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ABSTRACT

Tuberculosis continues to be a major adversary of human health and life since time immemorial. The expanding AIDS pandemic has gravely boosted incidence, prevalence, and severity of tuberculosis. Two decades earlier, therefore, the WHO has proclaimed tuberculosis as an emergency in health care. The disease is integrated with weak spots of human living, environment, habits and socioeconomic profile. Mycobacteria are essentially fought with drugs and development of resistance to antitubercular drugs is a great medical challenge. The traditions of prevention and control of tuberculosis are historically established and continue to progress in parallel to unending disease burden. Perpetual adaptations of strategies for control exemplifies holistic understanding in medicine and particularly tuberculosis. In the scientifically advanced but economically modest national context, tuberculosis control programmes remain major frontier of medicine. This article attempts to briefly overview the context.

Keywords: Antitubercular drugs, HIV/TB comorbidity, RNTCP, Tuberculosis

INTRODUCTION

Tuberculosis including multidrug resistant forms constitutes major disease burden and infective killers in the third world nations. The synergy of TB and AIDS has now posed emergency for global health care. Enduring chemotherapy is an essential strategy to fight tuberculosis. National tuberculosis control programme (NTCP) in India was launched in 1962. Soon followed the availability of very effective and well-tolerated drugs such as rifampicin and pyrazinamide, serving core for combination regimens. Most of the currently used two dozen drugs became available many years before. Discovery of new drugs is very slow in tuberculosis. Varied treatment strategies for mitigation, cure and prevention of TB include, directly observed treatment short course [DOTS] and DOTStplus. Recombinant human interleukin2 aerosol, recombinant interferon-gama, improvised BCG etc are being employed as adjuncts.

ANTITUBERCULAR CHEMOTHERAPY

The WHO guideline provides for initial INTENSIVE phase which is intended to make sputum culture mycobacterium negative. Four basic drugs employed in initiating treatment in newly diagnosed [presumably drug sensitive] cases of tuberculosis, are called PRIMARY antitubercular drugs. These are ISONIAZID, RIFAMPICIN, PYRAZINAMIDE, and ETHAMBUTOL. Young children and pregnant women may be given only three drugs. Treatment is continued after INTENSIVE phase with two drugs, isoniazid and rifampicin for another 4 months [extended up to 7 months as per clinical judgement].

The patients need to take drugs daily [three weekly in some instances]. Any interruption of drug or dose imposes a risk of therapy failure and development of resistant infection. Inadequate treatment may eliminate weaker and allow stronger drug resistant mycobacterial strains. Patients highly likely to get multi-drug resistant TB [MDR-TB] are those with weakened immune competence, those suffering a relapse, the contacts of MDR-TB patients often in prison, shelters for homeless, hospitals etc.

DOTS AND THE RNTCP

The reemergence of tuberculosis led WHO to declare TB as a global emergency in 1993 and recommend adoption of DOTS [directly observed treatment short course] strategy in member countries for control of Tuberculosis. The DOTS strategy is based on governmental commitment and sustained funding to the TB control programmes. The functional infrastructure is a must for diagnostic testing of sputum smear; uninterrupted supply of high-quality antitubercular drugs; supervised direct drug intake by patients and accurate record keeping and reporting of registered cases. DOTS strategy was the cardinal adoption. A health professional directly observes medicine intake by TB patients through the daily office or home visits. Chemotherapeutic sensitivity profile of infecting mycobacterial strains is also supposed to be worked out. The government of India launched Revised National Tuberculosis control programme [RNTCP] in 1997. The RNTCP centre should be competent also in managing MDR-TB cases.

MDR-TB

TB infection resistant to the two most potent anti-TB drugs isoniazid and rifampicin is termed MDR-TB. When the mycobacterium is also resistant to any or more second line drugs it is termed XDR-TB [extensively drug resistant]. Resistant infection is not curable by short course chemotherapy. Extended treatment even beyond two-year period employing alternative costly, toxic drugs is indicated which may not be highly effective.

Drugs available to treat a resistant form of infection are grouped as per effectiveness, use experience, and class. The Group 1 includes First Line drugs except streptomycin injection. Group 2 consists of injectable drugs streptomycin, kanamycin, amikacin, and capreomycin. Group 3 comprises of Fluoroquinolones, viz levofloxacin, ofloxacin, moxifloxacin. Group 4 includes oral bacteriostatic agents as PAS [para-amino salicylic acid], thionamide, prothionamide, cycloserine, terizidone. An additional Group 5 includes agents having yet unsettled efficacy profile. These provide a treatment option for XDR-TB or TDR-TB [ Totally resistant]. The agents exemplifying the class are clofazimine, linezoid, thioacetazone, amoxicillin/ clavulinate, imipenem/ cilastatin, clarylthromycin, supra dose isoniazid etc.

PMDT AND DOTS-PLUS

WHO has put forth guidelines for Programmatic Management of Drug Resistant Tuberculosis [PMDT] in 2006. This strategy was incorporated as DOTS-Plus, under the RNTCP in 2007. The DOTS-Plus is a complex strategy. Timely detection of cases needing drug sensitivity testing of infecting mycobacteria is imperative to success. Pressing requirements include, strong diagnostic laboratory capable of rapid molecular [PCR] testing; efficient supply mechanism for drugs; standardised recording and reporting of treatment status of patients; prompt detection and management of drug side effects and adverse effects; and vigilance and support to promote patient adherence to poorly tolerated drug regimen for long period. Uplift of diagnostic capacity with cost feasibility, however, are the critical perspectives.

In countries with high incidence of tuberculosis, identification of overt secondary cases and their prompt treatment remains the
goal of TB control programmes. In countries with low incidence, contact tracing for detection of latent disease to exhaust reservoir of future cases by appropriate treatment is adopted as a strategy [4]. Short course chemotherapy regimens primarily aim at enhancing treatment adherence. Resistance to anti-TB agents results consequent to inadequate treatment, a poor case holding, substandard drugs and irregular supplies, ignorance of health worker of consequences of interrupted treatment [often following apparent side effects]. The patient population may be vulnerable on account of illiteracy, low socioeconomic status, heavy load of infection, delay in laboratory diagnoses and results of mycobacterial sensitivity tests.

Treatment default is defined as interruption of anti-TB treatment for at least two consecutive months and is the major threat to TB control. Subpopulations of TB patients, more likely to default, in a given area, need characterisation for appropriate adjustments possible in the treatment regimen. Defaults tend to associate older age, smear-negative and extrapulmonary disease and longer treatment course. Most often defaults occur in the continuation phase of chemotherapy, although early defaults were also reported[5]. Resolution of symptomatic disease and perceived harshness of direct/indirect cost of therapy appear to be contributory.

The laboratory facilities available at RNTCP units lack uniformity and quality standards[6]. Weak laboratory capacity is a major barrier to identification of MDR-TB. The MDR-TB currently constitutes 2-3% per 1000 of active TB cases. This has very serious implications for TB control. The World witnesses about 0.4 million cases of multi-drug resistant TB occurring each year. While, second line drug therapy may not be problematic, ensuring adherence is crucial. This may implicate hospitalisation as well. Patient safety issues call for enhanced facilities for personalised selection of therapeutic regimens. The mycobacterial non-tuberculosis of the lung is caused by mycobacterium avium complex in 80% instances. Infection is believed to be soilborne. Drug regimens are still being ascertained for choice, however, Rifampicin, ethambutol, CAM 400 to 800 mg and an aminoglycoside are quite effective[7].

DEALING WITH LATENT INFECTION [INFECTION RESERVOIR]

One-third of the global population is TB infected. Only 5 to 10 % of these develop the disease, and rest 90-95% constitutes latent infection. It is challenging, as the available tuberculin skin test and interferon gama release assay are poorly predictive of who would develop the disease. Its detection in high-risk persons, eg. HIV-infected persons, with the autoimmune inflammatory disease, cancer etc is crucial[8]. World wide, the treatment of latent disease is considered to be TB control. For treating high-risk individuals, isoniazide is the first choice. Alternatives are considered for increasing therapy adherence, cost savings etc[9]. Upcomming novel molecular assays for diagnosis and drug susceptibility testing offer advantages. Approach to TB control involves new effective vaccines, more effective and rapid diagnostic tools as well as new drugs. Most studies of mycobacterial immunity attribute focus on the proliferation of T cells, production of cytokines and cytolytic activity. A proper vaccine for TB can be developed by using a combination of antigens and adjuvants capable of inducing appropriate and long-lasting T cell immunity [10].

THE HIV/AIDS IMPACT

The emergence of HIV/AIDS pandemic and widespread use of immunosuppressing medications has impacted epidemiology of tuberculosis infection. Classical clinical symptoms and signs have changed. Concomitant TB diagnosis would frequently require molecular tests such as PCR and histopathological examination of biopsy specimen[11]. The risk of developing TB increases 20 to 40 times in HIV-infected people, including a higher risk of extra pulmonary disease[12]. HIV/TB coinfection is prone to cause the emergence of MDR-TB [13]. Over a quarter of the HIV infection related deaths are attributable to co-infection with tuberculosis[14] Co-ordination of activities common for HIV and TB, including the reciprocal inclusion of TB/HIV interventions, is crucially assimilated in national health policies in India[15].

The short course TB treatment remains relevant for treating TB/HIV coinfected cases. The recommended anti retroviral regimen in India for HIV/TB coinfected patients is a combination of two non-NRTI [nucleoside reverse transcriptase inhibitor] drugs plus Efavirenz or less often Nevirapine. The NRTI combination used are, zidovudin with lamivudine and lamivudine; tenofivir with lamivudine. Occasionally, abacavir with lamivudin or didanosine with lamivudine may be used [15]. A common side effect of HAART [highly active antiretroviral therapy] is worsening of tuberculosis due to IRIS [immune reconstitution inflammatory syndrome][16].

Investigation of HIV status is now part of routine check-up of TB patients. The medical colleges mostly house the ARTs [antiretroviral treatment centres] in India. The need for high-level specialization at RNTCP units for successful implementation of DOTS-Plus and TB/HIV coinfection management makes medical colleges the preferred locations. In any case integration of medical colleges in close co-ordinating framework of healthcare is crucial to efficient prevention and control of these diseases.[17].

NEW ANTIBIOTIC DEVELOPMENT

The XDR-TB and TDR-TB are rational targets for surgical removal of infected tissue. Disease in these instances, however, is too widely spread, compromising the effort. New anti-TB drug discovery aspires to make available, shorter, simpler and affordable drug regimens with better tolerability, efficacy, and safety. The Possibility of drug interaction with antiretroviral treatments is also an important consideration. A new anti-TB drug should be effective in combination, including combination with ART. The new agent should permit effective combination in exclusion of isoniazid or rifampicin. This implies use to prospect for treating drug-resistant TB. Nitro-imidazo-oxazole agents are promising as possible future drugs. Fluoroquinolones moxifloxacin and gatifloxacin may hopefully provide substitute for isoniazid or ethambutol for shorter 4-month regimen [18]. Rifamycins are potent inhibitors of mycobacteria. Semisynthetic rifamycins viz. rifampicin, rifabutin, and rifampentine have been employed against various infections. Rifampicin is a key component of first line anti-TB chemotherapy. Rifapentin may be used in the shorter course and intermittent chemotherapy regimens for tuberculosis.

As facets of microbial metabolism have largely been exhausted for anti-microbial drug development, host proteome now promises targets for manipulation for eradicating intracellular bacteria, including mycobacteria [19]. Current evidence indicates that mycobacterial infection causes a time-dependent increase in PPAR-gamma expression, resulting in increased formation of lipid droplets that downregulate macrophage function. This provides escape to mycobacteria from macrophage killing. Inhibition of PPAR-gama enhances macrophage mycobacterial killing, suggesting potential scope for adjunctive anti-TB therapy [20].

NEWER UNDERSTANDING OF PATHOGENESIS AND SCOPE FOR STEM CELL IMMUNOTHERAPY

After invading the host, mycobacteria behave as intracellular pathogens and elicit Th1 immune response resulting in the granuloma. The subsequent second phase of disease development, however, involves survival of TB bacilli in the extracellular state. This mystery forms major research focus and its resolution would place the TB care on better footing. Some well-documented studies describe the smear negative cases as responsible for transmission of 15to20% new infections. Lesser than 5to10 thousand bacilli per field may not be visualized microscopically. There can be a failure of visualization of extracellular bacilli adopting pellicle form, detectable only by fluorescent microscopy. M.tuberculosis form biofilm as a mechanism to tolerate anti-TB chemotherapy. Pellicle shields the bacilli from an attack of host immune cells and thus source for disease reactivation persists. Reactivation occurs in immunodeficient states as old age, HIV infection, other lung infection, immunosuppressive therapy in autoimmune disease etc. The extracellular bacilli are beyond the reach of host immune T
cell attack as well as conventional chemotherapeutic agents[21]. Overall immune response to mycobacterial antigens decreases in tuberculosis, while inflammatory cytokines play a major role in the perpetuating destruction of lung tissue. Current research shows tissue specific mesenchymal stem cells can modify dendritic cell function inducing T cell unresponsiveness. This would check tissue destruction that enables mycobacteria to persist and cause disease. Overtly, this would appear to also shield mycobacteria from immune attack. The immunotherapeutic concept is gaining ground [22].

**VACCINE PERSPECTIVE**

BCG is found to provide protection against childhood miliary tuberculosis but offers no consistent protection against pulmonary tuberculosis in the adult. Attempts to vaccine development include boosters of BCG [the only approved TB vaccine], or its replacement. It is indicated that route of immunization determines the geographical location of TB-reactive T cells. It is this distribution that predicts protective immunity conferred by the vaccine. Such vaccines that are able to localize the TB lymphocytes to lung and airway mucosa may enhance immune protection as desired.[23].

Most vaccines do not prevent infection but prevent the occurrence of disease. Enormous prevalence of tuberculosis makes a scope for protection on top of established infection quite relevant. New vaccines aim to elicit robust long-lasting T cell responses against mycobacterial antigens, with implications to reduce disease transmission. There is emerging trend of developing synthetic peptide-bound immunogens for anti-TB vaccination [24].

**PERSPECTIVE OF NUTRITION CARE**

Wasting is a well-recognized feature of TB, found in 75% of patients with active disease [25]. In contemporary tuberculosis management, nutrition care is precariously neglected. Malnutrition being a major contributor to poor immune competence may allow eruption of active disease from latent infection. A grade of malnutrition significantly associates reduced cellular immune response, the ratio of CD4+/CD8+ T cells and IL2 production by mononuclear cells and NK cells. Protein-energy malnutrition is found significant in tuberculosis [26].

Dietary supplements in patients exhibiting pronounced wasting must be considered [27]. Evidence of gains in lean mass and grip strength in patients with nutritional care leading to a faster recovery in TB is furnished in clinical studies [28]. Recent data show that chronic worm infestation and micronutrient deficiencies, eg., vitamin D, arginine, are potential areas of intervention to optimize host immunity. Nutritional supplements to enhance nitric oxide production and vit D mediated effector functions as well as treatment of worm infestation reduce immunosuppression [meditated vide Treg over activity]. The approach may be more suitable than adjuvant immunostimulant cytokine therapy, for endemic areas [29].

**EPILOGUE**

STOP-TB motto of WHO envisages eliminating TB as a global public health problem by 2050 [30]. The collaboration of physicians, corporations, religious bodies, NGOs etc is mandatory for effective propagation of people’s awareness of critical issues of TB infection and its control, which is a crucial facilitator for diagnosis, management, and control. Major challenges in India include substandard primary health care infrastructure in rural areas in many states. The virtual absence of regulation of private health care is leading to the widespread irrational use of anti-TB Drugs. Unfortunately consequences of weak political will would compound with abundant administrative corruption. HIV infection is on the rise. National Rural Health Mission has the intention to reform rural primary health care and strengthen Tuberculosis control programmes in India in not so distant, future.

**REFERENCES**