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Editorial

MOLECULAR DIAGNOSTICS IN TUBERCULOSIS REVISITED WITH CLINICIANS' PERSPECTIVE

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"The strain is pan sensitive or showing only a single drug resistance in a Category II patient who is smear and culture positive even after five months of re-treatment regimen but cannot be put on second line drugs as the culture although positive is not showing resistance to both H and R..." a situation which is often seen in practical field conditions."

Statistics reveals that that there are more deaths due to TB than any other single infection[1] (1.45 million deaths each year as estimated by WHO in 2010), and there is an increase in drug resistance[2]. Modest estimates by the scientific community state that out of the 500,000 people who roughly develop MDR-TB in a year, only about seven per cent get diagnosed and about 20% of these receive a standardized regimen or a correct treatment[3] anywhere in the world. Various studies from TRC and NTI, have put MDR-TB levels at less than 3.4% in new cases and about 12% in re-treatment cases. These figures were corroborated by a sample state-wide survey[4] in Gujarat, in which MDR-TB was detected in 2.4% among new patients and in previously treated patients, MDR-TB was detected in 17.4%.

Drug resistant tuberculosis (DR-TB) is a laboratory-based diagnosis. Smear microscopy and culture are the only laboratory tests for TB that are available to most of the country's population. Smear microscopy has very high specificity (99%), but also harbours two key inadequacies: (a) a low sensitivity (50-60%); and (b) it cannot detect drug resistance. Drug resistant patients require prompt referral to second-line drugs to prevent dissemination of the increasingly resistant MDR-TB and XDR-TB[5,6]. With the advent of MDR-TB and XDR-TB, it has become imperative to take stock of the situation and make a strategy for the future in line with the MDGs by concentrating on innovations and steps to shorten the time period of diagnosis for DR-TB.

Traditional TB culture (LJ medium) for diagnosing smear-negative TB and testing for resistance takes about three months (average 84 days), which is too slow. Newer rapid diagnostic tests for TB and drug resistance such as MGIT (liquid culture), and new molecular tests or WHO approved hemi nested Real Time-TB PCR assays (Manual and Automated Nucleic Acid Amplification Tests)[7,8] are potential solutions but require large scale investment, specialized laboratories.

India is in the expansion phase of setting up a network of national accredited TB laboratories, especially for rapid diagnosis of DR-TB through new molecular tests both manual (LPA/HAIN/PCR hybridization assay) and Automated CB-NAAT (GeneXpert MTB/RIF test) and Liquid culture (MGIT 960)

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DST. Hence a clinician's perspective into these new diagnostic modalities for optimum utilization of resources is the foremost in identifying a maximum number of cases with least inputs. Molecular diagnostic tests have compromised the role of a clinician. These tests are not gospel truths with 100% accuracy and our over-reliance on them needs to be balanced with an eye for the benefit of the major stakeholder which, in this case, is the TB patient who may be showing deterioration on serial X-rays and producing positive sputum smears and cultures. The clinician should not be a mere bystander with near zero weightage, whose view is often sidelined by these new diagnostic modalities. Molecular diagnostics combined (in tandem) with the clinician's point of view which is missing currently is the way forward to solving the problem of TB patients not getting cured on first line TB drugs despite regular treatment with standardized regimens.

Since the drugs being used for DR-TB are few (with only bedaquiline being introduced recently), the physicians seeing cases of DR-TB must be able to diagnose drug resistance fast (within days instead of months). The new molecular diagnostic tools for TB namely LPA (Line Probe Assay or manual NAAT) and *automated CB-NAAT* test can diagnose MDR TB in matter of two days to two hours respectively. The Xpert MTB/RIF test (120 minute test) offers a potential solution for expediting TB diagnosis with higher sensitivity and also offers rapid screening of MDR-TB but should be endorsed by a clinician's acumen on basic radiology and detailed history of previous treatment taken by the patients. WHO endorsed[9] GeneXpert test for the rapid diagnosis of TB as well as rifampicin resistance as recently as December 2010 following its validation report which was published in September 2010 in New England Journal of Medicine.

GeneXpert is an automated (fully automated sample processing and analyzing technique), cartridge-based MTB specific nucleic acid amplification assay, using real-time PCR assay. Trials carried out at multiple sites (four distinct settings) for clinical validation revealed that 92.2 per cent of culture-positive patients were diagnosed by a single direct Xpert MTB/RIF test as compared to single direct smear sensitivity of 59.5%[10]. The specificity of Xpert MTB/RIF was 99 per cent and this makes a doctor very confident of his/her diagnosis. HIV co-infection can substantially decrease sensitivity of smear microscopy (to 47%), but does not significantly affect Xpert MTB/RIF sensitivity[11]. The Xpert MTB/RIF assay has been endorsed by the WHO as a potential alternative to smear microscopy for diagnosis of pulmonary TB.

However, few data are available to inform recommendations for use of the assay for testing non-sputum clinical samples when investigating suspected EPTB. Diagnosis of EPTB remains especially challenging since the number of *Mycobacterium tuberculosis* bacilli present in tissues at sites of disease is often very low and clinical samples from normally inaccessible deep-seated organs are difficult, if not impossible, to obtain. Nucleic acid amplification tests for rapid TB diagnosis are increasingly being used. The US CDC, Atlanta recommends the use of CB-NAAT to be performed routinely on each patient with signs and symptoms of pulmonary TB on at least one respiratory specimen such as sputum or BAL. However, no recommendation exists for their use in patients suspected of having EPTB as the evidence base is still limited.

GeneXpert or CB-NAAT will offer higher diagnostic yield in EP TB in the coming years as is evident from several published data on this subject. It has shown much higher sensitivity for smear-positive disease (99.0%) as compared to smear-negative disease (70.3%). In a recently published study[12], the sensitivity of Xpert MTB/RIF was 81.3% for EPTB and this was found consistent with several other published studies. The data from this study adds to a rapidly growing literature that collectively shows that Xpert MTB/RIF provides a rapid EPTB diagnosis in approximately 50–80% of cases in a majority of studies with a specificity of 99.8%. This test is likely to play a key role again along with clinician's opinion in providing rapid diagnostic assessment in a suspected EPTB case.

CB-NAAT can detect rifampicin resistance with 99.1% sensitivity and exclude its resistance with 100 per cent specificity[13,14]. The average time taken to detect these anomalies was less than 24 hours for Xpert MTB/RIF, same for smear microscopy (one day), about two-three weeks (17 days) for liquid culture and more than thirty days for solid culture[10,11]. Thus the consensus was that this test seems to have the potential to complement the current means of TB diagnostics and increase the yield of both TB cases and detect drug resistance early.

Many mutations can make *M. tuberculosis* drug resistant[15,16]: a prime example of this is the mutation in the rpoB gene, which, if mutated, makes the bacilli resistant to Rifampicin. By the virtue of this mutation, Rifampicin can no longer bind to the beta subunit (encoded by it) and prevent translation. CB-NAAT or Gene Xpert RT-PCR assay serves as a useful marker for diagnosing MDR-TB, as isolated Rifampicin resistance is rare (less than 5%). Mutations leading to INH resistance have been identified in varied gene targets like katG, inhA, ahpC and some other genes that still remain to be established.

LiPA (Line Probe Assays) are available for both Rifampicin (rpoB) and INH (KatG, inhA). Molecular mechanisms of drug resistance have been elucidated for all major first- and second-line drugs rifampicin (rpoB), isoniazid (KatG, inhA), pyrazinamide (pncA), ethambutol (embB), the aminoglycosides (rrs) and the fluoroquinolones (gyrA, gyrB). Although the mechanisms of resistance have been described and even well established for most agents, our cumulative knowledge of drug resistance is by no means complete and even today we see that new strains continue to emerge with many fresh resistance-related mutations. These facts are an important reminder for a clinician's viewpoint which can play a pivotal role in diagnosis of DR-TB by taking an exhaustive and accurate history of previous treatment and not treat it as a mere acaedemic exercise to fill some forms.

As a clinician, it is reasonable to get sputum smear examination and X-ray chest done as the preliminary examination, which can be followed by CB-NAAT for detection of MTB for diagnostic purpose and rapid screening of Rifampicin resistance in MDR-TB suspects. We can also use LPA or MTBDRplus test for this purpose. It can save us weeks of crucial time in starting appropriate treatment and order DST on MGIT (Rapid BACTEC or Liquid Medium) for first and second line drugs to start treatment with reserve drugs. We can use LPA (MTBDRsl) for second line drugs like aminoglycosides and fluoroquinolones with rrs and gyrA mutations in XDR-TB suspects for rapid screening and augmenting their treatment in a timely fashion[17]. The above algorithm will be the driving force for all clinicians working in the field of TB for many years to come. Some old tools like a good detailed history of intake of anti-TB drugs taken in the past with doses and duration along with chronological display of sputum smear and culture results in a tabular form (Drug-O-Gram) and thoroughly motivating all patients with systematic motivation by way of Motivation Assessment Scoring Scale[18] can help increase the success rate of treatment.

In fact the role of a clinician need not be undermined by algorithms not considering their view point at all. It is a clinician's prerogative to protect the major stakeholder i.e. the TB patient with a detailed history of previous medicines and put his/her mind to the drug-O-gram in tandem with these new diagnostic modalities to take care of 15-20% of the patients who may be pan sensitive or showing single drug resistance based on laboratory tests.

The way to a TB free India can be expedited by using these new tests for diagnosing DR-TB quickly along with both automated Liquid (MGIT) and good old Solid (LJ) culture media so as not to miss

any resistance. But the clinician's gold standard should always be the end point of smear and culture conversion in any TB patient on follow up and any persistent culture positivity after an adequate standardized regimen should be eyed with suspicion for MDR-TB despite the strain being pan sensitive or showing single drug resistance. All our old professors used to emphasize the fact that one should treat the patient and not the report.

The introduction of MDR-TB treatment (PMDT) as part of routine programme activities will succeed only if the national reference laboratories establish the new molecular diagnostic tests along with rapid culture (MGIT or Liquid media) for DR-TB diagnosis. These molecular diagnostic tests with higher sensitivity offer a ray of hope for increasing the yield of both DR-TB and EP TB in the years to come; but the key inputs from the treating physician (clinical acumen, history taking and serial radiological films) should never be ignored and shall be the saving grace in all pan sensitive cases wherein smear and culture conversion is delayed.

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Viewpoint

HYPOTHESIS: CAN CLOFAZIMINE PREVENT IRIS IN HIV/TB CO-INFECTED INDIVIDUALS?

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Antiretroviral therapy (ART) must be started during treatment for tuberculosis yet starting ART very early in the course of tuberculosis therapy increases the pill burden, the potential drug interactions and toxicity, and the risk of tuberculosis associated immune reconstitution inflammatory syndrome (IRIS).[1-10] From a recent meta-analysis, IRIS occurred in 16.1% (95% CI 11.5-22.9) of 13,103 HIV-infected persons starting ART.[1] The occurrence of IRIS varied by the associated opportunistic disease and CD4+ cell count. Tuberculosis (TB) associated IRIS was reported in 15.7% (95% CI 9.7-24.5) of those diagnosed with TB; however, risk can double among those who start ART with a CD4+ cell count < 50 cells/mm.[3,1] Trials of early *versus* later ART in HIV-TB have shown both a reduction in mortality and an increased occurrence of IRIS with the early introduction of ART, particularly among those having <50 CD4+ cells/mm.[3] Reported rates of 46.8 events/100 person years have been observed among persons with < 50 CD4+ cells/mm^3, compared to 15.8 events/100 person years among those with greater counts.[2-4] Mortality due to IRIS can be significant. In a randomized placebo-controlled trial of prednisone for paradoxical TB-associated IRIS, the syndrome was diagnosed 7-21 days after ART began in the 110 participants.[5] The CD4+ cell count prior to ART ranged from 55-243 cells/mm^3. Prednisone reduced morbidity but not mortality, which was 4.5%. In the CAMELIA study, 6/59 deaths (10.2%) among those who received early ART were attributed to IRIS.[2] In a South African study, neurological TB-IRIS accounted for 12% of all paradoxical TB-IRIS (median pre-ART CD4+cellcount 61 cells/mm^3) and had a mortality of 15.8% (3/19) including 2/7 with meningitis.[6] In India, 12.6% of 103 persons who received anti-tubercular treatment (ATT) and ART developed IRIS (median baseline CD4+ cell count 74 cells/mm^3); 38% (5/13) died with three deaths among four diagnosed with meningitis.[7] Of the 98 HIV+ individuals (median CD4+ cell count 64 and 66 cells/mm^3 among dexamethasone and placebo reci.[8] However, ART was unavailable in this trial. In a review of all-cause IRIS, investigators attributed 24% of all deaths to this syndrome.[9] These studies indicate that although early initiation of ART in the setting of HIV-TB leads to an overall reduction in death, there is an increased incidence of IRIS, which may then contribute to mortality and to considerable morbidity.[10] The risk of death may be greatest among persons with neurological TB. The potential consequences of neurological IRIS are exemplified in the Cryptococcal Optimal Timing of ART (COAT) trial for cryptococcal meningitis. The study was stopped early due to a 1.7 fold increased risk of death in those given early *versus* delayed ART: 42% mortality in the early arm compared to 27.6% in the later ART arm.[11] Therefore, interventions are justified to prevent or mitigate the clinical complications associated with IRIS. On a global scale, compared to other major opportunistic diseases, HIV-TB has accounted for the largest number of reported cases of IRIS.[1,11]

Randomized controlled studies have shown clofazimine (CFZ) to be beneficial for the treatment of erythema nodosumleprosum (ENL), chronic graft-*versus*-host disease, systemic lupus erythematosis, Crohns disease, and pustular psoriasis.[12-14] Furthermore, there is experience with CFZ use in HIV-infected persons with *Mycobacterium avium* complex (MAC) co-infection and experience with CFZ in the treatment of TB.[15-18] In that it has activity against MTB, CFZ can be initiated with standard ATT. If ART is initiated at week 2 of ATT, there is a greater than two week window from the start of CFZ to the start of IRIS. Therefore, a preventive effect of CFZ may be measurable.

The experience with CFZ for HIV-MAC has not been favourable. A randomized trial compared clarithromycin plus ethambutol with or without CFZ (100 mg once daily) in 106 persons with advanced

HIV (median CD4+ cell count 10 cells/mm^3) and disseminated MAC. Death was significantly associated with baseline MAC colony ≥1000 CFU/ml (relative hazard 1.95; 95% CI: 1.02-3.73) and assignment to the CFZ arm (relative hazard 1.79; 95% CI: 1.02-3.17). The quantitative decline of MAC from serial blood cultures was similar in both arms. The reason for this decreased survival was considered unrelated to direct drug toxicity. However, those randomized to CFZ had a median mycobacteremia level that was more than one log greater than those in the two drug arm, which may have contributed to increased mortality.[15,19] In addition, the MIC for CFZ against MAC ranges from 8-125 ìg/ml which can exceed CFZ serum concentration by more than 10-100 fold.[15] Although ART was found protective, not all participants received antiretrovirals. Finally, the enrollment period, from 2/1993-3/1994, preceded the availability of highly active combination therapy. The possibility that the immunosuppressive effects of CFZ contributed to the excess mortality observed in this study cannot be excluded. Given the survival benefit conferred by the available ART at that time, the current availability of highly active combination ART, the absence of excess mortality in other patient populations given CFZ,[20,21] and avoidable IRIS-related mortality or morbidity, CFZ can be considered as a potential safe therapeutic option to prevent or mitigate IRIS in the setting of HIV-TB.

CFZ is classified as a WHO Group 5 drug, along with linezolid, amoxicillin-clavulanate, thiacetazone, clarithromycin, and carbapenems. These are agents of unclear efficacy and not recommended for routine use in the treatment of TB.[20] CFZ was synthesized in 1954 for the treatment of TB, but inconsistent efficacy in both animal models and in humans have limited its use. However, the emergence of MDR-, XDR-, and TDR-TB has rekindled interest in this agent. The mechanisms of antimicrobial action are still incompletely understood. The agent may lead to the generation of bactericidal levels of reactive oxygen species (ROS). CFZ is extremely hydrophobic and appears to act at the plasma membrane level on a redox cycling pathway, which involves the reduction of CFZ by the NDH2:quinoneoxidoreductase of mycobacteria and the generation of ROS.[22]There is evidence for other mechanisms of action including interference with K+ transport through interactions with phospholipids, and alterations in mycobacterial lipid metabolism.[23,24] In common, these actions occur at the level of the mycobacterial membrane.

The MIC of CFZ against *Mycobacterium tuberculosis* (MTB) ranges from 0.06-2.0 µg/ml, with 1.0 µg/ml considered as a breakpoint.[20] It is active *in vitro* against intracellular organisms and does not show cross-resistance with strains resistant to other agents.[25] CFZ is also active against persisters, low oxygen adapted non-replicating MTB, suggesting a sterilizing capacity.[26]Gopal reviewed PubMed, Embase, and the Cochcrane Library for studies in all languages that reported the use of CFZ for MDR- or XDR-TB up to Feb 2012.[18] None of the six MDR studies (involving 531 patients, or four XDR studies, including 68 persons) were randomized controlled studies. Overall response rates for MDR-TB were 65% (52% CI: 52-79) and 65% (95% CI: 54-76) for XDR-TB. In the largest study of 427 individuals from Bangladesh, who received CFZ for MDR-TB, 75.6% had a favourable response.[27]All received CFZ in the intensive phase of treatment, and 244/247 received CFZ in the continuation phase. Response rates were highest in those who received CFZ for both phases (> 80%). Because regimens differed (six regimens were compared), it is not possible to draw firm conclusions about the role of CFZ in the treatment of drug-resistant TB. However, it is tempting to speculate that, given the activity of CFZ against non-replicating MTB, its use in the continuation phase may have contributed to a greater success rate. CFZ was generally well tolerated in these studies at daily doses that ranged from 50-300mg, with 100mg once daily as the most widely prescribed dose. Randomized controlled studies are needed to define the utility of CFX for the management of TB.

IRIS is an antigen-driven process in which normal immune homeostasis is dysregulated. There is a complex interaction of TH1 memory cells, promoting into CD4+ TH1 effector cells, functional T helper (TH) cells such as interferon-ã (IFN- ã) producing TH1 and interleukin (IL)-4 producing TH2 cells and various cytokines. TH1 cells are crucial for clearance of intracellular pathogens, such as MTB. TH17 cells

produce IL-17, IL-17F, and IL-22 and appear to play a critical role in inflammatory responses.[28,29] The maintenance of a homeostatic state is made possible by Tregs. Tregs suppress the proliferation of effector CD4+ and CD8+ cells and suppress their cytokine production, thus limiting the immune response to microbial antigens. The differentiation of naïve helper T cells (Th0) into Tregs is *via* signaling by TGF-ß, IL-7, and IL-10. Disruption of Treg signaling may upset the balance between an appropriately controlled immune response to MTB and the development of exaggerated inflammatory state. A critically important cytokine is IL-6. In the presence of TGF-â, IL-6 preferentially induces TH17 cells, and in the absence of IL-6, Treg differentiation can occur.[30, 31] Normally, there is an approximately 2:1 ratio between pro-inflammatory TH17 cells and the Tregs. During immune reconstitution, various subsets may reconstitute at differing rates, and this ratio may become unbalanced [32]. Altered or absent TREG function may be an integral part of the cellular and cytokine dysregulation leading to IRIS. However, the role of TH17 cells and Tregs may vary with the inciting pathogen.

Many studies have examined the immunological mechanisms of TB-IRIS and have sought to define biomarkers and immunologic profiles that might predict its occurrence.[33] As yet, there are no specific predictive markers or diagnostic tests for TB-IRIS. Mahnke in a study of 19 persons with IRIS (compared to 48 without IRIS) associated with 12 different coinfecting pathogens found a significant upsurge of pathogen-specific CD4+ cells, mainly polyfunctional effector memory cells (Tem), IFN-ã+ CD4+ cells (IFN-ã+ IL-2+ TNF+ and IFN-ã+ IL-2- TNF+) particularly among those with fungal and mycobacterial organisms.[34] There was no increase in responses to HIV or other coinfecting organisms not implicated as a cause of IRIS. In addition, CD8+ cells displayed a delayed recovery of CD28 and CD127. Among 20 TB-IRIS cases compared to non-IRIS TB controls, investigators observed that IRIS was accompanied by greater CD4+T cell responses to PPD compared to controls; however, CD4+ (IFN-ã+ IL-2+ TNF-Ü+) responses after CD3/CD28 stimulation were impaired, both before during and for six months after IRIS, compared to controls.[33] TB-IRIS was associated with both an exaggerated T cell response to TB antigen and diminished responsiveness to broad T-cell activation. PD-1 expression on CD4+ T cells (including effector memory CD4+ cells) was greater among those who developed IRIS and preceded the initiation of ART, among 16 persons with IRIS *versus* 29 controls.[33] Coexpression of CTLA-4, LAG-3, and ICOS was also more frequent at baseline. Even before ART initiation, those who developed IRIS had a higher proportion of activated but possibly dysfunctional T cells (including a greater proportion of activated Tregs). In addition Bourgarit reported that V ô2+TCR ãô + T cells were also increased among those who were eventually diagnosed with TB-IRIS.[35] These cells are important in the response to MTB and may facilitate subsequent ÜâT cell proliferation.

It is unclear if the more intensive restoration of Ag-specific T cell responses is either the primary trigger or driver of IRIS. Individuals who develop IRIS have lower plasma levels of CCL2 before the start of ART, suggesting a role for innate immune responses.[36,37] Pean demonstrated the greater expression of the degranulation surface marker, CD107a, prior to ART among 37 TB-IRIS patients compared to 91 non-IRIS TB patients and postulated that NK cytolytic activity may lead to higher MTB antigen load and thereby play a role in the development of IRIS.[38] In recent observations, IL-10 and IL-22 were increased in serum and yielded higher transcript levels in stimulated PBMCs among those with TB-IRIS.[39] While IL-10 may lead to a dampening of the immune response to MTB, the role of the pro-inflammatory cytokine, IL-22, (elevated in Crohns disease, rheumatoid arthritis, and other T cell mediated diseases) is less clear. That cytokines were more frequently associated with stimulated CD14+ cells, suggests a further role for innate immunity in the evolution of IRIS.

Although the exact mechanisms that lead to IRIS are incompletely known, the syndrome appears to follow recovery of innate immune function, an upsurge of pathogen-specific T cell function (largely

derived from CD4+ effector memory subsets), and the release of pro-inflammatory cytokines and chemokines. These immunological events may occur in the setting of significant immune dysfunction and dysregulation due to both HIV and MTB infection. IRIS may represent a continuum dependent on external factors such as the nature of the pathogen, the Ag load, and the timing of ART, in addition to host factors, including innate and adaptive immunity; not all individuals develop a clinically recognizable syndrome. Pathogen-specific therapies for IRIS are unlikely to be developed in the near future. While the initiation of immunosuppressive therapy must be approached with caution, early initiation pre-ART or at the time of ATT, may be able to lessen or prevent IRIS and its consequences.

While CFZ is a non-selective immune modulator, this agent may preferentially target effector memory T lymphocytes, believed to be a major factor in the development of IRIS. Two major K+ channels are expressed on lymphocytes: the Shaker-related voltage-gated Kv1.3 and the intermediate conductance Ca2+-dependent KCa3.1 K+ channels. Late effector memory cells preferentially express and up regulate Kv1.3. Blockade of these channels inhibit Ca2+ signaling and then proliferation and migration of CCR7- Tem cells.[40,41] CFZ inhibited human Kv1.3 K+ channels and perturbed the oscillation frequency of the calcium-release activated Ca^{2+} channel, leading to inhibition of the calcineurin-NFAT signaling pathway. CFZ effectively blocked T cell-mediated skin graft rejection in the mouse model of human skin transplantation.[42] As noted, CFZ has been used successfully in other T cell –associated conditions such as lupus, Crohns disease, rheumatoid arthritis, and graft-*versus*-host disease.[12-14] Lipid metabolism is modulated by CFZ in *M. leprae*-infected macrophages, which leads to increased expression of IFN-ß and IFN-ã in infected cells and may lead to enhanced clearance of organisms.[24] CFZ has also been observed to induce apoptosis in macrophages associated with caspase-3 activity.[43]

In mice, CFZ was largely found initially in adipose issue then largely redistributed to liver and spleen with accumulation in macrophages in lymphoid organs. This was associated with the up regulation of the anti-inflammatory protein, IL-1 receptor antagonist, and also down regulation of CCL5 and CXCL9 and CCL4 CCL17, and TNF-alpha in the lung. In addition to up regulation of CCL2 in the lung, which may lead to enhanced macrophage recruitment, it also led to increases in TIMP-1; this endogenous tissue inhibitor of matrix metalloproteinase activity may play a role in the containment of MTB infection and decrease virulence.[31,44] Distribution of CFZ was low in the brain, perhaps, the most life-threatening target of IRIS. Yet, intraperitoneal injection of CFZ was able to protect against granzyme B mediated neurotoxicity in the rat hippocampus by blocking the Kv1.3 K+ pathway.[45]

MTB-specific Tem cells have an important role in the generation of TB-IRIS but are also important in the host response to MTB. Because CFZ targets Tem cells, this agent warrants further study as a measure to prevent or mitigate TB-IRIS. On the other hand, CFZ may also dampen cellular immune defenses against MTB. However, CFZ does have activity against MTB; hence, there may be additional gain. Although not well studied, CFZ has been used safely, but with mixed success, in the management of TB. The short-term use of CFZ in the induction phase of ATT can provide the opportunity to examine the immunological, anti-mycobacterial effects of CFZ and its safety.The onset of antimicrobial action may take weeks to be manifest.[20]The delayed tissue distribution and onset of action suggest that CFZ must be started as early as possible before the initiation of ART. Since it has anti-MTB activity, CFZ would be started with ATT and then followed by the initiation of ART.

In patients with TB and HIV coinfection, the early initiation of ART is associated with a reduction in mortality, particularly among those with severe immunosuppression. However, ART is also associated with IRIS, again, particularly among those with the lowest CD4+ cell counts. Clofazimine is an interesting

agent in that it targets two potential avenues that lead to IRIS: it is active against *M. tuberculosis* including multidrug resistant strains and thus may reduce antigen burden. Importantly, it may target a key pathway in the generation of IRIS, the effector memory T cell. Because IRIS causes significant morbidity and mortality, exploration of strategies that can prevent or dampen its potentially devastating effects are warranted.

Norman Markowitz[1], Upasna Agarwal[2] and Dwayne Baxa[3]

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EVALUATION OF MEDICAL INTERNS' LEARNING OF EXPOSURE TO REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME GUIDELINES

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Summary

Background: As per the Medical Council of India (MCI), the posting in the Chest and TB department is elective during internship. Hence, they lack hands on exposure to various components of RNTCP programme. This gap in treating TB patients by using RNTCP guidelines may be bridged by sensitizing the interns through early exposure of medical interns to training programmes.

Objective: The workshop was conducted and evaluated, 1) To know learners' immediate reaction and 2) To know its effects on their learning and practice.

Methods: A series of training workshop on RNTCP guidelines was organized for Interns by the Core-committee of the State Task Force (STF), RNTCP and Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital (SMVMCH), Puducherry, during January2012 - November 2012. A Pre and Post test self-administrated questionnaire, immediate feedback and other open-ended feedback after six months was obtained from Interns to know its effect on their clinical practice.

Results: The pre and post test mean scores were highly significant ($p<0.001$). In the analysis of feedback, the consensus score for all the responses was above 75%. As per the responses of the feedback from interns taken after six months, the three broad categories of common responses from the manual content analysis emerged were: 1) Effect of training in patient care, 2) Acquaintance of RNTCP Guidelines, 3) Future Plan of application of lessons learned.

Conclusion: This training programme has been well received by the medical interns and has now been incorporated as a regular activity for the Interns posted in the Department of Community Medicine. ***[Indian J Tuberc 2014; 61: 288-293]***

Key words: Interns, RNTCP, Pre test and post test, Likert scale

INTRODUCTION

Since a decade of Revised National Tuberculosis Control Programme (RNTCP) implementation in India, still tuberculosis (TB) has remained a major public health problem in India. It has been estimated that in the South-East Asia Region, 60-70% of all patients with tuberculosis prefer to use the private sector.[1] In, India 80% of patients prefer private sector for treatment of minor illness.[2] It has been reported that there is lack of reporting mechanism and adherence to treatment guidelines in private sector.[3]As per the Medical Council of India (MCI), the posting in TB and Respiratory Medicine is elective during internship.[4] Hence, they lack hands on exposure to various components of RNTCP Programme. But, the CRRIs (Compulsory Rotatory Residential Internship) (also called as Intern) are the first point of contact with the TB suspects in other clinical departments like Medicine, Surgery, pediatrics, Orthopedics, etc. This gap in identifying and treating TB patients by using RNTCP guidelines may be bridged by sensitizing the interns through training programmes, symposia, Continuing Medical Education(CME) and student conference. Arora VK *et al*, Mohan A and Bogam RR had mentioned that Directly Observed Treatment Short course chemotherapy (DOTS) training needs to be imparted to the treatment providers.[5-7] So, the Core-committee of State Task Force (STF), RNTCP and Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital, Puducherry planned to conduct hands on exposure for the interns in the RNTCP guidelines. The workshop was evaluated with following objectives, 1) To know learners immediate reaction and 2) To know its effects on their learning and practice.

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Methods

Study Setting and design

The present study was based on a training workshop organized for interns. The event was organized by the Core-committee of State Task Force (STF), RNTCP and Department of Community Medicine of Sri Manakula Vinayagar Medical College and Hospital (SMVMCH), Puducherry.

A series of training workshop was organized once in two months for the interns posted in the Department of Community Medicine. Six such training workshops were held between January 2012 and November 2012 and 72 interns were trained during this period. Immediate feedback was taken after the training workshop. Six months later, a qualitative feedback was collected from the medical Interns, who had participated in this training workshop.

What was done?

The main focus of this workshop was to explain and illustrate the key concepts which support the treatment of tuberculosis using the guidelines of RNTCP.[8] The sessions were interactive with brief lectures followed by hands-on-exposure on AFB staining, identifying of bacilli under binocular microscope, how to fill and read laboratory form for sputum examination. Participants were shown TB laboratory register, Referral register, Referral form, TB treatment card, monitor drug collection and recording. There was a case-based discussion on sputum examination and categorization of patient for Anti-TB treatment (ATT).

Data collection

Pre and post test questionnaire: To assess the level of knowledge and skill acquired from the training, pre test and post test self administrated structured questionnaires were distributed to all the participants before and after the training Programme.[7] The data was entered in Epi-info (version 3.4.3) software. The difference in the mean pre and post test scores was found using paired-t test.

Feedback

At the end of the workshop, feedback was obtained immediately to know their learning after the training Programme. We used four point likert scale to avoid the neutral stand taken by the learners.[9]

Qualitative feedback on application of the learning in patient care (end of six months)

Six months later, Interns were given a feedback questionnaire having four open-ended questions [What did you learn in the training programme, Could you apply these learning to your work setting (patient care), If yes, how? (please elaborate with giving example), If no, why (please elaborate with giving example)] to respond. To avoid social desirability bias, information such as name, and background characteristics were not collected. The interns' qualitative feedback was assessed to judge their acquired knowledge/skills during the training and its application in patient care. Out of 72 interns participated in training workshop, we obtained feedback from 40 of them, those who had completed six months after workshop. The manual content analysis was done.

RESULTS

Pre and Post test

Out of 72 interns, there were 41 females and 31 males. The pre and post test mean scores were 9.8 ± 4.2 and 13.7 ± 3.7 respectively, which was highly significant (t value 9.941, $p<0.001$).

Feedback on Training Programme

All 72 participants' data was complete, and were included for analysis (Table.1). In the analysis of feedback, the consensus score for all the responses were above 79%. The item on the identification of TB suspects had a maximum consensus score of 84.8%. The consensus score for understanding the scientific Basic of treatment of TB under DOTS was 79.3%.

Table.1: Feedback on training of Interns on 'RNTCP Guidelines'

Questions	Strongly agree	Agree	Disagree	Strongly disagree	Weighted average	consensus
I am sensitized to structure of RNTCP	32(47.8)	35(52.2)	0(0)	0(0)	1.5	80.77%
Now I can identify TB suspect(pulmonary/Extra pulmonary)	49(73.1)	18(26.9)	0(0)	0(0)	1.3	84.84%
I can Grade the sputum	27(40.9)	36(54.5)	3(4.5)	0(0)	1.6	79.54%
I can categorize the patient using diagnostic algorithm under DOTS	45(67.2)	22(32.8)	0(0)	0(0)	1.3	82.99%
I understand the scientific basics of treatment of TB under DOTS	34(50.7)	31(46.3)	2(3.0)	0(0)	1.5	79.28%
I know how to select the correct regimen for the patient	44(65.7)	23(34.3)	0(0)	0(0)	1.3	82.62%
I know safe disposal of contaminated material	35(52.2)	32(47.8)	0(0)	0(0)	1.5	80.77%

Feedback after six months

As per the responses of the feedback taken from 40 Interns' after six months, the broad categories of common responses from the manual content analysis are mentioned in Table.2. The three categories of common responses were as follows:

1) Effect of training in patient care: The interns could apply the knowledge gained in a training workshop in patient care. One of the interns has identified a suspect of MDR TB and the adverse effect due to Isoniazid drug. Another Intern posted at RHTC (Rural Health Training Centre) had referred three TB suspects to nearby designated microscopy centre. Other Intern stated that during his/her posting in the Department of Medicine, S/he diagnosed five cases of Pulmonary Tuberculosis without the help of Assistant Professor.

2) Acquaintance of RNTCP Guidelines: Most of the interns had noted that they were aware of the Revised guidelines of RNTCP in diagnosis and treatment, three of them had mentioned that they came to know that after diagnosis, the TB patients should be referred to a respective DOTS centre for further treatment.

3) Future Plan of application of lessons learned: Around seven of the interns can identify the suspects for Pulmonary Tuberculosis for AFB sputum and can categorize on their own.

Table 2: Qualitative feedback from the CRRIs after six months of attending the training programme

Categories of common responses N = 16	CRRIs' Points (number of students making point)
Effect of training in patient care.	• I followed up a case of pulmonary TB (3) • I Identified a suspect of MDR TB already under Anti Tuberculosis Treatment (2) • I identified a TB default patient and referred (1) • I treated a patient of Isoniazide toxicity with pyridoxine. (1) • I entered the case in referral register and filled the referral slip (2) • During my posting at RHTC(Rural Health and Training center) , I referred 3 TB suspects to nearby DOTS center (1) • I sent 3-5 patients for sputum examination, categorized and registered these patients to our DOTS center(4) • I counseled sputum positive TB patients for treatment (2) • I could diagnose 5 cases of Pulmonary Tuberculosis during the Medicine posting without the help of Assistant Professor • I could diagnose a case of Extra Pulmonary Tuberculosis
Acquaintance of RNTCP Guidelines	• I came to know that our institute is a DMC (Designated microscopy center) (1) • Procedure for Registration of New sputum cases (23) • Revised guidelines of RNTCP in diagnosis and treatment (25) • Adverse effects of ATT(3) • I came to know that after diagnosis, to refer the patients to respective DOTs center for further treatment (5) • Identifying the suspects of TB (5) • Diagnosis of Pediatrics patient(1) • Diagnosis of Extrapulmonary cases(1) • MDR TB(4) • Learnt about the role of RNTCP state task force (STF) (1) • Proper Disposal techniques(1)
Future Plan of application of lessons learned	• I can identify the suspects for Pulmonary Tuberculosis for AFB sputum and categorize (7) • I can register the cases in our DMC & refer the Tuberculosis patient to the respective DOTS center to receive ATT (1) • I give health education to cases of TB (1) I can apply this knowledge in clinical practice (1)

DISCUSSION

Medical colleges play an influential role in training the future medical practitioners competent to manage TB patients, in their individual capacity. The Task Force for Involvement of Medical Colleges in the RNTCP has clearly highlighted the importance of training as an important contributor in RNTCP implementation.[10] Our study also assessed the application of their learning in their clinical practice.

The pre test and post test mean scores of participants were 9.8 and 13.7 respectively, which demonstrated that the training workshop significantly improved the knowledge on the RNTCP guidelines ($p<0.0001$). Bogam RR and Aggarwal P *et al* have reported similar finding among postgraduates and interns respectively. [7, 11]

Overall evaluation of the training programme assessed by feedback questionnaire showed that the Interns self-reported improvement in knowledge. In the analysis of feedback questionnaire, the consensus score for all the items were above 75%, it shows that the guidelines of RNTCP were well taken by the Interns. They could retain their learning and were confident in categorizing the patients and selecting the correct treatment regimen, which is one of the important steps for the success of treatment. In India, V.K. Arora *et al* have reported the 'Need to sustain DOTS training' as majority of patients prefer private clinics which dominate the health for treatment and their treatment success rate has been less than 50%.[5] Also, Khan J has emphasized that for effective control of TB, the knowledge of undergraduates and interns should be improved by continuing medical education.[12] Hence, the sensitization of Interns to the RNTCP guidelines will help to improve the treatment success rate in near future.

Most of the interns had stated that they were sensitized to the guidelines of RNTCP and they could retain and apply the knowledge at their workplace. About 20 interns could apply this sensitization in their clinical posting. One of the Interns claimed that she/he identified a suspect of MDR TB and the adverse effect due to Isoniazid. It is interesting to note that another Intern could diagnose five cases of Pulmonary Tuberculosis without the help of the teaching faculty during his/her posting in the Department of Medicine. It is of paramount importance to retain the knowledge pertaining to the guidelines and apply in situations needed so as to control TB. Mohan A *et al* have clearly discussed about the discordance between what is preached and practised and suggested that by actively associating with the RNTCP for DOTS implementation, medical schools can train the doctors in the making to actually practise what is taught to them regarding TB control.[6] It was an attempt by us to evaluate their application (what is thought) in their clinical practice keeping in mind that, these future private practitioners might apply this learning in their real practice. Our collateral beneficiaries to coordinate the TB cases diagnosed in other clinical departments through the DOTS centre of our institute. Most of the interns in their feedback had mentioned that they were aware of the referral system of TB patients.

CONCLUSION

Thus, the session on the topic of public health importance was well taken by the interns. Learning as an individual, the exposure of the interns to the guidelines of RNTCP will help them in future to treat the TB cases as per the guidelines. This training programme has been incorporated as a regular activity in our institute for the interns posted in the Department of Community Medicine.

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PRIORTISING AIRBORNE INFECTION CONTROL IN HIV/AIDS CARE SETTINGS IN INDIA

Ashok Kumar *

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India with 1.22 billion populations is the second most populous country in the world with one fourth of the global incident TB cases and has third highest number of estimated people living with HIV in the world. In 2012, out of the estimated global annual incidence of 8.6 million TB cases, 2.3 million were estimated to have occurred in India.[1] According to the HIV estimations 2012, the estimated number of people living with HIV/AIDS in India was 2.1 million; with an estimated adult (15-49 age group) HIV prevalence of 0.27% in 2011. The HIV epidemic in India is concentrated epidemic among high risk groups and is heterogeneous in its distribution[2]. Tuberculosis is the most common opportunistic infection in people living with HIV. India accounts for 10% of global burden of HIV-associated TB. In 2012, HIV prevalence among incident TB patients in India was estimated to be 5.95% (95% CI 5.93%–5.97%) translating about 1,30,000 HIV-associated TB patients are emerging annually.

The transmission of TB and Drug resistant TB (DRTB) is a recognized risk in HIV care settings as TB is transmitted through droplet infection by airborne route of transmission and is associated with high mortality[3]. Transmission of tuberculosis to persons with HIV infection is of particular concern in developing countries with high burden of TB and HIV with limited infection control practices. Overcrowding at outpatient departments (OPDs), waiting areas and wards with minimum ventilation measures expose people living with HIV (PLHIV) to risk of transmission of TB, drug resistant TB or other respiratory diseases in various health care settings[4]. With their low immune status and secondly due to exposure to the other PLHIV patients with TB ,the HIV patients are at high risk of developing TB in HIV care settings[5].

Presently under HIV care settings there are 15,606 Integrated Counselling and Testing Centres (ICTCs), 425 Anti-retroviral therapy (ART) Centres, 870 Link ART centres(LACs), 10 Centre of excellence(COEs) and 1,137 designated STI/RTI clinics .Under TB care settings there are 13,325 Designated Microscopic centres (DMCs) and 122 Drug Resistant TB (DR-TB) centres in the country. The HIV care facilities are by and large located in Medical colleges and General hospitals, District hospitals, Community Health Centres, and now also being expanded to Primary Health Centres within the General Health care system. Whereas most of the TB care facilities are located in PHCs, CHCs, District Hospitals, Medical Colleges and General Hospitals. Both the National AIDS Control Organisation and Central TB Division are further expanding these facilities to cover larger health care units to reach near the door steps of people, throughout the country.

Considering TB as the most common opportunistic in PLHIVs also heading to high risk of mortality, there is an urgent need for action necessary to minimize the risk of tuberculosis transmission in these HIV care settings like ICTC, ART centres, LACs, COEs, STI/RTI Clinics. WHO policy on TB/HIV collaborative activities and National Framework for HIV/TB collaborative activities in India (Nov 2013) recommends control of TB Infection in health-care facilities and congregate settings as an important strategy to reduce burden of TB in PLHIV[6, 7].

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Airborne Infection Control Measures

National Airborne Infection Control Guidelines in India have been developed with the objective to prevent transmission among suspects, patients, health care workers and even visitors at the health care settings[8]. Airborne infection control measures include three-main approaches, namely administrative, environmental, and personal respiratory protection measures[8,9].

Administrative controls are procedures for implementing, enforcing, monitoring, evaluating, and revising infection control plan and serve as the first line of defence for preventing spread of tuberculosis in health-care settings. This includes rapid triage and treatment of infectious cases, to identify facilities needing AIC activities, persons with respiratory symptoms, separate them into appropriate environment, fast-track them through the health care facility to reduce exposure time to others, and diagnose or treat them with minimal delay. Hospitalization should be minimized or avoided to the greatest extent possible. In many health care facilities, there is over crowding of patients in waiting areas, registration counters, investigating units and drug dispensing counters. Fast-tracking of respiratory symptomatic and decompression of crowded OPDs can be done with the help of paramedical workers or volunteers trained in air borne infection control measures who can take responsibility to segregate and decompress the crowded areas by fast tracking to reduce the risk of nosocomial *M. tuberculosis* transmission. Use of alternative spaces with natural ventilation for waiting areas and safe sputum collection will reduce the risk of transmission.

Inpatient administrative controls like minimizing hospitalization and visitors entry, educating patients and visitors on cough hygiene, routine segregation of patients to separate wards or separate areas within same ward in order to reduce risk of transmission, particularly to immune-compromised, maintaining spacing in the beds at least six feet, ward decompression, emphasising on opening the doors and windows to ensure adequate ventilation for inpatient areas are recommended.

Environmental controls aim to reduce the number of infectious particles in the air. This may be achieved by natural ventilation where possible and mechanical ventilation where there is limited scope for natural ventilation. In high-risk settings where optimal ventilation cannot be achieved through natural or mechanically-aided means, ultraviolet germicidal irradiation devices should be considered as a supplementary control measure. Mechanical ventilation systems include use of fan driven positive pressure mechanical ventilation and exhausts negative pressure mechanical ventilation systems. Hybrid (mixed-mode) ventilation systems use combined natural driving forces and mechanical ventilation for augmentation. It is important to ensure that mechanical ventilation measures like fans and exhausts are used in proper place and in adequate quantities. Ultraviolet germicidal irradiation (UVGI) devices should be considered as a supplementary measure if minimum air changes could not be achieved but the maintenance of these should be ensured[10]. UVGI should be considered adjunctive measures to be used in high risk settings only after administrative controls and ventilation measures have been addressed. In some settings, TB services and HIV services are in close proximity which increases the risk of transmission of TB in HIV patients. Proper infection control measures with attention regarding patient flow are required in such settings with reorganised design to provide integrated TB HIV services.

Respiratory Protection: Personal protective equipment e.g. N95 or FFP2 is important in TB infection control measures and should be routinely used by health care workers in high-risk settings , especially in TB wards, ART Centres, DRTB centres, and other high risk settings drug resistant tuberculosis, and during high-risk aerosol-generating procedures such as bronchoscopy or sputum induction.

Infection control measures for HIV care settings: Unsuspected TB cases contribute to TB transmission because they are not being treated and may go unsuspected for days or weeks, and may visit

multiple health-care facilities or be admitted indoors. Spread of TB and drug resistant TB in health care settings has highlighted the need for health care facilities to implement standard infection control precautions and to improve airborne infection control measures in health care settings especially high risk settings like ART Centres. National Airborne Infection Control guidelines recommend special infection control considerations for ART settings as under:

1. Fast-tracking of chest symptomatics should be done to ensure minimizing the risk of nosocomial transmission.

2. Screening of patients for respiratory symptoms and TB diagnosis should be done as soon as possible in the ICTC, ART, LAC centres for early referral for diagnosis and initiation of treatment.

3. ART centres should be located not adjacent to Designated Microscopy Centre (DMC)/DOT centres, with waiting area that is not shared by DMC/DOT centres. ART centres should have a well-ventilated waiting and seating areas.

4. Health education to patients and communities about TB transmission, Infection control and cough etiquette should be stressed upon by staff. IEC material on cough etiquette should be prominently displayed.

5. Ventilation standards for ICTC and ART centres should be adhered to.

6. Training Health Care Workers on respiratory protection to be conducted.

Surveillance of TB in Health Care Workers (HCWs): Recent increases in rates of TB and Drug resistant TB among health care workers have led to greater concern about the risk of nosocomial transmission in health care settings.With the better detection mechanism, there is rise in number of multi drug-resistant (MDR) and extensively drug resistant (XDR) TB among health care workers, a greater emphasis on the protection of the healthcare workers is required.

Considering the TB notification in India[11], the hospital infection control committees should ensure regular reporting of cases of TB among health care workers and collect data in a health worker TB registry. The Infection control committee should designate a nodal person to collect information of TB in health care workers.

Training of Public health building engineers, Administrators and Health Care Workers in Infection control in Universal workplace Precaution, waste segregation and disposal and Air borne Infection Control Practices, with special reference to tuberculosis, HIV and drug resistant TB, use of Personal Respiratory Protection i.e. N95 particulate respirators is essential component of Infection control plan.

Patient education: With the increase in number of TB and MDRTB contact cases, it is important to counsel and educate patients regarding cough hygiene, cough etiquettes, sputum disposal and adequate advocacy, communication and social mobilisation (ACSM) activities will reduce the risk of transmission in households and community. Similarly HIV and TB care settings should display Information, Education and Communication (IEC) material related to AIC at the appropriate places.

Although the National Infection Control Guidelines and the National Framework for HIV/TB collaborative activities highlight the need for implementing the infection control measures in HIV/TB care settings, there is a necessity of focused efforts in this direction .National AIDS Control Programme phase IV

has Infection control as key priority and the NACO has already issued guidelines to all the HIV /AIDS care facilities through the State AIDS Control Societies to implement the infection control measures for HIV / AIDS care settings as recommended in National Infection Control Guidelines. Programme Managers at State level, Admistrators of health care facilities, Microbiologists, Engineers, etc., are key personnel who can play a vital role in implementing the Airborne Infection Control measures in the facilities. With the efficient implementation of Airborne Infection Control measures at HIV/AIDS care settings, there would be substantial benefits in terms of reduction of TB transmission thereby break in chain of transmission and new TB cases will be averted. There will be reduction in transmission of TB and other respiratory infections like H1N1, H5N1 etc. among individuals attending the health care facilities. Transmission of TB among health care workers and close contacts will be reduced with effective implementation of these measures.

In conclusion, there is need of urgency to expedite implementation of airborne infection control measures in all the health care facilities, especially in HIV/AIDS care settings. This is a beneficial intervention to prevent transmission of TB disease among people living with HIV. Success in implementing these measures will depend on the facility administrators taking ownership to implement these measures on priority and appropriately address barriers to implement airborne infection control in the facilities.

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Review Article

PROGRESS IN ACHIEVING UNIVERSAL ACCESS TO CARE FOR MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

Fraser Wares and Dennis Falzon

Summary: Each year there are about nine million new cases of tuberculosis (TB) in the world and over one million people die of the disease. The emergence of resistance to the drugs that are used to treat TB threaten to undo much of the progress achieved in controlling it in recent decades. In some countries, up to one third or more of TB cases have multidrug-resistant TB (MDR-TB; combined resistance to at least isoniazid and rifampicin), requiring a much longer and toxic treatment than that suffices for other TB patients. Countries have committed to achieve universal access to care for MDR-TB for their populations by 2015. In this article, we use national data collected by the World Health Organization (WHO) to assess global progress in detection (against WHO estimates) and treatment of MDR-TB. Over one half of all the world's MDR-TB patients are concentrated in three countries: India, China, and the Russian Federation. In 2012, about 78,753 TB cases were reported to have been started on MDR-TB treatment, about 25% of the estimated MDR-TB case load in the world. Only 48% of over 35,000 MDR-TB patients started on treatment in 2010 were reported to have completed their treatment successfully. The global MDR-TB targets for 2015 will not be achieved unless barriers to the expansion of reliable diagnosis and effective treatment of MDR-TB are not urgently overcome in many countries. New diagnostics and medicines will be required to speed up this drive within the new WHO global strategy which now looks well beyond 2015. ***[Indian J Tuberc 2014; 61: 298-306]***

Key words: Tuberculosis, Multidrug-resistance, Diagnosis, Treatment, Control, Care, Targets, Strategy

INTRODUCTION

"Prevention of drug-resistant tuberculosis is relatively simple. It is a matter of good doctoring and adhering to a few straightforward rules." stated Sir John Crofton, the eminent figure in the field of tuberculosis (TB), in 1987.[1] Fast forward to World TB Day on 24 March 2013, when in a joint press release from the World Health Organization (WHO) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GF), headed "World Health Organization and Global Fund cite tuberculosis threat", Dr Margaret Chan, Director-General of WHO, stated that "We are treading water at a time when we desperately need to scale up our response to MDR-TB. We have gained a lot of ground in TB control through international collaboration, but it can easily be lost if we do not act now."[2]

In early 2012, WHO released its latest global roundup on multidrug-resistant tuberculosis (MDR-TB, defined as resistance to, at least, rifampicin and isoniazid).[3] The highest levels of MDR-TB ever documented have been reported in recent years. Globally in 2012, 3.6% of newly diagnosed tuberculosis (TB) cases and 20% of those previously treated for TB had MDR-TB [footnote[1]]. The highest risk of MDR-TB in TB patients is reported in eastern Europe and central Asia, where in some countries more than 20% of new TB cases and more than 50% of those previously treated for TB have MDR-TB.[4] In Belarus, for example, 32% and 76% respectively of new patients with TB and those previously treated for TB have MDR-TB.[5] By the end of 2013, 92 countries had reported at least one case of extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone and at least one second-line injectable agent).[4,6] An estimated 9.6% of MDR-TB cases have XDR"TB.[4]

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[1] A new case is a TB patient who has never received anti-TB treatment for active TB disease in the past or has completed less than one month of such a treatment. A previously treated case is a TB patient who has completed at least 1 month of anti-TB treatment for active TB disease in the past. It includes, among others, persons who relapse after a previous cure, or who present with TB after having interrupted treatment or after their previous treatment failed.

Despite the increased focus on tuberculosis as a public health problem since WHO declared it a global public health problem in 1993,7 with an estimated 8.6 million people developing TB and 1.3 million dying of the disease in 2012, TB still remains a major public health problem.[4] However, through effective public health action driven by political commitment and the required mobilisation of resources guided first by the WHO's DOTS Strategy and subsequently by the Stop TB Strategy, there has been major progress towards the 2015 targets established within the framework of the United Nation's Millennium Development Goals (MDG).[4,8-10] The TB incidence rate has been falling worldwide for about a decade at an average 2%/year, meaning that the MDG target has been achieved globally. By 2012, the TB mortality rate had fallen 45% compared with 1990, and the target of a 50% reduction by 2015 is within reach. Seven of the 22 high TB burden countries (HBCs) have already met all of the 2015 targets, and a further four are on track to do so by 2015. Treatment success – one of the most important indicators of global progress – reached 87% in 2011, up from 69% in 2000.[4]

The need to scale-up the diagnosis and effective treatment of MDR-TB was clearly recognized in the Global Plan to Stop TB 2006 - 2015.[11] The plan set a target to increase the number of MDR-TB treated to 100,000 per year by 2015, with all diagnosed patients being enrolled in programmes following international guidelines. Subsequently a more ambitious target was set out in the Global M/XDR-TB Response Plan that was launched in 2007.[12] In this plan, the target was to expand diagnosis and treatment such that 85% of TB patients with MDR-TB would be diagnosed and treated by 2015. The year 2009, saw two major events which increased the momentum and commitment to address the problems of M/XDR-TB. A ministerial conference held in Beijing, China in April 2009 brought together high level representatives from the 27 high MDR-TB countries that account for around 85% of the global MDR-TB cases, and led to a "Call to Action" on the part of the attending governments and international agencies.[13] Soon after, a resolution on MDR-TB was passed at the WHO's 62nd World Health Assembly (WHA) which called on all countries to implement the measures needed to achieve universal access to diagnosis and treatment of MDR-TB by 2015.[14] The major obstacles and approaches to controlling MDR-TB were described, and analyses of data from groups of countries pointed to a conclusion that MDR-TB could be set on a path albeit a slow one - to elimination.[15,16] An updated Global Plan to Stop TB 2011- 2015 was released in 2010, with the MDR-TB related goal of reducing the global burden of drug-resistant TB, and an overall target of a declining MDR-TB incidence by 2015.[17] The plan envisaged that 20% of new TB patients and 100% of previously treated TB cases would be tested for resistance to first line drugs each year by 2015, a total of about one million people placed on treatment for MDR-TB (between 2011 and 2015), and treatment success achieved in 75% or more of those treated.

However, of the 8.6 million people falling ill with TB in 2012, WHO estimates that only two-thirds were reported to public health systems.[4] For nearly three million (the one-third "missed"), it is unknown whether they reached health services, were diagnosed or received quality care. In addition, progress towards targets for universal access to diagnosis and treatment of MDR-TB (as called for by the WHA Resolution 62.[15] in 2009) is still modest, and in many countries the situation is serious enough to be described as a public health crisis. This despite the establishment in 2000 of the Green Light Committee to provide a mechanism for facilitated access to second-line drugs, inclusion of prevention and management of MDR-TB in the 2006 Stop TB Strategy, and issuance of guidelines and WHA resolutions from WHO.[6,9,14,18,19] How did this situation arise given the optimistic statement of Sir Crofton in 1987? What progress has been made in the intervening years and what do the future years hold?

METHODS

Source of data

The data used in this article were those officially reported by the countries to WHO using an online web-based system which has been in operation since 2009.[4] These data are submitted in

aggregated format by the representatives of the national authorities responsible for TB control. During and following submission, the data undergo validation until they are consolidated with legacy data in a single electronic register hosted by the Global TB Programme at the WHO Headquarters in Geneva, Switzerland. The data in this paper were as reported by countries until 30 June 2014.

Countries assign treatment outcomes to MDR-TB patients using definitions which were standardised in 2005.[20] For the purposes of this paper, treatment success refers to the total of cases who were cured or completed their treatment.

Indicators

MDR-TB estimates: The estimates of MDR-TB burden for the WHO's 27 "high MDR-TB burden countries" [Footnote[2]] presented in Table 1 are the number of MDR-TB cases who would be expected to be detected were drug-susceptibility testing (DST) for isoniazid and rifampicin to be performed routinely on all pulmonary TB cases notified in the country. It thus does not include those MDR-TB cases amongst TB cases which were not diagnosed (out of those estimated to have emerged) or who were diagnosed but not reported by the surveillance system in the respective country on which no information is available. The MDR-TB estimate is derived using the latest available value for the proportion of TB cases with MDR-TB and multiplying this proportion by the number of pulmonary TB cases notified by the respective country in 2012. The proportion of MDR-TB among TB cases is measured separately for new and previously-treated TB cases by drug-resistance surveys conducted on a nationally-representative sample of TB patients presenting for care.[22] Some countries use routine surveillance systems based on diagnostic DST to measure the proportion. In countries without a measured value, a modelled estimate is used based on observed data from countries considered to have a similar TB epidemiological profile. The point (best) value of the MDR-TB estimate is shown in Table.

Three sets of indicators are presented in Table to highlight progress in the efforts in scaling up services to address the MDR-TB burden in the respective country, namely:

1. *Detection*: Number of MDR-TB cases diagnosed and notified by a country in the years 2010 to 2012, expressed as (i) an absolute number and (ii) as a percentage of the 2012 point value of the MDR-TB estimate in the same year.

2. *Enrolment*: Number of TB cases with confirmed or presumptive MDR-TB reported by a country to have been placed on second-line TB treatment [footnote[3]] in the years 2010 to 2012 expressed as absolute numbers.

3. *Treatment outcomes*: Reported as the percentages of confirmed MDR-TB patients placed on treatment who had an outcome assigned as *treatment success* for the 2008 to 2010 patient cohorts. The denominator used in the calculation is all the MDR-TB cases started and followed up on treatment in the course of one calendar year ("cohort") and includes cases who are not evaluated owing to lack of information on the final outcome. Owing to the long duration of MDR-TB treatment, the monitoring of outcomes is performed 36 months after the start of the year of enrolment. Thus we present the outcomes for patients who started treatment in the years 2008 to 2010.

Detection, enrolment on treatment and treatment outcomes

The impressive global scale-up of rapid molecular diagnostics helped increase the detection of TB cases eligible for treatment in 2012 by 42% over 2011[footnote[4]].[4] However, these approximately 95,000 TB cases still only represented a 21%

[2] The 27 high MDR-TB burden countries refer to those Member States estimated by WHO in 2008 to have had at least 4,000 MDR-TB cases occurring annually and/or at least 10% of newly registered TB cases with MDR-TB.[21]

[3] Second-line TB treatment refers to the regimens used in the treatment of drug-resistant TB which include drugs from the second-line group and usually last 20 months or more.[23]

[4] This includes both confirmed MDR-TB cases (85,197) and confirmed rifampicin resistant TB cases (over 10,200).

Table: Estimated, notified, enrolment and treatment success of MDR-TB cases, by country and WHO region

Country	Best estimate of MDR-TB among notified pulmonary TB cases, 2012	Notified MDR-TB cases				Cases enrolled on MDR TB treatment			% Treatment success (patients in cohort)		
		2010	2011	2012	2012 % Notified / Estimated	2010	2011	2012	2008	2009	2010
Armenia	250	177	79	92	37	154	88	101	55 (77)	51 (134)	45 (132)
Azerbaijan	2 800	552	811	596	21	286	592	404	57 (23)	74 (100)	55 (286)
Bangladesh	4 200	339	509	513	12	339	390	513	83 (124)	63 (167)	75 (329)
Belarus	2 200	1 576	1 594	1 604	73	200	1 446	2 478	na	40 (1422)	31 (1442)
Bulgaria	100	56	55	49	49	56	42	36	23 (31)	19 (43)	16 (56)
China	59 000	2 792	1 601	3 007	5.1	1 222	1 155	1 906	46 (13)	46 (260)	42 (1222)
DR Congo	2 900	87	121	81	2.8	191	128	262	56 (202)	33 (177)	36 (105)
Estonia	70	64	78	62	89	63	75	54	48 (73)	41 (85)	47 (64)
Ethiopia	2 100	140	212	284	14	120	199	289	na	90 (73)	84 (114)
Georgia	630	359	475	346	55	618	737	665	56 (417)	54 (503)	54 (504)
India	64 000	2 967	4 237	16 588	26	2 967	3 384	14 143	43 (120)	53 (715)	34 (2182)
Indonesia	6 900	182	383	428	6.2	142	260	426	na	74 (19)	72 (140)
Kazakhstan	8 800	7 387	7 408	7 608	86	5 705	5 261	7 213	74 (2268)	73 (3897)	73 (5777)
Kyrgyzstan	1 800	566	806	958	53	566	492	775	50 (262)	35 (545)	42 (556)
Latvia	120	88	105	110	92	87	103	110	62 (128)	59 (131)	66 (88)
Lithuania	300	310	296	271	90	310	296	271	26 (276)	30 (322)	29 (310)
Myanmar	6 000	192	690	778	13	192	163	442	na	73 (64)	70 (188)
Nigeria	3 600	21	95	107	3	23	38	125	na	na	61 (23)
Pakistan	11 000	444	344	1 602	15	424	344	1 045	na	61 (74)	70 (195)
Philippines	13 000	522	1 148	679	5.2	548	2 397	1 918	53 (520)	54 (394)	42 (783)
Republic of Moldova	1 700	1 082	1 001	894	53	791	765	853	48 (522)	na	49 (791)
Russian Federation	46 000	13 692	13 785	13 612	30	13 692	18 902	18 452	51 (1537)	na	43 (4681)
South Africa	8 100	7 386	10 085	15 419	>100	5 402	5 643	6 494	48 (4383)	42 (4654)	40 (4882)
Tajikistan	910	333	604	694	76	245	380	535	na	71 (52)	62 (245)
Ukraine	6 800	5 336	4 305	6 934	>100	3 870	4 957	7 672	na	27 (3299)	29 (3902)
Uzbekistan	4 000	1 023	1 385	1 728	43	628	855	1 491	66 (294)	61 (464)	58 (628)
Viet Nam	3 800	101	601	273	7.2	101	578	713	na	73 (101)	78 (97)
High MDR TB burden countries	270 000	47 774	52 813	75 317	28	38 942	49 670	69 386	55 (11270)	48 (17695)	47 (29722)
WHO Regions											
African	38 000	9 340	12 390	18 156	48	7 209	7 467	9 386	50 (5496)	45 (6143)	46 (6176)
Americas	7 100	2 660	3 475	2 967	42	3 248	3 088	3 101	47 (1732)	47 (2298)	59 (2413)
Eastern Mediterranean	18 000	873	835	2 246	12	967	756	1 602	56 (262)	44 (511)	56 (676)
European	74 000	33 870	34 261	36 877	50	28 336	36 313	42 477	55 (7181)	48 (12133)	49 (20598)
South-East Asian	90 000	3 942	6 615	19 202	21	3 901	4 597	15 845	63 (413)	58 (1140)	46 (3113)
Western Pacific	74 000	4 295	4 394	5 749	7.8	2 210	4 946	6 342	58 (758)	57 (1027)	46 (2455)
Global	300 000	54 980	61 970	85 197	28	45 871	57 167	78 753	53 (15842)	48 (23252)	49 (35431)

na – not available; MDR-TB – multidrug-resistant tuberculosis; WHO – World Health Organization (for country classification by WHO Regions see data source reference 4)

coverage of the estimated 450,000 incident cases per year. Despite the number of notifications increasing in the 27 high MDR-TB burden countries from 47,774 in 2010 to 75,317 in 2012, only six countries (Estonia, Kazakhstan, Latvia, Lithuania, South Africa and Ukraine) notified 80% or more of the estimated cases in 2012 (Table).

Furthermore globally just under 79,000 of the patients eligible for MDR-TB treatment in 2012 were actually enrolled on treatment. There is thus a shortfall between global numbers of cases detected and those started on treatment; worryingly, gaps between numbers diagnosed and enrolled on treatment were observed to be growing in many countries, with patients reported to be on waiting lists for treatment in a number of countries.

Moreover, the global treatment success rate for MDR-TB is under 50% as a result of high levels of mortality and patients being lost to follow-up due to lack of effective services.[4] Globally, this indicator has not changed much between the cohorts of 2008 to 2010, even if the number of cases evaluated has increased markedly (Table). However, where high-quality care is provided, treatment success can surpass 70%.[24,25]

What the future holds for progress in scaling up access to diagnostic and management services for MDR-TB?

In 2013, WHO in its annual Global TB Report identified five priority actions to accelerate progress in TB control between now and the end of 2015, one of which targets drug-resistant disease:

i. To reach the estimated three million people with TB who are 'missed' by public health services each year;
ii. To address MDR-TB as a public health crisis;
iii. To accelerate the response to the TB/HIV epidemic;
iv. To increase financing to close all resource gaps, including *via* the full replenishment of the Global Fund; and
v. To ensure rapid uptake of new innovations.[26]

In each case, specific solutions are provided. For example, in high MDR-TB burden countries the increasing capacity to diagnose MDR-TB must be matched with supplies of quality drugs and scaled-up country capacity to deliver effective treatment and care; high-level political will and leadership as well as more collaboration among partners, including drug regulatory authorities, donors and technical agencies, civil society and the pharmaceutical industry.

Expansion of the introduction of molecular based diagnostics for DR-TB continues rapidly. As of March 2014, 2,343 GeneXpert machines (12,103 modules) and 6.3 million Xpert MTB/Rif cartridges have been procured in the public sector in 104 of the 145 countries eligible for concessional prices (Figure). Introduction of the Xpert MTB/RIF greatly facilitates the detection of TB and rifampicin resistance at decentralised (often district) levels, also outside conventional laboratory settings. However, additional laboratory capacity for DST of drugs other than rifampicin and for monitoring TB and MDR-TB treatment is needed. This requires both microscopy and culture services to be retained and optimised, with a remaining need for specialized laboratory infrastructure at the regional and/or national levels. Despite the great advance made with the availability of Xpert, the need for a simple, cheap and robust point of care diagnostic test for TB and drug resistance still remains. Also, whatever the current technique used, inadequate referral networks and inefficient commodity and supply chain management systems mean that most drug-resistant TB patients in low- and middle-income countries are still unable to access diagnostic services.

As highlighted by the growing waiting lists observed in a number of countries, currently alignment between diagnostic and management services is not in place. There has been impressive improvements in the global pooled procurement mechanism of second line drugs *via* the Global Drug Facility of the Stop TB Partnership (www.stoptb.org/gdf/), with an increase in the number of suppliers

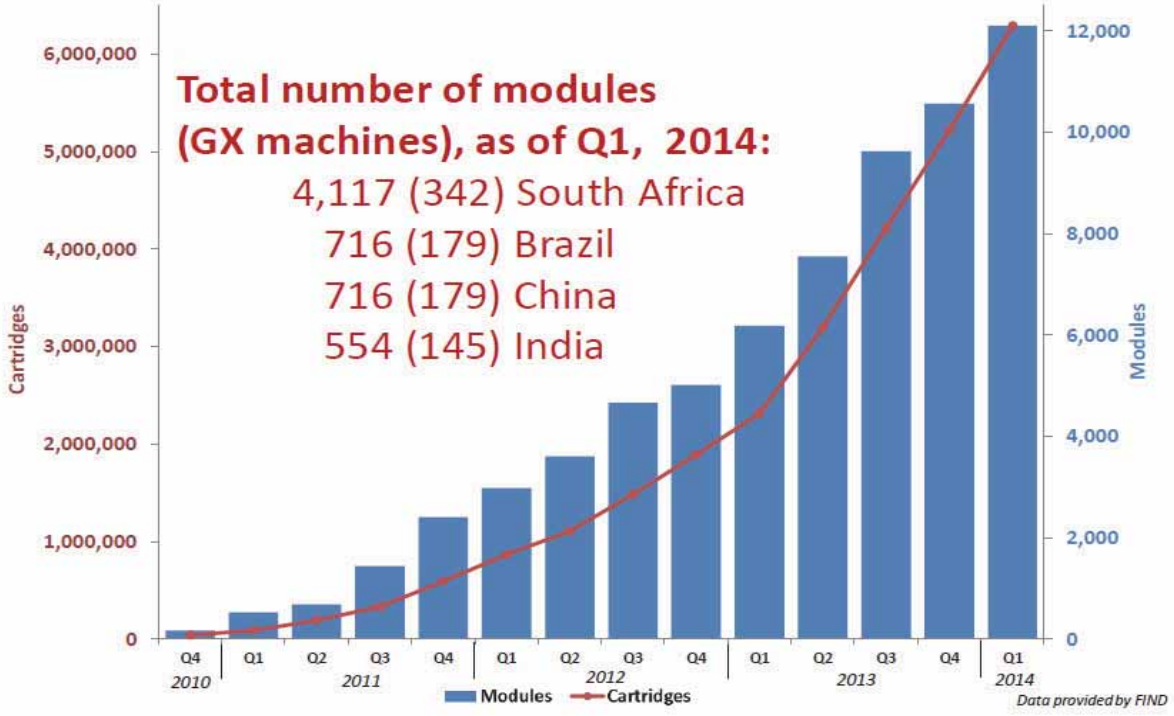

Figure: Cumulative number of GeneXpert instrument modules and Xpert MTB/RIF cartridges procured under concessional pricing

and the number of quality assured second line drug products available, and a price decrease of almost one-third of the drug regimens.27 However, treatment of an MDR-TB patient is still prohibitively costly for patients, their families, health systems and society at large. Current treatment regimens for drug-resistant TB are far from satisfactory. Whereas most patients with drug-susceptible TB can usually be cured with a 6-month course of treatment, in most MDR-TB cases, a treatment duration of 20 months or more is used, requiring the daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB. In addition, a significant proportion of MDR-TB patients may be infected with strains with additional resistance to fluoroquinolones and/or injectable drugs (aminoglycosides or capreomycin), rendering their treatment even more difficult, with recourse to highly toxic drugs. The lack of effective and affordable drugs for the treatment of MDR-TB is known to weigh heavily among the reasons that programmes cannot scale up their treatment efforts to the required level.

However, the landscape of drug development for treatment of TB has evolved dramatically over the last 10 years, and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB.[28] After 40 years of no new drugs for TB, bedaquiline, a diarylquinoline, was approved by the U.S. Food and Drug Administration in December 2012, and the WHO issued interim guidance for its use in the treatment of MDR-TB in June 2013.[29] Another new compound, delamanid, a nitro-imidazole, has been recommended for conditional marketing authorisation by the European Medicines Agency Committee for Medicinal Products for Human use in November 2013. WHO will be providing interim advice on the use of delamanid in MDR-TB treatment in the coming months. However

uptake by countries of bedaquiline has been slow, due mainly to a combination of cost and challenges to register the drug in countries. Lessons need to be learnt from the experience with the introduction of bedaquiline in order to speed up the introduction of other new drugs such as delamanid.

In addition to the introduction of new drugs, there is great interest shortening their treatment regimens. The results from an observational study in Bangladesh showed high rates of treatment success using regimens having a duration of 12 months or less compared with those usually achieved when the longer regimens are used.[30] However, there is much less evidence on the effectiveness and safety of these so-called "short-regimens" compared with regimens lasting 20 months.[31] Clinical trials (e.g. TB STREAM study) are underway to provide the required evidence on effectiveness and safety of these so-called "short-regimens" to inform future global policy making.[32] Interest is also being shown in the repurposing of existing drugs such as linezolid and meropenem-clavulanate for use in patients with MDR-TB and other advanced patterns of resistance. However, their use is restricted by the high cost of the drugs, methods of administration, adverse effects, and current limited evidence of their effectiveness and long-term safety.[33,34]

In addition to the challenges of ensuring an early diagnosis of MDR-TB and the availability of quality-assured and effective SLDs, there are many additional issues related to the strength of the health systems that are expected to deliver care for the MDR-TB patients. There need to be adequate and trained human resources available to deliver said services. These can be in the public or private health sectors, and in the community itself. The actual infrastructure to safely deliver the services, including in-patient facilities, are required to be in place with infection control measures implemented at all levels.[35] Information systems need to be strengthened with an increased focus on electronic systems which can enhance the management of data for patient monitoring including active pharmaco vigilance in patients on novel treatments.[36,37] All care needs to be patient-centred, and hence based on the requisite ethical and human rights standards, with the required social protection to protect against the catastrophic costs to patients and their families and to support adherence to treatment and care.[38]

Of the USD $7-8 billion per year required in low and middle income countries in 2014 and 2015, 20% is estimated to be needed for the treatment of MDR-TB and 10% for rapid diagnostic tests and associated laboratory strengthening.[4] Since 2002, there has been a noticeable increase in domestic funding for TB activities, and as a result in 2013, 87% of the USD $6.1 billion funding available was from domestic sources. However this total figure falls well short of the amounts needed to mount a full response to the TB epidemic up to 2015. In 2013, there remained an estimated USD $1 billion gap in funding for TB activities, of which 13% was for MDR-TB activities. The so-called BRICS countries (Brazil, the Russian Federation, India, China and South Africa) are relatively self-sufficient, although India is an exception with a minority of funds coming from domestic sources. With the majority of MDR-TB cases estimated to live in upper-lower and middle income countries, international donor agencies need to be flexible in their future financing mechanisms to ensure that especially middle income countries can continue to access funding, even as they transition to higher economic status.

CONCLUSIONS

Despite an increase in the numbers of MDR-TB cases detected and placed on treatment in recent years, overall progress is slow and lagging far behind the global targets set. Progress in achieving universal access to diagnostic and management services for MDR-TB patients will require a refocused commitment from both national governments and international agencies, including the commitment of the required funding. Multisectoral collaboration and coordination will be crucial. Alignment of the scale-up of diagnostic capacity and treatment capacity is needed, whilst accelerating the uptake of new tools and strategies. The removal of existing inefficiencies in the current health systems is a fundamental requirement for achieving the targets set in global plans and strategies. These concepts, as well as others relating to broader concerns in TB

control (eg, social protection), will remain relevant for TB and MDR-TB control into the future. As a result, they have been firmly rooted across the three pillars of the post-2015 TB strategy, that has been endorsed by the World Health Assembly in May 2014.[39]

> "The day when we will be able to provide access to care for M/XDR-TB in the bush of Swaziland and other remote inaccessible places will be the start of the elimination of MDR-TB from the world"
> Dr Mario Raviglione, Director, Global TB Programme, WHO Geneva, at the Global Laboratories Initiative's Annual Global Meeting, 29 April 2014.

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Original Article

STUDY TO EVALUATE IMPACT OF IEC ACTIVITIES ON AWARENESS OF TUBERCULOSIS AND RNTCP-DOTS AMONG OPD PATIENTS AROUND BATHINDA AREA

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Summary

Introduction: Tuberculosis (TB) is still a major public health problem in India. This study was aimed to know the awareness and impact of Information, Education, Communication (IEC) activities about TB and RNTCP & DOTS among general population around Bathinda area of Malwa region of Punjab through patients attending chest OPD of a tertiary care hospital attached to a medical college of this region.

Material & Methods: A cross-sectional study was conducted in above stated hospital from 1st June, 2012 to 31st May 2013, for a period of one year using a questionnaire and a pictorial poster, which was pilot-tested and results were included in the main study.

Results: A total 0f 19259 patients attended chest OPD in the given time period. It included 11412 (59%) male and 7847(41%) female patients. Average age of the patients was 46.8 years. Majority of patients were in the age-group of 26-50 years which is a most active and economically productive age group.

Conclusion: Although this study shows that knowledge about symptoms, mode of transmission of infection, treatment under RNTCP by DOTS is satisfactory but still IEC activities for RNTCP and DOTS need more and more and repeated sensitization of the general population. It is recommended that such studies are to be conducted for better implementation of RNTCP and DOTS programme in the country, particularly in the light of HIV and drug resistant Tuberculosis. ***[Indian J Tuberc 2014; 61: 307-311]***

Key words: Awareness, Tuberculosis, RNTCP, DOTS, Knowledge.

INTRODUCTION

The foreword of the book "Clinical Tuberculosis" written by Sir John Crofton is still appropriate to sum up the current scenario of the global epidemic of Tuberculosis. It states, "It is the sad reflection of the society's incompetence that more than thirty years after the methods for cure and prevention were evolved and before the advent of HIV/AIDS pandemic there were more patients with active tuberculosis in the world than there had been in 1950.[1] Tuberculosis is a public health problem in India accounting for one-fifth (21%) of the global Tuberculosis burden with over two million incident cases annually.[2] In 1962, national tuberculosis control programme (NTCP) was incorporated with general medical and health services of Government of India. This programme was reviewed after 30 years in 1990-92, and it was found that it had not fulfilled its targets. Success rate of cure was as low as 8% due to poor supply of drugs, poor diagnostic methods, poor regimens, poor patient compliance and poor planning. New policies and planning were put into the programme with the name of revised national tuberculosis control programme (RNTCP) after a pilot project tested programme in 1990-1995. Information, Education and Communication, 'IEC' as per World Health Organization, are defined as a public health approach to change/ reinforce health related behaviour in target audience within a predefined period of time through communication methods and principles. Target audience was divided into Primary, Secondary and Tertiary Audience. IEC activities for RNTCP and DOTS were started along with this programme to educate, inform and sensitize the community to create awareness about Tuberculosis and RNTCP-DOTS.

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Communication skills are a vital philosophy in the development of any health programme. With the implementation of RNTCP-DOTS in 1992-94, it was felt that success of this programme depends on the acceptance of the programme by the community. These activities were monitored by Central Tuberculosis Division (CTD), the State Tuberculosis Societies and District Tuberculosis Societies. Introducing a professionally managed IEC campaign was one of the main strategies to achieve the objectives of RNTCP. Feedback data were collected through various mechanisms to improve the activities for the programme.

Every year 1.8 million persons develop this disease of which eight lacs are infectious, 3.7 lacs die- truly a captain of deaths. An estimated 100 million workdays are lost due to this disease, 3000 children are dropped out from schools and 1000 women from families. Society and country also incur a huge loss of nearly three billion USD indirect cost and 300 million USD direct cost.[3] RNTCP's success - case finding and cure- depends on the passive reporting of chest symptomatics to the health institutes.[4] One essential step for adequate containment of TB is to ascertain the understanding of its risk factors, mode of spread and diagnosis by the society.[5] Therefore, it is very important that basic knowledge about TB, its causative agent, signs and symptoms should be known in the community. Unless they possess basic knowledge about tuberculosis and its management, they are not likely to make the best use of the available facilities.[6] It is the need of the hour to review repeatedly about awareness of tuberculosis and its programme in the community so as to prevent one more pragmatic failure which our country cannot afford due to its limited resources. The present study was planned and conducted aiming to test the knowledge and awareness about TB and RNTCP-DOTS among the patients attending Chest OPD in a tertiary-care medical college hospital in Bathinda-Punjab.

AIM AND OBJECTIVE

1. To know the awareness of the patients regarding TB.
2. To know the impact of IEC activities of RNTCP-DOTS programme in the community.

MATERIAL AND METHODS

This was an observational and descriptive type of epidemiological study. The study design was cross-sectional. Study setting was the chest outpatient department of a tertiary care medical college and hospital of Punjab. Target Audience in this study was primary audience. It was carried out for one year i.e. from 1st of June 2012 to 31st May 2013. All the patients who attended the chest OPD during this period were included in this study. A pre-designed, pre-tested anonymous questionnaire containing both written questions about TB in vernacular language and pictorial representation about RNTCP-DOTS was administered to the patients. The questions were adapted from the literature available i.e. RNTCP-DOTS module and its operational guidelines. It had 10 questions on general knowledge, risk factors, diagnosis and treatment of TB. Pictorial representations were taken from the charts of RNTCP programme, Government of India media division. A pilot study was done on first 100 patients and its results were included in the main study. Necessary corrections and modifications were adopted in the Proforma for the main study. The collected data was tabulated, analyzed and interpreted by using Microsoft Excel programme. Percentages were calculated wherever required. Patients who answered 25% questions correctly were categorized as having 'Poor' knowledge, up to 50% questions as Average knowledge, 75% questions as good and more than 75% as very good awareness for TB and RNTCP-DOTS programme.

RESULTS

A total of 19259 patients attended the chest OPD in the given time period. It included 11412 (59%) male and 7847 (41%) female patients (Table 1). Their age ranged from 15 – 99 years with a mean age of 46.8 years and Standard Deviation (SD) 13.65 years. There were 1513 (7.8%) patients in the age group of less than 25 years and 10760 (56%) patients in the 26-50 years' age group. Age group 51-75 years had 6680 (35%) and there were only 306 patients in the last age group i.e.>75 years.

Table 1: Age-Sex wise distribution of the patients (n=19259)

Sex	Age (in years)				
	Up to 25	26-50	51-75	>75	Total (%)
Male	777 (4.03)	5840(30.32)	4545(23.59)	250(1.29)	11412(59.25)
Female	736(3.82)	4920(25.54)	2135(11.08)	56(0.29)	7847(40.75)
Total	1513(7.85)	10760(55.86)	6680(34.67)	306(1.58)	19259(100.0)

Figures in parenthesis indicate percentage of total patients (n=19259)

Findings related to awareness about TB and RNTCP (Age and sex-wise separately) are shown in tables 2 and 3.

- 2124 (11%) patients had very good knowledge and awareness about TB and RNTCP, out of which 1099 were males and 1025 males.
- 9930 (52%) patients had good knowledge and awareness about TB and RNTCP; there were 5519 (56%) males and 4411 (44%) females.
- 6900 (36%) patients had average knowledge and awareness about TB and RNTCP (4547male and 2353 female patients).
- Very few patients i.e. 306 (1.5%) had poor knowledge and awareness about TB and RNTCP (Table 3).

Most of the patients had traditional source of information about TB. Many had come to know through posters put on various peripheral health institutions (PHIs). Some of them learnt from visual

Table 2: Age-wise distribution of the patients (n=19259)

Age (years)	Knowledge -Awareness				
	Poor	Average	Good	Very Good	Total (%)
Up to 25	115 (0.60)	21 (0.10)	50 (0.26)	1327 (6.89)	1513 (7.85)
26-50	9 (0.04)	856 (4.44)	9133 (47.42)	763 (3.96)	10760 (55.87)
51-75	8 (0.04)	5907 (30.67)	732 (3.80)	33 (1.71)	6680 (34.68)
>75	174 (0.90)	116 (0.60)	15 (0.07)	1 (0.005)	306 (1.58)
Total	306 (1.5)	6900 (35.7)	9930 (52)	2124 (11.0)	19259 (100.0)

Figures in parenthesis indicate percentage of total patients (n=19259)

Table 3: Sex-wise distribution of the patients (n=19259)

Sex	Knowledge -Awareness				
	Poor	Average	Good	Very Good	Total
Male	248 (1.28)	4547 (23.60)	5519 (28.65)	1099 (5.70)	11412 (59.25)
Female	58 (0.30)	2353 (12.22)	4411 (22.90)	1025 (5.31)	7847 (40.74)
Total	306 (1.58)	6900 (35.42)	9930 (52)	2124 (11)	19259 (100.0)

Figures in parenthesis indicate percentage of total patients (n=19259)

communication media like television, films hoarding, etc. It was seen that female patients had less knowledge as compared to male patients.

- 2124 (11%) patients had very good knowledge and awareness about TB and RNTCP.
    - 1327 patients in age group "< 25 years" (87.70 % of 1513 patients),
    - 763 patients in age group "26-50 years" (7.09 % of 10760 patients),
    - 33 patients in age group "51-75 years" (0.50 % of 6680 patients),
    - 1 patient in age group "> 75 years" (0.32 % of 306 patients).
- 9930 (52%) patients had good knowledge and awareness about TB and RNTCP.
    - 50 patients in age group "< 25 years" (3.30 % of 1513 patients),
    - 9133 patients in age group "26-50 years" (84.87 % of 10760 patients),
    - 732 patients in age group "51-75 years" (10.95 % of 6680 patients),
    - 15 patients in age group "> 75 years" (4.90 % of 306 patients).
- 6900 (36%) patients had average knowledge and awareness about TB and RNTCP.
    - 21 patients in age group "< 25 years" (1.38 % of 1513 patients),
    - 856 patients in age group "26-50 years" (7.95 % of 10760 patients),
    - 5907 patients in age group "51-75 years" (88.43 % of 6680 patients),
    - 116 patients in age group "> 75 years" (37.90 % of 306 patients).
- 306 (1.5%) patients had poor knowledge and awareness about TB and RNTCP.
    - 115 patients in age group "< 25 years" (7.60 % of 1513 patients),
    - 9 patients in age group "26-50 years" (0.08 % of 10760 patients),
    - 8 patients in age group "51-75 years" (0.12 % of 6680 patients),
    - 174 patients in age group "> 75 years" (56.86 % of 306 patients). (Table 2)

It showed that our IEC activities were being well received by the younger generation.

DISCUSSION

India is among the highest TB burden countries in the world.[2] This disease is more prevalent in developing countries with poor economy, limited infrastructure, overcrowding and undernourishment.[7] RNTCP is a passive process limited to the chest symptomatics in the community who attend the health institutions on their own for relief of symptoms. Therefore, it is essential that community at large and younger generation in particular are aware about the basic facts about tuberculosis.[6] It was very alarming that even today there was tendency to discriminate tuberculosis patients.[8] Further, ignorance and incomplete knowledge lead to all kinds of prejudices, social taboos and stigma on one hand and improper response by patients to fight their disease on the other hand. RNTCP is characterized by free diagnosis and treatment of tuberculosis. However, the mass survey carried out by CTD, Ministry of Health, Government of India, reported poor level of awareness among general population. A study done in urban slums in Puducherry showed that 16% patients were not aware of the free treatment for TB. Treatment for TB is costlier in private settings pushing the family into poverty trap, and it may lead to treatment default after a few weeks of treatment.[9] In our study we found that 62.8% of chest OPD patients had good and very good knowledge about TB programme. This may be due to the type of hospital where these patients reported for relief of their symptoms i.e. a tertiary care hospital. Similar results were seen in some other studies also.[10,11] There were more male than female patients in this study. Similar observations were made in a study carried out in Delhi[12] and in NFHS-3 data . In this study, 56% of patients reported in 26-50 years age group. It is well documented in the literature that TB affects maximum male patients and that too in economically productive age group.[13] However survey carried out in Delhi[12], reports highest prevalence in > 55 years of age. It was seen that

87.7% of under-25 years of age group patients scored more than 75% correct responses in the administered questionnaire. It shows that our health education activities on RNTCP are being received well in the younger population, may be due to more education level and being more receptive to mass-media activities like watching television and using internet, etc. Further strengthening of IEC activities will help in the control of TB as this younger age group is going to be sexually active and there is danger of increasing TB and HIV/AIDS. Free diagnosis and free treatment of TB should be known to all, and it will help in improving the health seeking behaviour and adherence to treatment of TB. Social issues such as stigma associated with TB have to be dealt with during health education sessions.[9]

CONCLUSION AND RECOMMENDATIONS

This study revealed that although knowledge regarding symptoms, mode of transmission and aetiology was satisfactory, there is still a great need to educate females and older individuals about TB and RNTCP. Repeated and multiple efforts are required to reinforce the messages in the community. Attempts should be made to improve the awareness about TB and RNTCP-DOTS, to remove myths and misconceptions and to allay the social stigma attached with TB. The AYUSH and other such NGOs, corporate and private practitioners delivering health services to the societies should be involved in this programme. It is also recommended that such studies need to be carried out in many more institutions to evaluate awareness in the community about RNTCP-DOTS and TB.

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Original Article

GENITAL TUBERCULOSIS: AN IMPORTANT CAUSE OF ECTOPIC PREGNANCY IN INDIA

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Summary

Objective: To assess the role of genital tuberculosis as an etiological factor for ectopic pregnancy.

Method: A total of eighteen women of ectopic pregnancy with concomitant female genital tuberculosis and a total of one hundred thirty six patients of ectopic pregnancy over a period of three years were enrolled.

Results: Mean age of patients with ectopic pregnancy and concomitant female genital tuberculosis was twenty-six and mean parity was 0.7. Most of these patients were in poor socio-economic group. Diagnosis of female genital tuberculosis was made by presence of granuloma in histopathological examination of endometrial aspirate or tubal specimen, positive acid fast bacilli in microscopy or culture, positive polymerase chain reaction in endometrial tissue and positive findings of genital tuberculosis during laparoscopy or laparotomy. Genital tuberculosis was responsible for 13.2% of all cases of ectopic pregnancy in the present study.

Conclusion: Genital tuberculosis appears to be an important cause of ectopic pregnancy in India.

[Indian J Tuberc 2014; 61: 312-317]

Key words: Genital tuberculosis, Ectopic pregnancy, Laparoscopy, Laparotomy.

INTRODUCTION

Nearly one third of the world population (estimated 1.7 billion) is infected with *Mycobacterium tuberculosis* out of which about 10% progress to clinical disease with 1.3 million deaths annually.[1,2]

Female genital tuberculosis (FGTB) is an important type of extrapulmonary tuberculosis which causes significant morbidity in the form of menstrual dysfunction, infertility, ectopic pregnancy and tubo-ovarian masses.[3-5]

FGTB has been described as a disease of young women with 80-90% women being diagnosed between the age of 20-40 years, especially in developing countries[6,7] as compared to premenopausal women over the age of 40 years in western countries.[8-9] Fallopian tubes constitute the initial focus of genital tuberculosis in majority of cases with bilateral tubal involvement and endosalphinx is usually involved causing tubal blockage and peritubal adhesions.[10]

Ectopic pregnancy is a significant cause of maternal morbidity and mortality, especially in developing countries where women often present late to the hospitals.[11-13] Most (about 95%) ectopic pregnancies occur in fallopian tubes while the rest occur in ovaries, cervix, caesarean scar, broad ligament, and abdominal cavity.[11-14] Combined intrauterine and extrauterine pregnancy (heterotropic pregnancy) is rare in spontaneous pregnancies but has been reported to be high (1-3%) in assisted reproduction.[14] Etiological factors include interference with the cilliary function of the fallopian tubes with pelvic inflammatory disease (especially due to chlamydial infection) being the commonest risk factor followed by endometriosis, previous tubal surgery, infertility and infertility treatment.[11,15,16]

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Genital tuberculosis is an important risk factor for ectopic pregnancy in developing countries like India where it is very common also.[6,17-19]

In his review on 7000 cases of genital tuberculosis from the literature, Schaefer[6] observed full term pregnancies in 155 (2.2%) abortions in 67(0.9%) and ectopic pregnancies 125 (1.8%) patients.

Tripathy *et al* also observed poor pregnancy outcome and higher ectopic pregnancy rate in genital tuberculosis.[18] Bapna *et al*[17] observed ectopic pregnancy needing laparotomy in nine out of 82 patients with FGTB(1.09%) making it an important cause of ectopic pregnancy in India.

MATERIAL AND METHODS

The present study was performed between January 2010 to December 2012 on 18 women with ectopic pregnancy and found to have concomitant female genital tuberculosis, admitted in Unit 3 of the Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi and from Santosh Medical College, Ghaziabad, Uttar Pradesh. The study was part of a larger ongoing study on diagnosis and management of FGTB for which ethical clearance had been obtained from the institute ethical committee. Written informed consent was obtained from all the subjects. Another 118 women who underwent expectant, medical or surgical management for proven ectopic pregnancy but without evidence of FGTB clinically, on laparoscopy/ laparotomy or on evaluation of endometrial sample, were taken as controls.

The main research question of the study was whether or not the FGTB(FGTB) causes increased incidence of ectopic pregnancy in India and is involved in the etiopathogenesis of ectopic pregnancy.

A detailed history was taken and a general physical examination and abdominal examination was performed on all women. All women underwent urine pregnancy test followed by quantitative serum âhCG level measurement. Transvaginal ultrasound (TVS) was performed on all women which confirmed the finding of empty uterus and adenexal mass with gestational sac with or without fetal cardiac activity.

Patients were managed for their ectopic pregnancy by expectant management, medical management or surgical management as per protocol of the hospital depending upon their general condition, beta HCG value and ultrasound findings. During laparoscopy and laparotomy, pelvis and abdomen were thoroughly visualized for any other finding apart from ectopic gestation, especially for evidence of FGTB like tubercles on fallopian tubes, ovaries or peritoneum, any tubo-ovarian mass, caseous nodules, encysted ascites, other pelvic mass, finding on tubes like hydrosalpinges, payosalpinges, beaded or blocked tube as reported in our previous study on the subject.[20] Endometrial samples were taken for microscopic examination for AFB, AFB culture, histopathological evidence of TB granuloma and polymerase chain reaction in only those cases with positive finding of FGTB on laparoscopy or laparotomy and in patients who were managed conservatively or medically. Biopsies were not taken from control cases due to financial constraints as testing the PCR and BACTEC was expensive. Biopsy was also taken from suspicious nodules on peritoneum during laparoscopy/laparotomy and sent for histopathological examination. Women with laparoscopic/laparotomy finding of TB with evidence of TB on endometrial or peritoneal biopsy were diagnosed as FGTB with ectopic pregnancy. Among patients managed medically, four had evidence of TB on endometrial biopsy (two with positive AFB culture, two with epithelioid granuloma in histopathology) and were also labelled as ectopic pregnancy with FGTB. Three of these patients underwent laparoscopic salpingectomy after failed medical management. All of these women (ectopic pregnancy with FGTB), after immediate management of ectopic pregnancy (medical or surgical depending upon clinical scenario) were started on category I directly observed treatment short course (DOTS) anti-tubercular therapy (ATT) under Revised National Tuberculosis Control Programme (RNTCP) from local DOTS centre.

All women receiving ATT were followed up regularly for any side effect of the treatment. Taking

alpha and beta error into consideration, a sample size of 15 cases of genital tuberculosis in ectopic pregnancy was calculated in the study group. Considering loss of follow up of 10-15%, we took 18 cases in study group and 118 cases which occurred at the same size in control group.

The results of women with ectopic pregnancy with FGTB were compared with women having only ectopic pregnancy. Statistical analysis was done using SPSS software version 12.0 (SPSS Chicago, IL, USA) with p value <0.05 taken as statistically significant.

RESULTS

There were 18 women in study group (women with ectopic pregnancy with FGTB) and 118 women in control group (women with only ectopic pregnancy). The comparison of women in these two groups is shown in table 1. There was no significant difference in the mean age of women in two groups. However, mean parity was 0.7 in study group compared to 1.8 in control group which was statistically significant (p=0.032). Similarly, socio-economic status as per modified Kuppuswami classification was different in two groups. There were significantly more poor women (77.3%) in the study group as compared to control group (46.6%) while moderate status was seen in 22.2% and 40.7% and rich status was seen in 0% and 12.7% cases respectively. There was statistically significant difference in number of poor women between two groups (p=0.024). Table 2 shows various methods of diagnosis of FGTB in study group. All cases of study group had positive findings of FGTB on laparoscopy/laparotomy as per author's previous study in this subject. Endometrial aspiration was positive PCR in all 18 cases while AFB was seen in microscopy and AFB culture was positive in three (16.6%) cases each and histopathological examination showed granuloma in seven cases (38.8%). There was positive epithelioid granuloma on peritoneal biopsy and tubal specimen in two cases (11.1%). Biopsies were not from control cases due to financial constraints

The management of ectopic pregnancy in the study and control groups is shown in table 3.

Expectant and medical management was successful in significantly higher number of cases in control group as compared to study group. Laparoscopic surgery (salpingectomy or salpingostomy) was performed in higher percentage of cases in study group (47.5%) as compared to cases in control group (33.3%), which is a statistically significant difference (p=0.03). Laparotomy had to be performed in 61% cases of study group while 22% cases of control group had

Table 1: Characteristics of women in two groups

Serial No		Group 1 (n=18)	Group 2 (n=118)	P Value
1. Age	Range	18-42	20-39	0.32
	Mean	26.5	29.54	
2. Pariety	Range	0-4	0-6	0.03
	Mean	0.7	1.8	
3.Socioeconomic status	Rich	0(0%)	15(12.7%)	
	Moderate	4(22.2%)	48(40.7%)	
	Poor	14(77.3%)	55(46.6%)	0.02

Table 2: Diagnosis of genital tuberculosis in study group (18 cases)

Serial No.	Tests done	Positive cases	percentage
1.	Endometrial aspirate		
	I. Acid fast bacilli on microscopy	3	16.6%
	II. AFB culture	3	16.6%
	III. PCR	18	100%
	IV. Epithelioid granuloma on histopathology	7	38.8%
2.	Epithelioid granuloma on tubal specimen or peritoneal biopsy	2	11.1%
3.	Finding of genital TB on laparoscopy/laparotomy(Tubercles, straw colored fluid, pelvic adhesions)	18	100%

Table 3: Management of ectopic pregnancy in patients

SERIAL NO	STUDY GROUP (n=18)	CONTROL GROUP (n=118)	P VALUE
1.EXPECTANT MANAGEMENT	0(0%)	8(6.7%)	0.0125
2.MEDICAL MANAGEMENT	1(5.5%)	28(2.7%)	0.0215
3.LAPAROSCOPIC SURGERY	6(33.3%)	56(47.51%)	0.035
a.unilateral salpingectomy	6(33.3%)	52(44%)	
b.salpinsostomy	0(0%)	4(3.3%)	
4.LAPAROTOMY	11(61.1%)	26(22%)	0.010
a. unilateral salpingectomy	11(61.1%)	22(20.3%)	
b.salpinsostomy	0(0%)	2(1.6%)	
5.BLOOD TRANSFUSION	18(100%)	107	
a.no blood transfusion	0(0%)	11(9.3%)	0.001
b.one unit	3(16.6%)	88(74.5%)	0.002
c.two units	13(72.2%)	19(16.1%)	0.002
d.three or more units	2(11.1%)	0(0%)	0.002

laparotomy, the difference being statistically significant (p=0.01). These were due to higher number of patients in study group with pelvic adhesion which made laparoscopy difficult.

The need for blood transfusion and number of blood transfusions required was significantly higher in women with ectopic pregnancy with FGTB. Two or more units of blood transfusion was required in 72.2% cases of study group as compared to 16.1% cases in control group (p=0.002).

DISCUSSION

Ectopic pregnancy is responsible for significant maternal mortality, morbidity and gynaecological emergencies in developing countries with an incidence of about 1.5%.[11]

Ectopic pregnancy is more common in age group 26-30 years.[11] The commonest associated etiological factor is previous tubal infection due to pelvic inflammatory disease (actually due to Chlamydial trachomatis) which could be due to previous induced abortions followed by pelvic infection.[11] Other causes include assisted reproduction, dysfunction in tubal smooth muscle activity and embryonic abnormalities.[11,15] FGTB is an important cause of ectopic pregnancy especially in developing countries where its prevalence is also high. Tripathy *et al*[18] observed only 19.2% conception rate in genital TB with live birth rate being only 7.2% and the rest being miscarriages and ectopic pregnancies.

Schaefer[6] *et al* also observed 1.8% ectopic pregnancy rate in his review on 7000 women on genital tuberculosis. Bapna *et al* also observed 1.09% ectopic pregnancies in their study on FGTB necessitating laparotomy.

In a recent study from India, Banerjee *et al*[19] found genital tuberculosis to be high (32.29%) on endometrial aspirate in 17 adolescent subjects with ectopic pregnancy in contrast to only 5% in miscarriages cases confirming that FGTB is an important cause of ectopic pregnancy in India.

We observed that out of total 136 cases of ectopic pregnancy, 18 women had concomitant FGTB making it responsible for 13.2% of all cases of ectopic pregnancy as was confirmed by finding of FGTB on laparoscopy and positive AFB on microscopy, culture or positive PCR. We also observed more need for blood transfusion in cases of surgical management of FGTB with ectopic pregnancy cases as compared to ectopic pregnancy alone possibly due to increase in adnexal adhesion, especially vascular adhesions. The results are consistent with our previous studies in which we found more difficulties and increased complications while performing various surgeries like hysteroscopy, laparoscopy, laparotomy and vaginal hysterectomy in women of FGTB.[20-24] There was also higher prevalence of pelvic and peri hepatic adhesions (Fitz Hugh Curtis syndrome) in FGTB as referred by us in our previous study.[25]

The limitation of our study was that due to financial constraints we could not do testing for Chlamydia or neisseria gonorrhoea in women. We relied on laparoscopy or laparotomy findings to exclude FGTB. We did not perform endometrial biopsy in control cases with negative findings of genital TB on laparoscopy or laparotomy, because of financial limitations. It may be that the incidence of FGTB may have been higher if we had done EA for AFB, histopathology and PCR in all the cases of ectopic pregnancy.

To conclude, our study highlights the role of FGTB as an important cause of ectopic pregnancy in India contributing to 13.2% cases. Hence, FGTB should be meticulously looked for in all cases of ectopic pregnancy during laparoscopy and laparotomy and suspected cases should be subjected to endometrial aspiration for FGTB testing so that timely and appropriate treatment of FGTB can be started to avoid further damage to fallopian tube and to avoid its long term sequelae.

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Original Article

PROFILE OF ADVERSE DRUG REACTIONS IN DRUG RESISTANT TUBERCULOSIS FROM PUNJAB

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Summary

Objective: The aim of the study was to elucidate the profile of adverse drug reactions (ADRs) associated with second-line anti-tubercular treatment for drug-resistant tuberculosis.

Material and methods: ADR profile of diagnosed drug-resistant tuberculosis cases on supervised second-line anti-tubercular drug regimen under Programmatic Management of Drug-resistant Tuberculosis under Revised National Tuberculosis Control Programme, were studied over two years' period. Adverse reactions were categorised into mild, moderate and severe types with subsequent systematic data-analysis.

Results: Out of total 207 patients in the study, 81.16% reported with adverse drug reactions. Out of total 195 adverse events, 63.58%, 18.46% and 17.94% were of mild, moderate and severe types respectively. Gastrointestinal events, hepatitis, hearing impairment, arthralgia, psychosis, hypothyroidism, visual disturbances, giddiness, peripheral neuropathy, skin reactions, swelling or pain at injection site, anorexia and sleep disturbances were important amongst these. High proportion of drug and/or alcohol abuse was an important observation. The offending drug(s) had to be terminated in 12.08% of the patients.

Conclusion: Early detection, management and pharmaco-vigilance reporting of ADRs remain key factors in the management of drug-resistant tuberculosis with remarkable relevance of the need for early diagnosis and treatment of 'drug-sensitive tuberculosis', to prevent emergence of drug-resistant tuberculosis. ***[Indian J Tuberc 2014; 61: 318-324]***

Key words: Drug-resistant TB, Adverse drug reactions

INTRODUCTION

Management of drug resistant tuberculosis (DRTB) requires prolonged and harsh chemotherapy using second-line drugs (SLDs) that are more toxic and less efficacious.[1] The available data from the several drug resistance surveillance studies conducted in the past suggest the prevalence of multi-drug resistant tuberculosis (MDR-TB) to the tune of 1-3% in new cases and around 12% in retreatment cases in India.[2,3]

Though India is the second-most populous country in the world after China, more than one-fifth of the global incident tubercular cases occur in India annually[4], with immense consequences. Accordingly, the DRTB case percentage amongst them translates into a large absolute number of such cases in the nation, posing a major threat in control of tuberculosis. Furthermore, treatment of DRTB is almost invariably associated with various ADRs which pose numerous challenges, worsening the disease scenario, affecting the cure rates and outcome and resulting in escalation of disease in the community. The severity of ADRs sometimes warrant reduction in the drug dosage or stoppage of the offending drug(s) temporarily or even permanently, which further curtails the drug options from the already almost exhausted armamentarium of anti-tubercular drugs, making the fight against the disease still more tough and hard to win. Cure is possible but prolonged treatment with less effective, more toxic and more expensive therapies[5] (born by the nation) with the fear of impending ADRs are the hallmarks of DRTB treatment.

The side-effect profile of the SLDs in DRTB cases is further worsened in patients with concurrent seropositive HIV infection, prior history of hepatitis/ jaundice, renal involvement, drug and/or alcohol abuse, diabetes mellitus, mental illness, thyroid disorders, malnutrition, pregnancy and lactation, etc.[1]

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After discharge from the hospital after initiation of second-line drug chemotherapy, major part of the treatment administration is carried out at home by the health worker, these ADRs sometimes remain unrecognised or are reported very late, leading to dire consequences.

The treating physician and attending health staff should be well versed with such ADRs, so as to detect these at the earliest, lest the patient is lost to follow up or stops the therapy, increasing the disease mortality and its spread in the family and the society. The literature reports very few studies regarding ADRs due to SLDs in drug resistant tuberculosis.

Revised National Tuberculosis Control Programmeme (RNTCP) introduced the Programmematic Management of Drug Resistant Tuberculosis (PMDT) services since 2007 in India to address the problem of MDR-TB in the country following the internationally recommended guidelines.

AIM

Keeping in view the enormity and seriousness of the prevailing situation (with large absolute number of DRTB cases in the community), the aim of the present study was to elucidate the profile of the ADRs associated with second-line treatment which invariably affects and poses serious challenges while managing DRTB, lest we confront a situation of 'MDR-TB epidemic' in future.

MATERIAL AND METHODS

The study was conducted on diagnosed DRTB cases admitted to the DRTB centre, Chest Diseases and Tuberculosis Hospital, Government Medical College, Amritsar (Punjab), put on second-line anti-tubercular drugs as category 4 regimen or were referred to this institution for the management of ADRs during second line chemotherapy under Programmematic Management of Drug Resistant Tuberculosis (PMDT) from other areas during the period of 1st February 2012 to 1st February 2014.

Under the Revised National Tuberculosis Control Programmeme (RNTCP) with PMDT in India, an MDR-TB case is defined as a tubercular patient in whom *Mycobacterium tuberculosis* is resistant *in vitro* to isoniazid and rifampicin with or without other anti-tubercular drugs based on DST results from an RNTCP-certified culture and DST laboratory. Notably, the RNTCP has taken the programmematic decision that patients who have any rifampicin resistance, should also be managed as if they are an MDR-TB case, even if they do not formally qualify as an MDR-TB case as per the above definition of MDR-TB.

Therefore, programme and clinical action will be driven primarily by rifampicin DST results.[6] Rapid molecular assays such as Line Probe Assay (LPA) and similar Cartridge Based Nucleic Acid Amplification Test (CB-NAAT) remain the preferred diagnostic methods for early and appropriate case detection of DRTB because of the rapid and highly-accurate results under PMDT. RNTCP views the treatment of MDR-TB patients as a 'standard of care' issue and follows the internationally recommended guidelines under PMDT.[6]

A review of patients' medical records was conducted using a standard form and the following variables were extracted: age, sex, weight, treatment history details and duration with special reference to the complaints related to various ADRs as narrated by the patients/family members/hospital staff/ attending health workers along with the related signs present thereof and the relevant investigation results were taken into consideration. Depending on their presentation, accordingly ADRs were categorised into 'mild', 'moderate' and 'severe' types as:

- **Mild**: If patient made one or two complaints during the 12 months period and required only symptomatic treatment
- **Moderate**: If more than two complaints or repeated every month/more times or of prolonged duration, but still manageable with symptomatic treatment.
- **Severe**: If the nature of ADRs warranted reduction in drug dosages or termination of the offending drug(s) temporarily or permanently.

The standardised treatment regimen (category 4) consisted of an intensive phase (IP) of six months with six drugs namely kanamycin (Km), levofloxacin (Lvx), ethionamide (Eto), Pyrazinamide (Z), ethambutol (E) and cycloserine (Cs) given daily. IP was extended beyond six months; upto7/8/9 months in patients who had a positive culture result taken in fourth/fifth/sixth month of treatment correspondingly, thus with a total IP of six-nine months as per the situation. This was followed by a continuation phase (CP) of 18 months with four drugs, namely Lvx, Eto, E and Cs. All patients enrolled to the study were treated with a daily supervised regimen. Special adjustments to the standard regimen for MDR-TB included: Pyridoxine was administered to all patients on category 4 regimen; in case of intolerance to any oral drug, it was substituted with para-amino salicylic acid (PAS); in case of intolerance to Km, then with capreomycin (Cm) or when unable to tolerate any injectable, then PAS was the substitute drug.

Decisions regarding management of the ADRs to any of the second-line anti-TB drugs, regarding dosage reduction/ withholding/ termination of any drug(s) were taken as per the advice of the DRTB centre committee of experts constituted under PMDT-RNTCP guidelines.[6]

Inclusion criteria: DRTB patients on second line drugs under PMDT-RNTCP.

Exclusion criteria: Patients having concurrent major psychiatric illness or serious medical illnesses, HIV seropositive cases, pregnant women.

RESULTS

A total of 207 DRTB patients on SLDs qualified for inclusion in the study during the stipulated period, as per the laid down criteria. There was a dominance of male patients, with 131 (63.28%) males *vs* 76 (36.72%) females (Table 1); with age range of 12-68 years; the youngest patient was an unmarried girl child, 12 years' old of urban background, whereas the oldest one was a 68 years' married male of rural background; the average age being 42 years.

From total 207 patients who received SLDs under PMDT, 168 patients (81.16%) reported with ADRs of mild, moderate or severe type, with a total of 195 adverse events. Thirty one patients (14.98%) amongst them developed severe type of drug reactions leading to reduction of drug dosage or temporary/ permanent withdrawal of the offending drug(s).

Ten patients developed severe hearing impairment and ataxia, and injection kanamycin had to be terminated permanently in six of them while in another four, the frequency of administration was reduced to alternate days. Two patients developed blurred vision and ophthalmic examination warranted stoppage of ethambutol. Another patient developed optic atrophy within two months of initiation of SLDs, compelling withdrawal of ethambutol with its replacement with PAS powder; but four months later patient developed photopsia and ethionamide was labelled to be the offending drug and had to be withdrawn permanently.

Five patients developed severe hepatitis with deranged liver function tests (LFTs), resulting in stoppage of all SLDs, till the LFTs returned to baseline. The drugs were then restarted stepwise, but addition of pyrazinamide led to re-deterioration of patients' condition and LFTs amongst three of them, hence pyrazinamide had to be terminated ultimately. However, hepatoprotective agents were also administered to all of them concurrently. Ethionamide had to be stopped because of the

Table 1: Sex distribution of patients in the study ($n = 207$)

Year	No. of patients	Male	Female
2012-13	102	63	39
2013-14	105	68	37
Total	207	131	76

development of hypothyroidism amongst six patients, who were initiated on thyroxine treatment. Another six patients developed psychosis, out of which three revealed having suicidal tendencies. Psychiatric opinion and detailed assessment resulted in withdrawal of cycloserine permanently from the regimen for all these six patients. Pyrazinamide was found to be the culprit drug in a patient who developed severe skin reactions, which remained uncontrolled with anti-histamine and corticosteroid administration, thus warranted withdrawal of Z.

Three patients who were being considered clinically to be having severe adverse reactions with severe abdominal pain, loose stools, fever and tender cervical lymphadenopathy, did not reveal any co-relation of their presentation in the relevant investigation reports including the HIV status; were kept under observation with symptomatic management and were later diagnosed to be having immune reconstitution inflammatory syndrome (IRIS). However, they responded well to a course of NSAIDs and corticosteroid therapy given for a total period of two weeks.

Of the total 195 adverse events, 124 (63.59%) were mild, 36 (18.46%) moderate and 35 (17.95%) severe type events (Table 2). Gastrointestinal events (including nausea, vomiting) were reported by maximum patients to the tune of 94 events (48.21%), hepatitis with 24 events (12.31%), followed by giddiness, arthralgia, swelling or pain at injection site, psychosis, hypothyroidism, skin reactions, peripheral neuropathy, anorexia and sleep disturbances being the important 'mild' and 'moderate' type of events registered as ADRs (Table 3). Proton pump inhibitors and/or anti-emetics had to be added prior to ingestion of the medication in about 15% of the patients to prevent such GI symptoms especially emesis, during the initial weeks of therapy.

Table 2: Categorisation of adverse events

Types of ADRs	No. of events (n=195)	Percentage
Mild	124	63.58%
Moderate	36	18.46%
Severe	35	17.94%

Table 3: Frequency of adverse events

Type of ADRs	Mild	Moderate	Severe	Total
Gastrointestinal	79	15	-	94
Hepatitis	12	7	5	24
Giddiness	10	4	-	14
Hearing impairment	-	-	13	13
Arthralgia	8	2	-	10
Psychosis	-	3	6	9
Swelling or pain at injection site	8	-	-	8
Hypothyroidism	-	-	7	7
Skin reactions	2	1	1	4
Visual disturbances	-	-	3	3
Peripheral neuropathy	2	1	-	3
Anorexia	2	1	-	3
Sleep disturbances	1	2	-	3
Total events	124	36	35	195

A significant proportion of male patients (~42%) revealed history of drug and/or alchohol abuse. Drug abuse included cannabis ('bhang') and opioids with opium, morphine, cocaine, opium husk ('bhuki') and heroin in various forms which included powder, crude form, smokable form and injections etc. Tobacco smoking was seen as a less prevalent habit amongst male patients, existed to the tune of 11%. However, tobacco chewing was observed amongst 28%.

Twenty patients were lost to follow up (erstwhile defaulters) during the course of treatment, of which nine were migratory labourers and could not be traced, three left due to personal reasons and another four being drug/alcohol addicts could not be persuaded for retrieval, whereas successful retrieval action brought four patients back to treatment schedule. Twenty-three patients (11.11%) died during the course of therapy. Six of these deaths occurred in the DRTB centre of this institution. Three patients died during the initial two weeks of initiation of SLDs, were having extensive bilateral pulmonary disease; two were having hydropneumothorax and were being managed with intercostal tube drainage with underwater seal, but died later; one more who had disseminated tuberculosis suddenly went into shock, failed to respond to therapy and died. None of the patients reported as of extensively drug resistant tuberculosis (XDR-TB) case during the study period.

DISCUSSION

The management of MDR-TB is a complex health intervention requiring multi-drug therapy for 24-27 months. This study demonstrates that at times, ADRs appear to be a major obstacle in the management of such patients and is associated with numerous challenges with a need of close monitoring.

The high incidence of ADRs observed in the study highlights the need for adequate clinical backup for managing these adverse events while decentralizing the treatment of MDR-TB. It is advisable that adverse events be detected by the community health worker or nurse or the attending staff at the earliest with confirmation of the diagnosis by the physician, followed by appropriate action.

Adherence to treatment with early recognition of ADRs can be attained by adequate health education to the patient and their family members while initiating the treatment regimen and at periodic intervals thereof, rigorous supervision by experienced health care staff providing directly observed therapy (DOT), intense monitoring, prompt identification and management of ADRs thereof.

This study showing a dominance of male patients (131M *vs* 76F) with average affected age of 42 years depicts the socio-economic impact and behaviour of the disease itself conforming to the fact from the earlier studies that tuberculosis primarily affects people in their productive age group with important socio-economic consequences. Literature depicts that tuberculosis hinders socio-economic development: 75% of TB cases are in the economically productive age group of 15-54 years[7] and that two-thirds of the cases are males.[8]

In the present study, 81.16% patients reported with ADRs including those of mild, moderate and of severe type with second line drugs. Other studies have reported adverse reactions ranging from 19-72 percent.[9-11] A higher proportion of adverse events as seen here, may be due to drug and/ or alcohol abuse history to the tune of 42% amongst males which included cannabis ('bhang') and opioids with opium, cocaine, opium husk ('bhuki') and heroin, etc. Majority of patients with history of alcohol intake, were consuming local made liquor, being cheaper and easily available than the Indian made foreign liquor (IMFL). This local made liquor has higher content of methyl alcohol as its constituent, being more injurious to the health and thus adding to the ADRs of the SLDs amongst these patients. Pertinent to note that the wide prevalence of the drug menace, with easy availability of such substances is because of the fact that this region of the country shares a long international border with a neighbouring country - infamous for drug trafficking. Illegal drug trade from that country *via* this region with resultant drug addiction and wrecking a sizeable population is a serious concern for this nation and such alarming state has been quoted in the media time and again.[12,13] These factors probably contributed to higher

percentage of ADRs reported in the present study, as compared to the earlier studies.[9-11]

Less prevalent tobacco smoking (~11%) amongst males was a heartening finding. This probably owes to the religious leanings of the majority of the population in the region of Punjab, which discourages tobacco smoking.

The offending drug(s) had to be terminated in 25/207 (12.08%) patients reporting 'severe' type of adverse events out of thirty-one such patients while in other six, modifications in the drug dosages and frequency of administration were sufficient; whereas a previous study[11] with data from Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russia, carried out more than a decade ago, showed that on an average 30% patients (19.7- 49.4%) required removal of the suspected drug(s) from the regimen due to adverse reactions. The possible explanations for the differences in the findings can be that treatment regimens varied across projects, as the treatment was tailored according to drug susceptibility patterns in that study and also that aminoglycosides including capreomycin were used for a longer duration of 6-18 months and similarly the other drugs were administered for 18-24 months duration in these countries. However, PMDT-RNTCP in India does not advocate such lengthier period of treatment nor too much variation in the regimen under the prescribed national programmeme guidelines.[6]

From the study, it seems feasible to treat MDR-TB patients more effectively in India, with certain additional inputs into the existing healthcare system. Close attention needs to be paid to ensure adherence to therapy, timely recognition of ADRs and their treatment. Minor adverse events are extremely common and should be expected and built into patient counselling from the beginning; most such side effects are manageable with reassurance and symptomatic treatment. Patients experiencing higher rates of ADRs may be at increased risk of non-adherence. In most cases, management of adverse events could be accomplished using relatively simple and low cost interventions without compromising the integrity of the MDR-TB treatment regimen, consistent with reported literature.[14] A detailed history of drug and/or alcohol abuse may prove to be an important indicator to forecast impending ADRs while managing such DRTB patients.

Having MDR-TB was an emotionally devastating experience for some patients and their families; as was narrated by them on knowing about the diagnosis, the long duration of therapy with multiple drugs and the social stigma[15] attached to the disease with negative social consequences. But provision of emotional support, helping attitude and listening with patience to them by the attending doctors and staff with regular reassurance and counselling helped them to resolve minor ADRs including depression, anxiety, sleep disturbances, giddiness etc. at times with minimum medication.

Pertinent to mention the fact that major part of the treatment of DRTB cases on category IV is carried out at their home with the administration of 'multiple' and 'toxic' second line antitubercular drugs for a 'lengthier period' to the tune of 24-27 months, resulting in higher ADR incidence amongst those referred to us from the periphery (either by DOT provider or by the family members directly). Majority amongst these had ADRs of 'moderate' to 'severe' type; with those of 'severe' type warranting reduction in drug dosage(s) or withholding the offending drug(s) temporarily or permanently; emphasising that the attending health staff should have adequate knowledge and training about such ADRs which are expected at every moment, especially in those with history of drug and/or alcohol abuse.

An effective system should be in place (at the periphery) that allows prompt patient retrieval, in case patient fails to attend a DOT appointment. The DOT provider should visit the patient's home on the same day to find out why the patient has not appeared for his/ her DOT, and ensure that treatment is resumed promptly and effectively; of course in a sympathetic, friendly, convincing and non-judgmental manner. Many times, the reasons for this can be ADR(s), requiring prompt action by the DOT provider to bring the patient to the DRTB centre for early expert management, lest patient's condition deteriorates.

However, caution needs to be taken to extrapolate the findings of this study with a small number of patients to the much larger group of MDR-TB patients in India, as patients were managed at this tertiary health care institution.

CONCLUSION

Early detection of ADRs while treating DRTB with second-line drugs remains a key factor in the management of DRTB- a man-made phenomenon. Patients, family members, DOT providers and attending staff should be well educated about such ADRs, enabling early detection with confirmation of the diagnosis by the physician followed by appropriate action and pharmaco-vigilance reporting. DOT remains integral for close follow up and monitoring resulting into rapid intervention.

A huge absolute number of MDR-TB cases in India, is both startling as well as a depressing fact, which needs early, careful and effective management so as to curtail further spread of MDR-TB in the society. With only limited drugs in our armamentarium so far, the quest for new and better drugs for treatment of DRTB is still on; regular clinical trials to revolutionize this treatment remains a challenge.

Confronting the future challenge of 'MDR-TB epidemic', the remarkable relevance of the fact needs to be re-emphasised that there is no substitute for early diagnosis and prompt treatment of drug-sensitive tuberculosis under RNTCP, so as to prevent the emergence of DRTB; endorsing the fundamental principle: 'prevention is better than cure'.

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Case Series

OROFACIAL TUBERCULAR LESIONS

Jigar Dhuvad[1], Brijesh Patel[1], Sonal Madan[2] and Mukesh Dhuvad[3]

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Summary

Aim: The aim of this study was to evaluate the clinical characteristics of orofacial lesions like ulcer, swelling, discharge (with or without fistulae), nodules (tubercles), granulomatous growth, induration, diffuse inflammation, and extraction socket involvement in an Indian population through the case reports and review of literature.

Material and Methods: Four case reports are presented of patients who had orofacial lesions which turned out to be tuberculous. The diagnosis of tuberculosis was possible because it was kept high on the list of differential diagnosis of orofacial lesions. In our study, we used the following clinical criteria: 1) Suspicious lymph nodes should be biopsied. 2) Excision of non-healing, fistulous, or non-responsive lesions should be considered for biopsy. 3) Histopathological evidence of granulomatous inflammation with epithelioid cells and Langhan's giant cells or acid-fast bacilli should on Ziehl-Neelsen staining. 4) The patients' medical records were reviewed for details relating to presenting signs and symptoms, site and appearance of the lesions, chest x-ray findings, and sputum smear and tuberculosis culture results.

Results: In all cases, the patients were prescribed antituberculosis therapy (ATT) by the physician. Strict follow-up was done to ensure completion of intensive phase therapy and both oral as well as pulmonary lesions were resolved.

Conclusion: Dentists and physicians treating orofacial lesions should be alert to the possibility of orofacial tuberculosis. Medical history should be taken very carefully and lymph node biopsy as well as other radiological and microbiological investigations should be carried out to rule out oral tuberculosis. Antituberculous therapy leads to successful resolution of the orofacial lesions. ***[Indian J Tuberc 2014; 61: 325-330]***

Key words: Tubercular lesions, Orofacial region, Dental treatment

INTRODUCTION

Tuberculosis is not only a medical problem, but a socio-economic one as well. India has approximately two to three million people infected with Tuberculosis[1]. According to WHO estimates, India has the world's largest tuberculosis epidemic[1]. Paul Nunn, coordinator of WHO's STOP TB department in Geneva, described the cases as "a wake-up call for countries to accelerate provision of proper care, particularly for multi drug-resistant patients[1].

The aim of this study was to evaluate the clinical characteristics of orofacial lesions like ulcer, swelling, discharge (with or without fistulae), nodules (tubercles), granulomatous growth, induration, diffuse inflammation, and extraction socket involvement in an Indian population through the case reports and review of literature.

In our study, we used the following clinical criteria: 1) Suspicious lymph nodes should be biopsied. 2) Excision of non-healing, fistulous, or non-responsive lesions should be considered for biopsy. 3) Histopathological evidence of granulomatous inflammation with epithelioid cells and Langhan's giant cells or acid-fast bacilli should on Ziehl-Neelsen staining. 4) The patients' medical records were reviewed for details relating to presenting signs and symptoms, site and appearance of the lesions, chest x-ray findings, and sputum smear and tuberculosis culture results.

We hereby discuss a series of four cases of orofacial lesions but ultimately turned out to be tuberculous and well responded to anti-tubercular treatment.

CLINICAL RECORD

Case 1:

A 35-year-old female came with a complaint of pus discharge from buccal aspect of upper left

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anterior teeth. During the intraoral examination, a localized swelling at the labial aspect of maxillary anterior teeth was noticed. IOPA (Intraoral Periapical) revealed the periapical radiolucency at the maxillary lateral incisor, and obturation was also done in the same. Apicoectomy was performed and the periapical specimen (Fig. 1) of histopathological examination revealed granulomatous inflammation containing Langhan's-type cells. General examination revealed a febrile episode associated with evident and palpable lymph nodes at levels 1 and 2 on the left side of the neck. Her chest X-ray showed a typical tuberculous Koch's picture of the involved lung (Fig. 2), all of which confirmed the diagnosis.

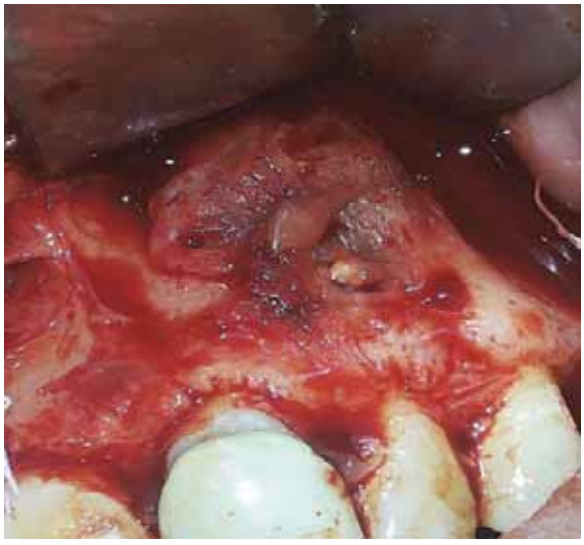

Figure 1: Periapical lesion in relation with upper left lateral incisor

Case 2:

A 38-year-old man presented with a white, reticular lesion on the dorsolateral aspect of the tongue. A provisional diagnosis of oral lichen planus was made, even though an ulcerated lesion (Fig. 3). Two incisional biopsies were performed. In addition to a definitive diagnosis of oral lichen planus, a histopathological examination of the ulcerated lesion revealed chronic inflammation characteristic of tuberculous granulomas, which consisted of epithelioid cells and Langhan's giant cells, surrounded by lymphatic infiltration. A second section of the tissue was taken and the culture was positive for *M. tuberculosis*.

Case 3:

A 42-year-old man reported with the swelling in relation with submental area. Patient's primary complaint was a single enlarged, firm swelling in relation to the left submental area. Clinically, there was

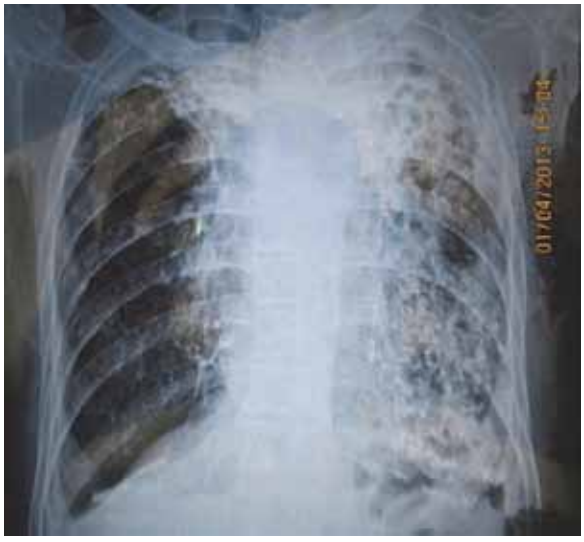

Figure 2: Chest X-ray showing a typical tubercular Koch's in the lung

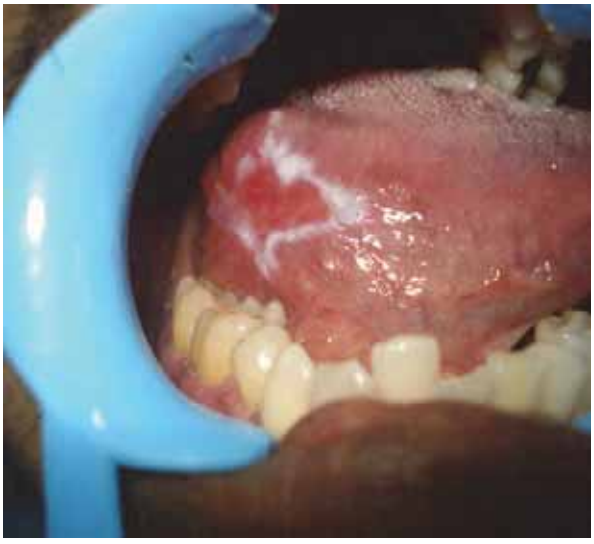

Figure 3: Clinical view showing an erythematous ulcer resembling oral lichen planus

an extraoral scar, so provisional diagnosis of foreign body post trauma was made (Fig. 4). OPG (Orthopantomograph) revealed nothing significant. Submental incision was made and the mass was sent for histopathological examination. A histopathological study revealed a chronic granulomatous lesion consisting of multiple granulomas, Langhan's-type cells with some necrotic areas. A tuberculin skin test was positive and subsequent Ziehl-Neelsen staining demonstrated acid-fast bacilli (Fig. 5). These symptoms are highly suggestive of TB, which was subsequently confirmed on general examination of losing about ten kilograms' weight in the past six months and had a history of smoking up to twenty-five bidis a day for about twenty years.

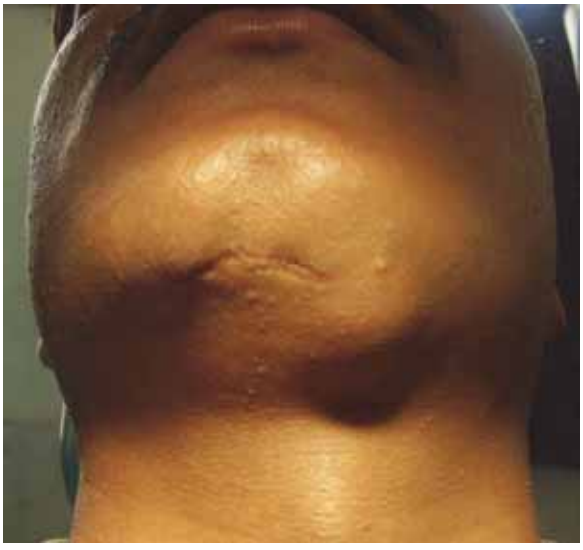

Figure 4: Clinically extraoral scar suggesting post trauma foreign body

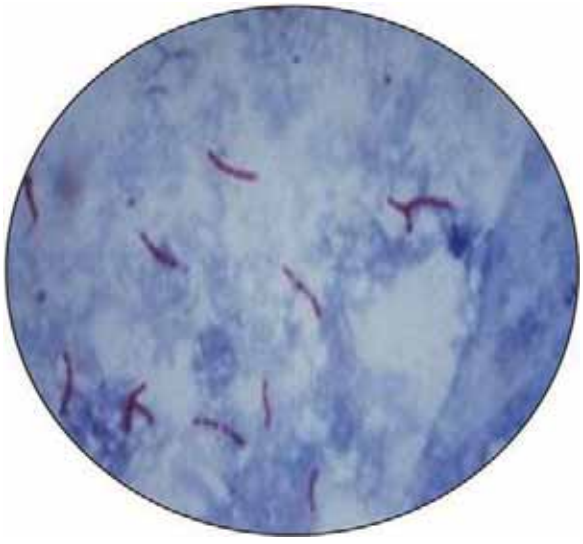

Figure 5: Acid-fast bacilli seen in ZN stain

Case 4:

A 28-year-old male was referred for the evaluation of a gradually increasing swelling on the lower left side of the face. Local extraoral examination revealed a unilateral, firm, non-fluctuant, mildly tender and 3*2 cm measuring swelling fixed to the underlying structures. The overlying skin of swelling was erythematous and showed the presence of a fistula with a serosanguinous discharge (Fig. 6). Fine needle aspiration cytology (FNAC) of the swelling showed a typical caseous material with a white cheesy appearance was aspirated, which on microscopic examination demonstrated necrotic material, a large number of neutrophils, a few lymphocytes and a few clusters of epithelioid cells, suggestive of a tuberculoid

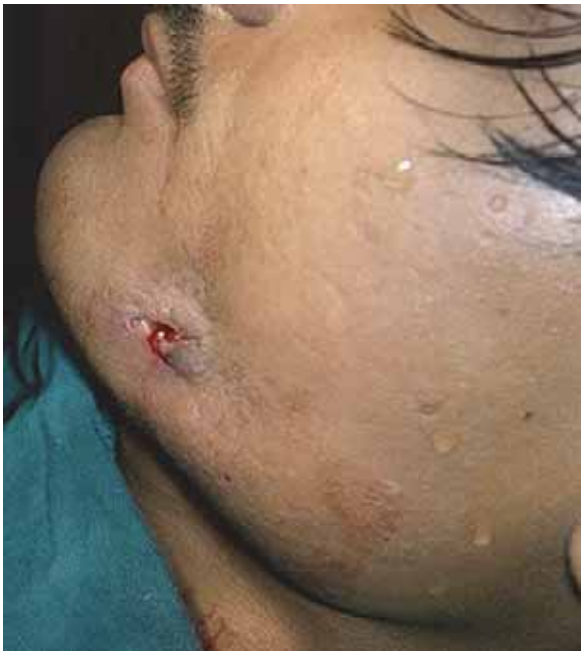

Figure 6: Swelling at left body of the mandible with an extraoral fistula

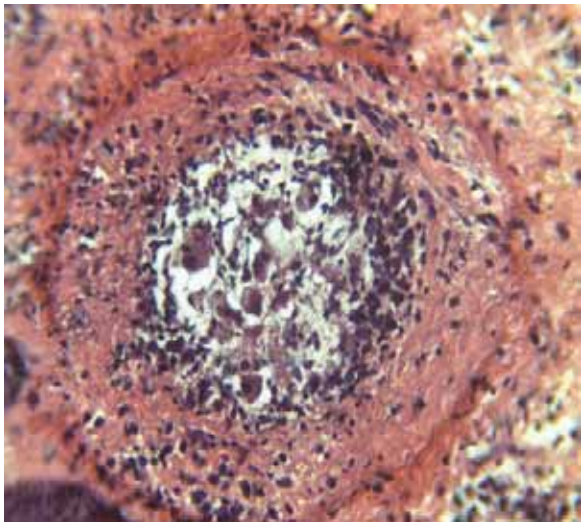

Figure 7: Photomicrograph of ulcer biopsy showing typical tubercular granulation tissue (H&E - 40x)

or caseating granuloma (Fig. 7). This clinched the diagnosis of tuberculous osteomyelitis because the patient's history of generalized weakness, weight loss and an evening rise in temperature for one month and various investigations were in favour.

All the patients were then prescribed antituberculosis therapy (ATT) consisting of isoniazid, ethambutol, pyrazinamide and rifampicin by the physician. They had completed intensive phase therapy, both oral as well as pulmonary lesions showing the signs of improvement.

DISCUSSION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, is a non-mobile, non-spore forming, rod-shaped bacillus, 1 to 4 mm long and 0.3 to 0.5 mm wide, which stains weakly gram positive. The cell wall is rich in lipids and retains carbolfuchsin red dye after acid washing; therefore, the mycobacterium bacilli are said to be acid fast bacilli[2].

Primary infection is in the lung parenchyma and adjacent lymph nodes. The disease usually resolves after symptoms of a mild respiratory illness, but the organisms remain alive, contained in a lung focus by host cell-mediated defences. Reactivation can occur through subsequent illnesses or immune suppression, leading to disease. In some cases, the primary tuberculous infection becomes progressive, and subsequent bacteremia results in TB (Tuberculosis) meningitis or a debilitating generalized acute infection called miliary TB. Miliary TB is so named because the radiographic lesions look like disseminated millet seeds[3]. Organs with high oxygen tension are most susceptible to TB infection, including lung, kidney, and bone[4]. TB of the TMJ also has been reported[5,6]. Disease is more prevalent in infants, children, adolescents, elderly, and in individuals who have immuno-suppressive diseases[5,7].

Approximately, 95% of individuals exposed to *M. tuberculosis* remain clinically asymptomatic[8]. The remaining 5% develop primary TB, which is most often localized to the lungs. In the lungs, caseous foci and hiliary nodes undergo healing by fibrosis and occasionally calcification. In primary TB, mucosal lesions are caused by direct inoculation of the micro-organism into the oral mucosa and are most common in younger patients. In contrast, secondary lesions are more common in older subjects[8]. In a minority of subjects, secondary TB occurs when the progressive pulmonary disease spreads to other organ systems through self-inoculation *via* infected sputum, blood, or the lymphatic system[8].

Physical findings may include fever, muscle weakness, findings of a pleural effusion, or a focal mass or lymphadenopathy[5]. Fever is common in the afternoon and evening, falling at night with drenching night sweats. A chronic hacking cough produces haemoptysis 20% of the time[9]. Thorough evaluation of the suspected tuberculosis patients is paramount, as it may be present in almost any organ system. In extrapulmonary tuberculosis, symptoms may include an obvious mass or lesion with local pain, swelling, and occasionally fistula formation[5]. Extrapulmonary lesions may be ulcerative, but granulomatous disease is more common[10]. Specific symptoms should be evaluated thoroughly with radiographs and CT to evaluate the major organ systems and skeleton for the presence of disease.

Excluding tuberculous lymphadenitis of the neck, which overall is present in up to 10% of persons suffering from extrapulmonary TB, disease occurrence in the head and neck is rare (seen in only 1% of patients)[11-13]. Oral tuberculosis is a rare entity and affecting approximately 0.05% to 5.00% of patients with tuberculosis[11,14]. In this way, this disease rarely features in the differential diagnosis of orofacial lesions.

Oral TB occurs at any location of oral cavity, but the dorsum of tongue is most commonly affected[11,15]. Other sites include the palate, palatine tonsil, uvula and floor of the mouth, lips, buccal mucosa, gingiva, salivary glands, maxilla, and mandible[11,16]. The involvement of the mandible by tuberculous infection is extremely rare as it contains less cancellous bone[17]. However, mandibular involvement is more frequent than maxillary, with the alveolar and angle regions showing greater affinity[18]. Salivary glands are rarely infected. TB is normally confined to the intraglandular and periglandular lymph nodes in the major salivary glands, and any invasion of the parenchyma usually originates from the nodes themselves[8].

Mucosal lacerations, leukoplakia, poor oral hygiene, and dental extractions have been implicated as predisposing factors for the development of oral TB[11,16]. Intact and healthy oral mucosa seems to provide a sufficient barrier to mycobacteria, with saliva also helping to control the organisms[14]. Secondary oral TB usually appears in the setting of pulmonary disease[16]. Patients may present with odynophagia and fever[16]. Lesions of the oral mucosa typically consist of ulcers, nodules, fissures, tuberculomas, periapical granulomas or swellings[14,16]. Other manifestations like cervical lymphadenitis, focal pain, and non-healing extraction socket should not be excluded to diagnose TB[10].

The history reported by the patients, clinical and radiological examination, laboratory confirmation along with the biopsy play an important role in the diagnosis of tuberculosis. Once the diagnosis of TB is confirmed, the patients should be started with Antituberculosis therapy (ATT)[11].

In India, after achieving the successful results of DOTS strategy (Directly Observed Treatment Short course chemotherapy), the "Revised National TB Control Programme" is being implemented under the umbrella of National Rural Health Mission. Objectives of this programme are early detection and treatment of at least 90% of estimated all types of TB cases in the community, including Drug resistant and HIV associated TB, successful treatment of at least 90% of new TB patients, and at least 85% of previously-treated TB patients, reduction in default rate of new TB cases to less than 5% and re-treatment TB cases to less than 10%[19].

CONCLUSION

Dentists and physicians treating oral lesions should be alert to the possibility of oral tuberculosis. Medical history should be taken very carefully and lymph node biopsy as well as other radiological and microbiological investigations should be carried out to rule out oral tuberculosis. Anti-tuberculous therapy leads to successful resolution of the oral lesions.

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Case Report

CANCER-LIKE PRESENTATION OF FEMALE GENITAL TUBERCULOSIS

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Summary: Tuberculosis of the female reproductive tract affects usually reproductive age group and is a common cause of infertility with tubal pathology. Diagnosis of the female genital tract tuberculosis is challenging and, very often missed due to the unusual presentations and lack of specific diagnostic tests. This may occasionally lead to unnecessary surgical procedures. We present two case reports of female genital tuberculosis (FGTB) who presented to us with symptoms mimicking malignancy diagnosed TB only on histopalthology. ***[Indian J Tuberc 2014; 61: 331-335]***

Key words: Female Genital Tuberculosis, Cancer Mimic, Diagnostic Challenge, Polymerase Chain Reaction.

INTRODUCTION

Tuberculosis is the oldest disease known to mankind[1] and yet, one of the leading causes of mortality and morbidity in the present era, especially with the emergence of HIV/AIDS and multidrug resistant strains of the microbes[2]. Though pulmonary tuberculosis is the commonest presentation, there are a number of cases of extra pulmonary tuberculosis. Amongst extra pulmonary tuberculosis, female genital tuberculosis (FGTB) poses a diagnostic challenge.

Tuberculosis affecting the female genital tract came into light in the late 18th century.[1] Affecting mostly the reproductive age group, it is a common cause of infertlity. The actual incidence of FGTB is not known as it is mostly mis-diagnosed or unrecognized due to atypical presentations and paucity of investigation.[3]

FGTB often presents as infertility, oligomenorrhoea or severe dysmenorrhea[2]. All of these have a low predictive value for TB and therefore a battery of investigations are required to confirm diagnosis. Quite often, the diagnosis is missed because the tests are inconclusive. We report two cases of genital tuberculosis which posed a diagnostic challenge and the final diagnosis was made only on histopathology.

CASE REPORTS

Case 1

A 29-year-old nulliparous woman, reported with severe menorrhagia, dysmenorrhea and white discharge per-vagina. Her medical history was insignificant and investigations for infertility were inconclusive . She had history of failed attempt of *in vitro* fertilization. She underwent hormonal therapy for menorrhagia, but her symptoms persisted. She also had significant weight loss over the past few months. She had no history of tuberculosis or contact with tuberculosis.

Excepting pallor systemic examination which was normal, gynecological examinations revealed bulky uterus and bilateral tender fornices. Ultrasound and MRI showed thickened endometrium(31mm), left ovarian mass with multiple heterogenous echotexture, fluid in the pouch of Douglous and enlarged para aortic, retroperitoneal lymphnodes. With provisional diagnosis of endometrial carcinoma, the patient was subjected to dilatation and curettage which revealed hyperplastic endometrial glands admixed with hemorrhage and necrosis on histopathology. Cervical biopsy was inconclusive. Cytology of fluid from pouch of Douglas and ovarian mass showed only lymphocytes. Patient underwent

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staging laparotomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed.

On gross examination, the uterus appeared with 6x5x4 cm sided adnexa tubo-ovarian mass. Cut sections revealed cheesy material filling the endometrial cavity, cervical cavity and tubo-ovarian mass. Cut sections of the five enlarged lymph nodes were grey white.

Microscopic examination showed multiple well-formed caseating epithelioid granulomas with Langhan's giant cells in the endometrium, myometrium including adenomyotic foci, cervix, left-sided tubo-ovarian mass, right intact tube ovary and also lymph nodes (Figure 1). AFB staining of the microscopic sections revealed acid fast bacilli. Diagnosis of tuberculosis was confirmed by PCR (polymerase chain reaction) of the endometrial tissue.

Case 2

A 57-year-old lady with one living child, reported complaints of post menopausal bleeding, discharge per vagina, pain abdomen for three years

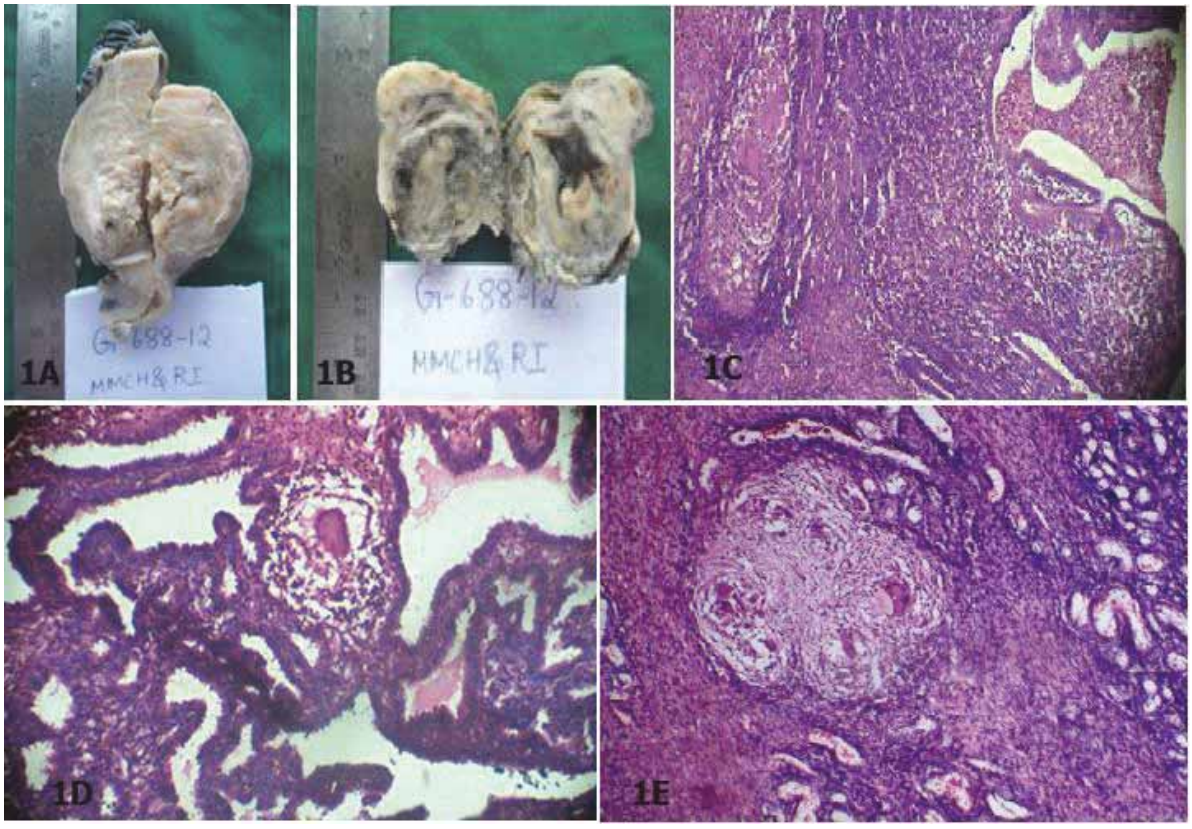

Figure 1: 1A: Serial section of the hysterectomy specimen showing cheesy necrotic material in the endometrial cavity, 1B: Cut section of tubo-ovarian mass showing necrotic material, 1C: Microsections of endomyometrium showing multiple granulomas with caseating necrosis.(H&E staining x100), 1D: Microsections of fallopian tube showing tubal mucosa revealing collection of epithelioid cells along with a Langhan's giant cell(H&E staining x400), 1E: Microsections of ovary showing a well-formed granuloma along with Langhan's giant cells in the ovarian tissue (H&E staining x100).

and significant weight loss over the last one year. Past history or family history was non-contributory.

Patient was pale and systemic examination was normal. Gynecological examination showed ulcerated cervix, which bled on touch. Uterus was of normal size with bilateral tender fornices. Per rectal examination, X-ray chest and sputum examination were normal. Cervical PAP(Papanicolaou) smear showed inflammatory cells and was negative for intraepithelial lesion or malignancy. MRI abdomen showed endometrial thickening and soft tissue streaking in parametrium. Cervical biopsy was inconclusive. Endometrial biopsy showed focal collection of atypical cells along with proliferative glands. Patient underwent total abdominal hysterectomy. Histopathological examination of endometrium and cervix revealed multiple caseating granulomas of tubercular etiology (Figure 2).

DISCUSSION

Tuberculosis is an important cause of reproductive and genital tract morbidity in women. The prevalence of FGTB cannot be determined accurately, as many cases are asymptomatic and get detected incidentally during the investigation for infertility.[4] FGTB accounts for 9% of extra

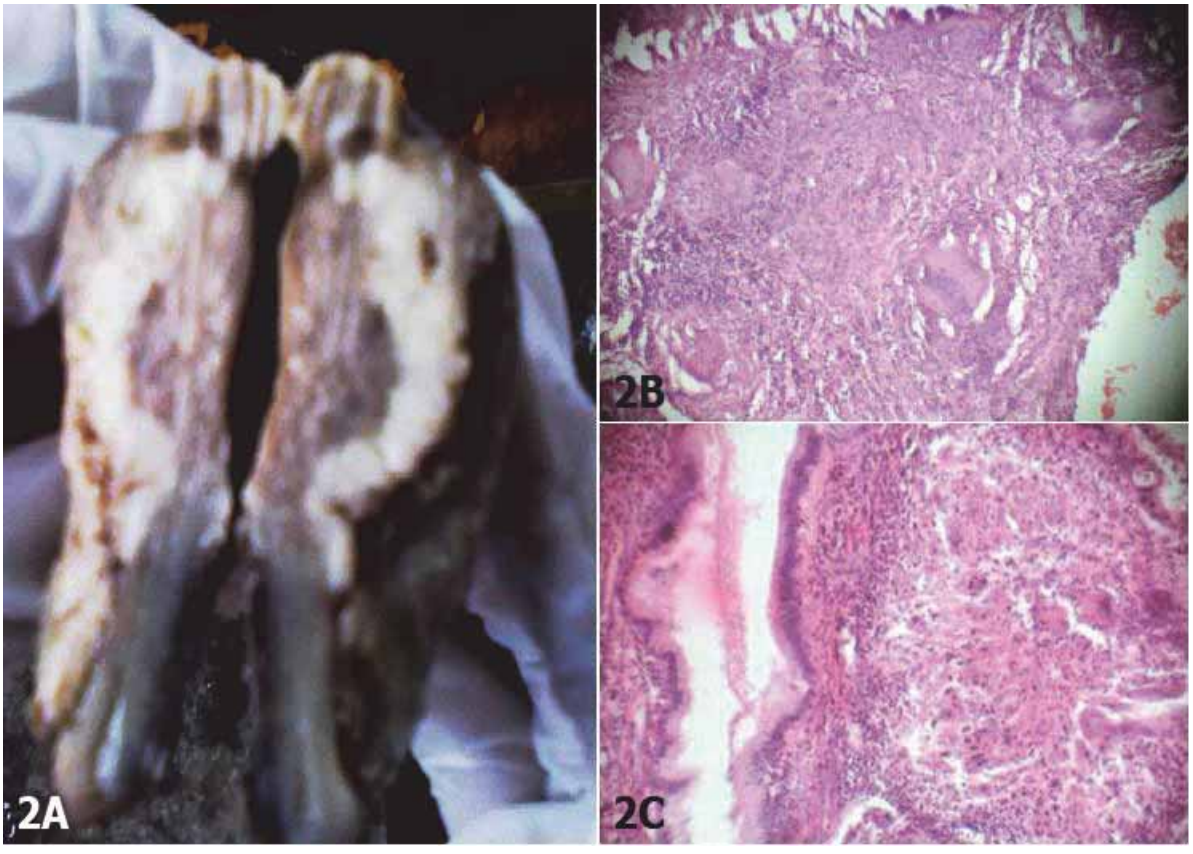

Figure 2: 2A: Serial section of the uterocervix showing the gray-white tubercles in the myometrium, 2B: Microscopy of endomyometrium showing epithelioid granulomas with multiple giant cells(H&E stainingx400), 2C: Microscopy of cervical tissue showing endocervical gland with well formed caseating granuloma(H&E staining x400).

pulmonary tuberculosis and also contributes to more than 3% of patients with infertility in developing countries.[5] The disease is commonly seen in reproductive age group and is very rare in postmenopausal women.[6]

Tripathy and Tripathy stated that genital TB is mostly a secondary manifestation of primary TB of the lungs. They reported that the genital tract is vulnerable to this disease after puberty, and often detected during the childbearing period. It spreads to female genital tract by hematogenous or lymphatic route.[2,7] However, sexual mode of transmission has also been reported.[8]

The most common presentations of FGTB are infertility, pelvic pain, vaginal bleeding, amenorrhea, vaginal discharge and postmenopausal bleeding. Less common presentations are ascites, abdominal mass, tubo-ovarian abscess and vague abdominal distension.[9] In the present case, one patient presented with infertility, menorrhagia, and dysmenorrhea and other case with postmenopausal bleeding. In postmenopausal women, genital TB is rare and comprises 1% of cases of postmenopausal bleeding. The exact cause of low incidence of the disease in this age group is not known. Most authors believe that an atrophic endometrium is a poor milieu for the growth of *Mycobacterium tuberculosis* bacilli.[10] Pelvic tuberculosis can also mimic ovarian malignancy with falsely elevated CA-125, which returns to normal after anti tubercular treatment.[1,2,7]

Various studies show a pattern of involvement of FGTB. Mondal SK *et al* showed that fallopian tubes were the commonest to be affected (100%), followed by endometrium(50%), ovaries (20%), cervix(5%), vulva and vagina (<1%).[11] In Case 1 of our study, extensive involvement of the endometrium including the adenomyotic foci, and myometrium was seen. Bilateral adnexa with left tuboovarian mass, as well as the cervix were involved. Case 2 showed the involvement of endometrium and cervix.

The presence of caseous material on cut surface of the uterus is a rare feature, especially in woman of reproductive age with incidence of 5%.[11] In first case, there was evidence of caseous material in endometrial cavity on gross examination, with extension into cervix and bilareal adenexa.

The tubercular granulomas generate from the basal layer of the endometrium, where it is lodged during the hematogenous spread. It develops into numerous well-formed granulomas and sheds off with menstruation.[1] In case of postmenopausal women, granulomas get enough time to develop caseous necrosis. Hence, it is commoner to find caseous material in a postmenopausal uterus than in that of reproductive age group. As the granulomas are well developed in the late secretory phase hence D and C is recommended in pre-menstrual phase.[7]

FGTB is baffling and challenging because of its non-specific presentations and its notoriety for evading diagnosis. Pelvic sonogram, chest x-ray and laparoscopic examination are the first line of investigation in case of FGTB. Ideally, hysterosalpingogram should be avoided in suspected cases of FGTB, but if done may also aid in diagnosis. Presence of epithelioid granulomas, on histopathological examination with positive AFB staining usually aids in the diagnosis of FGTB, but AFB staining lacks sensitivity. Culture on L-J medium, even though time consuming, is more sensitive. PCR has emerged as the most sensitive, rapid and specific mode of diagnosing FGTB. Studies have found that PCR is useful in early diagnosis and confirmation in clinically suspected cases of FGTB.[12] In our cases, the diagnosis was confirmed by PCR done on the tissue block. PCR also has a draw back of false negative results.[12]

CONCLUSION

FGTB being a clinically and diagnostically challenging disease, requires a high degree of suspicion, followed by elaborate investigations including repeated biopsies, D and C examination, culture, AFB staining and PCR.

These cases emphasize that though uncommon, one should keep tuberculosis as an

important alternative in the differential diagnosis of malignant appearing lesions of female genital tract. All steps should be taken to rule out TB before undertaking hysterectomy, especially in the reproductive age group.

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Case Report

RESOLUTION OF TUBERCULAR ABSCESS WITH ANTITUBERCULAR TREATMENT

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(Received on 22.4.2013; Accepted after revision on 14.7.2014)

Summary*:** Tubercular brain abscess is a rare manifestation of neurotuberculosis. Large brain absceses are usually surgically treated. We report a case of tubercular brain abscesses in left cerebellar hemisphere and right parietal lobe in a child who was treated surgically for the cerebellar abscess and conservatively with antitubercular drug for parietal abscess. The patient showed significant clinical improvement and healing of brain abscess on follow up imaging. The resolution of relatively large abscess by conservative management with antitubercular treatment is very rare. ***[Indian J Tuberc 2014; 61: 336-339]

INTRODUCTION

Central nervous system tuberculosis often manifests as meningitis or tuberculoma. Tuberculous brain abscess is relatively uncommon[1,2]. We report a case with two brain abscesses over left cerebellar hemisphere and right parietal lobe. The cerebellar abscess was surgically treated and the evacuated pus revealed acid fast bacilli on Ziehl-Neelsen stain. The parietal abscess was managed conservatively with antitubercular drug. Follow up imaging of brain shoed evidence of healing of both abscesses.

Case Report

A two and half years' old male child came with his parents to neurosurgery out-patients' department with a complaint of low grade fever for six months, weakness of right side of body for the last one month, headache and vomiting for the last three months. There was no history of trauma, seizure, rash, loose motion or ear discharge. On the day of admission, the child was drowsy and febrile with body temperature of 37.4 degree Celsius. On clinical examination, localization to painful stimulus, bilateral papilledema, normal reacting pupils to light were present. Right side limbs showed increased muscle tone, extensor plantar reflexes and brisk tendon reflexes. An intracranial space occupying lesion was suspected clinically. Mantoux skin test and human immunodeficient virus serology were negative. Chest radiograph study and ultrasonography of abdomen were normal.

Contrast-enhanced magnetic resonance imaging of brain revealed two large ring enhancing lesions over left cerebellar hemisphere and right parietal lobe with perilesional edema and supratentorial hydrocephalus. Fourth ventricle was compressed. The lesions were hypointense on T1W, hyperintense on T2W image. Diffusion weight images were not available with the patient. Left cerebellar and right parietal lobe abscess with supratentorial hydrocephalus was the radiological diagnosis (Figure-1).

Surgical management of left cerebellar abscess and conservative management for right parietal lobe abscess were planned. The patient was operated through suboccipital approach. Thin yellow coloured pus was drained which revealed acid fast bacilli on Ziehl-Neelsen stain. Biopsy of abscess wall showed tubercular infection (Figure-2).

The pus culture yielded mycobacterium tubercle. The post operative period was uneventful. The child was given antitubercular treatment with rifampicin, isoniazid, and pyrazinamide combination for the first two months followed by rifampicin and isoniazid combination for 10 months duration. The

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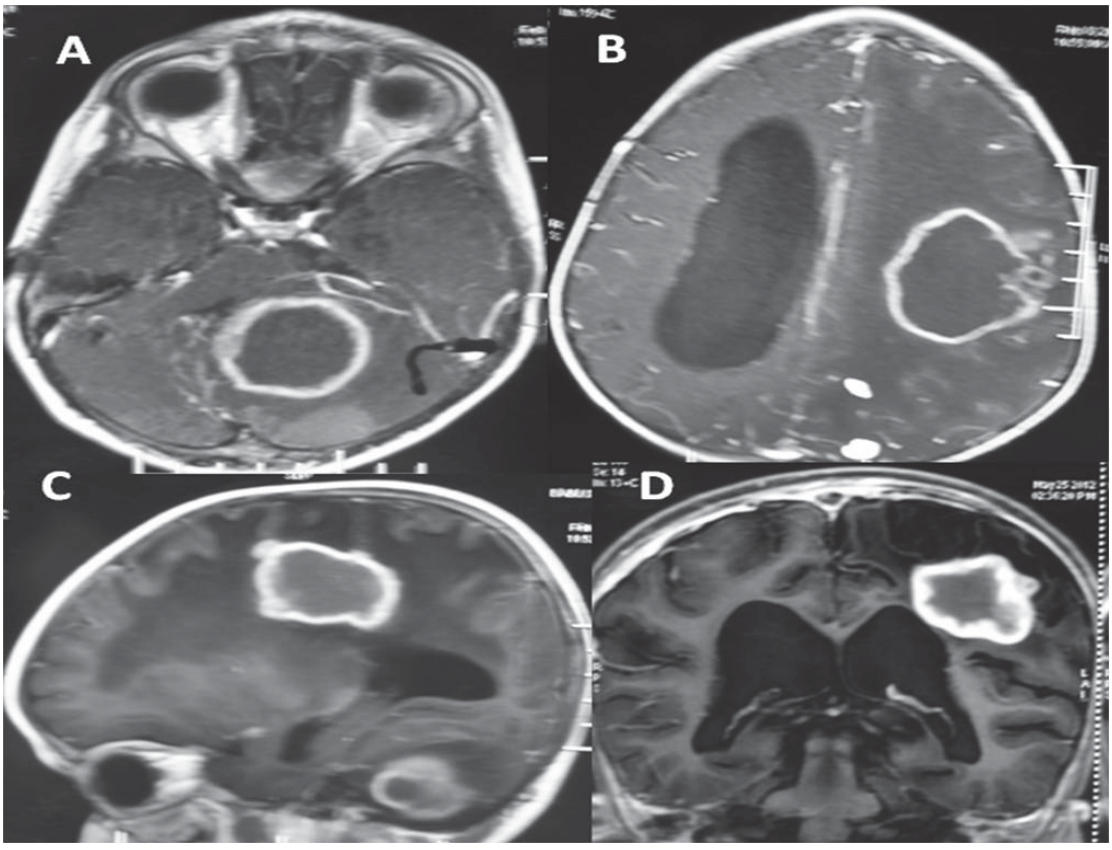

Figure 1: Contrast-enhanced MRI of brain showing large cerebral abscess as ring enhancing lesions in left cerebellar hemisphere (A) and right parietal lobe (B,C and D) causing compression of fourth ventricle and supratentorial ventriculomegaly.

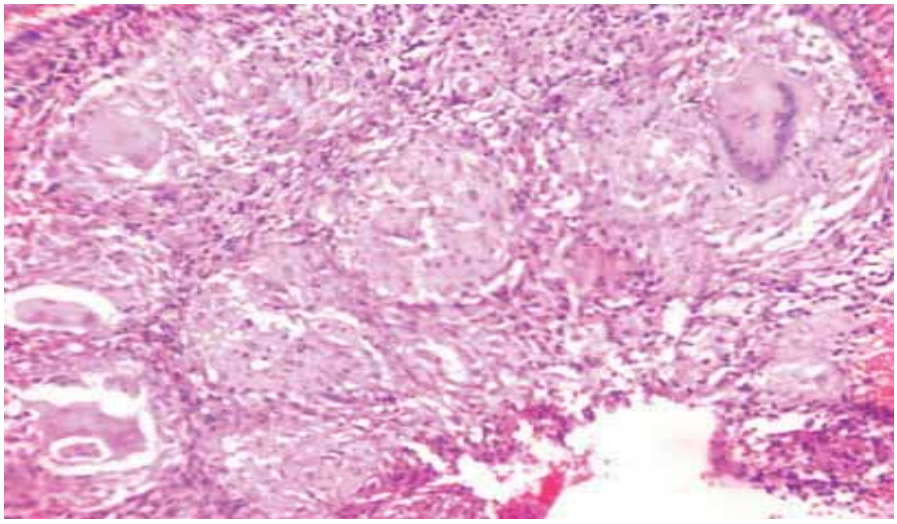

Figure 2: Microphotograph showing discrete and coalescent granulomas comprised caseation necrosis along with epithelioid cells and Langhan's giant cells surrounded by glial tissue. (H&E 400X)

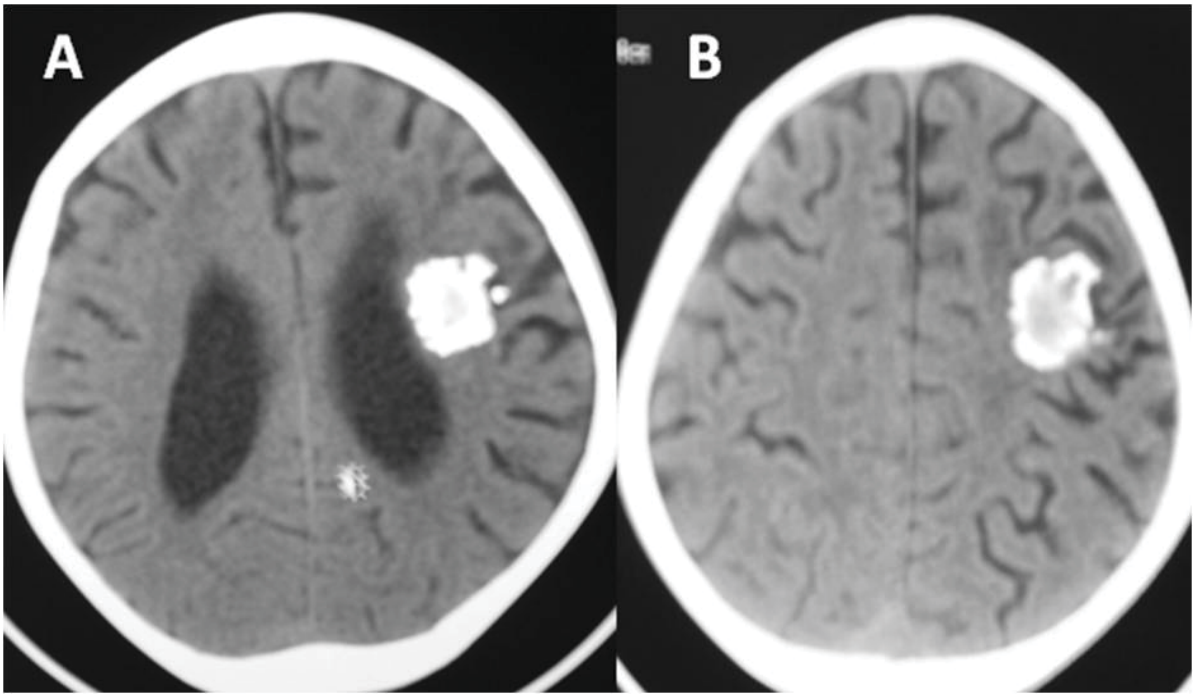

Figure 3: Non-contrast computed tomography of head after six months of antitubercular drug treatment showing decreased size and dense calcification of left parietal abscess (A and B) suggesting healing of the lesion.

follow up computed tomography scan of head after six months' showed decreased size and calcification of right parietal abscess and near complete resolution of left cerebellar abscess (Figure-3).

After six months and one year of follow up, the child had no signs and symptoms of systemic illness or neurological deficit. His sensory and motor functions were normal.

DISCUSSION

Mycobacterium tuberculosis is the most common pathogenic agent of tuberculosis (TB). Tuberculous abscesses occur in approximately 10% of all patients with neurotuberculosis.[3] The Brain abscess formation is rare in central nervous system tuberculosis and is seen most commonly in immunocompromised patient[1,4-6]. Tubercular brain abscess develops either from tubercular granuloma or spread of tubercle from meninges. Tubercular granuloma mimics tubercular abscess by its central caseation mimicking pus. However, acid fast bacilli need to be demonstrated in the pus of tubercular brain abscess.[1] The tubercular abscess is larger in size than tuberculoma and contains plenty number of tubercular bacilli in contrast to tuberculoma with a few bacilli inside granuloma. They elicit more vasogenic edema than tuberculoma.[7,8] Tubercular brain abscess is often multiloculated and has a much thicker abscess wall in comparison with bacterial brain abscess. [9] In our case, pus within brain abscess was positive for acid fast bacilli and biopsy of the abscess wall revealed tubercles giving bacteriological and histological confirmation of tubercular brain abscess.

The clinical manifestation of tubercular abscess of brain depends on the size, location of abscess. Most common clinical features are partial seizures, focal neurological deûcit, and feature of raised intracranial tension[10].

On computed tomography scan, they appear as hyperdense lesions with a hypodense centre. On magnetic resonance imaging, T1-weighted images showed the centre of the abscess to be hypointense, and its wall slightly hyperintense. On T2-weighted images, the centre is hyperintense and the wall hypointense. Large, irregular perifocal edema is typically present. Peripheral ring enhancement is evident after contrast administration[11]. In MRI imaging, tubercular abscess is differentiated from granulomata as the central portion of tuberculous abscesses is hyperintense on T2-weighted images, in contrast to the central T2 hypointensity seen in granulomata. This is due to the fact that tubercular abscess contain non-specific inflammatory cells whereas tuberculoma contain epithelioid cells, giant cell mixed with mononuclear cells around the caseation centre.[12]

Some authors recommended early excision of tubercular abscess as thicker fibrotic capsule of fully developed tubercular abscess (TBA) hampers catheter drainage while others recommend prolonged antitubercular therapy alone for TBA with early poorly formed capsule.[13, 14] Mathisen *et al*[15] recommend for initial diagnostic aspiration followed by prolonged antitubercular therapy for one year in case of suspected TBA. Open surgical option may be reserved for enlarging abscess with mass effect and lesion not responding to antitubercular therapy. In our case we decided for surgical management of the cerebellar abscess due to its mass effect and conservative management of the parietal abscess.

Resolution of solitary and multiple tuberculoma on anti-tubercular treatment treatment has been well documented.[16] However, total resolution of relatively large tubercular abscess is very uncommon.

CONCLUSION

Large brain abscess formation due to tuberculosis is uncommon. Contrast-enhanced magnetic resonance imaging of brain is the preferred modality for tubercular abscess of brain. The tubercular abscess in supratentorial compartment with no significant mass effect can be managed conservatively with antitubercular drug. Abscess in infratentorial compartment with mass effect is to be managed surgically.

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Case Report

COEXISTENT SQUAMOUS CELL CARCINOMA OF THE CERVIX AND GENITAL TUBERCULOSIS

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Summary

Background: Tuberculosis and genital malignancies are two common but separate pathologies that rarely coexist. Despite various theories depicting a cause - effect relationship between the two, their association is rarely reported in genital malignancies. ***Case report:*** We report a case of keratinising squamous cell carcinoma of the cervix associated with pelvic granulomatous lymphadenitis, with post-operative flare up of disease responding to anti-tuberculosis treatment. Since coexistence of genital tuberculosis and genital malignancy has been reported rarely, the literature for these cases is reviewed. ***[Indian J Tuberc 2014; 61: 340-342]***

INTRODUCTION

Tuberculosis and genital malignancy are two common pathologies known worldwide. However, the pathophysiology and cause-effect relationship of the two conditions has remained a mysterious domain despite the fact that research for carcinogenesis has indicated a possible correlation between chronic inflammation and cancer development.[1,2]

CASE REPORT

A 30-year-old P3L3 presented to us with complaints of intermenstrual bleeding and post coital bleeding along with blood mixed vaginal discharge since three months. Past history of the patient was not suggestive of any chronic disease and personal history did not reveal any high risk factors for cancer cervix. Clinical suspicion of cervical carcinoma stage II A1 was confirmed to be keratinizing squamous cell carcinoma on biopsy.

MRI findings revealed 4.3 x 4.2 x 2.1 cm soft tissue mass lesion arising from the external os of cervix and bulging into the upper half of vaginal canal, associated with a few enlarged lymph nodes along the bilateral external iliac region. There was no evidence of bowel and bladder involvement.

Patient underwent radical hysterectomy (type III) with pelvic lymphadenectomy. Intraoperative findings revealed a 4 x 4.5 cm cauliflower growth involving posterior lip of cervix extending upto the cervicovaginal junction and bilateral parametrium and paracolpos were free. (Figure) There were two enlarged lymph nodes in the external iliac group which were removed along with the other pelvic nodes.

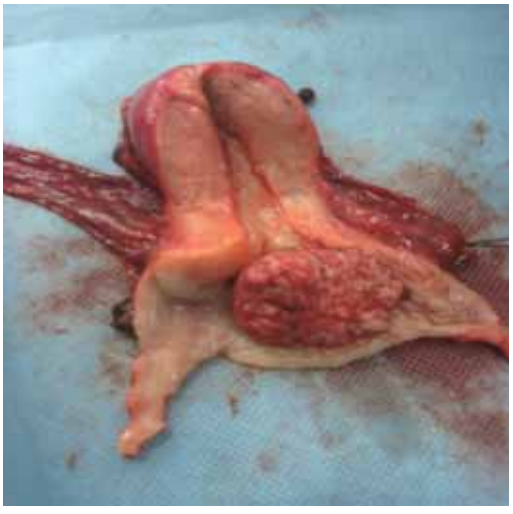

Figure: Malignant growth involving the posterior lip of cervix

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Table: Coexistence of genital malignancy with genital tuberculosis before and after 1985

Type of genital malignancy and site of tuberculosis	Till 1985	After 1985
Cervical carcinoma with cervical tuberculosis	Nine [5]	None
Cervical carcinoma with tubercular pelvic lymphadenitis	One [5]	One [present case report]
Cervical carcinoma with endometrial tuberculosis	Eleven [5]	One [6]
Endometrial carcinoma with endometrial tuberculosis	Eight [5]	Three [7,8,9]
Carcinoma of the fallopian tubes with tubercular salpingitis	None	Two [10,11]

In the post operative period, patient developed high grade fever refractory to antibiotics. No cause for fever was detected on clinical examination and investigations. Histopathology report revealed keratinizing squamous cell carcinoma of the cervix with free surgical margins along with granulomatous lymphadenitis of one of the enlarged lymph nodes while the other lymph nodes were normal. In absence of caseous necrosis, PAS staining was planned but could not be taken up due to financial constraints. Although her ESR was raised and Mantoux was positive, more specific investigations like BACTEC and AFB smear did not detect mycobacterium bacilli in the lymph node biopsy. Looking at the high incidence of tuberculosis in our country, patient was started on anti-tuberculosis treatment (category I). After 48 hours of ATT, patient became afebrile and there was significant improvement in her appetite and general well being. She was discharged on six month course of ATT and was advised routine follow up.

DISCUSSION

The association of TB with carcinoma was initially described 200 years ago by Bayle who considered " cavitation cancereuse" as one of the various types of TB.[3] In general, chronic inflammatory conditions have been thought to create the appropriate microenvironment for malignancy by increasing the rate of cell turn over which in turn may increase the risk of genetic errors.[4] But, despite this potential association between TB and malignancies, it has been reported infrequently. In 1985, Hsu *et al* described two cases of coexistent cervical tuberculosis and malignancy, one of which had several enlarged lymph nodes infected with tuberculosis. They also reviewed all the cases of coexistent genital tuberculosis and genital malignancies.[5] After 1985, literature has revealed only six cases of coexistent genital TB and genital malignancy among which one case was of cancer cervix and we hereby report the second case of cervical cancer coexistent with genital TB (Table).

CONCLUSION

The association of cancer cervix with tuberculous lymphadenopathy is rare. Presence of granulomatous lymph nodes with or without other histological features of tuberculosis like central necrosis and giant cell reaction in a case of genital malignancy should be considered for further evaluation of tuberculosis and treatment with ATT if the situation so commands as in our case, especially in TB endemic countries where extensive diagnostic tests may not be always affordable.

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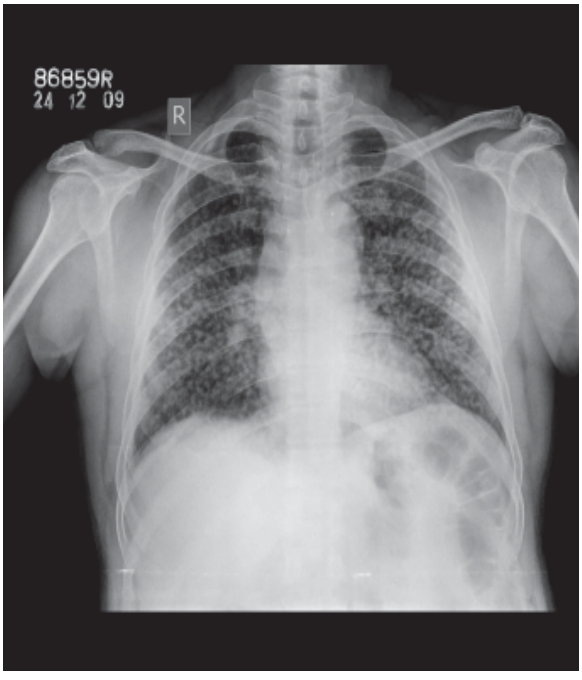
TUBERCULOSIS OR AN UNUSUAL OCCUPATIONAL EXPOSURE?

Ketaki Barve, Vinaya Karkhanis and J.M. Joshi

(Received on 2.4.2014; Accepted after revision on 14.7.2014)

A 56-year-old man, non-smoker, working in a flour mill for the last 30 years, presented with three-year history of dry cough and progressive dyspnoea. He had received empirical tuberculosis therapy multiple times in the past without any relief in symptoms. His vital parameters were normal with pulse oximetry showing oxygen saturation of 98%, which decreased to 90% after an exercise. Chest auscultation revealed bilateral crackles.

Laboratory investigations including complete hemogram, renal function test and liver function test were within normal limits. Mantoux test was negative. Chest radiograph showed bilateral reticular opacities (Figure 1). High resolution computed tomography (HRCT) showed bilateral randomly distributed nodules (Figure 2). Sputum smear and bronchial washings were negative for acid fast bacilli, and culture revealed no growth of *Mycobacterium tuberculosis*. Sputum and bronchial washings cytology were negative for malignant cells. Spirometry showed forced vital capacity (FVC) was 1.99L (58% predicted), forced expiratory volume in 1 second (FEV1) was 1.41L (50% predicted) while FEV1/FVC ratio was 71% suggesting a restrictive abnormality. The DLCO was



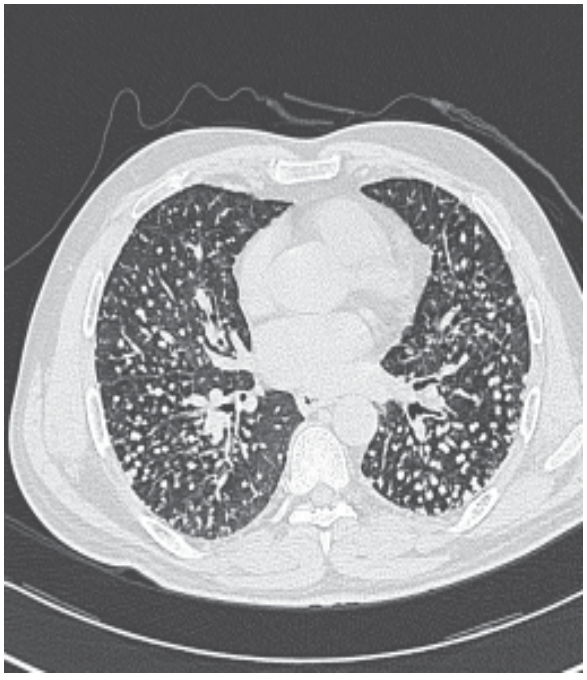


Figure 1: Chest radiograph showing bilateral nodular opacities.
Figure 2: High resolution computerised tomography of the thorax showing bilateral randomly distributed nodules without fibrosis.

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60% predicted. The patient used a red coloured stone commonly known as "Agra stone" (Figure 3) in the flour mill grinder, which generated significant silica dust during chiselling. The patient was, therefore, diagnosed as a case of silicosis due to occupational exposure to silica dust.

Silicosis is a disease of lungs caused by inhalation, retention, and pulmonary reaction to crystalline silica due to an occupational exposure to silica particles of respirable aerodynamic size[1]. Radiologically, it is characterized by nodular opacities. Coalescence of the nodules may lead to large masses called progressive massive fibrosis (PMF). Silicosis is seen commonly in occupations like mining, quarrying, drilling, tunnelling, sandblasting, construction work, and foundries. However, a significant exposure to silica dust can also occur in unusual occupation like working in flour mill[2,3] due to an exposure to "Agra stone"- a stone with a high silica content. These uncommon occupational exposures usually go unrecognized and patients are commonly misdiagnosed to be having tuberculosis. This may lead to erroneous treatment with empirical antituberculous therapy as in our patient thereby subjecting the patient to various drug related adverse effects and also wastage of resources.

Figure 3: Agra stone used in the flour mill industry for grinding.

This case serves as a reminder of the fact that, a high index of suspicion for occupational lung diseases is required, particularly in small scale industries without which these unusual occupational exposures may be missed.

Key words: Silicosis, Flour Mill Lung, Agra Stone

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FORUM

DIABETES MELLITUS IN PATIENTS WITH TB

The recent report on "diabetes mellitus in patients with TB" is very interesting[1]. Chachra *et al* concluded that "higher prevalence of diabetes mellitus in DOTS patients[1]" and proposed that "some strategy on the lines of HIV disease should be formed under DOTS for the concomitant treatment of TB and diabetes[1]." There are many considerations on this report. First, it is interesting how the "strategy on the lines of HIV disease" can be applied. Second, how to set a proper diabetes screening among the TB patients should be widely discussed. Harries *et al* noted that "implementation research is needed to assess the value and ways of screening for DM in patients with TB and *vice versa*[2-3]." In fact, screening for DM can be easily done by blood test and can be performed in any patient diagnosed with TB.

Beuy Joob[1] and Viroj Wiwanitkit[2]

Authors' Response

The authors extend sincere thanks for the interest shown in our article.

In India, HIV testing of TB patients is routinely done through "Provider initiated testing and counselling" (PITC) in all states. At country level, as on fourth quarter 2013 report, 61% of TB patients knew their HIV status which has increased from 1% in 2013. The 8,87,903 TB patients (63% of total TB patients registered) were tested for HIV, 45,999 (5% of those tested) were diagnosed as HIV positive and were offered access to HIV care. It was therefore suggested that on the same lines, Diabetes Mellitus (DM) can be tested through PITC without any additional manpower on periphery/district/state/ national level.

We agree that the screening of DM with TB can be easily done in patients by blood test, and based on findings of bidirectional referral study among TB and DM cases, Revised National TB Control Programme in INDIA has decided to screen all TB patients above the age of 30 years for DM by checking random blood sugar level among TB patients attending DOT Centres by DOT providers.[4]

Vaibhav Chachra , V.K. Arora[3]

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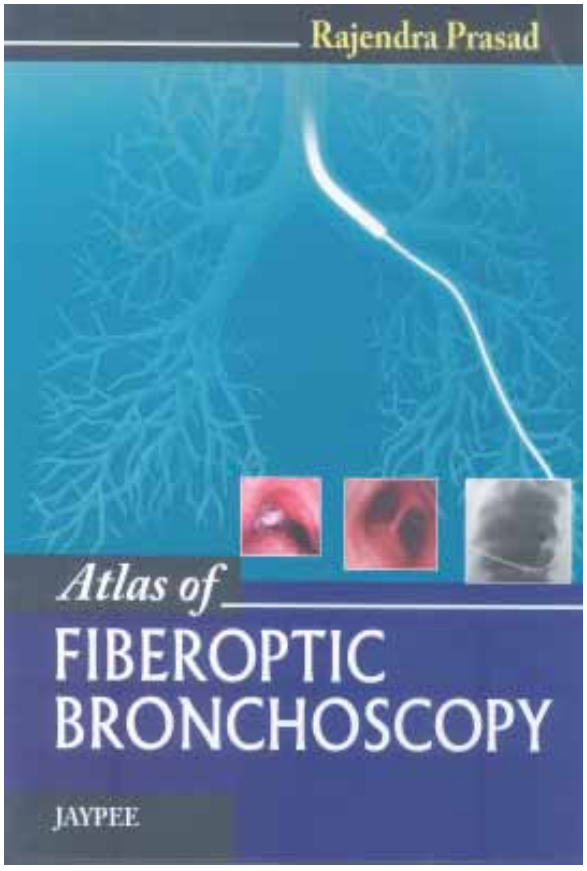
BOOK REVIEW

ATLAS OF FIBEROPTIC BRONCHOSCOPY; EDITED BY: DR RAJENDRA PRASAD; PUBLISHERS: JAYPEE BROTHERS, NEW DELHI.



'Fiberoptic bronchoscopy', which has revolutionised the practice of pulmonary medicine, has become an important therapeutic and diagnostic tool in pulmonary medicine. The present book consists of 17 chapters in which more than 64 cases of respiratory medicine varying from endobronchial polyp to squamous and undifferentiated carcinoma have been discussed with broncoscopic visualizations.

The chapter on '*Advances in Fiberoptic Bronchoscopy'* i.e. Use of laser in bronchoscopy, Endobronchial electrocautery, Argon plasma coagulation, Cryotherapy for endobronchial lesions, Endobronchial brachytherapy, Photodynamic therapy, Tracheobronchial stenting, Autofluorescence bronchoscopy, Indication for fluorescence endoscopy, Endobronchial ultrasound has been discussed in great detail. The correlation of X-ray picture , CT scan and bronchial visualization gives an added advantage in understanding of different conditions.

This book will be an excellent addition in the Indian libraries along with other bronchoscopic books/atlases from the Western countries. Thermoplasty, Navigation bronchoscopy, Interventional pulmonology and EBUS can further be added in detail to this book to make it a comprehensive bronchoscopic guide for postgraduates and chest physicians.

V.K. Arora
Executive Editor, IJT

ABSTRACTS

Isoniazid preventive treatment in children in two districts of South India: does practice follow policy?

H. R. Shivaramakrishna, A. Frederick, A. Shazia, L. Murali, S. Satyanarayana, S. A. Nair, A. M. Kumar and P. K. Moonan. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(8)**: 919-24.

The objectives were to determine the proportion of household contacts aged <6 years of patients with tuberculosis (TB) with positive sputum microscopy results who initiated and completed isoniazid preventive treatment (IPT), and to determine reasons for non-initiation and non-completion of IPT. Household visits were conducted on a random sample of adult patients registered during January–June 2012 to identify household contacts aged <6 years. Among 271 children living with 691 index patients, 218 (80%) were evaluated and nine (4%) were diagnosed with TB. Of 209 remaining contacts, 70 (33%) started IPT and 16 (22.9%) completed a full course of IPT. Of 139 contacts who did not start IPT, five developed TB disease. Reasons for non-initiation of IPT included no home visit by the field staff (19%) and no education about IPT (61%). Reasons for non-completion included isoniazid not provided (52%) and long duration of treatment (28%). This study shows that Revised National TB Programme guidance was not being followed and IPT implementation was poor. Poor IPT uptake represents a missed opportunity to prevent future TB cases. Provision of IPT may be improved through training, improved logistics and enhanced supervision and monitoring.

New Approaches to TB Vaccination

Zhou Xing, Mangalakumari Jeyanathan and Fiona Smaill. *Chest* 2014; **146(3)**: 804-12.

Pulmonary TB remains a leading global health issue, but the current Bacillus Calmette-Guérin (BCG) vaccine fails to control it effectively. Much effort has gone into developing safe and effective boost vaccine candidates for use after the BCG prime vaccination. To date, almost all the lead candidates are being evaluated clinically *via* a parenteral route. Abundant experimental evidence suggests that parenteral boosting with a virus-based vaccine is much less effective than respiratory mucosal boosting, because the former fails to activate a type of T cell capable of rapidly transmigrating into the airway luminal space in the early phase of the *Mycobacterium tuberculosis* infection. The next few years will determine whether parenteral boosting with some of the lead vaccine candidates, particularly the protein-based vaccines, improves protection in humans over that by BCG. Much effort is needed to develop respiratory mucosal boost vaccines and to identify the reliable immune protective correlates in humans.

A study of *Mycobacterium tuberculosis* genotypic diversity & drug resistance mutations in Varanasi, north India

Anamika Gupta, Savita Kulkarni, Na1in Rastogi and Shampa Anupurba. *Indian J Med Res* 2014; **139(6)**: 892-902.

One-fifth of the world's new tuberculosis (TB) cases and two-thirds of cases in the South East Asian region occur in India. Molecular typing of *Mycobacterium tuberculosis* isolates has greatly facilitated to understand the transmission of TB. This study was aimed to investigate the molecular epidemiology of *M. tuberculosis* genotypes in Varanasi, north India, and their association with clinical presentation among patients with pulmonary TB. *M. tuberculosis* isolates from 104 TB patients attending a tertiary referral hospital of north India were screened for susceptibility to isoniazid (INH), rifampicin (RIF), ethambutol

(EMB) and streptomycin (STR) by proportion method and multiplex-allele-specific-polymerase chain reaction (MAS-PCR). These were genotyped by spoligotyping. The spoligotype patterns were compared with, those in the international SITVIT2 spoligotyping database. Eighty three of 104 isolates were distributed in 38 SITs, of which SIT3366 was newly created within the present study. The mass of ongoing transmission with MDR- TB isolates in Varanasi, northern India, was linked to Beijing genotype followed by the CAS1 Delhi lineage. HIV-seropositive patients had a significantly higher proportion of clustered isolates than HIV-seronegative patients and compared with the wild type (wt) isolates, the isolates with katG315Thr mutation were considerably more likely to be clustered. This study gives an insight into the *M. tuberculosis* genetic biodiversity in Varanasi, north India, the predominant spoligotypes and their impact on disease transmission. In this region of north India, TB is caused by a wide diversity of spoligotypes with predominance of four genotype lineages: Beijing, CAS, EAI and T. The Beijing genotype was the most frequent single spoligotype and strongly associated with multi drug resistant (MDR)-TB isolates. These findings may have important implications for control and prevention of TB in north India.

Xpert® MTB/RIF assay for tuberculosis diagnosis: evaluation in an Indian setting

V. P. Myneedu, D. Behera, A. K. Verma, M. Bhalla, N. Singh, J. Arora, R. Singhal, M. Mathur, P. Lal and R. Sarin. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(8)**: 958-60.

The present study was conducted to evaluate the performance of the Xpert® MTB/RIF assay and compare Xpert results with solid and MGIT 960 liquid culture system. A total of 134 patients who had failed the Category I or II regimen were recruited for evaluation. Xpert correctly identified all *Mycobacterium tuberculosis* isolates. The sensitivity and specificity of the Xpert assay for the detection of rifampicin resistance was respectively 98.2% and 97.0% when compared with MGIT 960 results.

Health-related quality of life in women exposed to wood smoke while cooking

I. N. Aggarwal, K. Umasankar and D. Gupta. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(8)**: 992-4.

Using the abbreviated World Health Organization Quality of Life (WHOQOL-Bref) questionnaire, we evaluated the effect of exposure to smoke from wood combustion while cooking on health-related quality of life (HRQL) in 85 women using wood and 85 women using liquefied petroleum gas (LPG) as cooking fuel in India. Age, years of cooking and hours spent daily in the kitchen were similar between women in the two groups. WHOQOL-Bref transformed scores in psychological, social relationships and environment domains were significantly lower in women in using wood than in those using LPG, suggesting that HRQL was impaired across domains among these women.

Value of adding an IGRA to the TST to screen for latent tuberculous infection in Greek health care workers

A. Charisis, A. Tatsioni, C. Gartzonika, A. Gogali, D. Archimandriti, C. Katsanos, A. Efthymiou, S. Katsenos, G. Daskalopoulos, S. Levidiotou, S. H. Constantopoulos and A. K. Konstantinidis. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(9)**: 1040-6.

The objective was to evaluate the value of adding an interferon-gamma release assay (IGRA) to the tuberculin skin test (TST) for detecting latent tuberculous infection (LTBI) in a Greek university hospital among health care workers (HCWs) predominantly vaccinated with Bacillus Calmette-Guerin (BCG). Of 788 HCWs enrolled, 68.1% were BCG-vaccinated. A TST □10 mm was considered positive and was followed by the QuantiFERON-TB® Gold In-Tube assay (QFT-GIT) in a two-step strategy. Of the enrolled HCWs, 36.4% were TST-positive, of whom only 14.4% were IGRA-positive. Agreement between the tests was poor (ê = 0.019; 95%CI -0.014-0.05, *P* = 0.355). Both TST and IGRA positivity increased with TST diameter, from 5.7%

in TST 10–14 mm to 48.8% in TST □20 mm. TST-positive, IGRA-negative results were most likely in younger, recently BCG-vaccinated HCWs (84.6% in those aged 20–29 years) and less likely in older HCWs (45% in those aged 50–59 years). The two-step strategy would have been more cost saving compared to the TST-only approach if adherence to LTBI treatment in our cohort had been □24%. Poor overall agreement between TST and QFT-GIT was found. Use of IGRA as a second step in TST-positive cases offers an appropriate tool for LTBI detection among BCG-vaccinated HCWs in low-TB-incidence settings.

Malnutrition associated with unfavourable outcome and death among South African MDR-TB and HIV co-infected children

R. M. Hicks, N. Padayatchi, N. S. Shah, A. Wolf, L. Werner, V. B. Sunkari and M. R. O'Donnell. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(9)**: 1074-83.

Pediatric multidrug-resistant tuberculosis (MDR-TB) is complicated by difficult diagnosis, complex treatment, and high mortality. In South Africa, these challenges are amplified by human immunodeficiency virus (HIV) co-infection; however, evidence on treatment outcomes among co-infected children is limited. Using conventional and new pediatric definitions, the objective was to describe treatment outcomes and identify risk factors for unfavourable outcome and mortality in children aged <15 years with MDR-TB or extensively drug-resistant TB (XDR-TB) in KwaZulu-Natal, South Africa. It was a retrospective cohort study in a regional TB referral hospital. From January 2009 to June 2010, 84 children (median age 8 years, IQR 4–12) with MDR-TB (n = 78) or XDR-TB (n = 6) initiated treatment. Sixty-four (77%) were HIV-positive and 62 (97%) received antiretroviral therapy. Sixty-six (79%) achieved favorable treatment outcomes. Overall mortality was 11% (n = 9) at 18 months after initiation of treatment. Malnutrition (aOR 27.4, 95%CI 2.7–278.7) and severe radiographic findings (aOR 4.68, 95%CI 1.01–21.9) were associated with unfavourable outcome. New pediatric outcome definitions increased the proportion classified as cured. It is possible to successfully treat pediatric MDR-TB-HIV even in resource-poor settings. Malnutrition is a marker for severe TB-HIV disease, and is a potential target for future interventions in these patients.

Effectiveness of directly observed treatment of tuberculosis: a systematic review of controlled studies

J. H. Tian, Z. X. Lu, M. Bachmann and F. J. Song. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(9)**: 1092-8.

There is controversy about the effectiveness of directly observed treatment (DOT) for anti-tuberculosis treatment. This systematic review aimed to synthesise evidence from studies that compared DOT and self-administered treatment (SAT) or different types of DOT for anti-tuberculosis treatment. Multiple databases were searched by two independent reviewers to identify relevant randomised (RCTs) and non-randomised studies. The risk of bias was independently assessed by two reviewers, and studies at high risk of bias were excluded. Data extraction was conducted by one reviewer and checked by a second reviewer. Primary outcome measures were cure and treatment success. We included eight RCTs and 15 non-randomised studies that were predominantly conducted in low- and middle-income countries. There was no convincing evidence that clinic DOT was more effective than SAT. Evidence from both RCTs and non-randomised studies suggested that community DOT was more effective than SAT. Community DOT was as effective as, or more effective than, clinic DOT. There was no statistically significant difference in results between family and non-family community DOT. Community DOT by non-family members might be the best option if it is more convenient to patients and less costly to health services than clinic DOT.

Understanding private retail drug outlet dispenser knowledge and practices in tuberculosis care in Tanzania

E. Rutta, A. Tarimo, E. Delmotte, I. James, S. Mwakisu, D. Kasembe, N. Konduri, R. Silumbe, K. Kakanda and R. Valimba. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(9)**: 1108-13.

The objectives were to assess 1) the level of knowledge about tuberculosis (TB) among dispensers in Tanzania's retail pharmaceutical sector; 2) practices related to identification of patients with suspected TB; 3) the availability of educational materials and training; and 4) the availability of first- and second-line anti-tuberculosis treatment in retail drug outlets. It was a cross-sectional descriptive study involving the administration of a structured questionnaire among drug dispensers in 122 pharmacies and 173 accredited drug dispensing outlets. Private retail drug outlets are convenient; most are open at least 12 hours per day, seven days/ week. Although 95% of dispensers identified persistent cough as a symptom of TB, only 1% had received TB-related training in the previous three years; 8% of outlets stocked first-line anti-tuberculosis medicines, which are legally prohibited from being sold at retail outlets. The majority of respondents reported seeing clients with TB-like symptoms, and of these 95% reported frequently referring clients to nearby health facilities. Private retail pharmaceutical outlets can potentially contribute to TB case detection and treatment; however, a coordinated effort is needed to train dispensers and implement appropriate referral procedures.

Airflow obstruction among street vendors who refill cigarette lighters with liquefied petroleum gas

S. Moitra, P. D. Blanc and B. B. Brashier. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(9)**: 1126-31.

The objective was to assess respiratory status among LPG-exposed workers and non-exposed controls. We quantified the exposure and evaluated respiratory symptoms and lung function among 113 LPG refilling workers (aged 41.9±9.9 years) and 79 controls (aged 40.8±7.2 years). We used multiple linear regression analysis to estimate the LPG exposure response within the group of refilling workers, adjusting for age, height and smoking status. Compared to the controls, the LPG-exposed lighter refillers manifested a 190 ml decrement in 1-second forced expiratory volume (FEV1) (2.55±0.4 *vs*. 2.26±0.3 l) and a 6% decrement in FEV1/forced vital capacity (FVC) (both $P < 0.05$). We found a significantly negative exposure response among the LPG workers: for FVC and FEV1, 44 ml per ml of reported daily LPG use in refilling ($P < 0.05$). Likely heavy exposure to LPG through manually refilling cigarette lighters is associated with airflow decrements. This adverse effect may be relevant to other occupational groups heavily exposed to volatile hydrocarbons, especially those in marginal employment sectors.

Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients

K. J. M. Aung, A. Van Deun, E. Declercq, M. R. Sarker, P. K. Das, M. A. Hossain and H. L. Rieder. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(10)**: 1180-7.

The objective was to summarize the outcome and its determinants of the first treatment for multidrug-resistant TB using a standardized regimen consisting of a minimum nine months. This was a prospective, observational study of a gatifloxacin (GFX) based directly observed regimen, mainly with initial hospitalization. The 4-month intensive phase was extended until sputum smear conversion. Patients were monitored using culture for up to two years after treatment completion. Of the 515 patients who met the study inclusion criteria and were successively enrolled from 2005 to 2011, 84.4% had a bacteriologically favourable outcome. Due to extensive disease with delayed sputum conversion, only half of the patients completed treatment within nine months; however, 95% were able to complete treatment within 12 months. Eleven patients failed or relapsed, and 93.1% of the 435 patients who were successfully treated completed at least 12 months post-treatment follow-up. The strongest risk factor for a bacteriologically unfavourable outcome was high-level fluoroquinolone (FQ) resistance, particularly when compounded by initial pyrazinamide (PZA) resistance. Low-level FQ resistance had no unfavourable effect on treatment outcome. Amplification of drug resistance occurred

only once, in a patient strain that was initially only susceptible to kanamycin and clofazimine. The excellent outcome of the Bangladesh regimen was largely maintained. Bacteriological treatment failures and relapses were rare, except among patients with high-level GFX resistance, notably in the presence of PZA resistance.

Chest radiography for active tuberculosis case finding in the homeless: a systematic review and meta-analysis

K. Paquette, M. P. Cheng, M. J. Kadatz, V. J. Cook, W. Chen and J. C. Johnston. *The International Journal of Tuberculosis and Lung Disease* 2014; **18(10)**: 1231-6.

In low-incidence regions, tuberculosis (TB) often affects vulnerable populations. Guidelines recommend active case finding (ACF) in homeless populations, but there is no consensus on a preferred screening method. We performed a systematic review and meta-analysis to evaluate the use of chest X-ray (CXR) screening in ACF for TB in homeless populations. Articles were identified through EMBASE, Medline and the Cochrane Library. Studies using symptom screens, CXRs, sputum sweeps, tuberculin skin tests and/or interferon-gamma release assays to detect active TB in homeless populations were sought. Data were extracted using a standardised method by two reviewers and validated with an objective tool. Sixteen studies addressing CXR screening of homeless populations for active TB in low-incidence regions were analysed. The pooled prevalence of active TB in the 16 study cohorts was 931 per 100,000 population screened (95%CI 565–1534) and 782/100,000 CXR performed (95%CI 566–1079). Six of seven longitudinal screening programmes reported a reduction in regional TB incidence after implementation of the CXR-based ACF programme. Our data suggest that CXR screening is a good tool for ACF in homeless populations in low-incidence regions.

NATCON-2014

69TH NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES (NATCON 2014)

The 69th National Conference on Tuberculosis and Chest Diseases (NATCON 2014), under the joint auspices of the Tuberculosis Association of India and the Maharashtra State Anti-Tuberculosis Association, Mumbai, will be held at The Lalit from 5th to 7th February, 2015.

Papers/Posters on the following subjects are welcome for the above Conference:

1. Epidemiology of TB
2. RNTCP, HIV-TB, MDR-TB, XDR-TB
3. Pneumonia, COPD and Asthma
4. TB Diagnostics
5. Sleep-Disordered Breathing
6. Public & Private Partnership for DOTS Implementation
7. Tobacco & Lung Health
8. Paediatric Tuberculosis
9. Bird Flu (Avian Influenza)
10. Surgery in Pulmonary Tuberculosis
11. Advocacy, Communication and Social Mobilisation (ACSM)
12. Socio-behavioural studies in HIV and TB
13. Lung Health
14. TB & Diabetes
15. Pulmonary rehabilitation
16. Information Technology in Respiratory Diseases
17. Indoor Air Pollution
18. Air borne infection control

It will be appreciated if you can participate as well as kindly bring this circular to the notice of all TB and Chest Diseases Workers with you and in your area. The participants should let us know, whether they would like to present academic papers/posters on any of the above subjects and, if so, to forward the abstracts of the same **by 15th December, 2014 to the Secretary General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-110001;** Telephone: 23715217; Telefax: 23711303**; E-mail:** tbassnindia@yahoo.co.in**.** The guidelines for preparation of abstracts/slides/ transparencies are as follows:

GUIDELINES FOR AUTHORS

A) For preparing abstracts :

1. The length of an abstract should normally not exceed 250 words, including the heading.
2. The abstract should comprise (a) objectives of the study, (b) methodology of investigation and (c) main findings. In respect of some papers, (b) and (c) may comprise the idea/hypothesis, discussion and conclusion. Phrases like “findings will be presented at the Conference” are unhelpful.
3. If analysis is incomplete at the time, a revised abstract should be sent, at least six weeks prior to the Conference to be included in the “Programme and Summaries” for distribution among delegates.
4. An inadequate abstract may not be selected by the Programme Committee for presentation.

B) For preparing projection slides :

1. Material on the slide should be relevant, minimum, in bold letters/figures and computer composed.

2. Material should normally cover 3/5 of the available space on the slide (35mm) with margins on all sides. Professional assistance is preferable.
3. Blue on white background is better than black and white slides. For multi-colour slides, the preferable colours are red, black and green on white background.

C) For preparing posters :

1. The dimensions of your poster should not exceed 60cm horizontallyx120cm in vertical length.
2. Avoid putting too much material and text on the poster.
3. The heading should have letters at least 35mm high listing the title of the paper, authors, institution and its location.
4. Lettering for text and illustrations must be at least 10mm high, or typed clearly.

5. Divide your poster into Introduction, Objectives, Methods, Results, Discussion and Conclusions. Each of these sections should be in sequence to guide the reader through the poster.
6. The introduction should contain 3 to 5 sentences outlining essential information necessary to understand the study and why it was done.
7. The objective of the study, the questions to be asked or the hypothesis to be tested should be clearly stated in as few words as possible.
8. Outline your methods briefly.
9. Results should be presented as graphs or tables. They should be self-explanatory and therefore please provide a clear legend including symbols. You may also want to provide an interpretation of the results below each panel.
10. The discussion (if necessary) and conclusions should be succinctly stated on large type. Many viewers read this first, hence it should be easy to understand.

For further details, you may please contact: Dr.V.K. Arora, Vice-Chairman (P&R), E.mail:vijaykumar1945@gmail.comm; Mobile No.; 9818001160; Mr. Tejinder Ahluwalia, Secretary General, Mobile No.9810550888; Dr.Y.N Dholakia, Honorary Secretary & Honorary Technical Adviser, Maharashtra State Anti-TB Association; E-mail: yatindholakia@gmail.com, msatba@gmail.com; Mobile No.9869105521.

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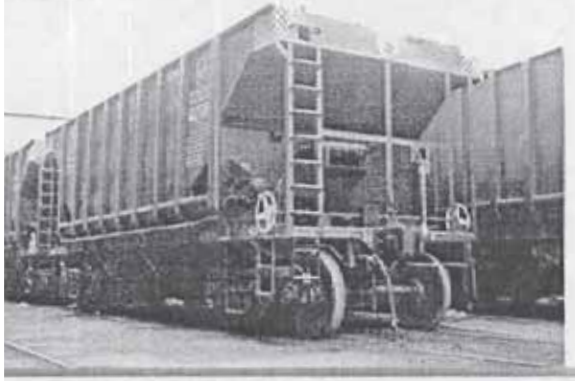

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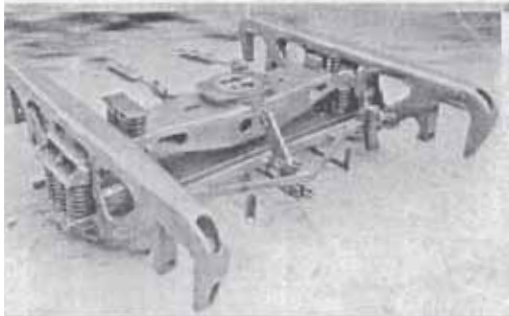

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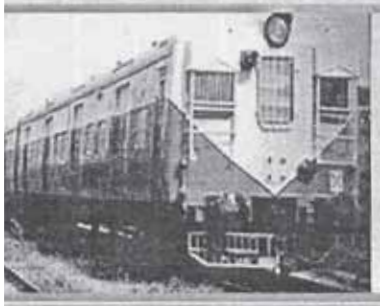

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