Update in Tuberculosis/Pulmonary Infections 2015

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The year 2015 included both innovations and setbacks in mycobacterial lung disease, especially tuberculosis (TB). In November, the World Health Organization (WHO) announced that TB is once again the leading infectious killer of adults globally, and there remain serious diagnostic and treatment gaps (1). At the same time, there are exciting new developments in diagnostics for latent and active TB disease and in medical therapy, especially for persons with drug-resistant disease. In addition, real progress is being made in diagnosing and treating other forms of mycobacterial lung disease. Many of these important developments have been reported in the *Journal*. We summarize these findings here, with a focus on TB immunology, diagnosis of latent and active disease, TB prevention, and TB treatment. Finally, we present updates in nontuberculous mycobacterial lung disease.

TB Immunology

Understanding the immune response to *Mycobacterium tuberculosis* is important, given that although more than 2 billion individuals are infected with the bacteria, only a fraction of them go on to become sick. Furthermore, such an understanding is essential for developing a successful TB vaccine. The complex interaction between the pathogen and the human immune system was the topic of a paper by Mehra and colleagues who looked at the role of the DosR regulon in a TB model in macaques (2). DosR regulates the

response of *M. tuberculosis* to hypoxia and appears to have an important role in modulating immune responses to the bacteria (3). In their study, the team of investigators evaluated strains of *M. tuberculosis* that had mutations in the DosR region and found that although mutant strains could initially replicate, they did not cause disease in the monkey model, whereas strains with complemented DosR regulons were able to cause both infection and disease. They conclude that the complemented DosR regulon modulates both the magnitude and the timing of adaptive immunity and is associated with persistent infection. The study has important implications not only for better understanding the different immune responses *M. tuberculosis* evokes in its human hosts but also for better targeting responses that could lead to an effective TB vaccine.

Diagnosis of Latent and Active Disease

In the absence of an effective vaccine, much attention has been focused on finding persons who have been infected with and are sick from TB as soon as possible so that active disease can be both prevented and cured. Given that TB elimination is now the stated global TB strategy, identifying infected individuals and eradicating the bacteria in these individuals is essential (4). A number of studies published in the *Journal* in 2015 evaluated strategies to better determine who has been infected

with TB, with a focus on IFN- γ releasing assays (IGRAs), especially in high-risk populations. The two IGRA tests that have been the focus of evaluation are the Quantiferon-TB Gold In-Tube assay (QGIT; Cellestis Limited, Carnegie, VIC, Australia) and the T-SPOT.TB (Oxford Immunotech, Oxford, England).

Since the IGRAs were introduced almost 15 years ago, there has been great hope that these tests would radically alter the diagnosis and management of TB infection and disease, but studies have provided mixed results. The four IGRA-focused papers that were published in the *Journal* in 2015 continued to show an unclear benefit to using these tests, although they may have some utility in high-risk populations. A paper by Zellweger and colleagues reported the TB Network European Trials Group (TBNET) findings from a prospective cohort on the performance of both IGRAs in contacts of patients with active TB disease (5). Overall, they found that both tests were poor at predicting which contacts would go on to develop active TB disease. They also found that a majority of contacts who did go on to develop active disease did so in a relatively short time period (81 d) and that clinical follow-up and active screening for signs and symptoms of TB remains the most beneficial strategy for diagnosing active TB in contacts (6).

A study by King and colleagues, however, seemed to contradict the earlier poor predictive performance of the IGRAs in the high-risk population of health care

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workers reported in 2014 (7, 8). This study analyzed results from the T-SPOT.TB assay in more than 42,000 health care workers from 19 hospitals in the United States. The samples came from a repository kept by Oxford Immunotech, the company that makes the T-SPOT.TB assay. They found that the test had a specificity of 98.6% for ruling out TB infection but also noted that rates of positivity were higher in hospitals where the geographical incidence of TB was high. The study, however, lacked individual clinical and epidemiologic data, and therefore the findings may be limited. It is possible, however, that the T-SPOT.TB may be the preferred IGRA screening method for health care workers.

A study done in South African children by Mandalakas and colleagues also suggests that the T-SPOT.TB may offer advantages over the QGIT in the pediatric population, where diagnosis of latent and active TB is notoriously difficult (9). This prospective, observational cohort study assessed the likelihood of the tuberculin skin test (TST), the QGIT, and the T-SPOT.TB to predict latent disease in more than 1,300 children aged 6 months to 15 years. The authors found that the TST and IGRA tests were more likely to be positive in children who had a known TB contact, that QGIT indeterminate test results were more frequent in children infected with HIV, and that T-SPOT.TB had a lower indeterminate rate that was not affected by HIV status. For this reason, T-SPOT.TB could offer advantages in populations with a high HIV prevalence. In a study conducted in South African adolescents—another population with a high prevalence of HIV—Andrews and colleagues compared the TST and QGIT and found high rates of annualized conversion in a group of 12- to 18-year-olds living in Cape Town. For TST the rate was 13%, for QGIT the rate was 14%, and both the TST and QGIT conversion correlated well with one another (10). They also found that the magnitude of the QFT value at conversion was a strong negative predictor of the risk of reversion—a significant problem in some low-burden settings and one that can obscure the true rate of TB transmission.

Given the mixed results seen with IGRAs in diagnosing TB infection and disease, there has been interest in exploring other means for making these diagnoses and for determining who is most at risk for developing disease among those who are

infected. This has led to an interest in combining IGRAs with TB biomarkers, and an article by Escalante and colleagues provided evidence that a combination of the QGIT and a flow cytometry assay looking at CD4⁺ T cell coexpression of CD25 and CD134 could identify immunologic profiles of individuals who may be at increased risk of developing active TB (11). A similar approach combining the QGIT, TST, and cytokine profiles was assessed by Tebruegge and colleagues looking at 149 children with possible TB (12). The cytokine profiles assessed included IFN- γ , IFN-inducible protein-10 (IP-10), tumor necrosis factor- α , IL-1 α , IL-2, IL-13, and macrophage inflammatory protein-1 β , and the study assessed whether combinations of the cytokine profiles in addition to the results of the TST and QGIT could distinguish between latent and active TB. The investigators found that several combinations were found more often in children diagnosed with active TB, those with latent disease, and those who were uninfected, and that these signatures should be a topic of future study.

Rounding out the update on diagnosis, there has been some interest in improving the utility of an older diagnostic test—smear microscopy—through use of an automated digital microscopy protocol. In this study, Ismail and colleagues found that the TBDx System (Signature Mapping Medical Sciences Inc., Herndon, VA) performed as well as an experienced TB microscopist, with 62% sensitivity and 99.7% specificity (13). Although this tool may offer some diagnostic options in areas where there are limited human resources, its inability to detect resistance and its low sensitivity may limit its utility in the field.

Disease Prevention

As a field, TB has suffered from a lack of effective methods for primary and secondary prevention of disease. In terms of primary prevention, infection control in institutions that diagnose and treat TB is still a significant challenge in many settings in the world, and nosocomial transmission of TB remains a major problem (14). Two studies published in the *Journal* in 2015 added important data on potential improvements in both primary and secondary prevention of TB. Mphahlele

and colleagues assessed the potential of upper room ultraviolet (UV) air disinfection to prevent TB transmission in a controlled trial looking at TB transmission from patients to guinea pigs (15). This study not only found that an upper room UV germicidal irradiation system consisting of five fixtures with 216 W total exposure could prevent TB infection in guinea pigs but also made “UV dosing” recommendations for either a total fixture output of 15 to 20 mW/m³ total room volume, or an average whole-room UV irradiance of 5 to 7 μ W/cm², to effectively prevent TB. Finally, it appears there is environmental control somewhere on the spectrum between natural ventilation and negative-pressure isolation that can reduce the spread of TB.

Preventing disease in persons who are already infected with TB is necessary for TB elimination, but although there are clear recommendations for doing this in persons exposed to drug-susceptible TB, there are, as yet, no guidelines on preventive therapy in persons who are exposed to multidrug-resistant TB (MDR-TB), even though the consequences of becoming sick with drug-resistant (DR) strains are so severe. A modeling exercise done by Fox and colleagues assessing the use of fluoroquinolone-based preventive therapy in persons exposed to DR-TB found that not only was the use of such therapy effective in reducing mortality, the incidence of MDR-TB, and health care costs, but the model also predicted there would be a decrease in fluoroquinolone-resistant TB given that cases of active disease would be prevented (16). Although there are several ongoing and planning randomized clinical trials looking at the role of fluoroquinolone preventive therapy in persons exposed to MDR-TB, it will be years before those results are available. Although this model does not consider some of the complexities of field implementation of preventive therapy, nor does it account for potential toxicity associated with preventive therapy, it is one piece of evidence that could be used to support increased use of preventive therapy for MDR-TB in high-risk situations.

The landmark TEMPRANO trial included HIV-infected participants with a CD4 count of less than 800 cells/ μ l who did not meet WHO eligibility criteria for antiretroviral therapy (ART) initiation at the time of the study (17). The participants

were randomly assigned to deferred ART (until meeting WHO criteria), deferred ART plus isoniazid prophylaxis, early (immediate) ART, or early ART plus isoniazid prophylaxis. The risk of death or severe HIV-related illness was lower with early ART than with deferred ART and lower with isoniazid prophylaxis. This study provides further evidence for the benefit of secondary prophylaxis for TB in HIV-infected patients, even with early HIV disease, and, along with the START (Strategic Timing of Antiretroviral Treatment) study, was largely responsible for the change in WHO guidelines to recommend ART for all HIV-infected patients, regardless of disease stage or CD4 count (17, 18).

Current and Novel TB Treatment Regimens

Several studies addressed potential improvements in the treatment of TB and MDR-TB. Boeree and colleagues conducted a dose-ranging trial to evaluate the safety and tolerability of increasing doses of rifampin (19). Although the standard dose of 10 mg/kg was developed more than 40 years ago, a dose-finding study with an assessment of the maximum tolerated dose had never been conducted, and cost considerations played a role in dose selection. In the study, consecutive experimental groups each received progressively higher doses of rifampin, up to a maximum of 35 mg/kg for 14 days. The investigators found that rifampin was safe and well tolerated at all doses and that peak serum concentrations of rifampin showed a more than proportional increase with dose, with a greater fall in bacterial load in the higher-dosing groups. Later time points in treatment were not reported. Dorman and colleagues conducted a randomized dose-ranging study to determine tolerability, safety, and antimicrobial activity of daily rifapentine (20). Adults with sputum smear-positive pulmonary TB were assigned to rifapentine 10, 15, or 20 mg/kg or rifampin 10 mg/kg daily for 8 weeks, with standard companion drugs. They found that daily rifapentine was well-tolerated and safe and that higher rifapentine exposures were associated with high levels of sputum sterilization at the end of the intensive phase of treatment. These study findings provide support for the evaluation of high-dose daily

rifapentine with combination therapy in further studies to shorten the duration of TB treatment.

In a study evaluating a novel regimen, Diacon and colleagues evaluated the 14-day bactericidal activity of clofazimine and pyrazinamide in monotherapy and in combination with pretomanid and bedaquiline (21). Participants with sputum smear-positive pulmonary TB were randomized to receive one of the novel drug combinations or standard therapy. They conducted daily sputum culture over the first 14 days of treatment and found that bedaquiline, pretomanid, and pyrazinamide had equivalent efficacy to the current standard four-drug regimen. Clofazimine did not add to the activity of the other drugs, potentially because sufficient free serum drug concentrations were not achieved or due to a delay in clofazimine effectiveness (22).

Bastard and colleagues conducted a retrospective cohort study of data routinely collected in MDR-TB treatment programs in Armenia, Georgia, Kenya, Swaziland, and Uzbekistan (23). Patients were enrolled between 2001 and 2009 and received individualized treatment regimens on the basis of drug susceptibility testing results, according to WHO guidelines (24). The investigators compared outcomes using the 2008 and 2013 WHO definitions, which changed for cure and failure. In the 2013 definition, cure is defined as a patient who has completed treatment with no evidence of failure and at least three consecutive negative cultures taken at least 30 days apart after the intensive phase. Failure is defined as termination of treatment or need for permanent regimen change of at least two anti-TB drugs because of lack of conversion by the end of the intensive phase, culture reversion from negative to positive in the continuation phase, acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions. With 2008 definitions, the proportion of patients categorized as cure, treatment complete, death, failure, default, and not evaluated were 35, 21, 9, 11, 23, and 2%, respectively. With 2013 definitions, these changed to 35, 7, 4, 38, 15, and 1%, respectively. The most striking finding is the large increase in the proportion of patients reported as failures with the updated definition. More than one-third of patients who had been categorized as defaulters by the 2008 definition were

recategorized as failures, and many deaths were recategorized as failures. This study also highlights the poor efficacy of current MDR-TB treatment regimens.

Nontuberculous Mycobacterial Lung Disease

Although *M. tuberculosis* is responsible for the most significant burden of mycobacterial lung disease experienced worldwide, there has been an increasing understanding of risk factors for, diagnosis of, and treatment of nontuberculous mycobacteria (NTM), especially *Mycobacterium avium* complex (MAC). Several significant articles on these topics appeared in the *Journal* in 2015. Boyle and colleagues reported on clinical characteristics of the different species in the *M. avium* complex (25). In a retrospective cohort study of all pulmonary MAC isolates from a single hospital collected between 2002 and 2012, they found there were different clinical presentations depending on whether the isolate was *M. avium*, *Mycobacterium intracellulare*, or *Mycobacterium chimera*. They found that *M. avium* and *M. intracellulare* isolates were more likely to meet the clinical criteria for infection and that those with *M. intracellulare* and *M. chimera* were more likely to have disease recurrence. They propose that MAC isolates should be speciated to better predict clinical disease and outcomes. In addition to differences observed in pulmonary disease based on pathogen characteristics, host factors affecting disease were also identified and reported by Szymanski and colleagues (26). They assessed genetic variations in individuals with NTM lung disease compared with healthy family members and a nonrelated control group, specifically looking at variants in the immune, cystic fibrosis transmembrane conductance regulator, cilia, and connective tissue gene sets. They found that patients with NTM pulmonary disease have more protein affecting variants in these regions, suggesting a multigenic predisposition to NTM disease.

Advances were also reported in the treatment and monitoring of patients with symptomatic *M. avium* complex lung disease. A retrospective cohort study reported by Jeong and colleagues found that thrice-weekly therapy with a macrolide

(azithromycin or clarithromycin), rifampin, and ethambutol was as effective as daily therapy with the same regimen in a population of patients with noncavitary, nodular, bronchiectatic disease (27). The rates of symptomatic, radiographic, and bacteriologic improvement were the same in the two groups, but the rate of treatment modification due to adverse events was higher in the daily therapy group. This study adds to the growing evidence supporting thrice-weekly therapy for patients with this type of *M. avium* pulmonary disease, and this treatment approach could be adopted for clinical practice, even as randomized controlled trials are being developed. Such trials will require clear and objective endpoints, and a paper by Griffith and colleagues demonstrated the potential role for semiquantitative culture in monitoring response to therapy (28). They assessed the semiquantitative culture results of

180 patients being treated with macrolide-based regimens for *M. avium* complex lung disease and compared these with clinical and radiographic evidence of disease improvement. They found that 82% of the patients ultimately converted their cultures to negative and that although differences in baseline culture results did not correlate with sustained culture conversion, changes in sputum culture semiquantitative scores from baseline to Month 3 were highly predictive of long-term sputum conversion. Monitoring these changes from baseline to Month 3 could allow for earlier identification of individuals at risk for treatment failure and subsequent modification of therapy.

Conclusions

The year 2015 saw both great progress and great setbacks in the field of TB. Several

studies have improved our understanding of TB epidemiology, diagnosis, and management, and there is growing momentum to develop better diagnostic strategies and to improve outcomes by optimizing current medications and developing novel and shorter treatment regimens. With further investment in comprehensive strategies to stop transmission by the initiation of timely and effective therapy, treat latent TB in those at highest risk of developing active disease, and develop shorter regimens for the treatment of drug-sensitive and drug-resistant disease, TB elimination can be a reality not only in low-prevalence settings but also in countries that face a high burden of disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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