): in particular, ethambutol was more frequently discontinued in the daily therapy group than in the intermittent therapy group (24 vs. 1%, p <0.001). Based on this study, as well as previously published studies, intermittent treatment of pulmonary noncavitary nodular bronchiectatic disease appears to have similar outcomes compared with daily therapy and is tolerated better. These findings support the current American Thoracic Society and Infectious Diseases Society of America recommendations to use intermittent therapy to treat patients with noncavitary nodular bronchiectatic MAC lung disease.

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Discrimination Between Active and Latent Tuberculosis – Immunological Tools

Tuberculosis continues to be a global health problem. The 2014 WHO Global Tuberculosis Report estimates that 9 million new cases of tuberculosis and 1.5 million tuberculosis–related deaths occurred worldwide in 2013 [1]. An estimated 2 billion people worldwide harbor the organism with no evidence of disease [2]. Effective global control of the disease rests on accurate diagnosis of active and latent tuberculosis, and prompt, effective treatment. Current diagnostic tests take advantage of the cell mediated response to TB antigens (the Mantoux skin test, based on the type IV delayed hypersensitivity response) and the IGRAs (interferon gamma release assays) that measure IFN-γ secreted by peripheral blood mononuclear cells following stimulation with tuberculosis antigens. These tests, however, do not differentiate active from latent tuberculosis, nor can they predict the risk of reactivation of latent TB. There has been considerable effort, therefore, to analyze the complex immune response to M. tuberculosis in order to better identify biomarkers of active tuberculosis infection.

The TB immune response is multifaceted, involves a number of players from the innate and adaptive immune systems, and is the product of cooperation between macrophages and T cells and the cytokines they produce. Several recent studies have indicated that a broader analysis of the immune response using multiplexed assays and measurement of multiple parameters may provide insight into development of more sensitive and specific tools that can discriminate between latent and active tuberculosis. We highlight some of these studies in this commentary.

Among the soluble mediators of the immune response, IP-10 has been investigated as a superior discriminator between active TB and latent TB infection (LTBI). In a study of 38 plasma cytokines in active tuberculosis or LTBI patients, and uninfected controls, Wergeland et al found IP-10 was able to distinguish active TB from LTBI with high accuracy [3]. An expanded cytokine panel including IP-10, IL-2, IL-6 and MIP-1 β indicated improved diagnostic sensitivity for Mycobacterium tuberculosis infection, in comparison with measurement of IFN-γ alone, as utilized in the IGRAs [4]. Th1/Th2 and IL-4/IL4δ2 ratios have been examined for their ability to predict the risk of reactivation of latent tuberculosis. J. Siawaya et al, in a study of LTBI showed that decreased ratios of IL-4/IL-4δ2 (IL-4 antagonist) predicted low risk of reactivation, whereas lower IFN-γ/IL-4 and IL4δ2/IL-4 was predictive of an elevated risk [5].

Also of great interest is the flow cytometry analysis of polyfunctional CD4 and CD8 cells in active and latent tuberculosis. Of note is the analysis of IFN-γ, IL-2 and TNF-α secreting T cells, as well as of the phenotype (naïve and memory) of TB-specific T cells in peripheral blood, all of which emphasize the need for multivariate analysis of biomarkers. Studies in this area include investigation of the ability of CD27 and PD-1 expressed on CD4 cells to distinguish between LTBI, healthy BCG vaccinated controls and clinically resolved M. tuberculosis infection [6]. Another study, comparing the response of CD4 and CD8 cells to PPD, ESAT-6 and CFP-10, showed that individuals with LTBI had a higher percentage of IFNγ+ CD4 and CD8 cells compared with individuals with active infection [7]. More recently, V. Rozot et al examined the ability of TB-specific, IFNγ+ and/or TNF-α positive CD4 and CD8 T cells to discriminate active infection from LTBI [8]. Analyzing a cohort of LTBI and active TB patients, they determined that while the individual measurement of TNF-α+CD4 cells or the percentage of TB-specific CD8 cells was capable, in isolation, of differentiating active infection from LTBI, a combination of these two parameters resulted in greater assay specificity and sensitivity, representing a significant improvement over single parameter measurements.

In addition to cytokines and cell associated biomarker studies, the gamut of biomarkers under investigation for discrimination between LTBI and active TB include antibodies to TB antigens, autoantibodies, cytokine receptors, markers of inflammation and differential gene expression studies [9]. All of these studies indicate that while single analytes (IFNγ) have been in use for a number of years, they have limited ability to discriminate active infection from LTBI. Development of multivariate assays that more accurately reflect the immune response to latent or active tuberculosis is crucial to accurate diagnosis and management of the disease.

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References:


Mycobacterial Taxonomy

Together with the genera Corynebacterium and Nocardia, the genus Mycobacterium forms a monophyletic taxon, the so-called CMN group, within the phylum Actinobacteria. The genus Mycobacterium is highly diverse, thanks to its ancient origin and years of evolution in multiple habitats. Historically, the species within the genus Mycobacterium have been classified based on their growth rate in a subculture as rapid (visible growth in <7 days) and slow growers (growth detection >7 days), and on their pigment production as scotochromogenic (pigment production in the dark), photochromogenic (pigment production after exposure to light), or nonchromogenic [Runyon classification, 1959].

The plethora of newly described species seen in the past decades is in part the consequence of the availability and increased reliability of new DNA-sequencing methods that are capable of differentiating even closely-related species and an increased frequency of isolation of mycobacteria. The latter may be the result of newly emerging manmade reservoirs for certain species. From 41 valid species in 1980, currently this genus encompasses 170 recognized species and 13 subspecies (http://www.bacterio.net/mycobacterium.html).

The Mycobacterium genus includes strict pathogens, potentially or opportunistic pathogens, and nonpathogenic saprophytic species. According to the presently prevailing terminology, the mycobacteria species that earlier were referred to as atypical mycobacteria or mycobacteria other than tuberculosis (MOTT) are now called nontuberculous mycobacteria (NTM). Gene sequence similarities within the genus sequences (>94.3% for 16S rRNA gene) and robust phylogenetic reconstructions using concatenated sequences of housekeeping genes have confirmed the natural division among slowly growing and rapidly growing mycobacteria, and also have demonstrated that all slow growers belong to a single evolutionary branch that emerged from the rapidly growing mycobacteria. This feature is intrinsically linked to their pathogenic ability to infect humans and, therefore, all obligatory pathogens and most opportunistic pathogens belong to the slowly growing evolutionary branch.

Revised Device Labeling for the Cepheid Xpert MTB/RIF Assay for Detecting *Mycobacterium tuberculosis*

Tuberculosis remains a major global health problem and rapid and accurate diagnosis of tuberculosis is critical for making decisions in regards to airborne isolation as well as for timely initiation of antituberculosis therapy.

Major efforts have been made in recent years to increase case detection of tuberculosis. Xpert MTB/RIF is an assay which enables the simultaneous detection of *Mycobacterium tuberculosis* complex (MTBC) as well as rifampin (RIF) resistance. One Xpert MTB/RIF test on sputum detects 90% of pulmonary tuberculosis (99% of smear-positive disease and about 75% of smear negative disease).

A single Xpert MTB/RIF Assay detected 97% of patients who were acid-fast bacilli (AFB) smear-positive and culture confirmed as infected with MTBC, and two serial Xpert MTB/RIF Assay results detected 100% of smear positive/MTBC culture-positive patients. This is compared to the results of two or three serial fluorescent-stained AFB sputum smears.

The Food and Drug Administration (FDA) recently cleared the Xpert MTB/RIF Assay for testing of either one or two sputum specimens to aid in decisions about airborne isolation for patients with suspected pulmonary tuberculosis.

The results of a recent multi-center international study showed that negative Xpert assay results from one or two sputum specimens is highly predictive of the results from two or three negative AFB smears.

Revised labeling for the Xpert MTB/RIF Assay includes guidance in regards to the decision about whether to test one or two sputum specimens to determine the need for ongoing airborne infection isolation, including the recommendation that clinical circumstances and institutional guidelines should be used in decision making. Negative Xpert MTB/RIF Assay results should not be the only factor dictating infection control.

Assay performance is similar in patients with human immunodeficiency virus (HIV) and those without. HIV-infected adults with pulmonary tuberculosis are more likely to be AFB smear negative at presentation.

Serial sputum collection for mycobacterial culture is still recommended since nucleic amplification methods do not identify all patients with pulmonary tuberculosis. Furthermore, microbiologic isolation of the organism is required for characterization and susceptibility testing, as well as necessary for identifying nontuberculous mycobacterial disease.

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References:


Slowly Growing Nontuberculous Mycobacteria Antimicrobial Susceptibility Testing Change

Recently the National Jewish Health Mycobacteriology Laboratory reached out to several key opinion leaders in treatment of nontuberculous mycobacteria (NTM) disease to determine relevant compounds for patient treatment. Opinion leaders agreed that testing for kanamycin, ethionamide, and cycloserine were no longer routinely necessary; however, the addition of linezolid was recommended.

Based on this feedback, the Mycobacteriology Laboratory no longer offers the 8-drug MIC and 12-drug MIC testing panels. Instead, the laboratory now offers a single 10-drug panel together with the combination MIC panel for rifampin and ethambutol.

Additionally, the Mycobacteriology Laboratory will perform antimicrobial susceptibility testing for *Mycobacterium avium* complex and other slowly growing NTM strains with a microdilution methodology, instead of utilizing a macrobroth-based system. This new methodology will not only offer a more concise testing panel to healthcare providers, but also help reduce testing turnaround time.

Meetings

The 52nd Semi-Annual Denver TB Course April 15-18, 2015; Molly Blank Conference Center at National Jewish Health Main Campus. [Click here](#) for more information and registration.

Carolyn and Matthew Bucksbaum NTM Lecture Series for Physicians, Patients, and Families Friday May 15, 2015; An educational collaboration with National Jewish Health and NTMir. History Colorado Center, 1200 Broadway, Denver, CO 80203. Free registration. [Click here](#) for more information and registration.

American Thoracic Society Public Advisory Roundtable (PAR) ninth annual patient/family forum; Saturday May 16, 2015 from 10:00 a.m. to 2:00 p.m. Sheraton Denver Downtown Hotel. [Free registration](#).