TUBERCULOSIS CONTROL: PERSPECTIVE AND PROGRAMMES

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ABSTRACT

Tuberculosis continues to be major adversary of human health and life since time immemorial. The expanding AIDS pandemic has greatly boosted incidence, prevalence and severity of tuberculosis. Two decades earlier therefore, the WHO has proclaimed tuberculosis as 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 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 exemplify 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. Synergy of TB and AIDS has now posed emergency for global health care. Enduring chemotherapy is 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 DOTS plus. Recombinant human interleukin-2 aerosol, recombinant interferon-gamma, 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 medications. 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 (thrice weekly in some instances). Any interruption of drug or dose imposes 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 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 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 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.
health professional directly observes medicine intake by TB patients through daily office or home visits. Chemotherapeutic sensitivity profile of infecting mycobacterium in patient is also supposed to be worked out. Government of India launched Revised National Tuberculosis control programme (RNTCP) in 1997 [1]. 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 [2]. Drugs available to treat 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, 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 treatment option for XDR-TB or TDR-TB (Totally resistant). The agents exemplifying the class are clofazimine, linezolid, thioacetazone, amoxicillin/clavulinate, imipenem/cilastatin, clarythromycin, 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 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 antitubercular drugs; efficient recording and reporting of treatment status of patients; prompt detection and management of drug side effects and adverse effects; and vigilence 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 [3].

In countries with high incidence of tuberculosis, identification of overt secondary cases and their prompt treatment remains 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 strategy [4]. Short course chemotherapy regimens primarily aim at enhancing treatment adherence. Resistance to anti-TB agents results consequent to inadequate treatment, 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, delays 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 treatment regimen. Defaults tend to associate older age, smear negative and extra pulmonary disease, and longer treatment course. Most often defaults occur in 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 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. 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 adherance is crucial. This may imply hospitalization as well. Patient safety issues call for enhanced facilities for personalized selection of therapeutic regimens. The mycobacterial nontuberculosis of 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 global population is TB infected. Only 5 to 10 % of these develop disease, and rest 90-95% constitute latent infection. It is challenging, as the available tuberculin skin test and interferon gama release assay are poorly predictive of who would develop disease. Its detection in high risk persons. HIV infected, persons with autoimmune inflammatory disease, cancer etc is crucial [8]. Worldwide, the treatment of latent disease is considered key to TB control. For treating high risk individuals, isoniazide is the first choice. Alternatives are considered for increasing therapy adherenece, cost savings etc [9]. Upcoming, 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 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

Emergence of HIV/AIDS pandemic and wide spread use of immunosuppressing medications has impacted epidemiology of tuberculosis infection. Classical clinical symptoms and signs have changed. Confirmation of TB diagnosis would frequently require molecular tests such as PCR and histopathological examination of biopsy specimen [11]. Risk of developing TB increases 20 to 40 times in HIV infected people, including higher risk of extra pulmonary disease [12]. HIV/TB co infection is prone to cause emergence of MDR-TB [13]. Over quarter of the HIV infection related deaths are attributable to co-infection with tuberculosis [14] Coordination of activities common for HIV and TB, including 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 co infection. The recommended anti retroviral regimen in India for HIV/TB co infected patients is combination of two non-NRTI (nucleoside reverse transcriptase inhibitor) drugs plus Efavirenz or less often Nevirapine. The NRTI combination commonly used are, zidovudin with lamivudine; stavudine with lamivudine; tenofovir with lamivudin. Occasionally, abacavir with lamivudin or diadenosine 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 checkup of TB patients. The medical colleges mostly house the ARTs (anti retyroviral treatment centres) in India. The need for high level specialization at RNTCP units for successful implementation of DOTS-Plus and TB/HIV co infection management makes medical colleges the preffered 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 ANTI TB DRUG 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 making available, shorter, simpler and affordable drug regimens with better tolerability, efficacy and safety. The Possibility of drug interaction with anti retroviral treatments is also an important consideration. A new anti TB drug should be effective in combination, including combination with ART. New agent should permit effective combination in exclusion of isoniazid or rifampicin. This implies use 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 rifapentine have been employed against various infections. Rifampicin is key component of first line anti TB chemotherapy. Rifapentin may be used in 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-dependant increase in PPAR-gama expression, resulting in increased formation of lipid droplets that down regulate 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 granuloma. Subsequent second phase of disease development however, involves survival of TB bacilli in 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 15 to 20% of new infections. Lesser than 5 to 10 thousand bacilli per field, may not be visualized microscopically. There can be failure of visualization of extracellular bacilli adopting pellicle form, detectable only by fluorescent microscopy. M.tuberculosis form biofilm as mechanism to tolerating anti-TB chemotherapy and persist. Pellicle shields the bacilli from 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 bacteria are beyond 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 major role in 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 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 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-reactive T lymphocytes to lung and airway mucosa may enhance immune protection as desired [23].

Most vaccines do not prevent infection, but prevent occurrence of disease. Enormous prevalence of tuberculosis makes 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 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 major contributor to poor immune competence may allow eruption of active disease from latent infection .Grade of malnutrition significantly associates reduced cellular immune response, 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 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 vitD mediated effector functions as well as treatment of worm infestation reduce immunosuppression (mediated 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 global public health problem by 2050 [30]. Collaboration of physicians, corporates, religious bodies, NGOs etc is mandatory for effective propagation of people’s awareness of critical issues of TB infection and its control, which is 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 widespread irrational use of anti TB Drugs. Unfortunate consequences of weak political will compound with abundant administrative corruption. HIV infection is on rise. National Rural Health Mission has intention to reform rural primary healthcare, which must strengthen Tuberculosis control programmes in India in not so distant, future.

REFERENCES


