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EPIDEMIOLOGY OF TUBERCULOSIS

The Centers for Disease Control and Prevention recently published the trends in tuberculosis (TB) incidence in the United States (1). In 2006, a total of 13,767 TB cases were reported in the United States, at a rate of 4.6 per 100,000, representing a 3.2% decline from 2005. The incidence of TB in 2006 was the lowest recorded since 1953, but the rate of decline has slowed since 2000. Foreign-born persons and racial/ethnic minority populations continued to be affected disproportionately. The TB rate among the foreign-born was 9.5 times that of United States–born persons. The slowing of decline in the overall national TB rate and the inability to effectively address persistent disparities in TB rates between United States–born and foreign-born persons, and between whites and racial/ethnic minority populations, may hamper progress toward the goal of TB elimination in the United States.

Current guidelines only recommend targeted tuberculin testing and treatment of latent TB infection (LTBI) for foreign-born subjects who have entered the United States within the previous 5 years. Cain and coworkers assessed the epidemiologic basis for this guideline (2). Although the reported cases of TB declined among United States–born individuals by 62% in the period 1993–2004, those among foreign-born persons increased by 5%. Over half of all reported cases of TB occurred among the foreign born. Among 14,517 cases of TB reported in 2004, 3,444 (24%) of these were among foreign-born persons who had entered the United States more than 5 years previously. The rate of TB disease was 21.5 of 100,000 among foreign-born individuals overall, and 11.9 of 100,000 among those having stayed for more than 5 years, as compared with 2.7 of 100,000 for United States–born persons. Thus, almost one-quarter of all TB cases occur among foreign-born persons who have resided in the United States for more than 5 years, and the case rates for such persons from selected regions of origin remain substantially elevated. Issues with these high-risk group should be specifically addressed to enable elimination of TB in the United States.

Because immigration from areas with high TB burden would theoretically threaten control efforts in countries with low disease incidence, Dahle and coworkers undertook a study in Norway to evaluate the effect of immigration on the genetic diversity of Mycobacterium tuberculosis isolates on a nationwide basis over a 12-year period (1994–2005) (3). Of the 1,865 M. tuberculosis isolates with more than four copies of IS6110 in restriction fragment length polymorphism (RFLP) analysis, 385 isolates (20.6%) were assigned to 135 clusters, and the remaining 1,480 isolates (79.4%) showed unique patterns. The percentage of clustered isolates, suggesting recent transmission, was reduced among nonimmigrants and remained stable among immigrants during the study period. Thus, import of M. tuberculosis as a result of immigration from high-incidence countries might not necessarily affect the transmission dynamics of M. tuberculosis in low-incidence countries. Although 69% of the isolates originated from immigrants from high-incidence countries, and the incidence of TB was increasing among such immigrants during the study period, the established TB control program appeared adequate in preventing disease transmission. It is clearly important that these well-functioning control strategies are maintained.

HIV infection has a major but unquantified impact on the risk of TB. DeRiemer and coworkers studied all patients with TB in San Francisco from 1991 to 2002 (4). The initial isolates of M. tuberculosis were genotyped using IS6110 RFLP as the primary method, resulting in delineation of clusters. Genotypic clusters with at least one HIV-positive person were larger, lasted longer, and had a shorter time between successive cases relative to clusters with only HIV-uninfected persons (all P < 0.05). Overall, 13.7% of TB cases were attributable to HIV infection, and an estimated 405 excess TB cases occurred. Thus, coinfection with HIV has amplified the local TB epidemic during this period. This relationship should lead to corresponding enhancement of control strategies in appropriate populations.

In countries with low prevalence of TB, the disease can be found at high rates among certain risk groups, including illicit drug users and homeless persons. These populations would likely benefit from targeted interventions for early case detection and enhanced treatment supervision. In response to the rising notification rates of TB among illicit drug users and homeless persons in Rotterdam, The Netherlands, after the discontinuation of a chest radiograph screening program in 1996, a mobile digital X-ray screening program was reinstituted in 2002 among these at-risk subjects. de Vries and coworkers studied trends and characteristics of TB among these risk groups and assessed the impact of the screening program on disease transmission using molecular epidemiology (5). During the study period, 206 TB cases among illicit drug users and homeless persons were found, representing 11.4% of the total caseload in the city. The annual number of TB cases declined from 24 at the start of the screening program to 11 in 2005. In 1997–2002, more than 80% of the illicit drug users or homeless persons were infected with one of the M. tuberculosis strains prevalent among these risk groups. After nearly 4 years of systematic chest radiograph screening, this proportion fell to 45% in 2005. Thus, the investigators concluded that radiographic screening among these risk groups decreased incident cases and reduced disease transmission. From the results of this study, such screening should be continued to prevent resurgence of TB. Because there has not been a consensus on whether tobacco smoking increases the risk of TB infection, disease, or mortality,
a systematic review and meta-analysis including 24 studies were performed by Bates and coworkers (6). For TB infection, the relative risk (RR) estimate was found to be 1.73 (95% confidence interval [CI], 1.46–2.04); for TB disease, estimates ranged from 2.33 (95% CI, 1.97–2.75) to 2.66 (95% CI, 2.15–3.28). The TB mortality RRs were mostly below the TB disease RRs, suggesting no additional mortality risk from smoking in those with active TB. Thus, the evidence shows that smoking is a risk factor for TB infection and disease, but it is still unclear regarding the role of smoking in causing additional mortality risk in active TB.

Pai and coworkers underlined in a commentary the strong evidence for association of smoking with TB disease, but less so for TB infection and mortality (7). Thus, these workers advocated that TB control programs must begin to address tobacco control as a potential preventive intervention, likely highly cost-effective from a societal perspective.

Obesity has become an increasingly common condition in both developed and developing countries. Although undernutrition is well known to be associated with TB, few studies have systematically examined the association between obesity and this disease. Leung and coworkers found in a prospective cohort of elderly individuals that the obese (body mass index [BMI], ≥30 kg/m²) and overweight (BMI, 25 to <30 kg/m²) subjects were at significantly lower risks of developing active TB than normal-weight individuals (BMI, 18.5 to <23 kg/m²), after adjustment for baseline demographic, social, and clinical variables (8). An inverse linear association was observed predominantly for pulmonary but not extrapulmonary TB. This association persisted after controlling for potential confounders or excluding individuals with known TB risk factors. These findings might have major biologic, clinical, and/or epidemiologic implications.

In recent years, the worldwide emergence of extensively drug-resistant TB, which denotes multidrug-resistant TB with additional bacillary resistance to fluoroquinolones, and one or more of the three injectable agents (kanamycin, amikacin, and capreomycin), has raised much concern in global TB control. The high mortality and transmissibility of this form of TB among HIV-infected patients, as reported in South Africa, have proved to be alarming (9). Thus, increasing attention needs to be focused on the epidemiology of extensively drug-resistant TB (10, 11). Within this context, several studies have attempted to address the issue of fluoroquinolone resistance among M. intracellulare isolates in different communities.

In South Korea and Taiwan, fluoroquinolone resistance among M. tuberculosis isolates is uncommon, and is largely accompanied by resistance to any first-line drug or multidrug resistance, as well as prior anti-TB treatment (12, 13). Thus, these data would suggest that the predominant mechanism of emergence of extensively drug-resistant TB in some countries is the suboptimal management of multidrug-resistant TB through inadequate administration of second-line reserve drugs, and other aspects of programmatic failure in the management of this disease.

The frequency of nontuberculous mycobacterial infections appears to be increasing, but it is unclear whether this represents enhanced detection or a true increase. Clinical and microbiological studies might be limited by surveillance bias. Khan and coworkers studied nationally representative cohorts of noninstitutionalized civilian populations participating in the 1971–1972 and 1999–2000 National Health and Nutrition Examination Surveys (NHANES) in the United States (14). Participants were skin tested with Mycobacterium intracellulare antigen, and sensitization prevalence was compared across NHANES and between participant subgroups. Logistic regression was used to identify associations between participant characteristics, environmental factors, and mycobacterial sensitization. Between 1971–1972 and 1999–2000, the prevalence of M. intracellulare sensitization rose from 11.2 to 16.6%. On multivariate analysis of the 1999–2000 cohort, age, sex, race, birthplace, education, and occupation were strongly associated with M. intracellulare sensitization. The observed rising prevalence of sensitization would be consistent with the observed increase in the rates of pulmonary infections/disease due to nontuberculous mycobacteria in the United States.

The relative contribution of environmental factors versus genetic factors in the development of TB is not entirely clear. van der Eijk and coworkers performed a reanalysis of the Prophit survey of twin studies in TB (15). A drastically different conclusion was reached with careful subgroup analysis of the old data. It was found that a known acid-fast bacilli–positive or –negative sputum markedly influenced the odds ratio of concordance of disease in the members of a twin pair. The difference between monozygotic and dizygotic twins in concordance for TB was confined to 106 twin pairs involving a smear-positive index case. The odds ratio of concordance was proportional to the intensity of exposure (sputum smear positivity, physical proximity between members of a twin pair, contagiousness of disease, and living together). Thus, susceptibility to TB among members of a twin pair likely depends on environmental factors rather than on hereditary or genetic factors. The tendency of monozygotic twins, necessarily of the same sex, to stay in closer proximity could have confounded the opposite conclusion in the previous analysis. The environmental context of transmission should be given more emphasis when studying interindividual and population differences in host susceptibility to TB.

GENETICS AND IMMUNOLOGY OF TB

Genetic polymorphisms can influence host susceptibility to developing active TB. Activation of the P2X(7) receptor on human macrophages induces intracellular killing of M. tuberculosis. Fernando and coworkers examined the association between polymorphisms in P2X(7) and the risk of TB among patients and control subjects from Southeast Asia (16). They found that only the 1513A→C polymorphism was present in this ethnic group. The 1513C allele was found to be strongly associated with extrapulmonary, but not pulmonary TB (odds ratio, 3.8; 95% CI, 1.6–9.0). ATP-mediated killing of mycobacteria was shown to be ablated in macrophages from subjects homozygous for the 1513C allele, and significantly impaired in macrophages from heterozygous subjects. Furthermore, a strong correlation was found between the degree of mycobacterial killing and ATP-induced apoptosis.

In a genetic polymorphism study in Mexican mestizo patients with pulmonary TB, Niño-Moreno and coworkers found no significant association of the P2X(7)-762 gene polymorphism with TB (17). In contrast, the P2X(7) A1513C polymorphism was significantly associated with TB, corroborating the results of the study by Fernando and associates (16).

Stein and coworkers took a unique approach to the study of genetic susceptibility in TB by developing an intermediate phenotype model for TB susceptibility, using levels of tumor necrosis factor (TNF)-α in response to culture filtrate as the phenotype (18). In the study, they analyzed candidate genes related to TNF-α regulation and found that IL-10, IFN-γ receptor 1, and TNF-α receptor 1 genes were linked and associated to both TB and TNF-α. They showed these associations with regard to progression to active TB disease, but not susceptibility to LTBI. This would represent the first report of an association between TB and the TNF-α receptor 1 gene in a human population.
TNF is commonly regarded to have an essential role in the immunologic response of *M. tuberculosis* infection. Although an increased rate of TB has been reported in humans treated with antibody against this cytokine, disparate rates of disease have been observed among those treated with the anti-TNF agents infliximab and etanercept. Plessner and coworkers compared the effects of antibody against TNF and soluble TNF receptor fusion protein in a murine model of TB (19). During chronic infection, administration of the former resulted in death within a month, but administration of the latter allowed control of infection, perhaps correlating with the clinically observed difference between the two therapeutic biological agents in exacerbating TB. The difference might be related to different ability of the two biological agents to penetrate into granulomas.

Prospective studies to evaluate the effect of vitamin D supplementation on antimonycobacterial immunity have not been previously performed. Martineau and coworkers embarked on a double-blind, randomized, controlled trial in TB contacts (20). Participants either received a single oral dose of 2.5 mg vitamin D or placebo. The primary outcome was assessed with a functional whole blood assay (BCG-lux assay) that measured the ability of whole blood to restrict luminescence, and thus growth, of recombinant reporter mycobacteria. IFN-γ responses to *M. tuberculosis* antigens early secretory antigenic target (ESAT)-6 and culture filtrate protein (CFP) were determined with a second whole blood assay. Vitamin D supplementation significantly enhanced the ability of whole blood samples to restrict, in vitro, BCG-lux luminescence as compared with placebo, but did not affect antigen-stimulated IFN-γ release. Clinical trials are warranted to determine whether vitamin D supplementation can prevent reactivation of LTBI.

The same group of investigators has also found that the protection of 1α,25 dihydroxyvitamin D against TB is not mediated via the effects of IFN-γ, IL-12 p40, or TNF, but probably occurs through nonclassical mechanisms, including induction of antimicrobial peptides, like cathelicidin (21).

Neutrophils contain antimicrobial peptides with anti-TB activity, but their contribution to immune resistance to TB infection has not been well investigated. Martineau and coworkers found that human neutrophil peptides could kill *M. tuberculosis* (22). The peptides cathelicidin LL-37 and lipocalin 2 restricted growth of the organism, the latter in an iron-dependent manner. Ethnic differences in neutrophil counts and circulating concentrations of human neutrophil peptides may be linked to differences in innate resistance to TB infection.

Rook reviewed the role of Th2 cytokines in susceptibility to TB (23). He postulated that the background Th1 component in developing countries would protect low-dose challenge with *M. tuberculosis* in mice and humans, but not after high-dose challenge with escalation of the preexisting IL-4 component blocking immunity, unless its antagonist, IL-4 62, could be released from the individual’s immune system. IL-4 (and IL-13) would thus be believed to undermine Th1-mediated immunity and drive inappropriate alternative activation of macrophages. The mechanisms mediating the effects of IL-4 might include impaired antimicrobial activity due to reduced TNF-α-mediated apoptosis of infected cells, reduced activity of inducible NO synthase, increased availability of iron to intracellular *M. tuberculosis*, and increased proliferation of antigen-specific FOXP3 regulatory T cells. IL-4 might also increase toxicity of TNF-α and drive pulmonary fibrosis, thus enhancing immunopathology. Thus, in developing countries, a new TB vaccine might need to do more than enhancing existing Th1 response. In these environments, it might be more important to block the Th2 component.

Although it has been observed that patients with LTBI develop strong IFN-γ responses to the protective antigen heparin-binding hemagglutinin (HBHA), and patients with active TB do not (24), the underlying mechanism remains elusive. Hougardy and coworkers evaluated the possible involvement of regulatory T cells and/or cytokines in the low HBHA T-cell responses (25). They found that depletion of CD4+ CD25+ FOXP3+ T cells resulted in the induction by HBHA of IFN-γ concentrations similar to those obtained for LTBI. Thus, these specific regulatory T cells would be likely to depress cell-mediated immune responses to protective mycobacterial antigens during active TB.

Although plasmid DNA immunogens have been explored as potential vaccines for protection against *M. tuberculosis*, little is known about host factors that might restrict long-term DNA antigen expression in vivo. Greenland and coworkers observed rapid damping of transgene expression from a plasmid DNA immunogen in wild-type, but not in T-cell–deficient mice (26). This damping of antigen expression was temporally associated with the emergence of antigen-specific cellular immune responses. A requirement for Fas and the appearance of apoptotic nuclei at the site of vaccine inoculation would suggest T-cell induction of Fas-mediated apoptosis of plasmid DNA vaccine antigen-expressing cells. The study has demonstrated that high levels of in vivo antigen expression could be associated with high-frequency cellular immune responses that, in turn, would rapidly down-regulate vaccine antigen expression in vivo. Thus, it might not be possible to maintain persistent high-level production of vaccine antigen in vivo to drive persistent immune responses, due to limitation of antigen production by the host immune responses.

**DIAGNOSIS OF LTBI AND TB**

Arend and coworkers conducted a prospective comparison of two IFN-γ release assays (IGRAs)—QuantiFERON-TB Gold In-Tube (QFT-GIT) and T-SPOT.TB—alongside conventional tuberculin skin test (TST) in the assessment of contacts of an index patient with TB (27). The main objective was to compare performance of these three tests, in the context of correlation with recent exposure, in the absence of previous bacille Calmette-Guérin (BCG) vaccination. Among 785 study participants, TST results were associated with age, whereas positive IFN-γ responses were significantly associated with cumulative shopping time in the store where the index patient worked, especially for QFT-GIT. Among participants with TST reactions 15 mm or larger, the sensitivities of QFT-GIT and T-SPOT.TB were 42.2 and 51.3%, respectively. Interassay agreement was 89.6% (kappa = 0.59). By varying the cutoff values of the IFN-γ release assays, agreement between these assays reached an optimal level of 93.6% (kappa = 0.71) using a cutoff of 0.20 IU/ml for QFT-GIT and 13 spots for T-SPOT.TB. Thus, it was concluded that the results of the two assays correlated with exposure parameters to TB, whereas the TST did not. A possible lack of sensitivity of these assays in detecting LTBI in individuals with a TST of 15 mm or larger, but no previous BCG vaccination, warrants further investigation.

The usefulness of TST and QFT-G assay in immunocompromised hosts was assessed by Kobashi and coworkers (28). Two hundred and fifty-two subjects had malignant diseases (n = 74), immunosuppressive therapy (n = 72), diabetes mellitus (n = 52), chronic renal failure (n = 50), and HIV infection (n = 4). Although the positive rate of the QFT-G assay for diagnosis of active TB or LTBI was 78.1%, that of TST was only 50.0%. However, 32 patients (13%) had indeterminate QFT-G results. The indeterminate results were significantly more common among subjects receiving immunosuppressive treatment (28%), especially in the presence of lymphopenia, than in those who had
other underlying diseases. Thus, care should be taken in the interpretation of QFT-G assays for these patients.

Although two forms of IGRA (T-SPOT.TB and QFT-G) are available commercially to detect TB infection, neither has been evaluated on comparable HIV-infected and uninfected subjects in an environment of high disease prevalence. Rangaka and coworkers performed such a cross-sectional study to compare these two assays with the Mantoux test among 160 healthy adults attending a voluntary counseling and testing center for HIV infection in a deprived urban community in South Africa (29). Seventy-four study subjects were HIV positive and 86 were HIV negative. A lower proportion of Mantoux positivity was found in HIV-infected as compared with HIV-uninfected subjects ($P < 0.01$). By contrast, the proportion of IGRA positivity was not significantly different among HIV-infected persons for the T-SPOT.TB (52 vs. 59%, $P = 0.41$) or the QFT-G (43 vs. 46%, $P = 0.89$). Fair agreement between the Mantoux (5/10-mm cutoffs) and IGRAs was seen in HIV-infected people. By contrast, poor agreement between the Mantoux test and either IGRA individually was observed among HIV-uninfected subjects. This study highlights the preserved sensitivity of IGRA in moderately advanced HIV infection, but also suggests unsatisfactory agreement of the assays with the Mantoux test. Further prospective studies will be warranted to determine which investigation could best predict the subsequent risk of TB.

Luetkemeyer and coworkers performed a comparison of the QFT-GIT assay with the TST in the diagnosis of LTBI in HIV-infected subjects (30). Concordance between the tests was 89.3% (kappa = 0.37, $P = 0.007$). However, in patients with positive results by either test, only 28% were positive by both modalities. TST-positive/QFT-GIT–negative discordant results were found in 5.1% of subjects, and TST-negative/QFT-GIT–positive discordance in 5.6%. Indeterminate IGRA results occurred in 5.1%, with a higher risk ($RR, 4.24; P = 0.003$) for lower CD4+ counts ($<100/mm^3$ vs. $\geq100/mm^3$). Thus, whereas the overall concordance between QFT-GIT and TST was high, agreement among subjects with positive tests by either modality was low.

Rangaka and coworkers, aside from finding that IFN-γ release appeared to be less impaired than TST by HIV coinfection, discovered that a novel approach relating the results of enzyme-linked immunospot method to CD4+ cell count by a ratio could assist the diagnosis of active TB in patients with HIV infection (31). This approach possibly merits further evaluation to determine its potential utility.

Dewan and coworkers evaluated the sensitivity of QFT-G for the detection of active TB among 242 persons with suspected disease (32). Thirty-seven subjects had culture-confirmed TB. Excluding one indeterminate result, 23 of 36 subjects had positive tests. The sensitivity of 64% suggested that QFT-G assay should not be used alone to exclude active TB.

Kang and coworkers assessed the usefulness of QFT-G and T-SPOT.TB in the diagnosis of active pulmonary TB in South Korea (33). The sensitivities of the IGRAs were found to be 89 and 92%, respectively, and their specificities were 49 and 47%, respectively. The negative predictive values of the IGRAs were higher than that of TST (84 and 87% vs. 64%). Thus, the high negative predictive values of the IGRAs might help in exclusion of active TB, but the low positive predictive values limited their usefulness in confirming the diagnosis of disease, due to the high prevalence of LTBI in South Korea.

Kobashi and coworkers previously demonstrated possible utility of the second-generation QFT assay in differentiation of active TB from nontuberculous mycobacteriosis (34). Among patients with the former diagnosis, only 4% had a negative result, but for those with Mycobacterium avium complex lung disease, only 7% had a positive result. Using an enzyme-linked immunospot assay for IFN-γ (T-SPOT.TB), Wang and coworkers found the sensitivity, specificity, positive predictive value, and negative predictive value of this test for diagnosis of active TB to be 87.2, 88.5, 91.9, and 82.1%, respectively, among patients whose clinical symptoms and radiographic findings were compatible with TB (35). The accuracy of this investigative tool for active TB was found to be greater than 80%, even in an area where nontuberculous mycobacterial disease prevailed.

In a hospital-based study, Detjen and coworkers assessed the diagnostic values of IGRAs and TST for active TB among a cohort of children with either bacteriologically confirmed TB or nontuberculous mycobacteriosis in a low TB incidence country (36). The specificities for TB of QFT-GIT and T-SPOT.TB were 100 and 98%, respectively, both considerably higher than that of TST (58%). The specificity of TST was as low as 10.5% in children with nontuberculous mycobacterial lymphadenitis, but was 100% in children with other nonmycobacterial respiratory tract infections. The sensitivity was 93% for both QFT-GIT and T-SPOT.TB and 100% for TST. Agreement between the two IGRAs was 95.6%; 68% of the IGRAs showed indeterminate results. Thus, both IGRAs showed high diagnostic value for bacteriologically confirmed childhood TB. Their advantage, when performed in addition to TST, was the ability to distinguish positive TST results caused by nontuberculous mycobacterial disease, thereby reducing overdiagnosis of TB and guiding clinical management appropriately.

There is currently no available test for monitoring the effect of treatment of LTBI, either to indicate cure or predict risk of subsequent progression to disease. Chee and coworkers performed a prospective study with 226 contacts who had positive T-SPOT.TB results by repeat testing on completion of treatment of LTBI (with isoniazid for 6 mo in the majority) (37). The pre- and post-treatment T-SPOT.TB results were analyzed according to the combined and separate responses to ESAT-6 and CFP10 antigens. Reversion of T-SPOT.TB results to negativity occurred in 37.6% of contacts at treatment completion. Treatment had a significant effect on the response to CFP10 ($P < 0.001$; reversion rate, 48.6%), but not on the response to ESAT-6 ($P = 0.081$; reversion rate, 21.6%). There was a significant difference between the median decrease in the spot-forming cells for CFP10 and ESAT-6 ($P < 0.0001$). Significantly different age-related T-cell responses to the two antigens were also found. These findings implicate the quantitative response to CFP10 as a potentially useful monitoring tool in LTBI.

After the demonstration by Kobashi and coworkers of the issues with decline in IGRA positivity after anti-TB treatment (34), Pai and coworkers studied the sensitivity of QFT-GIT among patients treated for pulmonary TB (38). They found changes in IFN-γ responses over time were highly inconsistent. Although the average IFN-γ levels decreased slightly during anti-TB treatment, the QFT-GIT sensitivity remained mostly unchanged. There was no clear correlation between antigen burden and T-cell responses. Their finding corroborated those of Kobashi and coworkers. Thus, further research appears to be necessary to unravel the kinetics of T-cell responses during treatment for TB.

Millington and coworkers assessed the kinetics and functional profile of M. tuberculosis antigen–specific T cells secreting IFN-γ and IL-2 in patients with untreated active TB when bacterial and antigenic loads were high, and after curative treatment with reduction of antigenic load (39). The frequencies of M. tuberculosis antigen–specific IFN-γ–secreting T cells declined during 28 months of follow-up ($P = 0.005$), whereas the frequencies of antigen-specific IL-2-secreting T cells increased during treatment ($P = 0.02$). These contrasting dynamics for the
two cytokines led to a progressive convergence of the frequencies of IFN-\(\gamma\) and IL-2-secreting cells over 28 months. Simultaneous measurement of IFN-\(\gamma\) and IL-2 secretion at the single-cell level revealed a codominance of IFN-\(\gamma\)-only secreting and IFN-\(\gamma\)/IL-2 dual-secreting CD4+ T cells in active disease, which shifted to dominance of IFN-\(\gamma\)/IL-2-secreting CD4+ T cells and newly detectable IL-2-only secreting CD4+ T cells during and after treatment. These distinct T-cell profiles before and after treatment of TB might serve as a novel marker of mycobacterial load and clinical status that merits further prospective validation.

Schoch and coworkers assessed the feasibility and yield of various diagnostic procedures after active case finding with radiologic screening for TB among asylum seekers to Switzerland (40). They studied 101 such subjects, and found that radiologic abnormalities compatible with TB had poor predictive value for active disease requiring treatment. Respiratory and systemic symptoms correlated weakly with culture confirmation of TB. This study indicates that all radiologically suspected cases should be examined with on-the-spot and early-morning sputum, regardless of symptoms. If both specimens do not show acid-fast bacilli on direct microscopy, bronchoscopy and, to a lesser extent, induced sputum (for 2 samples) would help to increase the diagnostic yield of TB. The examination of any single specimen has a low yield of 36 to 63%, and is thus insufficient for exclusion of active TB.

In another study performed by Brown and coworkers in the United Kingdom (41), 140 consecutive adult inpatients with chest radiograph findings suggestive of TB and unable to expectorate were recruited. Among 107 subjects who provided three gastric washing specimens and at least three induced sputum specimens, 43% had positive cultures for \(M.\) \textit{tuberculosis}. The use of three induced sputum specimens detected more cases than did the use of three gastric washings. Among 79 subjects with culture results for all five induced sputum specimens, there was no difference in yield between samples obtained by sputum induction performed in a single day or that performed over 3 days (with 3, 1, and 1 specimens collected consecutively). No additional cases were diagnosed in the 21 patients who underwent bronchoscopy.

**TREATMENT OF TB**

Ditah and coworkers evaluated TB treatment outcome in England, Wales, and Northern Ireland by redefining outcome criteria and investigated factors associated with unsuccessful treatment outcome 12 months after notification (42). In this prospective analysis, 87.5% of 2,209 new smear-positive pulmonary TB cases were classified as successful using new criteria, in contrast with only 76.8% using the conventional World Health Organization (WHO)/International Union against Tuberculosis and Lung Disease (IUATLD) criteria. Risk factors for unsuccessful treatment outcome included male sex, elderly age, pulmonary TB, and drug resistance. The investigators concluded that using the new criteria enabled the success rate to exceed the target of 85% advocated by the WHO/IUATLD. Although the TB treatment outcome criteria set by these organizations might be clear, mixing of measures of process and outcome could occur. Thus, refinement would be recommended in low-incidence, high-income countries, especially in those with a high mortality among the elderly patients.

The optimal duration of treatment for pulmonary TB in patients coinfected with HIV is currently unknown. Nahid and coworkers performed a retrospective analysis on all patients with TB who reported to the San Francisco Tuberculosis Control Program from 1990 through 2001 (43). Of 700 patients, 38% were HIV infected, 45% were not, and 17% were not assessed for the status. For a number of reasons, the duration of therapy was extended beyond 6 months for both HIV-infected and HIV-uninfected/unknown patients (mean: 10.2 vs. 8.4 mo; \(P < 0.001\)). Among 196 HIV-infected and 362 HIV-uninfected/unknown status subjects who completed therapy, the relapse rates were 9.3 versus 1.0 per 100 person-years, respectively (\(P < 0.001\)). HIV-infected individuals who received the standard 6-month rifampin-based regimen were more likely to relapse than those treated for longer duration (adjusted hazard ratio, 4.33; \(P = 0.02\)). HIV-infected subjects who received intermittent therapy were also about four times more likely to relapse than those treated on daily basis. These findings warrant further prospective investigations. As the use of highly active antiretroviral therapy (HAART) was associated with more rapid conversion of sputum smears and cultures, as well as improved survival, the potentially beneficial impact of such therapy merits further studies, especially regarding the optimal timing of its administration. In an accompanying editorial, Perlman and coworkers highlighted the need to improve our current knowledge regarding treatment of HIV-related TB (44), specifically including ways to circumvent the high risk of acquired anti-TB drug resistance in addition to recurrence of the disease, as well as how to use HAART optimally to reduce TB mortality. Using system dynamic simulation, Atun and coworkers found that a high coverage of HIV-infected population with HAART (≥75%), allied with high multidrug-resistant TB cure rates, could reduce substantially the number of deaths from TB (45).

Saukkonen and coworkers published, on behalf of the American Thoracic Society, an important and useful document regarding hepatotoxicity of anti-TB drug therapy (46). The mechanisms of drug-induced liver injury and the risk factors for hepatotoxicity were clearly addressed, as were the systematic steps for prevention and management of anti-TB drug-induced hepatotoxicity. In a study from Hong Kong, which has a high prevalence of chronic hepatitis B and TB, Chang and coworkers, using a conditional logistic risk model, identified hepatitis B surface antigen carriage as the only risk factor for hepatotoxicity during therapy for TB among patients carefully matched for sex and age (47). Advancing age was also shown to increase the odds of hepatitis. Dosing schedules in the first 9 weeks of therapy were found to have little impact on hepatotoxicity. Ruslami and coworkers from Indonesia performed a double-blind, randomized, phase II clinical trial to explore the pharmacokinetics and tolerability of a higher dose rifampin (>10 mg/kg) among patients with TB on treatment (48). Increasing the rifampin dose was associated with more than dose-proportional increases in the mean drug exposure. Mild (grade I or II) hepatotoxicity was more common in the higher-dose group (46 vs. 20%, \(P = 0.054\)).

Huang and coworkers found that the mutant C allele of manganese superoxide dismutase might increase the susceptibility to anti-TB drug–induced liver injury (49). Study of such genetic polymorphisms would help in identifying patients at high risk for drug-related hepatotoxicity. A study performed by Donald and coworkers (50) evaluated the pharmacokinetics (area under curve and 2-h serum concentration) of isoniazid associated with optimal early bactericidal activity, and the influence of N-acetytransferase-2 (NAT2) genotype and phenotype on the ability of patients with TB to reach the identified pharmacokinetic values after different isoniazid doses. At a 6-mg/kg dose, all except a minority of homozygous fast NAT2 acetylators could achieve such values, as did all homozygous slow acetylators receiving 3 mg/kg. Any dose reduction below 6 mg/kg body weight would be likely to disadvantage a significant proportion of fast acetylators, but conversely, homozygous
slow acetylators would require only a 3-mg/kg dose to achieve a satisfactory exposure to isoniazid. These data might have potential implications in isoniazid dosing among selected patients to optimize therapeutic efficacy and minimize hepatic toxicity.

Szko and coworkers retrospectively analyzed a cohort of patients with TB who were given streptomycin for 3 months, and ofloxacin plus ethambutol for 12 months, in the face of hepatic injury (51). Among 40 patients, 85% were cured. There were no treatment failures or relapses during 2 years of treatment and follow-up. Clinically recognized drug toxicity occurred in 12.5%, all attributed to streptomycin. Thus, this report again echoed the role of some fluoroquinolones in the management of TB in the face of hepatic dysfunction.

Somocurio and coworkers in Peru reported the outcomes of 121 patients with drug-resistant TB treated by adjunctive surgery (52). Of patients, 79.3% were culture positive before surgery, and sustained culture-negative status among survivors was achieved in 74.8%; 63% of those followed for at least 6 months after surgery were either cured or probably cured. Postoperative complications were observed in 22.6% of patients. This constituted one of the largest cohorts of patients with drug-resistant TB treated with surgery, and the first from a resource-poor country. These results argue for the feasibility of using surgery in this disease setting in poor countries. Indeed, these results were echoed by the findings of Mohsen and coworkers from Egypt where 23 HIV-negative patients with multidrug-resistant TB underwent lobectomy or pneumonectomy in addition to chemotherapy, with all attaining sputum-negative status postoperatively (53). Hospitalization mortality was only 4.3%, and morbidity was acceptable.

A retrospective cohort study, comprising 252 patients with multidrug-resistant TB, was performed by Torun and coworkers in Turkey (54). The highest long-term treatment success and survival rates were achieved in patients who both received fluoroquinolones and underwent surgery \( (P = 0.001 \) vs. other groups). However, an additional benefit from surgery could not be conclusively demonstrated, and larger scale studies may be warranted to clarify this issue.

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**References**


