Advances in tuberculosis 2011–2012

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ABSTRACT

Renewed global interest and funding for tuberculosis (TB) has led to increased research and publications, with several recent advances. The increased incidence of drug resistant TB and emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) TB globally has strengthened the need for improved rapid diagnostics and better treatment regimens. The HIV and TB epidemics have further impacted on TB research, necessitating the development of better preventive and treatment strategies. Important recent strides in adult TB include more widespread validation of molecular techniques and advances in therapeutics, including major drug trials with existing and novel agents and even a putative new regimen. Studies in childhood TB have led to increased understanding of the paediatric burden, new possibilities for rapid diagnosis and advances in preventive strategies. There are still several research priorities that must be addressed including development of better diagnostics, defining biomarkers of TB disease or correlates of protection, shorter more effective regimens for prophylaxis and for treatment, and development of an improved safe vaccine that offers protection against pulmonary disease. Operational research to inform more widespread implementation of research findings is needed in order to benefit optimally from recent advances.

Tuberculosis (TB) remains a major cause of disease globally, with an estimated 9 million new cases each year.[1] Morbidity and mortality are especially high in specific populations such as those with underlying immunosuppression or very young children. The spread of drug resistant TB and emergence of multidrug resistant (MDR), extensively drug resistant (XDR) and totally drug resistant TB poses a real threat to global TB control.[2 3] The need for better, more effective ways to diagnose, treat and prevent TB has led to increasing research and advances in several areas. This article summarises key advances over the last 2 years (from 2011 to 2012) and their potential impact, and suggests areas for future research.

ADVANCESIN ADULT TB

Epidemiology

India and China together account for 50% of the world's MDR-TB cases. While the epidemiology of MDR-TB in India is patchy and incomplete, China has recently completed a national survey in which the proportion of cases with MDR-TB was estimated by cluster randomised sampling of TB cases in 70 clusters across China.[3] Two sputum specimens were sent to China's central CDC microbiology laboratory; 25% of patients had disease resistant to isoniazid (INH) or rifampicin or both, 10% had MDR-TB and 8% of cases of MDR-TB were XDR-TB. A quarter of all previously treated patients had MDR-TB; those who had received multiple treatments had the highest risk of MDR-TB (OR 13.3). This important epidemiological study confirmed that MDR-TB is a major problem in China.

An important retrospective cohort study from Peru investigated transmission to household contacts of patients with MDR-TB or XDR-TB.[4] The primary outcome was the occurrence of active TB when the index patient began MDR-TB treatment and during 4 years of follow-up. In 693 households with MDR-TB or XDR-TB, 242 of 4503 contacts developed TB; XDR contacts developed TB at almost twice the rate of MDR contacts. None of the contacts received specific chemoprophylaxis. Most contacts (129/142) with TB whose isolates were tested for resistance had MDR-TB. This study confirms that household contact investigations should be performed in all patients with MDR-TB or XDR-TB. Contacts should be considered to have MDR-TB unless proven otherwise, and should commence treatment while awaiting culture results.

The epidemiology of XDR-TB from 2005 to 2008 was prospectively investigated in 2008 consecutive adults with MDR-TB at treatment initiation.[5] Patients with MDR-TB from eight countries were included; samples were sent to the CDC laboratory (Atlanta, Georgia, USA). XDR-TB, found in all countries, varied in incidence from 0.8% in the Philippines to 15.2% in South Korea.

Prior treatment with second-line injectable agents and fluoroquinolones emerged as the most important risk factors for XDR-TB (ORs 4.75 and 4.21, respectively). While this study was limited by lack of data from India and China, it demonstrated that previous treatment with second-line drugs is a strong consistent risk factor for XDR-TB.

Diagnostics

Two important studies added new insights into pleural and glandular TB. The former investigated diagnostic yield of different tests in tuberculous pleural effusions from 382 patients in Taiwan[6]; the combined yield of pleural fluid and sputum using liquid culture was 65%, while that of granulomas on pleural biopsy was 74%. A novel observation was that the percentage of lymphocytes in pleural fluid was negatively associated with the mycobacterial burden and inversely correlated with a positive culture.

The usefulness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) in patients with intrathoracic adenopathy was investigated in 156 patients with lymphadenopathy over 2 years from four centres in the UK.[7] The yield of EBUS TBNA was 93%. Factors predictive of a positive culture were the presence of necrosis on

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histopathology (OR 2.2) and sampling of more than one node (OR 1.9).

Molecular diagnosis

The performance of Xpert in extrapulmonary samples was evaluated in 1476 clinical specimens including pleural and ascitic fluid, cerebrospinal fluid (CSF), pus, urine, biopsies and gastric aspirates.[8] The sensitivity and specificity of Xpert was 81% and 99%, respectively, far better than the sensitivity of microscopy (48%). Comparing different extrapulmonary fluids, the sensitivity for pus, urine and CSF were 85% and for gastric aspirates 80%. In contrast, the sensitivity for pleural or ascitic fluid was 50%. The yield from paediatric specimens had high sensitivity and specificity of 87% and 99%, respectively. The use of Xpert in a high MDR, high HIV prevalence setting was investigated using single archived spot sputum samples from 496 South African patients with suspected TB.[9] The sensitivity (95%) and specificity (94%) were similar to other studies; sensitivity in smear-negative culture-positive patients was 60%. The key advantage of Xpert was that it consistently outperformed sputum smear, diagnosing 47% of smear-negative TB patients. Xpert showed a trend towards reduced sensitivity ($p=0.09$) and reduced negative predictive value ($p=0.01$) in HIV-infected patients, leading the authors to conclude that Xpert is a good rule-in test but has limited rule-out value compared with those who are uninfected with HIV.

The performance of the national UK molecular diagnostic service (Fastrack) over a decade using a line probe assay (Innolipa, LiPA) was audited.[10] Data from 7836 consecutive sputum samples, comparing LiPA with liquid culture, indicated that the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for diagnosing TB were 93.4%, 85.6%, 92.7%, 86.9% and 90.7%, respectively. The corresponding figures for detection of rifampicin resistance were 92.1%, 99.3%, 89.4%, 99.5% and 98.9%. Fastrack thus proved a rapid and reliable national service for diagnosing TB, saving 25.3 and 32.2 days for TB diagnosis and rifampicin resistance, respectively, in smear-positive samples. The sensitivity and specificity were comparable to Xpert.

Prevention

An open-label randomised non-inferiority trial comparing 3 months of once weekly treatment with 900 mg rifapentine and 900 mg INH (directly observed) versus the current gold standard of 9 months of 300 mg INH daily (self-administered) for latent TB infection (LTBI) was the largest LTBI trial ever performed, enrolling 8053 subjects.[11] The finding that just 12 supervised doses of combination therapy was as effective as 9 months of INH alone in preventing active TB over 2 years has great public health significance. As expected, rates of treatment completion were 82% in the combination group versus 69% in the INH group. Adverse events including hepatotoxicity were less common in the combination group. This combination may emerge as the standard of care for LTBI, but limitations were that only 3% of this population was HIV-infected and the daily INH group had unsupervised treatment, which almost certainly contributed to lower completion rates.

Another important study of preventive treatment with INH in HIV-infected adults compared the WHO recommended treatment period of 6 months with 36 months in a randomised double-blind placebo-controlled study in Botswana in 1655 participants.[12] Antiretroviral agents (ARTs) were provided to participants with CD4 <200 cells/μl. There were 34 (3.4%) cases of incident TB in 989 participants in the 6-month group and 20 cases (2.0%) in 1006 adults in the extended 36-month period. Thus, extending treatment to 36 months reduced the incidence of TB by 43%. This intervention was safe, with no increased incidence of hepatitis (10 cases in each group). The benefit of continued INH was most striking for those with a positive tuberculin skin test (TST), who had a 74% reduction in TB incidence. Interestingly, TST-negative individuals did not benefit. As expected, this study also documented the role of ARTs in reducing TB incidence, with ARTs reducing the incidence of TB by 50%.

A study of MDR-TB transmission showed that a simple measure like wearing of a mask by patients with MDR-TB could reduce transmission by 56%.[13] Working at the Airborne Infectious Research facility in South Africa, 17 patients occupying the ward wore face masks on alternate days. The ward air was exhausted to two identical chambers, each housing guinea pigs that breathed the ward air of patients. Thirty-six versus 69 guinea pigs became infected when breathing air of patients wearing masks representing a 56% reduction of TB transmission with masks. It should be noted that the masks were simple Green ear-loop face masks and that their use was supervised by nurses. Changes were allowed when the mask was soiled or moist (2–3 masks per 12 h period). This simple and cheap intervention therefore has the potential to render patients with MDR-TB less infectious in crowded wards and clinics.

Treatment

There were three important studies in the field of new drugs for MDR-TB. Most recently, the first prospective randomised study of linezolid for treatment of XDR-TB was reported.[14] Several case reports, retrospective studies and a recent meta-analysis[15] have confirmed that linezolid is an effective drug in MDR-TB and XDR-TB. In this phase IIa study conducted in South Korea, 41 patients with advanced microbiologically-confirmed XDR-TB, who had not responded to available chemotherapeutic options, were randomised to immediate or 2-month delayed treatment with 600 mg linezolid in addition to their background regimen.[14] The 2-month delay was to minimise the possibility that study effects other than linezolid could account for any improvement. At 4 months, patients underwent a second randomisation to continue linezolid at 600 mg or in a reduced dose of 300mg/day for an additional 18 months. The results of the study confirmed the excellent efficacy of linezolid in XDR-TB, with 79% of those starting immediate treatment and 35% of those starting delayed treatment culture converting ($p=0.001$). Overall, 89% had culture converted by 6 months (median of 75 days) after starting linezolid. A major concern was the emergence of acquired resistance to linezolid when it was added as a single drug to a clearly failing regimen. 11% of those who had received linezolid for more than 6 months developed resistance, linked to mutations either in the 23S rRNA or in the ribosomal protein L3. The excellent beneficial effect was tempered by considerable toxicity, with 87% of patients developing clinically significant adverse effects (21 cases of peripheral neuropathy, 7 cases of optic neuropathy and 7 episodes of myelosuppression). More toxicity occurred in those taking the 600 mg dose, with these patients being 2.7 times more likely to have an adverse effect than those taking the reduced dose ($p=0.03$). Whether the lower dose has sufficient potency remains to be evaluated.

There is a great need for novel agents for the large numbers of patients with MDR-TB and XDR-TB globally, some of whom have run out of almost all drug options. Delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, is one of the most promising. In an impressively large study conducted in 481 patients with MDR-TB across 17 centres in nine countries, Wells *et al*

randomised their subjects in a 1:1:1 ratio to placebo or two different delamanid doses (100 or 200 mg twice daily).[16] They achieved 2-month sputum culture conversion rates of 45% in the 100 mg twice daily group compared with 30% in the placebo group, a significant increase of 53% (95% CI 11% to 112%, p=0.008). The drug was well tolerated. Although QT prolongation on the ECG was more commonly reported, there were no instances of arrhythmia or syncope. A second larger trial of 6 months of delamanid has commenced and will include patients who are co-infected with HIV.

New drug regimens are urgently required to combat MDR-TB. In a TB Alliance study, treatment-naive patients with drug susceptible disease were randomised to multiple agent combinations to develop a next generation TB regimen.[17] They randomised patients to one of six groups with varying combinations of novel and old agents and found that the combination of PA-824 plus moxifloxacin plus pyrazinamide had a 14-day early bactericidal activity (EBA) comparable with that of the current standard regimen for drug-susceptible TB. More importantly, since this drug combination relied neither on INH nor rifampicin, it has the potential to treat patients irrespective of sensitivity to these two drugs and hence emerge as a potential new regimen for both drug susceptible and MDR-TB. Limitations of this study were the small sample size and the fact that 2-week EBA may not translate into cure. Larger phase IIB and phase III studies are needed, with inclusion of more HIV-infected patients.

Treatment outcomes

There have been no randomised controlled studies of treatment for MDR-TB. Three recent systematic reviews identified 92 studies with individual patient data on 9153 patients with MDR-TB from 32 centres.[18] Individual patient meta-analysis was used to estimate adjusted odds of treatment success. Treatment success was associated with use of latest generation fluoroquinolones (aOR 2.5), ethionamide or prothionamide (aOR 1.7), ≥4 effective drugs in the intensive phase (aOR 2.3) and ≥3 in the continuation phase (aOR 2.7). The treatment duration that best correlated with successful outcomes was 7–8.5 months and 25–27 months for intensive phase and total treatment, respectively. Despite limitations, the WHO has used these data to inform its recommendations in the 2011 MDR-TB treatment guidelines.[19]

CHILDHOOD TB

Recent studies in childhood TB have led to increased understanding of the paediatric burden, new possibilities for rapid diagnosis and advances in preventive strategies. The global burden of childhood TB is under-reported due to paucibacillary disease and the lack of capacity for obtaining a confirmed microbiological diagnosis in children.[20] For example, childhood TB was recently estimated to account for only 3.5% of the global TB caseload in 22 high-burden countries.[1] However, paediatric studies done in select high TB incidence countries suggest a much higher incidence in children. HIV infection has had a large impact on the epidemiology and severity of childhood TB, as HIV-infected children have an increased risk of developing disease and of dissemination. Initiation of highly active antiretroviral therapy (HAART) reduces the risk of TB disease, but the risk remains higher than that of HIV-uninfected children. Moreover, children living in a household with an HIV-infected adult have a higher risk of TB exposure and infection.

Diagnostic advances

Signs, symptoms and radiological findings in paediatric TB may be variable and non-specific. An international consensus definition, based on expert opinion, has recently been published to promote the use of standardised endpoints in diagnostic and vaccine trials.[21 22] Evidence of infection can be obtained using the TST or an interferon gamma assay (IGRA). Recent WHO recommendations advise against the use of IGRA assays in place of the TST, given the cost, need for laboratory infrastructure and a blood specimen and the relatively lower sensitivity in high compared with low TB incidence settings.[23] The recognition of a typical host response to *Mycobacterium tuberculosis* may be another approach to diagnosis of disease. To date, no biomarker has been identified that identifies disease with sufficient accuracy for clinical use.

Accurate microbiological diagnosis has been difficult due to poor sensitivity of existing routine tests, especially smear tests, and the reluctance or inability to obtain an appropriate sample in children.[24] However, microbiological diagnosis using induced sputum specimens has increasingly been reported to be feasible and effective in children of all ages including infants. Smear and culture of two induced sputum specimens increased the diagnostic yield for pulmonary TB by 22% in young children in a primary care setting.[25] The availability of the Xpert MTB/Rif assay allows for rapid diagnosis including accurate detection of rifampicin resistance. Studies in children indicate that Xpert done on two induced sputum specimens detected approximately 75% of culture-confirmed cases with very high specificity.[26 27] While two nasopharyngeal specimens provided a lower yield than induced sputum for culture confirmation, the yield from Xpert on two nasopharyngeal specimens was similar, detecting almost 70% of culture-confirmed cases.[27] The yield was more than double that for smears, and did not differ by HIV status. Results were available within a day compared with more than 2 weeks for liquid culture. A recent study of Xpert done on gastric lavage specimens in children unable to spontaneously produce a sputum specimen reported a sensitivity of 69% for culture-confirmed cases; no comparison with induced sputum was performed.[28]

Prevention and management of TB disease

Vaccination with BCG remains part of the expanded programme of immunisation in many high burden countries. While BCG is protective against the development of disseminated TB, no consistent protection for pulmonary disease has been shown and vaccination is contraindicated in HIV-infected children who may develop disseminated BCG. However, a case–control study in Tanzania reported that childhood BCG (as indicated by a BCG scar) was associated with a 70% reduced risk of active TB in adulthood in HIV-infected and uninfected adults (OR 0.3, 95% CI 0.2 to 0.7).[29] The protective effect occurred across all age groups and was not confounded by HIV status. This was thus the first study providing strong evidence that BCG vaccine may prevent TB disease among HIV-infected and uninfected adults.

Exposure to an adult with pulmonary TB was reported to increase mortality by almost 70% in children under 5 years of age in Guinea-Bissau; mortality was increased eightfold when the mother had TB.[30] Although the risk of mortality was highest following exposure to a smear-positive adult case, there was also a significantly increased risk after contact with a smear-negative adult. These results highlight the need for implementation of post-exposure prophylaxis in children, a highly effective

strategy to reduce the risk of TB disease. A comparison of the cost-effectiveness of screening strategies to identify child household TB contacts reported that provision of prophylaxis based on age and reported exposure (without TST or IGRA testing) was the most cost-effective strategy in children under 2 years of age.[31] However, studies of primary prophylaxis using INH in HIV-infected children living in high TB prevalence areas have produced conflicting results. In two papers, primary prophylaxis substantially reduced the risk of TB disease in HIV-infected children with advanced HIV disease.[32 33] The risk of TB disease was substantially reduced by use of HAART or INH, but using HAART and INH together resulted in an even greater reduction of risk by approximately 90%.[33] In contrast, a study of HIV-infected infants failed to show a benefit of INH prophylaxis.[34] Differences in patient population (older children with more advanced HIV in the former two studies), meticulous follow-up with use of INH prophylaxis on exposure to a household TB contact in children enrolled in the infant study and earlier use of HAART in those in the infant study may explain these differences. Consequently, the WHO has published guidelines recommending the use of primary prophylaxis in HIV-infected children older than 1 year of age living in high TB prevalence settings.[35]

In contrast, there have been few studies on new strategies for the treatment or management of childhood TB. A meta-analysis of dosing schedules of TB drugs and treatment efficacy reported that children who received daily treatment were more likely to be cured than those receiving intermittent treatment.[36] Similar results for daily treatment in adult TB cases were reported, especially when daily treatment was used in the initial phase in cavitary disease, INH-resistant infection or HIV co-infection.[36] A meta-analysis of children with MDR-TB encouragingly reported excellent outcomes, with a cure rate of 82%, mortality of 6% and adverse events in 39%.[37]

Future research

There is an urgent need for the development of more reliable clinical scoring methods for TB in children, especially in those with HIV infection. Improved and point of care methods for diagnosing TB disease are needed that provide incremental value over existing tests, as well as diagnostic platforms that can simultaneously detect multiple respiratory pathogens. Defining biomarkers that indicate TB disease or that are correlates of protection for infection and disease remain a priority. Proteonomic and genomic biomarkers to identify a host response specific for TB are needed. Shorter more effective treatment regimes for prophylaxis and for disease are also needed. Development of an improved safe vaccine that offers protection against pulmonary TB would be a real advance. Further study of the effectiveness of primary prophylaxis in HIV-infected children living in high TB prevalence areas is needed. Operational research to inform more widespread implementation of advances in microbiological diagnosis and use of sputum induction is required in children in order to benefit optimally from recent advances.

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