MDR TB - CURRENT ISSUES

[Indian J Tuberc 2004; 51:1-3]

Drug resistance in *M. tuberculosis* was observed even in the early days of chemotherapy. The current threat is due to the emergence of strains resistant at least to Isoniazid (H) and Rifampicin (R) (MDR TB). Despite TB being 100% curable, patients develop drug resistant tuberculosis due to various reasons. The level of initial drug resistance is said to be an epidemiological marker to assess the success of the National TB Programme. This also influences the design of the regimens to be employed as well as policy decisions. The response to treatment of patients with MDR-TB is poor and the mortality rate is usually high. Since these patients need to be treated with expensive and toxic second line drugs, and may require hospitalization to manage their toxic reactions and other complications, they require a sizable proportion of health care resources.

Currently available regimens to treat MDR- TB are 4 to 10 times more likely to fail than standard therapy for patients with drug-susceptible organisms. After the introduction of Rifampicin, no worthwhile anti-tuberculosis drug with new mechanism(s) of action has been developed in over thirty years. Moreover, no new drugs that might be effective in the treatment of MDR- TB are currently undergoing clinical trials. Recently, a series of compounds containing a nitromidazopyran nucleus that possess anti-tuberculosis activity has been described. After activation by a mechanism dependent on *M. tuberculosis* F420 co-factor, nitroimidazopyrans inhibited the synthesis of protein and cell wall lipid. In contrast to current anti-tuberculosis drugs, nitroimidazopyrans exhibited bactericidal activity against both replicating and dormant *M. tuberculosis*. Lead compound PA-824 showed potent bactericidal activity against multi-drug-resistant *M. tuberculosis* and promising oral activity in animal models. It is being hoped that these nitroimidazopyrans offer the practical qualities of a small molecule with potential for the treatment of tuberculosis.

Presently, flouroquines (Ofloxacin, Ciprofloxacin), aminoglycosides (Kanamycin, Capreomycin), PAS, Cycloserine, Ethionamide and Prothionamide are the second line drugs that are often used to treat MDR- TB. Though β-lactam antibiotics have shown impressive *in vitro* activity, they seem to have limited utility in the field setting. Though it may seem that the greater the number of drugs used, the greater would be the chance of having at least two drugs to which the organisms may be sensitive, this also means that there is greater chance of toxicity and an enormous increase in the cost of treatment.

MDR-TB is essentially a bacteriological diagnosis and it implies that the bacilli have been proved to be resistant to at least Rifampicin and Isoniazid by *in vitro* culture and sensitivity testing. Therefore, for the diagnosis and management of MDR-TB cases, existence of a well-functioning mycobacterial laboratory is mandatory.

Due to difficulties in collecting comparable data from different countries/regions and in order to assist NTPs in establishing policies, the WHO and IUATLD launched in 1994, with several partners, a global Drug Resistance Surveillance (DRS) programme. The first global report on DRS was released in 1997 and included data from 35 countries/geographical sites. This report showed that drug resistance was ubiquitous. Median prevalence of resistance to at least one drug among new tuberculosis cases was 9.9% (range: 2-41%) and MDR- TB was 1.4% (range: 0-14%). MDR-TB among new cases proved to be
a problem in some countries including Estonia, Latvia, Ivanovo Oblast in Russia, the Dominican Republic, and Cote d’Ivoire. As expected, high prevalence of drug resistance among previously treated cases was found in many of the countries surveyed. The median prevalence of resistance to at least one drug was 36% (range: 5-100%) and MDR-TB was 13% (range: 0-54%). A second global report followed in 2000 and included data from 58 countries/geographical sites and importantly, trends from 28 sites. Prevalence of resistance to at least one drug among new cases was 10.7% (range: 2-36%) and MDR-TB was 1% (range: 0-14%). These findings were not much different from the findings of the previous report. Several of the previous “hot spots” for MDR-TB were confirmed again; however, others were added to the list including new areas in Russia (Tomsi Oblast) and China (the provinces of Henan and Zhejiang). Among previously treated cases the prevalence of resistance to at least one drug was 23% (range: 0-94%) and MDR-TB was 9% (range: 0-48%). In summary, 72 countries/geographical sites were surveyed between 1994 and 2000; from these studies, the median prevalence of MDR-TB was found to be 1%.

The prevalence of multi-drug resistance in a community is of importance where drug regimens under DOTS are given, since the two main bactericidal drugs i.e. Isoniazid and Rifampicin used in the regimens are not expected to yield optimum desired results. Chronic sputum positive patients with an unfavourable outcome could continue transmitting the drug-resistant bacilli to healthy members of community, thereby increasing TB in the community. The response to primary SCC in initial HR resistance is very poor, irrespective of the regimen prescribed, the number of drugs used and the rhythm of administration. The favourable response in MDR-TB patients to various re-treatment regimens containing quinolones given along with other anti-tuberculosis drugs too is only 50%. Even when the regimens are individually tailored, the cure rate is low. Thus, there is an urgent need to evolve and evaluate suitable regimens for the MDR cases.

Second-line drugs are very difficult to obtain in small towns and rural areas in India. Therefore, reliable supply of drugs is a difficult problem. While the standard short-course regimen with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for 6 months may cost less than Rs. 1000, the cost of treatment with second-line drugs works out to be several times more. Reliable pharmacokinetic data regarding bioavailability of most of these formulations are not available either. Moreover, there is no assurance that the most expensive brand names have the best bioavailability profile. Even considering the cheapest brand names available, the cost of drug treatment alone is much beyond the means of the average Indian patient. Therefore, long term compliance is not very good. All these factors constitute significant challenges for the clinicians treating MDR-TB in a field setting.

While continuing to ensure that DOTS strategy is given top priority, WHO has realized that in areas where the prevalence of MDR-TB is high, it represents a special threat to tuberculosis control, and has advocated the policy of DOTS-plus. In populations where MDR-TB is endemic, the outcome of the standard short-course chemotherapy regimen remains uncertain. Unacceptable failure rates have been reported and resistance to additional drugs may be induced. As a consequence there have been calls for well-functioning DOTS plus programmes to provide additional services in areas with high rates of MDR-TB. These programmes may need to modify all five elements of the DOTS strategy: (i) the treatment may need to be individualized rather than standardized; (ii) laboratory services may need to provide facilities for culture and drug susceptibility testing; (iii) reliable supplies of a wide range of expensive second line drugs would have to be ensured; (iv) operational studies would be required to determine the indications for expanded programmes, and (v) their format. Financial and technical support from international organizations and developed nations would be needed in addition to that obtained from local governments. If DOTS-plus programmes are established, they may prove highly beneficial for patients with MDR-TB.
Several agents have evoked interest as potential adjunctive treatment for patients with MDR-TB. Though very little information is available regarding their clinical utility, they are described here considering their therapeutic potential. Thalidomide and pentoxifylline have been shown to combat the excessive effects of TNF-α. They may be useful in limiting the wasting associated with MDR-TB. Other agents which have occasionally been considered include, levamisole, transfer factor, inhibitors of transforming growth factor β (TGF β), interleukin-12, interferon-α (IFN α) and imiquod an oral agent which stimulates the production of IFN-α. Though there have been anecdotal reports of their usefulness, further studies are required to clarify their role.

Although there are barriers to widespread drug susceptibility testing, baseline screening to identify drug resistance early and to guide re-treatment efforts may be essential to stop the avalanche of acquired drug resistance. Anti-mycobacterial agents should be manufactured with strict quality controls to assure adequate bioavailability. National Programmes should apply modern techniques of molecular epidemiology to identify the entry and expansion of virulent clones of MDR-TB in the population. Support for drug discovery programmes should be given priority. Current availability of the complete genome of M. tuberculosis and considerable understanding of the metabolism of the unique mycobacterial cell wall will help accelerate the process. Operational [uninterrupted supply of drugs] and economic issues [affordable agents] are critical for the care of patients with drug susceptible and drug resistant tuberculosis. DOTS and DOTS-plus programmes are essential in the prevention and management of drug resistance.

M.M. SINGH
K.K. CHOPRA

REFERENCES

Dr. P.K. Sen was closely associated with Tuberculosis Association of India and the Indian Journal of Tuberculosis for a long time. He was nominated to the prestigious post of the President of the Association and remained in that capacity till 1996. He was editor of the Indian Journal of Tuberculosis for a long time and then Editor Emeritus till his sad demise in 1999.

Born on 31st December, 1904, Dr. P.K. Sen graduated from the Calcutta Medical College in 1929. He won the “SEHRGUT”, the highest distinction in M.D. Degree of the University of Berlin in 1933. He stood first in the TDD examination in the University of Wales in 1934 and was later awarded the Ph. D. by the University. He won the Deutsche Academic and Humboldt Scholarships in Germany and Scholarships of the Indian High Commissioner and British Medical Research Council in England. He was a Fellow of the American College of Chest Physicians, Indian Academy of Medical Sciences, the Medical Faculty of West Bengal and the National Institute of Science of India. The University of Calcutta awarded him “Coats Gold Medal” for distinguished contribution to medical sciences, in 1952. The third award of the Tuberculosis Association of India’s Gold Medal for outstanding work in tuberculosis field was conferred on Dr. P.K. Sen at the time of the 23rd National Conference on Tuberculosis and Chest Diseases held in Mumbai in January, 1968.

Dr. Sen was the Chairman of Bengal Tuberculosis Association and Chairman of the Committee on “Medical Education” of the Indian Medical Association, West Bengal. He was Honorary Professor of Medicine for Tuberculosis and Chest Diseases and the head of Department of Chest Diseases in the University College of Medicine, Calcutta. He was a consultant to the All India Institute of Hygiene and Public Health, visiting Professor of the Institute of Post-Graduate Medical Education and Research, and the Honorary Director of the B.C. Roy Research Institute of Tuberculosis. Dr. Sen’s earlier original studies on ‘Nutrition’, ‘Pneumoconiosis’, ‘Industry and Tuberculosis’, survey in Jute Industry and later his studies on “domiciliary treatment” on various aspects are well-known. As Honorary Director of B.C. Roy Research Institute of Tuberculosis, Dr. Sen continued to guide researchers in investigating various aspects of tuberculosis, including mode of action of anti-tuberculosis drugs.

A doctor of high academic eminence, he made original contributions to medical science and distinguished services to the anti-tuberculosis work. As Honorary Director of Dr. B.C. Roy Research Institute of Tuberculosis, Dr. Sen continued to guide researchers in investigating various aspects of tuberculosis, including mode of action of anti-tuberculosis drugs.

His sad demise on July 6, 1999 was a great loss to tuberculosis workers and Tuberculosis Association of India.

Indian Journal of Tuberculosis
CO-INFECTION OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND TUBERCULOSIS: INDIAN PERSPECTIVE

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Summary: Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) have resulted in a resurgence of tuberculosis the world over. Given that the South-East Asia Region of the World Health Organization accounts for nearly 40 per cent of all tuberculosis (TB) cases globally and 18 per cent of the world’s HIV infected also live in this region, the twin challenge of this “cursed duet” seems to be daunting. Treatment of patients co-infected with HIV and TB in India is very difficult especially because there is very little co-ordination between the Revised National Tuberculosis Control Programme (RNTCP) and HIV control. Clinical presentation of TB in early HIV infection resembles that observed in immuno-competent persons. In late HIV infection, the clinical presentation of TB can be atypical. Diagnosis of TB in HIV infected patients may be delayed because of atypical clinical presentation and involvement of inaccessible sites and low sputum smear positivity. Rational management of patients co-infected with HIV and TB in severely resource limited settings involves detailed history taking, thorough physical examination, clinical staging, assessment of CD4+ T-lymphocyte count or total lymphocyte count and institution of antiretroviral drugs and anti-tuberculosis treatment using the directly observed treatment, short-course (DOTS) strategy. HIV infected patients respond well to the standard anti-tuberculosis drug treatment regimens using the DOTS strategy. Thorough knowledge and familiarity regarding the adverse drug reactions and drug-interactions between antiretroviral and anti-tuberculosis drugs is essential for ensuring compliance and successful outcome.

Key words: Human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), pulmonary tuberculosis, extra-pulmonary tuberculosis, antiretroviral treatment, directly observed treatment, short-course (DOTS)

INTRODUCTION

The human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) pandemic is one of the most devastating diseases mankind has ever faced. Though the HIV pandemic began late in Asia, the situation is rapidly changing. Given that the South-East Asia Region of the World Health Organization (WHO) accounts for nearly 40 per cent of all tuberculosis (TB) cases globally and 18 per cent of the world’s HIV infected also live in this region, the twin challenge of this “cursed duet” seems to be daunting. In the developing countries, TB accounts for about a third of AIDS deaths and the deadly synergy between HIV and TB is a leading cause of mortality in the developing world. Moreover, HIV and TB are intricately linked to factors such as malnutrition, poverty, homelessness, over crowding and the social and economic consequences of co-infection with HIV and TB have been a tragedy in the making.

HIV/AIDS EPIDEMIOLOGY

Global

In December 2002, WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 42 million people worldwide were living with HIV/AIDS. Since the beginning of the epidemic, about 30 million people have died of AIDS; the AIDS deaths in 2002 alone were 3.1 million. In 2002, 5 million adults and children were newly infected with HIV. Of these, more than 95 per cent were living in the developing world.

India

The overall national HIV prevalence rate in India...
India has been estimated to be less than 1 per cent and India continues to be in the category of low prevalence countries. In a vast populous country like India, this low national prevalence rate blurs the actual picture of the epidemic. The number of HIV infected cases reported in the sentinel surveillance conducted by the National AIDS Control Organisation (NACO) is shown in Figure 4. In the year 2002 an estimated 4.58 million people were living with HIV infection in India—the second-highest figure in the world, after South Africa. HIV prevalence among women attending antenatal clinics was more than 1 per cent in Andhra Pradesh, Karnataka, Maharashtra, Manipur, Nagaland and Tamil Nadu states suggesting that there have been localised epidemics that are affecting millions of people.

Significantly, 75 per cent of the TB infected persons in the developing countries are estimated to be less than 50 years of age as compared to 20 per cent in the industrialised countries. These young adults are also at a high risk of developing infection with HIV. Given that HIV-infected individuals have an extraordinarily high risk of developing clinical TB gives cause for serious concern as the implications are most serious.

HIV Seroprevalence in patients with Tuberculosis

Studies from Sub-Saharan Africa have recorded HIV seroprevalence rates of 50 to 70 per cent in patients with TB. In Asia, where the HIV epidemic is still at an early stage, the rate of HIV infection in TB patients has been lower. Studies from India have reported HIV-seropositivity rates ranging from 0.4 to 20.1 per cent; higher prevalence has been observed in certain cities such as Chennai and Mumbai. This large regional variation could have been due to the occurrence of localised epidemics and in some instances due to selection bias.

Prevalence of TB in patients with HIV infection

Surveillance data and clinical observations suggest that TB is the most common life-threatening opportunistic infection in patients with HIV infection and AIDS. It has been reported that 25 to 65 per cent patients with HIV infection and AIDS had tuberculosis of any organ.
IMPACT OF HIV INFECTION

HIV infected persons are at markedly increased risk for primary or reactivation tuberculosis\(^3,19-21\) and for second episodes of tuberculosis from exogenous reinfection\(^22,23\). Upon antigenic challenge, CD4+ T-helper (Th) cells, are thought to differentiate along the separate pathways resulting in cell populations with different cytokine production profile termed Th1 and Th2\(^{24-26}\). In murine models, Th1 cells that produce interferon-\(\gamma\) (IFN-\(\gamma\)) and interleukin-2 (IL-2) confer resistance to infection with mycobacteria\(^{26,27}\). Th2 cells that produce interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6) and interleukin-10 (IL-10) do not contribute much to antimycobacterial immunity\(^3,26\). Reduced Th1 response observed in HIV-infected patients is thought to increase their susceptibility to tuberculosis\(^3,28\).

It is now well established that HIV-positive individuals have an extraordinarily high risk of developing active clinical TB as compared to HIV-negative persons and the estimated annual risk of breakdown among those infected with both HIV and TB is about 5 to 8 per cent with a cumulative lifetime risk of 30 per cent or more compared to a cumulative lifetime risk of 5 to 10 per cent in HIV-negative adult patients\(^{29}\). Infection with HIV is therefore one of the most potent risk factors for the development of tuberculosis\(^3,30-32\).

In persons with HIV infection/AIDS, factors such as (i) increased vulnerability to tuberculosis; (ii) increased opportunity to acquire tuberculosis due to over crowding, exposure to patients with multidrug-resistant tuberculosis (MDR-TB), increased hospital visits; and (iii) malabsorption of antituberculosis drugs resulting in sub-optimal therapeutic blood levels inspite of strict adherence to treatment regimen have all been postulated as the possible causes for increased risk of acquiring MDR-TB\(^{33}\). Recent studies have also demonstrated Rifampicin monoresistance in HIV patients\(^{34}\).

CLINICAL PRESENTATION

Clinical staging of HIV infection as described by the WHO is listed in Annexure I\(^{35,36}\). In HIV-negative and immuno-competent adult patients, pulmonary TB is the most common form of TB encountered and accounts for about 80% of the cases. While EPTB accounts for only 20 per cent of cases of TB in HIV-negative persons, it accounts for 53 to 62 per cent of cases in HIV-positive individuals\(^3,37\). The risk of tuberculosis increases as immunosuppression progresses\(^{38-40}\). The most common extrapulmonary site in HIV-positive individuals is the lymph node. However, neurological, pleural, pericardial, abdominal, and virtually every body site can be involved in HIV-positive patients\(^3,37-40\). In studies reported from India, EPTB constituted 45 to 56 per cent of all the cases of tuberculosis in persons with AIDS\(^41-43\).

Clinical presentation of tuberculosis in persons with early HIV infection has been found to be similar to that observed in immuno-competent and HIV-negative patients. Important differences have been observed in the clinical presentation of tuberculosis in patients with late HIV infection (CD4+ T-lymphocyte count less than 200/mm\(^3\)) (Table 1)\(^{44,45}\). Thus, the clinical presentation of TB in late HIV infection is atypical and this often results in a delay in the diagnosis.

DIAGNOSIS

Testing for HIV infection in patients with tuberculosis

The guidelines issued by the Centres for Disease Control (CDC), Atlanta, suggest that all patients with TB should be tested for HIV infection\(^{46}\). It has been observed that, up to 5 per cent of patients with tuberculosis without any evidence of risk factors have been found to have HIV infection\(^{37}\). However, in the Revised National Tuberculosis Control Programme (RNTCP) in India, there is no such provision. The total lack of co-ordination between the voluntary counseling and testing centres (VCTCs) and the RNTCP underplays the enormity
of the relationship between HIV and TB\textsuperscript{48}.

Testing for TB in patients with HIV infection

Targetted tuberculin testing for latent TB infection has been advocated in developed countries such as USA\textsuperscript{49}. However, in areas where TB is highly endemic, this approach is not useful.

Diagnosis of TB

Diagnosis of TB in HIV infected patients is difficult because of absence of fever and constitutional symptoms, negative sputum smears, atypical chest radiographs, higher prevalence of EPTB especially at inaccessible sites, resemblance to other opportunistic pulmonary infections, among others. However, the conventional methods of smear and culture must be applied to sputum, body fluids and secretions. Attempts must also be made to procure material for histopathological, cytopathological and microbiological testing employing radiologically guided procedures or minimally invasive diagnostic methods such as video-assisted thoracoscopy, laparoscopy and colonoscopy\textsuperscript{40,52,53} where relevant.

Indications for initiating antiretroviral treatment in patients with HIV infection in resource limited settings is listed in Annexure II\textsuperscript{52,53}. If the CD4+ T-lymphocyte counts cannot be assessed, total lymphocyte count of 1200/mm\textsuperscript{3} or less has been suggested as a substitute in patients with symptomatic HIV disease (WHO stages II or III). Even though the total lymphocyte count does not correlate well with CD4+ T-lymphocyte count, it is considered to be a useful marker of prognosis and survival in conjunction with clinical staging. Assesment of viral load using plasma HIV-1 ribonucleic acid (RNA) levels is not considered essential to initiate antiretroviral therapy\textsuperscript{52,53}.

TREATMENT

It is essential to start standard antituberculosis treatment promptly following the directly observed treatment, short-course (DOTS) strategy\textsuperscript{54} in HIV patients diagnosed to have TB as majority of these patients respond well to the standard antituberculosis treatment\textsuperscript{55,55,56}. It has also been shown that, in countries where HIV infection is

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-negative and Early HIV infection</th>
<th>L</th>
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<tbody>
<tr>
<td>Pulmonary: extra-pulmonary disease</td>
<td>80:20</td>
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</tr>
<tr>
<td>Clinical presentation</td>
<td>Often resembles post-primary TB</td>
<td>C</td>
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<tr>
<td>Chest radiograph</td>
<td></td>
<td></td>
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<tr>
<td>Intrathoracic lymphadenopathy</td>
<td>Less common</td>
<td></td>
</tr>
<tr>
<td>Lower lobe involvement</td>
<td>Less common</td>
<td></td>
</tr>
<tr>
<td>Cavitation</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Mantoux negative</td>
<td>Less common</td>
<td></td>
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<tr>
<td>Sputum smear positivity</td>
<td>Common</td>
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</tbody>
</table>

Adapted from references 44 and 45

Table 1: Clinical presentation of TB in HIV infected patients

Diagnosis of TB in HIV infected patients is difficult because of absence of fever and constitutional symptoms, negative sputum smears, atypical chest radiographs, higher prevalence of EPTB especially at inaccessible sites, resemblance to other opportunistic pulmonary infections, among others. However, the conventional methods of smear and culture must be applied to sputum, body fluids and secretions. Attempts must also be made to procure material for histopathological, cytopathological and microbiological testing employing radiologically guided procedures or minimally invasive diagnostic methods such as video-assisted thoracoscopy, laparoscopy and colonoscopy\textsuperscript{40,52,53} where relevant.
endemic, TB recurrence may be reduced by administration of treatment for at least six months in accordance with WHO recommendations\(^5\)

However, the management of HIV and TB co-infection is complicated and needs care by experts in this field because some antiretroviral agents produce unacceptable drug interactions with antituberculosis agents and/or can increase toxicity of TB treatment.

**Rifamycins** being inducers of the cytochrome P450-3A (CYP3A) system in the intestinal wall and liver, decrease the serum concentrations of drugs metabolised by this system. Among the Rifamycins, Rifampicin is the most potent, Rifapentene is intermediate and Rifabutin is the least potent inducer\(^3,5\). Thus, antiretroviral drugs such as protease inhibitors and non-nucleoside reverse-transcriptase inhibitors which are metabolised by the CYP3A may be affected by Rifamycins. Protease inhibitors such as delavirdine are potent inhibitors of the CYP3A and thereby increase the concentrations of the drugs metabolised by this enzyme system. These agents can increase the levels of Rifabutin which is a substrate of CYP3A. Though Rifampicin and Rifapentene are inducers of CYP3A, neither of them is a substrate for the CYP3A system and therefore it is unlikely that the inhibitors of the CYP3A have an effect on their concentrations\(^5\). This interaction is very important as there is a chance of rapid development of resistance to the protease inhibitors by HIV if their blood levels are sub-optimal\(^3,5\).

To tide over this problem, several options have been suggested in developed countries\(^3,5\). Some of these options include (i) using the standard four drug anti-tuberculosis treatment including Rifampicin for the initial intensive phase, then introducing highly active antiretroviral treatment (HAART) and using an extended non-Rifamycin continuation phase such as Isoniazid and Ethambutol; (ii) deferring HAART until standard anti-tuberculosis treatment is completed; (iii) discontinuing HAART and treating with a standard short-course regimen; and (iv) continuing protease inhibitor therapy with Indinavir, 800 mg every 8 hours and using a nine-month anti-tuberculosis regimen substituting Rifabutin, 150 mg daily for Rifampicin. Because protease inhibitors inhibit the metabolism of Rifabutin and increase the risk of uveitis, Rifabutin should be used in a reduced dosage of 150 mg/day\(^5\). The efficacy of these measures are being currently investigated and no consensus is available at present.**

**Treatment of HIV-TB Co-Infection in Resource Limited Settings**

Commonly used antiretroviral drugs and the guidelines for antiretroviral therapy for individuals with HIV-TB co-infection in resource-limited countries are listed in Annexures III & IV\(^3,5\). In patients with early HIV infection (CD4+ T-lymphocyte count greater than 200/mm\(^3\); or, when CD4+ testing is not available, total lymphocyte count greater than 1200/mm\(^3\)), TB should be first treated monitoring the CD4+ count. Antiretroviral treatment can be initiated after anti-tuberculosis treatment is completed.

In later stages of immuno-suppression (CD4+ T-lymphocyte count 50 to 200/mm\(^3\); or, total lymphocyte count less than 1200/mm\(^3\)), antiretroviral therapy should be initiated after the first two months, because the toxicity due to antituberculosis treatment is greatest during this period.

In late stages of immunosuppression (CD4+ T-lymphocyte count less than 50/mm\(^3\)) anti-retroviral treatment should be started as soon as it can be tolerated\(^3,5\).

Rifabutin should not be used with hard gel formulation of saquinavir as saquinavir levels are decreased by 45 per cent\(^1\). Ritonavir is the most potent inhibitor of the metabolism of Rifabutin and these two drugs cannot be used. Drug-interactions of Rifampicin with other drugs commonly used in patients with AIDS such as Ketoconazole, Itraconazole\(^6\), Fluconazole\(^6\) resulting in antifungal treatment failure and the problem of MDR-TB are special problems in these patients. However, many of these drugs are not available or are very expensive to procure in the Indian setting.
Paradoxical Reactions

Paradoxical reactions, also called immune restoration syndromes, have been reported in 32 to 36 per cent of patients with HIV-related tuberculosis within days to weeks after the antiretroviral treatment has been initiated. Manifestations range from isolated instances of fever to increased or initial appearance of adenopathy, new or worsening pulmonary infiltrates, serositis, cutaneous lesions, and new or expanding central nervous system mass lesions. These pose a problem and have to be distinguished from tuberculosis treatment failure, drug hypersensitivity, and other infections common among immunocompromised patients.

Treatment of MDR-TB in patients with HIV infection and AIDS

In the early reports of outbreaks of MDR-TB in HIV co-infected patients in hospitals and prisons, the mortality rate was very high ranging from 72 to 89 per cent. However, subsequent studies have documented decreased mortality and improvement in clinical outcome for HIV-seropositive patients with MDR-TB who were started on at least two drugs with in vitro susceptibility against the MDR-TB isolate.

Treatment of latent TB

Though practiced in the industrialised countries, preventive therapy for TB by treatment of latent TB infection is not practical in many resource-limited settings because of the difficulty in excluding active disease. If diagnostic testing is available to exclude active TB and where PPD skin testing is feasible, Isoniazid therapy (with Pyridoxine supplementation) for 9 months in tuberculin skin test reactors is recommended after exclusion of active disease.

Globally, HIV is threatening the control of TB. Treatment of co-infection with HIV and TB requires commitment and a focused approach. Appropriate use of antiretroviral drugs to treat HIV infection and ensuring high levels of coverage and compliance is required to prevent TB by preserving immunity. The DOTS strategy is very useful to ensure cure of TB in patients with HIV infection and AIDS. Coordination between the RNTCP and the AIDS control measures is required for effective management of these patients.

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Annexure I

WHO staging system for patients infected with HIV and TB

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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</table>
| Stage 1 | Asymptomatic  
Persistent generalised lymphadenopathy  
Performance scale 1: asymptomatic, normal activity |
| Stage 2 | Weight loss between 5% and 10% of body weight  
Minor mucocutaneous manifestations (seborrhoeic dermatitis infections, recurrent oral ulcerations, angular stomatitis)  
Herpes zoster within the past five years  
Recurrent upper respiratory tract infections (for example, bac And/or                  
Performance scale 2: symptomatic, normal activity |
| Stage 3 | Weight loss >10% body weight  
Unexplained chronic diarrhoea for longer than one month  
Unexplained prolonged fever (intermittent or constant) for lo Oral candidiasis  
Oral hairy leukoplakia  
Pulmonary tuberculosis within last year  
Severe bacterial infections (for example, pneumonia, pyomy And/or                  
Performance scale 3: bedridden for less than 50% of the day |

Clinical stage 4 (AIDS)  
HIV wasting syndrome*  
*Pneumocystis carinii* pneumonia  
Toxoplasmosis of the brain  
Cryptosporidiosis with diarrhoea for more than one month  
*Cryptococcus*, extrapulmonary  
Cytomegalovirus infection of an organ other than liver, splee  
Herpes simplex virus infection—mucocutaneous for mo
## Annexure III

### Commonly used antiretroviral drugs:

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Dosage schedule</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td><strong>Nucleoside reverse transcriptase inhibitors (NsRTI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>300 mg twice daily or with ZDV and 3TC</td>
<td>Hypersensitivity, nausea, vomiting, lactis, rashes, headache, irsteatosis (ra)</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>&gt;60 kg: 200 mg twice daily or 400 mg once daily</td>
<td>Pancratis, nausea, diar lactic acids</td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 125 mg twice daily or 250 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>150 mg twice daily</td>
<td>Minimal toxicity, nausea, diar lactic acids</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>&lt;50 kg: 2 mg/kg bid</td>
<td>Pancratis, steatosis (ra)</td>
</tr>
<tr>
<td>Zidovudine (ZDV, AZT)</td>
<td>&gt;60 kg: 40 mg twice daily</td>
<td>Anaemia, na headche, ir steatosis (ra)</td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 30 mg twice daily</td>
<td></td>
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<td></td>
<td>300 mg twice daily</td>
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<tr>
<td></td>
<td>250 mg twice daily (alternative dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC combination 300 mg/150 mg twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Nucleoside reverse transcriptase Inhibitors (NNRTI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>200 mg once daily for 14 days followed by 200 mg twice daily</td>
<td>Skin rash aminotransf</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>600 mg once daily (bed time administration is</td>
<td>CNS symptoms hallucination</td>
</tr>
</tbody>
</table>
All readers as well as other workers in the field of tuberculosis and other respiratory diseases are invited to contribute good review articles which will be of topical interest and useful for updating knowledge. The subject of the review articles may be on your speciality/area of experience or on any subject of your choice pertaining to tuberculosis & chest diseases.

The review articles received for publication will be peer-reviewed as per the Journal policy.
INITIAL DRUG RESISTANCE AMONG TUBERCULOSIS PATIENTS UNDER DOTS PROGRAMME IN BANGALORE CITY*

Sophia Vijay, V.H. Balasangameshwara, P.S. Jagannatha, and P. Kumar

Summary:
Background & Objectives: The level of initial drug resistance (IDR) and its trend is a sensitive indicator of the programme efficiency and provides indirect reflection of the quality of tuberculosis services in the area. Studies from some parts of India have reported an increase in the level of IDR to INH and Rifampicin. There is paucity of information on age specific pattern of IDR from India. Frequency of drug resistance in the younger age group provides a precise evaluation of the current situation. The published data from Bangalore (1985-86) pertaining to patients under the National TB programme reported an IDR of 20.6% to any drug. Subsequently, the RNTCP with DOTS strategy to achieve high cure rate was implemented in the area in late 1998. The present study was undertaken in a cohort of 324 new smear positive patients initiated on Cat-I regimen under RNTCP in Bangalore Mahanagara Palike from April to December 1999 to study the pattern of IDR among them, soon after RNTCP implementation in the area. This information would serve as a useful baseline data for the area to assess the impact of DOTS strategy on the levels of IDR subsequently.

Material & Methods: Two pre-treatment sputum samples were collected from these patients and subjected to microscopy, culture & susceptibility testing at the National Tuberculosis Institute. The susceptibility testing was done by economic version of proportion method, as per IUATLD guidelines. Information regarding the previous treatment was elicited using a pre-tested semi-structured schedule based on the WHO questionnaire for IDR surveillance and scrutiny of available records.

Results: Among the 271 correctly categorized new patients, 27.7% were resistant to one or more drugs. The resistance to streptomycin was highest (22.5%) followed by INH (13.7%), and MDR was 2.2%. The age specific resistance was highest in <25 years and declined significantly in the higher age groups, being lowest (17.7%) in ≥45 years. Effective RNTCP implementation is expected to show declining trends in the IDR, particularly in the younger age group during the subsequent surveys.

Key Words: Tuberculosis, Initial Drug Resistance, DOTS.

INTRODUCTION

The tuberculosis programme in India, till 1993, had short course chemotherapy regimen, given under unsupervised conditions and the performance of programme in terms of success rate was poor. This together with the easy availability and the haphazard use of Rifampicin, both in public and private sectors from mid eighties had created the fear of increasing level of acquired drug resistance (ADR), particularly the multi-drug resistance tuberculosis (MDR TB). ADR is bound to influence the level of initial drug resistance (IDR) in the community. There has been increased awareness that drug resistant TB poses a major threat to the patients as well as to the TB Control Programme.

The frequency of IDR, especially MDR TB, varies from place to place and is found to be generally low, even in high prevalence countries such as Malawi, Tanzania and China where DOTS strategy is implemented. In contrast, a poor or sub-optimal tuberculosis control programme can lead to a rapid emergence of drug resistance, especially in
the area with high prevalence of TB.

In India, Revised National Tuberculosis Control Programme (RNTCP) based on DOTS strategy had shown a success rate of 82.0% among newly diagnosed smear positive patients evaluated from 1993 to 1998. In contrast, the cure rate was 40.3% among patients treated with unsupervised SCC regimen during the year 1999. Efficiency of the treatment programme determines the level of ADR. Due to continued transmission of infection with resistant bacilli, ADR leads to increase in the levels of IDR, which in turn may cause increase in treatment failure cases, thereby decreasing the success rate of the existing programme.

Information available in some parts of India shows an increase in the level of IDR to Isoniazid (H) & Rifampicin (R). The IDR as reported from India is 18% to 20% for H, 14% to Streptomycin (S), and 3% to HR. This level of IDR reflects the effect of previous TB Control programme with unsupervised SCC regimen. Resistance to R started appearing late and has remained at a low level of about 1%. As per the published data from Bangalore in the year 1985-86, IDR to any drug was 20.6% (INH 17.4%, Streptomycin 4.8%, Rifampicin 2.9%, HR 1.4%). These data pertain to patients attending the District TB Centre situated in Bangalore Mahanagara Palike (BMP). The RNTCP was introduced in this area in late 1998. The strategy lays emphasis on direct supervision of treatment and aims at good treatment compliance, high success rate and minimizing the failures due to drug resistance.

With this in view, a study was taken up to estimate the baseline data on IDR for BMP, in a cohort of new smear positive patients initiated on CAT I regimen [2(EHRZ)/4(HR)]. The level of IDR would serve as useful information to assess the impact of DOTS strategy on the levels of IDR subsequently.

METHODS

Studies on IDR need to follow the guidelines prescribed by World Health Organization (WHO)/International Union against Tuberculosis and Lung Diseases (IUATLD). At least three conditions have to be kept in mind, namely, sampling procedure, complete and meticulous patients’ treatment history and standard drug susceptibility testing. Sample should be representative of the area under consideration and should be statistically valid. Complete patient history has to be obtained to distinguish IDR from ADR. Drug susceptibility testing should be in accordance with international standards with an ongoing internal quality control and external quality assessment.

Study area

The BMP, having a population of 3.7 million as per 1991 census, had 39 microscopy centres (MCs). All smear positive pulmonary tuberculosis patients classified as “new” and initiated as CAT I regimen, during the period April to December 1999 formed the study cohort (n=366). Two pre-treatment sputum samples were collected from these patients by Centre staff. The samples were transported to National Tuberculosis Institute (NTI), Bangalore laboratory for microscopy, culture and susceptibility tests. Tri-sodium phosphate (TSP) was used as the medium for transportation.

Bacteriological Investigations

Smear microscopy examination was carried out with Ziehl-Neelsen technique and smear grading was as per RNTCP guidelines. Isolation of mycobacteria was done using Lowenstein Jensen (LJ) media. Susceptibility testing was carried out by economic version of proportion method with critical drug concentration for INH (0.2mg/ml), Rifampicin (40mg/ml), Streptomycin (4mg/ml), and Ethambutol (2mg/ml), the critical proportion for declaring resistance to each of the drugs being 1%. Para nitro benzoic acid & Niacin tests were carried out for identification. The laboratory methods were uniform with a stringent internal quality control procedure as per the standard operating procedure manual, and external quality control procedures were in place with monitoring by WHO Supra National Reference Laboratory, Brisbane, Australia. The drugs used for the susceptibility testing were of pure quality.
Data collection

Initial interviews at the time of intake were done at the residence of patients by NTI staff using pre-tested semi-structured interview schedules. These schedules were designed based on the WHO questionnaire to elicit information on the previous history of treatment. If the patients did not volunteer the history of previous treatment, further elicitation was done by using indirect questions. Utmost care was taken to ascertain previous history of treatment. The interview schedules also obtained information on the patients’ identification details, demographic profile and knowledge about the disease. Brief training on study procedures was imparted to all Medical Officers (MO), Senior Treatment Supervisors (STS), Senior TB Laboratory Supervisors (STLS), and Laboratory Technicians (LT) of the BMP.

RESULTS

A total of 366 smear positive pulmonary tuberculosis patients were registered as “new” in this period. Among these, 324 (88.5%) were culture positive. On further interrogation by the study team, it was found that 53 (16.4%) had previous history of anti-TB treatment of ≥4 weeks and had been wrongly classified as ‘new smear positive’. The remaining 271 correctly identified as “new” formed the study group. Among these 271 patients, 196 (72.3%) were susceptible to all drugs.

The socio-demographic variables considered for analysis to compare the resistant and susceptible groups were age, sex, literacy, marital status, employment and history of contact.

Drug susceptibility pattern

Of the study group, 75 (27.7%) had resistance to any drug and could be labeled as IDR. The resistance to S was highest (22.5%), followed by H (13.7%). Resistance to R with or without other drugs was 2.6%. The proportion with MDR was 2.2% in this group (Table 1).

The median age of the study group was 35 years. The age distribution of resistant and susceptible group revealed that a significantly higher proportion of those resistant to any drug were in the age group <35 years (Table 2).

Further, stratified age group analysis revealed that the resistance to any drug was highest among those aged <25 years and declined thereafter, being lowest in the age group >45 years (Fig). The difference in proportion with drug resistance, between <25 year and >45 year age groups was significant (p<0.05). Only 2 out of 5 patients had IDR in the age group <15 years (not on table). Hence this age group was combined with the age group 15-24 years.

Other variables such as sex, literacy, marital status, employment and history of contact did not show statistically significant difference in those with susceptible and resistant isolates (Table 2).

<table>
<thead>
<tr>
<th>Resistance to</th>
<th>New culture positive cases (N=271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug#</td>
<td>Number (%)</td>
</tr>
<tr>
<td>H</td>
<td>37 (13.7)</td>
</tr>
<tr>
<td>R</td>
<td>7 (2.6)*</td>
</tr>
<tr>
<td>S</td>
<td>61 (22.5)*</td>
</tr>
<tr>
<td>E</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>One Drug+</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>R</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>S</td>
<td>36 (13.3)</td>
</tr>
<tr>
<td>E</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Two drugs+</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>HS</td>
<td>18 (6.6)</td>
</tr>
<tr>
<td>SR</td>
<td>0</td>
</tr>
<tr>
<td>Three drugs+</td>
<td></td>
</tr>
<tr>
<td>HRS</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>HSE</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>HRSE</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Any drug</td>
<td>75 (27.7)</td>
</tr>
</tbody>
</table>

# Resistance to the drug in question, either alone or in combination with resistance to others.
+ Resistance to the specified drug only
* p<0.05

Indian Journal of Tuberculosis
DISCUSSION

The current study was undertaken to assess the level of IDR in BMP area within six months of RNTCP implementation. It was ensured that all new smear positive pulmonary tuberculosis patients diagnosed in all the 39 microscopy centres of BMP were included in the study. The history of treatment was elicited meticulously by using the pre-tested questionnaire adopted from WHO. This resulted in exclusion of 16% of those wrongly classified as ‘new’ and hence, the drug resistance identified in this study could be termed as Primary Drug Resistance. All necessary pre-requisites for evaluation of IDR have been observed. The sample size was 100% from all designated microscopy centres of BMP, covering 75% of annual case detection and hence could be considered to be representative of BMP. NTI follows the standard norms for susceptibility testing with an ongoing internal quality control and an external quality assessment.

Studies conducted by Tuberculosis Research Centre (TRC), Chennai from 1956 to 1997 have clearly shown a gradual increase in the prevalence of resistance to H, S and SH. Resistance to R started appearing in 1990s and had remained at almost 1%. Although such trend studies have not been done for Bangalore area, the IDR has been reported from Bangalore in the studies done in 1980.

### Table 2: General Characteristics of New Culture Positive Cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Resistant to any drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 years</td>
<td>154</td>
<td>51 (33.1%)*</td>
</tr>
<tr>
<td>≥35 years</td>
<td>117</td>
<td>24 (20.5%)*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>191</td>
<td>47 (24.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>80</td>
<td>28 (35.0%)</td>
</tr>
<tr>
<td>Literacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>79</td>
<td>23 (29.1%)</td>
</tr>
<tr>
<td>Literate</td>
<td>192</td>
<td>52 (27.1%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>161</td>
<td>39 (24.2%)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>110</td>
<td>36 (32.7%)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>139</td>
<td>36 (25.9%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>132</td>
<td>39 (29.5%)</td>
</tr>
<tr>
<td>History of contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>91</td>
<td>27 (29.7%)</td>
</tr>
<tr>
<td>Absent</td>
<td>180</td>
<td>48 (26.7%)</td>
</tr>
</tbody>
</table>

* P<0.04

**Fig.** Age group analysis of Initial Drug Resistance
and 1985 – 86 by NTI (5.7% and 4.8% respectively). The results did not differ much in these two studies, probably because of the short interval between the two studies. The level of resistance to H, Ethambutol (E), R and HR in the present study is not comparable with the previous two studies because of the sampling technique followed in the earlier two studies. Only one centre from Bangalore was selected in earlier studies and hence cannot be considered as representative of Bangalore City, whereas the present study included cases from all the microscopy centres of RNTCP in BMP. Nevertheless, S resistance in the present study is high (22.5%) and the probable reason for this high level could be the indiscriminate use of Streptomycin containing regimens for treatment of tuberculosis in the earlier programme under non-DOT situations, both in the Government and private sectors.

One of the striking findings in this study is the high level of IDR among younger patients compared to older age group, indicating an exposure to drug resistant cases in the last two decades. A similar finding was reported in 1994 after a nationwide survey conducted in United States, wherein the age-specific resistance adjusted for demographic characteristics was highest in children below 15 years, suggesting a dangerous increase in the frequency of any resistance in USA17. The study of trend in IDR over a twelve-year period in Karonga district of Malawi shows a low IDR for any drug among those aged <20 years (8.1%) with no difference in IDR (11%) in those aged >20 years4. The low level of IDR among younger patients is probably the result of a good DOTS programme in Malawi.

The tuberculosis programme for Bangalore was hitherto limited to the non-DOTS regimens given at the District TB Centre (DTC). Other health institutions were not involved much and the involvement was limited to the extent of referring cases for diagnosis and treatment to the DTC. This might have led to incomplete treatment with more defaults, gradually increasing the ADR levels. The increase in ADR levels in the past twenty-five years could have increased the IDR levels in younger persons as seen in the present study. The age group analysis as done in this study, shows the impact of the TB control programme on IDR over the years. Studies of this type can also be easily conducted in RNTCP set-up by adopting either 100% or cluster sampling, using a modified questionnaire for eliciting the previous history of treatment and a reliable culture and susceptibility testing facility. Although cluster sampling is also recommended by WHO10, the present study adopted 100% sample for a period of nine months during 1999. This study was part of a main study to assess the treatment outcome among cohorts of new and re-treatment patients initiated on Cat I and Cat II regimen18.

The initial MDR in this study has remained low at 2.2%. Earlier studies from the District TB Centre of Bangalore have reported an initial MDR ranging from 0.9% to 1.2%8. The initial MDR for India has been stated to be low and ranges from 0 to 3.2%8, while that for BMP area is still low & within the observed values in India. Hence, the failure to treatment with Cat I regimen, among those correctly typed as ‘new’, should also remain low, provided the treatment compliance is good. The treatment outcome of these patients will be reported subsequently.

It is proposed to repeat the study after a gap of five to ten years in order to measure the impact of RNTCP on IDR in BMP area. It is expected that there would be a measurable drop in the level of IDR among younger group, as a result of continuous high success rate combined with high case detection rate due to an on going DOTS programme in BMP.

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and support. Constructive suggestions offered by
all the members of Technical Coordination Committee
of NTI are highly appreciated. Study would not have
been successfully completed without the cooperation
of all study patients and their family members.

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outcome of smear positive tuberculosis cases under DOTS

FOR AUTHORS

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Indian Journal of Tuberculosis
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PARAFFIN SLIDE CULTURE TECHNIQUE FOR ISOLATING NON-TUBERCULOUS MYCOBACTERIA FROM STOOL AND SPUTUM OF HIV SEROPOSITIVE PATIENTS

P. Narang1, Rahul Narang2, S. Bhattacharya3 and D.K. Mendiratta

(Received on 30.6.2003; Accepted on 3.9.2003)

Summary:
Objective: Paraffin slide culture method (PSC) was used to isolate Non-tuberculous mycobacteria (NTM) from stool and sputum samples of HIV seropositive and negative patients.

Material & Methods: Eighty stool and forty two sputum samples from both symptomatic or asymptomatic HIV sero-positive patients; and 40 stool and 128 sputum samples from symptomatic but HIV seronegative patients were cultured by PSC to assess its utility in isolating NTM from the clinical specimens. The samples were simultaneously processed by culture on Lowenstein Jensen (LJ) medium for comparison with regard to isolation rate, isolation time and contamination rate.

Results: The PSC proved to be as good as LJ in isolating NTM from clinical specimens and, in addition, had the advantage of in situ staining for acid fast bacilli and lower contamination rate. The PSC was also used for typing NTM by biochemical tests.

Key words: Paraffin slide culture, HIV, Non-tuberculous mycobacteria

INTRODUCTION

Non-tuberculous mycobacteria (NTM) or the so-called atypical mycobacteria or mycobacteria other than tuberculosis (MOTT) have been recognized since Koch’s time but did not gain as much importance as Mycobacterium tuberculosis. Today, the recovery of NTM from patients’ specimens and from environmental sources is of concern to microbiologists, epidemiologists and physicians.

In developed countries, as the incidence of tuberculosis decreased, the occurrence of NTM in pulmonary diseases increased1-3. Haematogenous dissemination of NTM has been reported with higher frequency after the advent of the acquired immunodeficiency syndrome (AIDS). The immunosuppressed individuals infected by human immunodeficiency virus (HIV) infection have become the most significant risk factor for disseminated NTM disease and of these, 95% are due to Mycobacterium avium complex (MAC)4,5.

In developing countries, little is known about NTM infections, either in AIDS or non AIDS patients. In India, there is paucity of data relating NTM to disease. They have, however, been isolated from patients’ specimens but are considered only as commensals or contaminants6-7.

Infetecth IdentikitTM which utilizes capacity of NTM to use paraffin wax as the sole source of carbon, was successfully used by our laboratory at the M.G. Institute of Medical Sciences, Sevagram, to culture known strains of NTM and Nocardia and also to speciate NTM by putting up biochemical reactions8. The present study was undertaken to find out the utility of this kit in isolating NTM from clinical specimens of stool and sputum of HIV seropositive and seronegative subjects. The growth was compared with the gold standard Lowenstein Jensen medium with regard to isolation rate, isolation time and contamination rate, and was also correlated...
with signs and symptoms of the patients.

**MATERIAL AND METHODS**

The study was conducted between November 1999 and March 2001. Stool and sputum specimens were collected from HIV seropositive patients, with or without symptoms of mycobacterial infection and disease (80 stool and 42 sputum), and HIV seronegative symptomatic patients (40 stool and 128 sputum) attending Kasturba Medical Hospital, Sevagram. Due to unavoidable reasons, only one sample of stool and sputum could be obtained from each patient, hence repeated isolation could not be demonstrated.

**Processing of faecal samples**

Fresh faecal suspension was prepared from stool by inoculating a loopful of sample into sterile saline. Aliquots of 500 l were added to 4.5ml of sterile Czapek broth (3.0g NaNO₃, 1.0g K₂HPO₄, 0.5g MgSO₄, 0.5g KCl, 0.01g FeSO₄ in 1L of distilled water at pH 7.5) with antibiotic cocktail of PANTA Plus, Becton and Dickinson (1:100) in a sterile test tube containing paraffin wax coated slide, PSC (Infectech Identikit™ USA). Two such tubes, one for staining and other for subculture, were inoculated. Stool samples were also cultured on two slopes of LJ medium after decontamination with 3% oxalic acid for 60 minutes.

**Processing of sputum samples**

For sputum samples, 500 l of sputum was added to 4.5ml of sterile Czapek broth with PANTA Plus (1:100) in each of 2 tubes containing paraffin wax coated slide (PSC). Before inoculation on 2 slopes of LJ medium, modified Petroff’s method was used to process the sputum samples.

The PSC tubes and the LJ bottles were incubated at 37°C in an incubator and were checked daily for growth. If visible growth was observed on PSC, one of the slides was removed from the tube for in situ acid fast staining by Kinyoun’s method. The slide was first fixed with alcohol and was then immersed in a tube containing the staining reagents. The stained slides were then examined under microscope (10x, 40x, and 100x) for presence of acid fast colonies and acid fast organisms. If acid fast organisms were seen, NTM species were suspected as they, along with Nocardia, are the only acid fast organisms which utilize paraffin as the sole source of carbon and grow on this media.

The growth from the other slide was then subcultured on to LJ media and 5 fresh tubes of PSC for further identification of the species. The growth on the freshly inoculated tubes was used for putting up tellurite reduction, nitrate reduction, urea hydrolysis and Tween 80 hydrolysis tests. Separate slides with growth of the isolated NTM were used for each test in the test tube containing Czapek broth and the reagents. Uninoculated media, with paraffin slide without growth were used as reagent control.

Speciation of growth on LJ medium was also performed by conventional methods.

**RESULTS**

From stool samples of 6 HIV seropositive patients, NTM grew by PSC, and five of them were suffering from diarrhoea. Out of these 6 isolates, 4 belonged to *Mycobacterium avium* complex (MAC) while 2 belonged to *M. fortuitum* complex. LJ could detect 5 NTM isolates, 4 MAC and 1 *M. fortuitum* (Table 1). None of the HIV seronegative subjects

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>HIV +ve subjects (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. tested</td>
</tr>
<tr>
<td>Diarrhoeal</td>
<td>17</td>
</tr>
<tr>
<td>Non-diarrhoeal</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
</tr>
</tbody>
</table>

**Table 1**: Isolation of NTM from stool samples

**Figures in parentheses indicate horizontal percentages**
had NTM isolated from their stool samples. Mean isolation time for MAC was 19 days by PSC, while on LJ it was 21 days. For M. fortuitum complex isolation time was the same (12 days by both methods). Contamination rate for stool samples by PSC and LJ was 9.16% and 13.33% respectively (Table 3).

As expected, no M. tuberculosis was isolated on PSC. However, on LJ medium, M. tuberculosis was the main isolate from sputum in both the groups but HIV seropositive subjects had more positivity (45.23%) than HIV seronegative (27.34%) (Table 2).

### DISCUSSION

PSC technique proved to be a good method of isolation for NTM from clinical specimens of the patients. Since M. tuberculosis does not grow on PSC, any growth on the paraffin slide is an immediate indication of NTM or Nocardia species. In addition, the in situ acid alcohol fast staining procedure allows differentiation between these organisms. The Nocardia species are not acid alcohol fast using Kinyoun’s method and are filamentous on PSC, and therefore can be differentiated in the first instance.

The risk of contamination was found to be low as compared to LJ. The reason could be that very few human pathogens and commensals are able to grow on paraffin wax and the technique is made more selective from the possible contamination by Pseudomonas aeruginosa or Candida tropicalis, the organisms which can contaminate the slides by the addition of antibiotic and antifungal cocktail, PANTA (Becton and Dickinson).

This technique was used in our laboratory to speciate the known strains of mycobacteria and was found to be easy and useful. In the present study, the technique has been used to isolate the NTM from clinical specimens and to speciate them. Six NTM species including 4 M. avium and 2 M. fortuitum from the stool specimens and 3 NTM species including 2 M. avium and one unspeciated from sputum samples were isolated.

Isolation of MAC was equally good on PSC when compared to LJ. For stool samples, isolation time for MAC was lesser while it was the same for}

**Table 2:** Isolation of mycobacterial species from sputum samples by PSC and LJ

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Specimen</th>
<th>Positive for AFB on ZN staining</th>
<th>Culture positive on PSC</th>
<th>Culture positive on LJ for MTB and NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV +ve (n=42)</td>
<td>Stool</td>
<td>16 (38.09)</td>
<td>3* (7.14)</td>
<td>19+3*</td>
</tr>
<tr>
<td>HIV -ve (n=128)</td>
<td>Sputum</td>
<td>24 (18.75)</td>
<td>1** (0.78)</td>
<td>35+1**</td>
</tr>
</tbody>
</table>

(*) NTM; (**) Nocardia
Figures in parentheses indicate horizontal percentages

**Table 3:** Comparison of contamination on PSC and LJ

<table>
<thead>
<tr>
<th>Specimen</th>
<th>LJ</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool (n=120)</td>
<td>16 (13.33)</td>
<td>11 (9.16)</td>
</tr>
<tr>
<td>Sputum (n=170)</td>
<td>12 (7.05)</td>
<td>9 (5.29)</td>
</tr>
<tr>
<td>Total (n=290)</td>
<td>28 (9.65)</td>
<td>20 (6.89)</td>
</tr>
</tbody>
</table>

In sputum samples also, NTM were isolated from samples of HIV seropositive subjects only. Three isolates of NTM (two MAC and one unspeciated) were isolated from a total of 42 sputum samples of HIV seropositive subjects. Positivity by PSC and LJ was the same. In one subject, MAC was isolated from both stool and sputum sample. The isolation time for MAC was the same (21 days) by PSC as well as LJ. The contamination rate was lower in PSC, 5.29% as compared to LJ, 7.05% (Table 3).

The risk of contamination was found to be low as compared to LJ. The reason could be that very few human pathogens and commensals are able to grow on paraffin wax and the technique is made more selective from the possible contamination by Pseudomonas aeruginosa or Candida tropicalis, the organisms which can contaminate the slides by the addition of antibiotic and antifungal cocktail, PANTA (Becton and Dickinson).

This technique was used in our laboratory to speciate the known strains of mycobacteria and was found to be easy and useful. In the present study, the technique has been used to isolate the NTM from clinical specimens and to speciate them. Six NTM species including 4 M. avium and 2 M. fortuitum from the stool specimens and 3 NTM species including 2 M. avium and one unspeciated from sputum samples were isolated.

Isolation of MAC was equally good on PSC when compared to LJ. For stool samples, isolation time for MAC was lesser while it was the same for
sputum. This method has also been utilized for putting up drug resistance tests in our department (data not given here) and by other workers. Also the PSC has been utilized for isolation of NTM from blood samples of HIV positive patients in our laboratory and other laboratories. In this case, the sample is first cultured in the 13 A medium and then subcultured in PSC. PSC growth has also been utilized for DNA extraction and further characterization of NTM at genetic level (Ollar R.A. personal communication).

Isolation of NTM using rapid methods and their identification up to species level using genetic probes is being done in the developed countries routinely. The exorbitant cost involved in these techniques is the major inhibitory factor for their incorporation in the laboratories of the developing countries. Hence, a simple, inexpensive and useful method like the PSC can be utilized in these countries without the specialized training of the technicians for isolation and speciation of NTM.

ACKNOWLEDGEMENTS

We are grateful to Dr. R.A. Ollar, Director, Infectech IdentikitTM for providing the PSC kit and his constant support and Dr. A.P. Jain, Professor and Head, Department of Medicine, M.G. Institute of Medical Sciences for permitting us to take specimens from the patients. We are also thankful to Mr. Diwakar Ingley, Technician, Mycobacteriology laboratory for technical support.

REFERENCES

ROLE OF SOCIO-ECONOMIC FACTORS IN TUBERCULOSIS PREVALENCE

Dheeraj Gupta, Kshaunish Das, Balamughesh T, Ashutosh N. Aggarwal and Surinder. K. Jindal

(Original received on 19.5.2002; Revised version received on 26.8.2003; Accepted on 26.8.2003)

Summary: Background: There is a need to re-assess the role of generally identifiable risk factors for development of tuberculosis (e.g. old age, poverty and poor socio-economic status). The present study was designed to look into the socio-economic and demographic characteristics of patients of tuberculosis (TB) vis-à-vis those with other respiratory diseases in the area and around Chandigarh.

Setting: Chest Clinic of a tertiary care hospital.

Design: Case-control study

Material and Methods: Two hundred and fifty consecutive cases of TB and an equal number of patients with pulmonary diseases other than tuberculosis as controls were interviewed as per a pre-designed, structured questionnaire that inquired into several socio-economic and demographic variables besides the clinical details. Univariate and multiple logistic regression analyses were carried out to obtain odds ratios separately for each variable.

Results: The mean age of patients suffering from tuberculosis was 35.56 years (SD 13.69). There were 168 men (67.2%) and 82 (32.8%) women among the cases. Persons suffering from tuberculosis were more frequently found to have the worst of the socio-economic conditions for all the variables. Odds ratio (OR) increased by 3.14 (95% CI 2.48-3.98, p<0.001) for every decrease of Rs.500/- in the income level per person per month below Rs.2000/-. Similarly, the OR increased by 3.66 (CI 2.9-4.61, p<0.001) with increasing number of persons per room. The ORs for poorer housing, toilet facilities, water supply and consumer articles were also significant. In multivariate logistic regression analysis, the age, level of education, crowding, type of housing, water supply and number of consumer articles in the household was found to be independently and significantly associated with a higher risk of TB.

Conclusion: There is a significant SES-health gradient in TB prevalence; tuberculosis risk increases with lowering of socio-economic status.

Key words: Tuberculosis, socio-economic factors, epidemiology, risk factors, poverty

INTRODUCTION

With the recent resurgence of tuberculosis world wide, there is an imperative need to reassess whether the age-old risk factors for the development of disease (e.g. old age, malnutrition, poverty, poor socio-economic status) are still operating or not, especially in the developing countries. A recent publication from the National Institute of Tuberculosis, Bangalore, has summarized all the available literature on the sociological aspects of tuberculosis. There are very few studies in recent times that have studied the socio-economic aspects of this deadly disease. In the present study we have looked into the socio-demographic characteristics of patients of tuberculosis seen at a tertiary care referral institute located in Chandigarh in Northern India and having a catchment area spread over the states of Punjab, Haryana, Himachal Pradesh, Jammu & Kashmir, western parts of Uttar Pradesh and Uttarakhal.

MATERIAL & METHODS

A case-control study design, which included 250 consecutive cases of tuberculosis, aged 12 years or more was adopted. The case definitions included 1) Pulmonary tuberculosis (PTB) with sputum smear positive for Acid Fast Bacilli (AFB) or a strong clinical/radiological suspicion of PTB with a documented response to anti-tubercular drugs. 2) Extra pulmonary tuberculosis with demonstrable AFB in smear/culture from clinical specimen or a histopathology consistent with tuberculosis. The control group consisted of 250 patients with pulmonary diseases other than tuberculosis. Each

Original Article

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case and control was interviewed as per a pre-designed structured questionnaire that enquired into several socio-economic and demographic variables besides the clinical details.

The data were analyzed on the basis of following variables:

a) Income level per person was calculated by dividing the total monthly income after excluding fixed expenses (rents, electricity, water bills, taxes) by the total number of members in the household (including children and infants). The income level was categorized in five groups (Group 1: <500, group 2: 501-1000, group 3: 1001-1500, group 4: 1501-2000 and group 5: >2000 Rupees per person per month).

b) Crowding was expressed as number of persons of more than one year of age sharing a single room (A child between 1-12 years was calculated as half). It was then divided into 5 categories (group 1=<0.25, 2=0.251-0.500, 3=0.501-0.750, 4=0.751-1.00 and 5=>1.000 persons per room, respectively).

c) Level of education was divided into 5 categories: Group 1 - No formal education, Group 2 - Primary Level (<Class VIII), Group 3 - Secondary level, Group 4 - Graduation, Group 5 - Postgraduate and above.

d) Type of housing: Scores assigned to type of construction (Pucca=0, Kutcha=1) and whether gets flooded/floor gets wet in rainy season (No=0, Yes=1). Based on the total score, the housing was graded as good (Score=0) to worst (Score=2).

e) Water supply: Graded as good (score=0) to worst (score=2) based on whether the supply was available throughout the day (yes=0, no=1) or location of the water supply (inside the house=0, outside=1).

f) Number of consumer items (refrigerator, television, radio, telephone) was categorized into 5 categories (1=none, 2=1 item and so on).

Odds ratio and 95% confidence limits were calculated for each variable after adjusting other variables.

RESULTS

The mean age of patients suffering from tuberculosis was 35.56 years (SD 13.69). There were 168 male (67.2%) and 82 (32.8%) female patients; 210 (84%) had pulmonary tuberculosis while 13 (5.2%) had diagnosis of multi-drug resistant tuberculosis. The mean age of controls was 42.6 years (SD=16.11). There were 160 (64%) male and 90 (36%) female patients, most of whom were diagnosed to have either bronchial asthma (n=140, 56%) or chronic obstructive pulmonary disease (n=86, 34%).

Persons suffering from tuberculosis were more frequently found to have the worst of the socio-economic conditions for all the variables as seen on the univariate analysis and the odd’s ratio (OR) of

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>S.E.</th>
<th>OR</th>
<th>Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.33</td>
<td>0.07</td>
<td>0.72</td>
<td>0.63</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.14</td>
<td>0.19</td>
<td>1.15</td>
<td>0.80</td>
</tr>
<tr>
<td>Education</td>
<td>-0.46</td>
<td>0.09</td>
<td>0.63</td>
<td>0.53</td>
</tr>
<tr>
<td>Decreasing income</td>
<td>1.15</td>
<td>0.12</td>
<td>3.14</td>
<td>2.48</td>
</tr>
<tr>
<td>Increasing crowding</td>
<td>1.30</td>
<td>0.12</td>
<td>3.66</td>
<td>2.90</td>
</tr>
<tr>
<td>Poorer housing</td>
<td>1.31</td>
<td>0.13</td>
<td>3.71</td>
<td>2.86</td>
</tr>
<tr>
<td>Poorer water supply</td>
<td>1.42</td>
<td>0.17</td>
<td>4.13</td>
<td>2.94</td>
</tr>
<tr>
<td>Toilet (out side)</td>
<td>1.18</td>
<td>0.20</td>
<td>3.25</td>
<td>2.20</td>
</tr>
<tr>
<td>Decreasing no. of consumer items</td>
<td>0.95</td>
<td>0.09</td>
<td>2.58</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Table 1. Univariate analysis to assess socio-economic factors influencing risk of having tuberculosis
In multivariate logistic regression analysis, only age, level of education, crowding, type of housing, water supply and number of consumer articles in the household were found to be independently and significantly associated with higher risk of TB (Table 2). The level of income per

Table 2. Multiple regression analysis to assess socio-economic factors influencing risk of having tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
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<tbody>
<tr>
<td><strong>Age (10 year intervals)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>35-44</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Male gender</td>
<td>168</td>
<td>160</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Graduate</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Secondary</td>
<td>47</td>
<td>69</td>
</tr>
<tr>
<td>Primary</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>None</td>
<td>111</td>
<td>71</td>
</tr>
<tr>
<td>Crowding index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=0.250</td>
<td>9</td>
<td>50</td>
</tr>
<tr>
<td>0.251-0.500</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td>0.501-0.750</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>0.751-1.00</td>
<td>151</td>
<td>51</td>
</tr>
<tr>
<td>&gt;1.00</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>78</td>
<td>207</td>
</tr>
<tr>
<td>Fair</td>
<td>65</td>
<td>16</td>
</tr>
<tr>
<td>Poor</td>
<td>107</td>
<td>27</td>
</tr>
<tr>
<td>Water supply</td>
<td></td>
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<tr>
<td>Good</td>
<td>80</td>
<td>167</td>
</tr>
<tr>
<td>Fair</td>
<td>137</td>
<td>82</td>
</tr>
<tr>
<td>Poor</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>No. of consumer articles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=4</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>1</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>None</td>
<td>138</td>
<td>20</td>
</tr>
</tbody>
</table>

*P<0.001
The association between poverty and health is well documented. The founders of social medicine have established the powerful relationship of poverty and ill health that was attributed to abysmal housing, overcrowding, insanitation and poor working conditions. With public health initiatives, the incidence of infectious diseases such as tuberculosis, smallpox, diphtheria, measles and syphilis declined dramatically in the West even before cure for any of these diseases was known. This is particularly evident in case of tuberculosis. TB mortality declined from 113 per 100,000 persons per year in 1920 to <10 per 100,000 persons per year in 1950’s before the introduction of Isoniazid and effective chemotherapy in the United States; this was attributed to improvements in housing, sanitation and general socio-economic status (SES). By the turn of the 20th century, the concept of SES-health gradient became established, i.e. the relative risk of mortality/morbidity from a particular disease increases at a relatively constant rate with decreasing SES across the entire SES-spectrum. In the present study, persons suffering from TB had increased odds for decreasing SES for all the studied SES-variables (viz. education, income, crowding, housing, type of water supply, toilet, and number of consumer articles per household) studied, on univariate analysis. In more recent times, TB continues to involve the groups which are socio-economically disadvantaged. This is supported by several studies from the West, even though data from India and other developing countries are relatively sparse.

In a study among urban residents of New York City, tuberculin positivity was present in 5.5% in the area of highest socio-economic status versus 22.4% in the lowest. Among the variables studied in that survey, tuberculosis infection was related to race/ethnic group, socio-economic status, age, and sex, in that order. Another study from Liverpool, England revealed that part of the rise in notification rates was attributable to the increasing incidence of TB in the economically deprived sections of the society.

Of the six socio-economic status indicators (over-crowding, income, poverty, public assistance, unemployment and education) in cases reported between 1987-1993 in the US, relative risk of TB increased with lower SES quartile for all the six SES indicators on univariate analysis. The same trend was observed in multivariate models containing individual SES indicators. Tuberculosis risk increased uniformly between SES quartile for each indicator except crowding, where risk was concentrated in the lowest quartile.

In the present study, the multivariate analysis showed an association of TB with overcrowding, poorer housing, lesser education and lower number of consumer articles. This is in agreement with results observed in literature. Low income had increased odds only in the lowest income category, which was statistically not significant. This could be attributed to the fallacies in reporting income, which could otherwise be assessed from other parameters such as the number of consumer items.

Exactly how poverty may lead to tuberculosis remains unclear. Poor SES with its attendant poor education is associated with poor knowledge of TB, risks of infection and dissemination, and with inadequate and/or delayed availability of health care. Poverty also results in poor nutrition and low body weight, which are likely to render the immune system more vulnerable to the invading organisms.

Over-crowding increases the risk of disease transmission. Aerosol droplets containing tubercle bacilli are discharged into the atmosphere when a open case of tuberculosis coughs or sneezes. Fine droplet nuclei remain suspended in the air stream that reaches the alveolar space, thereby starting the infection. Overcrowding, by decreasing the degree of air space that is shared, results in increased exposure to M. tuberculosis.

Like overcrowding, the independent
increased odds ratio for persons with poor housing (i.e. those living in ‘Kutcha’ house and/or houses which get wet/flooded during monsoon) to have TB, found in the present study has a plausible physical explanation. It is known that a viable bacillus that is dried out or exposed to sunlight often is phenotypically too weak to start an infection. Poor housing with its attendant poor ventilation (that prolongs contact with infectious droplet nuclei) and increased dampness (that promotes viability of tubercle bacillus) increase the risk of transmission and development of disease.

We also found an inverse relationship between age and increased risk for TB. This is contrary to the reported higher risk of tuberculosis in the elderly people. But the observations in this study are consistent with the results of the prevalence studies from this part of the country, where majority of patients belonged to 15-55 years of age. Although the increased susceptibility of the elderly to tuberculosis cannot be denied, the total load in the younger age groups is much larger in the developing countries.

Data on socio-economic risk factors for tuberculosis in India are sparse. In a study on socio-economic impact of TB, it was shown that tuberculosis imposes high direct and indirect costs on the patients, leads to loss of wages for an average of 3 months and leads to school drop-outs in about 20% children. The importance of socio-economic development in enhancing anti-TB efforts has been repeatedly emphasized. Also, successful implementation of tuberculosis control programme is likely to have a direct tangible economic and social benefit.

In summary, the present study indicates the existence of a SES-health gradient with respect to risk of tuberculosis. Most public health efforts are focused on control of tuberculosis through treatment of patients. It is not surprising that cost-effective strategies such as directly observed therapy have emerged and to a large extent have been successful, even within populations of lower SES. But, the current predominantly treatment-based approach to tuberculosis control cannot be expected to lead to eradication of tuberculosis unless matching and forceful efforts in prevention through improvement in socio-economic status are also initiated.

REFERENCES

PRE-TEST COUNSELLING FOR HIV

With the uprising HIV epidemic in the country, it has become imperative for every physician to acquire knowledge and skills for HIV counselling comprising general post-test and HIV-positive patient counselling. The guidelines for pre-test counselling are:

- Put the person at ease; establish personal rapport.
- Explain in layman's language what HIV is, how it occurs, any wrong perception that may be current, and its consequences (a possibility of progression to AIDS).
- Explain the benefits of HIV testing—medical as well as sociological.
- Detail the steps of HIV testing, the significance of positive or negative result, the margin of error in the test being offered and whether it is for screening or confirmation.
- Stress that a positive result does not mean AIDS or even a prediction that it must occur, sooner or later.
- Discuss at length the confidentiality issue and its implications. Frankly answer doubts and fears; who all shall be informed by the person concerned, if the test is positive. Explain explicitly the meaning and implications of giving written informed consent, the right to refuse the test and the potential consequences of refusal, especially for the spouse and family.
- Assure that medical help will be extended even if the test is refused.
- Allow adequate time for pondering over the situation and making the decision in favour of the test.

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OUTCOME IN MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS WITH AMBULATORY TREATMENT

S.P. Rai¹ and B.N. Panda²

(Original received on 31.3.03; Revised version received on 21.8.03; Accepted on 3.9.03)

Summary:
Background: Multidrug resistant tuberculosis (MDR-TB) is emerging as an increasingly important cause of morbidity and death. The patients continue to spread disease for a prolonged period and may pose a threat to the success of DOTS.

Aim: To evaluate response to chemotherapy with second line drugs given on domiciliary basis in cases of MDR-TB.

Methods: Retrospective case records of 36 proven MDR-TB patients treated from April 1998 to April 2001 were analyzed. The patients were defined as cured when they had continued to be smear and culture negative for more than one year in addition to clinical and radiological improvement. All patients were followed up for relapse for one year.

Results: Out of 36 patients, 27 had far advanced lesions and 8 had moderately advanced lesions. All patients had resistance to at least Isoniazid and Rifampicin. Additional resistance was observed to Streptomycin in 19, Pyrazinamide - 8, Ethambutol - 8, Ethionamide - 6, Cycloserine - 5, Thiacetazone - 4, Ciprofloxacin - 3 and PAS in one patient. Average duration of pre-treatment chemotherapy was 14 months. Twenty patients were cases of relapse. Ten patients had concomitant disease (NIDDM - 3, COPD-4, Bronchial asthma-2, IHD-1). Average time for sputum conversion was 5 months. Twenty-three patients had sputum conversion in less than 4 months after revised chemotherapy. Out of 36 patients, 28 patients were declared cured at the end of 24 months of therapy, 7 patients defaulted and one patient died due to massive haemoptysis. Adverse reactions to chemotherapy included photosensitivity to Sparfloxacin-4 patients, ototoxicity to Kanamycin-2 patients and hyperuricemia- one patient.

Conclusion: Problem of MDR-TB can be managed to some extent by ambulatory treatment with other logistic supports like drugs, laboratory services and sympathetic motivated staff.

Key words: MDR-TB, DOTS.

INTRODUCTION

Tuberculosis remains the world’s leading infectious cause of adult death¹. Multidrug resistant tuberculosis (MDR-TB) is emerging as an increasingly important cause of morbidity and death since patient continues to spread disease for a prolonged period in the society². The most important factors for the emergence of MDR-TB are poor compliance, improper dosages and inadequate duration of chemotherapy²⁴. Management of MDR-TB is more difficult, complicated, challenging, costlier and may pose a threat to the success of DOTS. All efforts should be made to prevent resistance i.e. by early diagnosis, using standard regimen in adequate dosage and achieving excellent compliance. Also strategies are required to manage these drug resistant tuberculosis patients with individualized and standardized second line regimens within the DOTS strategy³.

MATERIAL AND METHODS

Case records of 36 proven MDR TB patients treated by us from April 1998 to April 2001 were analyzed. The patients included family members of service and retired personnel coming from different parts of country as well as some retired personnel. Detailed history of previous chemotherapy was taken. Three specimens of sputum were examined for AFB

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E-mail: rch_sprai@sancharnet.in
by smear and culture. Sputum culture was done on Lowenstein Jensen medium. The identification and biochemical tests were performed as per standard guidelines of National Tuberculosis Institute laboratory. Standardized inoculum was incubated in medium containing required concentration of drugs. A control strain of H37 RV was set up with each batch of drug sensitivity testing. Resistance was defined as growth of 20 colonies or more observed in minimum inhibitory concentration of 5 mcg/ml for Isoniazid (H), a resistance ratio > 16 for Streptomycin (S), 64 mcg/ml for Rifampicin (R), 8 mcg/ml for Ethambutol (E), 100 mcg/ml for Pyrazinamide (Z) and 16 mcg/ml for Ciprofloxacin (C). In 15 patients, AFB culture and sensitivity was also done by radiometric method from Ranbaxy Clinical Reference Laboratory, Mumbai, using BACTEC 460 TB instrument.

X-ray chest, blood for HIV serology, total and differential leucocytes count, ESR and biochemical parameters like fasting and post prandial sugar, liver function tests, renal functions and serum uric acid were done in all cases on admission and subsequently at any time when there was clinical evidence of hepatic or renal dysfunction. Sputum smears for AFB and culture for M. tuberculosis were repeated monthly till the time negative status was achieved and after that only smear was repeated monthly. X-ray chest was repeated once in two months till sputum became negative and then at three monthly intervals. All patients were provided free supply of second line anti-tubercular drugs. Treatment was continued for 18 to 24 months after sputum negative status, the drug that was physically or financially not tolerable was withdrawn. This included Cycloserine in four patients due to high cost. These drugs were withdrawn, one by one, keeping in mind their efficacy in treatment of existing bacterial population.

RESULTS

We have analysed case records of 36 proven patients of MDR TB treated by us on ambulatory basis. They included 20 males and 16 females. The average age was 39 years (range 14 to 76 years). Far advanced lesions were seen in 27 patients, moderately advanced lesions in 8 patients and minimal lesion in one patient. Two patients had disseminated tuberculosis. All patients were negative for HIV infection. Average duration of pretreatment chemotherapy was 14 months (maximum 48 months). Seven patients had received less than 3 months’ chemotherapy, 20 patients were cases of relapse (7 patients had relapsed for the second time and 2 patients for the third time). Concomitant disease was seen in 10 patients (NIDDM-3, COPD-4, bronchial asthma-2 and coronary artery disease in one patient).

Table 1: Drug resistance for individual drugs in addition to H and R (n = 36)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>S</th>
<th>Z</th>
<th>E</th>
<th>N</th>
<th>Cy</th>
<th>T</th>
<th>C</th>
<th>P</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>19</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

(S-Streptomycin, Z-Pyrazinamide, E-Ethambutol, Cy-Cycloserine, N-Ethionamide, T-Thiacetazone, C-Ciprofloxacin, P-Para-amino-salicylic acid, K-Kanamycin)
Table 1 shows resistance to anti-tubercular drugs in addition to Isoniazid and Rifampicin. Table 2 shows pre-treatment chemotherapy, pattern of drug resistance and response to revised antitubercular regimens. Average time for sputum conversion was 5 months. Twenty-three patients had sputum conversion in less than 4 months after revised chemotherapy.

Out of 36 patients, 28 were declared cured at the end of 24 months of therapy, 7 patients defaulted (3 were sputum positive even after more than one year of second line chemotherapy). One patient died due to massive haemoptysis. Adverse reaction to chemotherapy included photosensitivity to Sparfloxacin - 4 patients, ototoxicity to Kanamycin - 2 patients and hyperuricemia in one patient.

**DISCUSSION**

While tuberculosis is curable, MDR-TB may be fatal and the cure rates are frustratingly low. Tuberculosis is easy to diagnose, but MDR-TB diagnosis depends on reliable and expensive culture and sensitivity tests that are not available in most parts of India. The second line drugs used in cases of MDR-TB are often less effective, more likely to cause side effects and are costly. Because of these constraints, they are not included in DOTS. Effective DOTS programmes should prevent the development of new cases of MDR.

Being in a tertiary care centre, we were fortunate to have facilities for doing culture and sensitivity and could provide free second line drugs for complete duration. Another problem faced is lack of reproducibility and standardization in most of culture and sensitivity reports. We have cross-checked culture sensitivity from New Delhi TB Centre and also got it done by radiometric method from Ranbaxy Laboratories for all those patients who could afford to pay. In some cases, we found difference in drug sensitivity reports.

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**Table 2: Pretreatment chemotherapy, pattern of drug resistance and response**

<table>
<thead>
<tr>
<th>Resistant to number of drugs</th>
<th>2 drugs</th>
<th>3 drugs</th>
<th>4 drugs</th>
<th>5 drugs</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of Resistance (no)</td>
<td>HR-13</td>
<td>SHR-6</td>
<td>SHRZ-2</td>
<td>SHRET-1</td>
<td>S C</td>
</tr>
<tr>
<td></td>
<td>HRT-1</td>
<td>HRE-1</td>
<td>SHR-1</td>
<td>SHRE-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR Cy-1</td>
<td>HRT-1</td>
<td>SHR-1</td>
<td>SHRE-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*HR C-1</td>
<td></td>
<td>SHRT-1</td>
<td>SHRET-1</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>13</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Defaulted</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>-</td>
<td>1*</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pretreatment Chemotherapy (Months)</td>
<td>15.4</td>
<td>11.2</td>
<td>13.8</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

*Died of haemoptysis*
Most of our MDR-TB patients had cavitary, far advanced disease indicating a much higher mycobacterial population, where, naturally, drug-resistant strains are more likely to be found. We found increasing proportion of drug resistant cases amongst relapse cases. In our earlier studies we found MDR in 1.8% of new cases in comparison to 13.8% in relapse cases after fully supervised, in-hospital based short course chemotherapy. In the present study, 20 patients (55.5%) were cases of relapse who had earlier received treatment from different practitioners for a much longer duration, average pre-treatment chemotherapy being 14 months. In these cases, drug treatment was not supervised and their compliance was questionable. Because of these reasons, the patients had shown high incidence of resistance to even second line drugs. All our patients were given pre-treatment counselling along with their relatives/spouses/guardians. Further monthly counselling was done when they reported for drug collection. Regularity in bacteriological surveillance was ensured. This gave a total success of 77.7% to our programme, more than what many previous studies achieved.

In the present study, we resorted to total OPD treatment of MDR-TB where more than 30% patients reported from a distance ranging from 50 - 300 Kms. But regular counselling, free supply of drugs along with clinical, radiological and bacteriological monitoring helped us to ensure better compliance and an excellent cure rate.

Success in controlling TB will depend on controlling MDR-TB and case management initiative, designed to manage MDR-TB should be incorporated within the DOTS strategy. We have noted remarkable (77%) cure rate in MDR-TB patients even with ambulatory treatment when other logistic supports like second line drugs, laboratory services and above all caring as well as motivated staff are ready to listen to the patients.

REFERENCES


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54th TB SEAL CAMPAIGN

His Excellency Dr. A.P.J. Abdul Kalam, the President of India and Patron of the Tuberculosis Association of India, inaugurated the 54th TB Seal Campaign on 2nd October, 2003 at Rashtrapati Bhawan, New Delhi. TB Seals depicting monuments of Bihar were presented to the President of India by Hon’ble Mrs. Sushma Swaraj, Minister of Health & Family Welfare, Government of India. Dr. S.P. Agarwal, Chairman, Tuberculosis Association of India and Director General of Health Services, presented the Special Souvenir to the President of India.

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Indian Journal of Tuberculosis
A 35-YEAR OLD MAN WITH A NON-RESOLVING PLEURAL EFFUSION

Chandramani Panjabi, Puneet Khanna, Sudhir Jain* and Ashok Shah

(Received on 8.12.2003; Accepted on 10.12.2003)

Key Words: Non-resolving Pleural Effusion, Sarcoidosis

CLINICAL SUMMARY

A thirty-five-year old male, a nonsmoker, was referred to us for evaluation of progressive pulmonary disease. His clinical course during the past 2 years was characterized by paroxysmal attacks of cough with scanty mucoid sputum. This was accompanied by intermittent fever and malaise. There was no history of wheezing, nasal symptoms or loss of weight. Eighteen months prior to referral, based on his symptomatic and roentgenologic profile, he was clinically diagnosed as a case of tuberculous mediastinal lymphadenitis. He was initiated on antituberculous therapy (ATT) comprising rifampicin 450 mg, isoniazid 300 mg, pyrazinamide 1500 mg and ethambutol 800 mg once daily. Prednisolone (10 mg thrice daily) was added after 2 months when the patient did not experience any relief. He was however irregular with the oral steroids and stopped it after 1 month. One year prior to referral, while on ATT for 6 months, he had few episodes of blood-streaked sputum, episodic exertional dyspnoea, and right-sided chest pain that increased on coughing and deep breathing. This was diagnosed as right-sided pleural effusion, and the patient was initiated on second line ATT in the form of kanamycin 1gm intramuscularly, sparfloxacin 400 mg, prothionamide 750 mg, clofazamine 200 mg, clarithromycin 500 mg, thiacetazone 150 mg and isoniazid 300 mg once daily. Kanamycin was stopped after 6 months but the other drugs were continued for a period of 1 year. In spite of regular second line ATT for 1 year, the patient remained symptomatic and as the effusion persisted, he was referred to us for evaluation.

Physical examination revealed a middle-aged male in no acute distress. There was no clubbing or cyanosis. Chest examination suggested a right-sided pleural effusion. Examination of other systems, including an ophthalmologic referral, did not detect any abnormality.

INVESTIGATIONS

A review of chest roentgenogram (Fig 1a) and computed tomography (CT) of the thorax (Fig 1b) showed bilateral pleural effusion. A pleural biopsy was done on the right side which showed non-specific inflammatory changes consistent with chronic pleurisy. The patient was then referred to the Department of Respiratory Medicine. A review of the chest roentgenogram (Fig 1a) and computed tomography (CT) of the thorax (Fig 1b) showed bilateral pleural effusion. A pleural biopsy was done on the right side which showed non-specific inflammatory changes consistent with chronic pleurisy. The patient was then referred to the Department of Respiratory Medicine.

Figure 1a: Chest roentgenogram (PA view), taken 18 months prior to referral, showing bilateral asymmetrical mediastinal lymphadenopathy with thickening of the right oblique fissure.
1b), taken 18 months prior to referral when ATT was first initiated, disclosed bilateral asymmetrical mediastinal lymphadenopathy without caseation or ring enhancement. The lung parenchyma was however normal. In addition, fissural thickening was seen on the chest roentgenogram and the CT scan (mediastinal window) revealed right-sided pleural involvement. At this time, the patient had a haemoglobin of 12.2 gm% with a total leucocyte count of 9200/mm$^3$. The differential counts were within normal limits. Other investigations, which included urine examination, blood sugar and urea, serum cholesterol, electrocardiogram and liver function tests were within normal limits. Several sputum stains and cultures for *Mycobacterium tuberculosis* were negative. Cultures for other aerobic organisms did not grow any pathogens. Tuberculin testing with 10 TU was negative.

**INVESTIGATIONS AFTER REFERRAL**

Chest roentgenogram (Fig 2a) and CT-thorax (Fig 2b) taken after referral showed persistent mediastinal lymph nodes and development of pleural effusion on the right side. Thickening of both the fissures on the right side was also seen (Fig 2a), which was suggestive of fissural effusions. The CT scan (lung window) (Fig 2c) now showed a wedge shaped consolidation along with air bronchogram in the right middle lobe. Poorly defined areas of consolidation with multiple air bronchograms were seen in the right lower lobe as also linear fibrotic band in the left lower lobe. A diagnostic pleural tap yielded 60 ml of straw-coloured exudate, with predominantly lymphocytes (62%), neutrophils (30%) and reactive mesothelial cells. Smear and cultures of the fluid were negative for *Mycobacterium*
tuberculosis, pyogenic organisms and pathogenic fungi. Fibreoptic bronchoscopy suggested the presence of a granulomatous disease. Bronchial biopsy (Fig 3) revealed well circumscribed noncaseating granuloma consisting of epitheloid cells and multinucleated giant cells. Pulmonary function tests were suggestive of severe restrictive airflow limitation with reduction in total lung capacity and a normal carbon monoxide diffusing capacity. Serum calcium and 24-hour urinary calcium were within normal limits while rheumatoid factor and antinuclear antibody were negative. However, serum angiotensin converting enzyme level was elevated (210 IU/ml, normal range = 22 - 120 IU/ml).

DIAGNOSIS

Pulmonary sarcoidosis with right-sided pleural effusion

Clinical course after diagnosis

The ATT was stopped on presentation. The patient was initiated on oral prednisolone 40mg once daily, which was reduced to 40 mg on alternate days after 2 weeks and gradually tapered after 6 months at the rate of 5 mg per month. There was remarkable clinical and roentgenologic improvement. His cough, fever, breathlessness and chest pain decreased, while the chest roentgenogram showed regression of the mediastinal lymph nodes and clearing of the effusion (Fig 4). After 8 months, steroid therapy was discontinued by the patient. Two months later, he...
developed a nodule on his chin, which on biopsy also demonstrated noncaseating granuloma. However, there was no pleural effusion or increase in the size of the lymph nodes on the chest roentgenogram. The chin nodule disappeared after prednisolone was restarted. The patient remains asymptomatic on regular maintenance therapy.

COMMENTS

At one point in time, the presence of pleural effusion was thought to exclude sarcoidosis. In 1962, Berte and Pfotenhauer, while reporting a case of massive pleural effusion in sarcoidosis, state that “a review of the American literature between 1953 and 1961 has failed to uncover a documented case report of pleural effusion resulting primarily from sarcoidosis.” However, involvement of the pleura in sarcoidosis was first demonstrated by Schaumann in 1933 following an autopsy of a 45-year-old Caucasian male. In 1974, Wilen et al reviewed the 32 communications describing 57 patients of sarcoidosis with pleural involvement and concluded that pleural involvement in a patient with sarcoidosis should be considered a part of this disease process. Subsequent series suggest that pleural effusion occurs in 0.7-7% of cases with sarcoidosis. In India, it has been seen in up to 6.6% patients. In our series of 73 patients with sarcoidosis, pleural effusion was seen in 2 (3%) patients.

Pleural effusion can either manifest as an incidental finding at the time of initial diagnosis of sarcoidosis or occur several years after the diagnosis has been established. Occasionally, patients have also presented with acute symptoms, viz. pleuritic chest pain and dyspnoea. Our patient experienced symptoms of acute pleurisy, which were erroneously thought to be due to the development of drug resistant tuberculosis.

Pleural effusions in sarcoidosis are often unilateral, with some series suggesting a right-sided predilection. Bilateral effusion has been reported in a third of the cases. It is usually mild to moderate, but can occasionally be massive. Our patient had a small right-sided pleural effusion. The pleural fluid characteristics in patients with sarcoidosis have been variable. Although the fluid is usually straw coloured, turbid or serosanguinous fluid has also been described. Biochemical examination suggests an exudate in most cases. Fluid cytology shows a variable amount of cells, chiefly lymphocytes. In our case, the pleural fluid was a straw coloured exudate with lymphocytic predominance. In tuberculous pleural effusion too, the fluid is usually straw-coloured and exudative, comprising mainly lymphocytes. This causes diagnostic difficulties due to the high prevalence of tuberculosis in our country, which has been picturesquely portrayed by the late Dr Samir K. Gupta as “searching for the needle of sarcoidosis in the haystack of tuberculosis.” Furthermore, the remarkable radiological similarity of sarcoidosis with pulmonary tuberculosis has important clinical implications in our country as these patients are often mistaken for tuberculosis and receive repeated courses of ATT while lung damage continues to progress.

Corticosteroids have been reported to be effective in the treatment of pleural effusion in sarcoidosis. However, cases of spontaneous resolution have also been reported. In our case, corticosteroid therapy resulted in resolution of the pleural effusion as well as marked improvement in the parenchymal infiltrates.

One of the important causes of the development of pleural effusion in a patient on ATT is a paradoxical response. This occurs mostly between 3 and 8 weeks of starting ATT, and the effusion usually subsides spontaneously on the same treatment. In our case, there was no response to both first and second line ATT, but the pleural effusion resolved with oral prednisolone that was started after the diagnosis of sarcoidosis was made.

Our case highlights the fact that although uncommon, sarcoidosis can also present with pleural effusion. In our country, a high index of suspicion is required to establish the diagnosis in such a case. Early diagnosis and initiation of appropriate treatment can not only prevent these patients from receiving unnecessary ATT for long durations but can also avoid significant morbidity and improve the prognosis.
ACKNOWLEDGEMENTS

The authors are thankful to Dr. R. K. Mathur, Director, Department of Imaging, Batra Hospital and Medical Research Centre, New Delhi for the computed tomographic scans.

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**RADIOLOGY FORUM**

As readers would have noticed, we have started a new section “Radiology Forum” from this issue of the *Indian Journal of Tuberculosis* in your hands. Readers as well as other workers in the field of Tuberculosis & Respiratory Diseases are invited to submit brief report of patients with interesting clinical and radiological features for publication. These will be published, provided that:

- the condition is of clinical and radiological interest;
- photographs (10 cm x 8 cm) are of excellent quality for printing;
- the diagnosis in each case has been confirmed;
- the chest radiograph is accompanied by brief clinical account, not exceeding one page typescript.

All the material received for publication in the Radiology Forum will be peer reviewed as per the Journal policy.
FOR AUTHORS

From the January 2004 issue, references in the Indian Journal of Tuberculosis will be published as per Vancouver style. All the numbered references in the text should be typed in detail, in the same consecutive order. Abbreviations of the titles of the cited journals should be according to the Index Medicus. Examples:

**Journal**

**Book**

**Chapter in Book**
Fraser RS, Muller NL, Colman N, Pare PD. Upper airway obstruction. In: Fraser RS, Muller NL, Colman N, Pare PD, Bralow L, ed Fraser and Pare’s *Diagnosis of Diseases of Chest*; 4th edn; Vol III. Philadelphia: W.B. Saunders Co.; 1999; 2021-2048.
Case Report

MULTI-DRUG RESISTANT EXTRA-PULMONARY TUBERCULOSIS IN A HIV-NEGATIVE PATIENT

S.K. Sharma¹ and A. Mohan²

(Received on 3.11.2003; Accepted on 25.11.2003)

Summary: A 25 year-old, HIV seronegative male presented with bilateral cervical lymphadenopathy with cold abscesses and sinus formation, peripancreatic lymphadenopathy and hypodense lesions in the spleen. Culture of pus aspirated from the cold abscess in the neck grew M. tuberculosis resistant to Rifampicin, Isoniazid, Ciprofloxacin and Para-aminosalicylic acid. In a resource-limited setting, he was treated with Ethambutol (E), Pyrazinamide (Z), Ethionamide (Eth), Cycloserine (Cyc), and Ofloxacin (Ofl). While on treatment, he developed drug induced hepatotoxicity; Z and Eth were stopped and clofazimine was added to the regimen. Subsequently, he developed splenic abscess and clofazimine induced generalized pigmentation of the body including tongue. After eighteen months of treatment, lymphadenopathy and splenic lesions regressed significantly. Thus, present case highlights several important basic principles of management of MDR-TB such as procuring tissue for microbiological testing, judicious use of imaging modalities, careful monitoring for adverse drug reactions, intercurrent infections and the need for pre-treatment counselling for ensuring compliance and completion of treatment.

Key words: Multidrug-resistant lymph node tuberculosis, drug induced hepatotoxicity, Clofazimine.

INTRODUCTION

In immuno-competent adults, it has been observed that extra-pulmonary tuberculosis (EPTB) constitutes about 15 to 20 per cent of all cases of tuberculosis. In human immunodeficiency virus (HIV) positive patients, EPTB accounts for more than 50 per cent of all cases of tuberculosis. Definitive diagnosis of EPTB involves demonstration of M. tuberculosis in tissue specimens and body fluids by microbiological and histopathological methods. Given the obscure location of the disease, reluctance of the patients to undergo invasive procedures for procuring body fluids and tissue specimens for examination and poor yield of the conventional histopathological and microbiological diagnostic methods, definitive diagnosis of EPTB is difficult. Furthermore, reliable mycobacterial culture and sensitivity testing is not widely available in India. Thus, there are very few reports of multi-drug-resistant tuberculosis (MDR-TB) at extra-pulmonary sites from India. We report the rare occurrence of MDR-TB involving the peripheral and peripancreatic lymph nodes and the spleen in a HIV-negative patient.

CASE REPORT

A 25 year-old male presented with a history of swelling on either side of neck, with pus discharge from some of them for the preceding two years. Physical examination revealed pallor, bilateral cervical lymphadenopathy with cold abscess and sinus formation. Rest of the physical examination was unremarkable. Base line haematological and biochemical investigations including liver function tests were normal. Chest radiograph was unremarkable. Contrast enhanced computerised tomographic scan (CECT scan) of abdomen revealed peripancreatic lymphadenopathy (Figure 1) and hypodense lesions in the spleen (Figure 2). He...
was put on anti-tuberculosis treatment with Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Streptomycin (S), awaiting the cold abscess pus mycobacterial culture and sensitivity report. Pus aspirated from the cold abscess in the neck grew *M. tuberculosis* resistant to Rifampicin, Isoniazid, Ciprofloxacin and Para-aminosalicylic acid. In a resource-limited setting, his anti-tuberculosis treatment regimen was modified to Ethambutol (E), Pyrazinamide (Z), Ethionamide (Eth), Cycloserine (Cyc), and Ofloxacin (Ofl) according to body weight.

During the fourth month of treatment, he developed anorexia and manifested icterus. Serum biochemistry revealed elevated serum bilirubin (3.5g/dl) and aspartate aminotransferase (AST) (110IU/l); and alanine aminotransferase (ALT) (134 IU/l) suggesting drug induced hepatotoxicity (DIH). Anti-tuberculosis treatment was modified; Z, and Eth were stopped and Clofazimine was added to the regimen.

Four weeks later he presented with moderate to high grade fever, chills and rigors with no other localisation clue. There was no recurrence of peripheral lymphadenopathy and the sinuses remained healed. The patient was admitted and investigated for the cause of fever. CECT scan of abdomen revealed splenic abscesses and air in the spleen (Figure 3). No communication could be
established between large bowel and spleen on performing colonoscopy and barium enema study. He was treated with intravenous ceftriaxone, amikacin and metronidazole. Modified anti-tuberculosis treatment with E, Cyc, Of1 and clofazimine was continued. Liver functions were monitored weekly. The patient responded to treatment and fever subsided. Meanwhile, he also developed clofazimine induced pigmentation all over body and over the tongue. The liver functions normalised and Z and Cyc could be successfully reintroduced into the treatment regimen. At nine months of treatment, there was no evidence of periphehral lymphadenopathy, the peripancreatic lymph nodes regressed considerably and splenic lesions decreased significantly. The patient completed 18 months of treatment and has remained asymptomatic and is under regular follow up.

DISCUSSION

Our patient presented with peripheral lymphadenopathy and discharging sinuses. Physical examination of the abdomen was unremarkable. However, CECT scan of abdomen revealed peripancreatic lymphadenopathy and hypodense lesions in the spleen. Thus, CECT scan of abdomen has been useful in identifying additional foci of involvement even when the physical examination was normal. It has been observed that, with the advent of CECT scan, more precise anatomical localisation of EPTB has been possible. Abdominal CT is useful in detecting high density ascites intra-abdominal lymphadenopathy and granulomas or abscesses in liver, pancreas and spleen 2,8. Caseous necrosis of lymph node may be discerned as low attenuating, necrotic centres and thick, enhancing inflammatory rim (Figure 1). As in case of our patient, CT scan also facilitates monitoring of response to treatment by documenting the reduction in size and disappearance of lesions.

EPTB is more common in HIV-positive individuals and in immuno-compromised patients 2,7. Less commonly, EPTB may occur in immunocompetent individuals also. Our patient was HIV-negative and did not have any obvious cause of immunosuppression. Though not widely or reliably available, mycobacterial culture and sensitivity testing is essential for labelling an isolate as multidrug-resistant (resistance to Rifampicin and Isoniazid with or without resistance to other anti-tuberculosis drugs). The present case also highlights the cardinal rule that, whenever possible, tissue and body fluid specimens from the site of EPTB must be subjected to smear, culture and sensitivity testing even though the diagnostic yield of these conventional diagnostic methods is low. This is essential because, MDR-TB is among the most worrisome elements of the pandemic of antibiotic resistance. While resistance to either Isoniazid or Rifampicin may be managed with other first line drugs, MDR-TB demands treatment with second-line drugs. These drugs have limited sterilising capacity and are not suitable for short-course treatment and these patients require prolonged treatment with less effective and more toxic second line drugs 2.

Our patient developed DIH which required modification of treatment regimen. Patients receiving anti-tuberculosis treatment especially with toxic second-line drugs, should be carefully monitored for development of DIH which can sometimes be fatal 10-11. When DIH develops, the choice of anti-tuberculosis drugs that can be used becomes limited and results in prolongation of duration of treatment. When patients with MDR-TB develop DIH, the choice of the drugs that can be used becomes further narrowed down. This not only affects the compliance with treatment but also prolongs the duration of treatment 2. Thus, treatment of MDR-TB should be taken up by experts at centres equipped with facilities for recording and monitoring the adverse drug reactions.

The pigmentation which developed due to clofazimine, though not fatal, can be alarming to the patient. Pre-treatment counselling regarding the possible adverse drug reactions, prompt recognition and modification of the treatment regimen will not only help in alleviating the symptoms but also will enhance treatment compliance which is essential for cure.

Our patient developed serious intercurrent infection during the course of treatment with second
line drugs which required hospitalisation. Intercurrent infections are known to occur in patients with tuberculosis\textsuperscript{12}. When patients with MDR-TB develop intercurrent infections, they may develop fever and toxemic symptoms. The inexperienced clinician may interpret this as lack of response and may attempt to alter the treatment regimen\textsuperscript{2}. Since the therapeutic choices are very few in MDR-TB, this issue is particularly relevant. Thus, meticulous search for other intercurrent infections must be made when patients with MDR-TB who have otherwise been responding well, if they develop fever or toxemic symptoms because prompt recognition and treatment of these infections can be rewarding. Our patient developed splenic abscess and gas in the spleen. In our patient, colonoscopy and barium enema did not reveal any communication between large bowel and spleen. Even though blood cultures were negative, we believe that this was due to superadded bacterial infection with gas producing organisms.

Thus, present case highlights several important basic principles of management of MDR-TB at extra-pulmonary sites such as procuring tissue for microbiological testing, judicious use of imaging modalities, careful monitoring for adverse drug reactions, intercurrent infections and the need for pre-treatment counselling for ensuring compliance and completion of treatment.

REFERENCES


Case Report

TUBERCULAR OSTEOMYELITIS OF NASAL BONES: A RARE ENTITY

Raman Wadhera1, Avinash Kumar2, S.P. Gulati3 and Sanjeev Arora4

(Received on 26.8.2003; Accepted on 6.10.2003)

Summary: A case of tubercular osteomyelitis of nasal bones in a 10 year old child is being reported because of its extremely rare occurrence.

Key words: Tubercular osteomyelitis, Nasal bone

INTRODUCTION

Tuberculosis is a common disease in developing countries. The disease affects bones in 1% of cases and involvement of skull occurs in 0.2-1.37% of these1. Since tuberculosis affects mainly the cancellous bones, there being little cancellous tissue in flat bones of skull, the disease is comparatively rare in skull2.

CASE REPORT

A 10 year old female child presented to the otolaryngology department of our hospital with a 1x1 cm slightly painful, diffuse, erythematous swelling over left side of bridge of nose for preceding one month. Patient had a history of minor fall preceding the onset of swelling. The swelling had persisted despite symptomatic treatment by local practitioners. On palpation, it was slightly tender and on compressing the swelling, thick pus oozed out from a point over it.

Patient was afebrile with no notable finding on systemic and general physical examination. Complete hemogram, ESR and skiagram of nasal bones were within normal limits. After hospitalization, surgical curettage of the lesion under general anesthesia was performed. Multiple small bony spicules were curetted out apart from the thick yellowish pus, which was drained. After debridement, presuming it to be a case of pyogenic osteomyelitis, wound was stitched and patient was put on a combination of amoxycillin with clavulanic acid in full dosage but the wound failed to heal despite a week long therapy. Rather, a week later another similar diffuse swelling appeared, this time over right side of bridge of nose. Repeat curettage was done and the curetted material, which was in the form of pale polypoidal granulation tissue and bony spicules, was sent for histopathological examination. Histopathological report was consistent with diagnosis of tubercular osteomyelitis.

By the time report of histopathological examination became available, patient had developed a 3x3 cm, smooth surfaced, mobile lymphnode in left submandibular region which too on fine needle aspiration cytology revealed features consistent with diagnosis of tubercular lymphadenitis (Fig.1). There was no past history of tuberculosis either in the patient or any family member. Meticulous search including X-ray chest failed to reveal any other tubercular focus in the body. Patient was put on standard four drug antitubercular regimen. Response to treatment was overwhelming with wound over nasal bridge healing over a period of two weeks (Fig.2). At the time of submitting this case report, patient had already been on ATT for about 1½ months; cervical lymphadenopathy had moderately decreased in size but was still present.

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Indian Journal of Tuberculosis
DISCUSSION

Primary tubercular osteomyelitis of nasal bones is a very rare entity. Though cases of tubercular osteomyelitis of zygomatic bone\(^3\) and other flat bones of skull have been reported in literature, we could not find any involving nasal bones. Non-healing nature of the lesion, appearance of another lesion despite meticulous curettage along with pale polypoidal caseous look of the granulation tissue at the time of second curettage and a history of trauma preceding the onset of swelling were the factors that made us suspect tuberculosis. Trauma has been suggested as playing a role in the genesis of the disease and review of literature revealed that 75-80% of all cases of tuberculosis of skull occurred before the age of 20 years and were more common in males\(^4\). The route of infection in these cases is either direct inoculation or via bloodstream\(^5\). In the present case, the infection was probably via direct inoculation as patient didn’t have any tubercular focus elsewhere.

CONCLUSION

Tuberculosis may involve virtually any organ, tissue or bone in the body. As such, a high level of suspicion for the condition may prove rewarding as in this case.

REFERENCES

Revised National TB Control Programme (RNTCP) is an application in India of the WHO-recommended Directly Observed Treatment, Short Course (DOTS) strategy to control TB with the objectives of curing at least 85% of new sputum positive TB patients and detecting at least 70% of such patients. Starting in October 1993, the strategy was pilot tested till 1996. Having proved both its technical and operational feasibilities, the implementation of RNTCP started in 1997. In the past years RNTCP has been expanding rapidly. By mid-November 2003, 765 million population has been covered under the programme. Status of implementation as on 30th October 2003 is reflected in the graph. Government of India is continuing to take aggressive steps to meet global TB control targets by covering the whole population with RNTCP by year 2005. It is planned to cover 85% of the country’s population by 2004 and the entire country by 2005. Around 730 million population is being covered with World Bank assistance. In addition, DFID, DANIDA and USAID are supporting RNTCP to cover the entire states of Andhra Pradesh, Orissa and Haryana respectively. Global Fund for AIDS, TB and Malaria (GFATM) is providing support for DOTS expansion in 3 states of Jharkhand, Chhattisgarh, and Uttarakhand (56 million populations) in the first round and 56 districts of Bihar and Uttar Pradesh.  

**Graph:** Status of RNTCP implementation in the country (as on 30th October 2003) and the future plan

*Dr. P. S. Chander, DDG (TB), Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, New Delhi*
Pradesh (110 million populations) in the second round. The Global Drug Facility (GDF) is also providing anti-TB drugs for Orissa and additional 200 million population as commodity grant.

**Status of RNTCP**

The programme is being implemented in a phased manner to ensure that quality of services is maintained. Currently, around 765 million of the country’s population in 418 units has been covered under the programme. Twelve States/Union Territories are fully covered under RNTCP (Arunachal Pradesh, Chandigarh, Delhi, Maharashtra, Manipur, Meghalaya, Mizoram, Rajasthan, Tamil Nadu, Kerala, HP and Sikkim).

A total of around 0.25 million patients have been initiated on treatment under DOTS in third quarter of 2003 out of which nearly 0.1 million are new sputum positive cases. The new sputum positive case detection rate for this quarter is 63%. It must be mentioned here that though this is slightly less than the expected levels of 70%, the current figure for detection rate is based on ARI of 1.7. The ARI is likely to be set at a lower level (1.5) when the findings of recently concluded ARI survey are finalised and consensus figure arrived at. The success rate continues to be high and 87% of the new smear positives registered in third quarter 2002 were successfully treated under DOTS. This is well above the global target of 85%. The sputum conversion rate and cure among the new sputum positives was 89% and 86%, respectively. The state wise details of performance of RNTCP implementing areas during third quarter 2003 are given in the Table. Around 80,000 cases are now being put on DOT in each quarter. Since the inception of the Programme in 1993, more than 25,000,000 patients have been placed on treatment under DOTS, thus saving more than 4,50,000 additional lives. Out of this more than 0.65 million cases have been put on DOTS in this year itself (first three quarters of 2003)

RNTCP has achieved around 40-fold expansion in its coverage since 1998. Every month, around 10 million additional population is being covered. With nearly three-fourth of the country’s population having access to DOTS, RNTCP is the second largest DOTS programme in the world. Since 1999, progress in global TB control has been determined by India’s success and this will continue over the coming years. As per the Global TB Report 2003, two-thirds (67%) of the additional smear positive cases reported under DOTS globally in 2001 were found in India alone.

Diagnostic facilities have been established in about 7,600 laboratories throughout the country. As a result, the proportion of sputum positive cases confirmed in the laboratory has doubled as compared to the previous programme and is at par with international standards.

The programme managers are well aware of the challenges that lie ahead, foremost being expansion of the programme to cover a population of 850 million by 2004 and the entire country by 2005. For sustainability, the programme activities need to be decentralised. Further, the programme proactively solicits involvement of NGOs and private practitioners (PPs) as per RNTCP guidelines. Till date, more than 550 NGOs and 2000 private practitioners are providing RNTCP services. Several Public-Private Mix (PPM) projects being implemented in various parts of the country have shown promising results. In addition, PPM projects are also being planned in 14 large urban areas with assistance from CIDA.

Medical colleges are being provided with manpower and logistic support to facilitate their participation in the programme. Seven RNTCP nodal centres have been identified and task forces have been formed at various levels. Presently, 131 medical colleges are participating in the programme. Recently in November, the second national level workshop for the involvement of Medical Colleges was held in Delhi. The work plan for the next year for the zonal nodal centres was developed in the workshop. Efforts are also on to involve ESI, CGHS, railways, armed forces, corporate sector and PSU in the programme.

Action plan for TB/HIV coordination is being implemented jointly by the RNTCP and NACO in six
### Table: State wise performance of RNTCP implementing areas as per 3rd Quarter 2003 (July-Sep) reports

<table>
<thead>
<tr>
<th>Implementing states</th>
<th>Population (in lakhs) covered by RNTCP (%)</th>
<th>Total no. of districts/DTCs reporting RNTCP</th>
<th>No. of districts/DTCs reporting smear positive patients</th>
<th>Smear positive patients diagnosed No</th>
<th>Percentage smear positive patients living in the district placed on DOTS</th>
<th>Total patients treated</th>
<th>Annualized total case detection rate</th>
<th>New smear positive patients treated</th>
<th>Annualized new smear positive case detection rate</th>
<th>3 month conversion rate of new smear positive patients $\dagger$</th>
<th>Cure rate of new smear positive patients $\ddagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andhra Pradesh</td>
<td>708 (91)</td>
<td>23</td>
<td>21</td>
<td>13916</td>
<td>98%</td>
<td>25808</td>
<td>146</td>
<td>11472</td>
<td>13520</td>
<td>88%</td>
<td>86%</td>
</tr>
<tr>
<td>Arunachal Pradesh</td>
<td>11 (100)</td>
<td>6</td>
<td>6</td>
<td>263</td>
<td>93%</td>
<td>500</td>
<td>175</td>
<td>203</td>
<td>71</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>Assam</td>
<td>109 (40)</td>
<td>23</td>
<td>8</td>
<td>1957</td>
<td>94%</td>
<td>3341</td>
<td>123</td>
<td>1405</td>
<td>52</td>
<td>82.6%</td>
<td>85%</td>
</tr>
<tr>
<td>Bihar</td>
<td>117 (13)</td>
<td>37</td>
<td>3</td>
<td>1326</td>
<td>98%</td>
<td>2763</td>
<td>94</td>
<td>995</td>
<td>34</td>
<td>94%</td>
<td>87%</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>10 (100)</td>
<td>1</td>
<td>1</td>
<td>353</td>
<td>84.95%</td>
<td>462</td>
<td>192</td>
<td>165</td>
<td>68</td>
<td>89%</td>
<td>84%</td>
</tr>
<tr>
<td>Chhattisgarh</td>
<td>94 (44)</td>
<td>16</td>
<td>4</td>
<td>1168</td>
<td>91%</td>
<td>2293</td>
<td>98</td>
<td>833</td>
<td>35</td>
<td>86%</td>
<td>79%</td>
</tr>
<tr>
<td>Delhi</td>
<td>149 (100)</td>
<td>20</td>
<td>20</td>
<td>5714</td>
<td>92%</td>
<td>10094</td>
<td>271</td>
<td>2880</td>
<td>77</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>Gujarat</td>
<td>502 (95)</td>
<td>27</td>
<td>25</td>
<td>13413</td>
<td>8597%</td>
<td>18196</td>
<td>145</td>
<td>7033</td>
<td>56</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>Haryana</td>
<td>80 (36)</td>
<td>19</td>
<td>5</td>
<td>1851</td>
<td>94%</td>
<td>3212</td>
<td>161</td>
<td>1177</td>
<td>59</td>
<td>85%</td>
<td>79%</td>
</tr>
<tr>
<td>Himachal Pradesh</td>
<td>63 (100)</td>
<td>12</td>
<td>12</td>
<td>2113</td>
<td>92%</td>
<td>3419</td>
<td>218</td>
<td>1264</td>
<td>81</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>Jharkhand</td>
<td>95 (34)</td>
<td>22</td>
<td>4</td>
<td>1207</td>
<td>97%</td>
<td>2219</td>
<td>100</td>
<td>961</td>
<td>43</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>Karnataka</td>
<td>489 (90)</td>
<td>26</td>
<td>23</td>
<td>19590</td>
<td>95%</td>
<td>14193</td>
<td>121</td>
<td>5966</td>
<td>51</td>
<td>87%</td>
<td>84%</td>
</tr>
<tr>
<td>Kerala</td>
<td>324 (100)</td>
<td>14</td>
<td>14</td>
<td>3603</td>
<td>94%</td>
<td>6512</td>
<td>80</td>
<td>2804</td>
<td>36</td>
<td>90%</td>
<td>89%</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>427 (68)</td>
<td>45</td>
<td>31</td>
<td>7171</td>
<td>8594%</td>
<td>10698</td>
<td>114</td>
<td>4321</td>
<td>46</td>
<td>87%</td>
<td>84%</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>992 (98)</td>
<td>48</td>
<td>46</td>
<td>17776</td>
<td>92%</td>
<td>33157</td>
<td>134</td>
<td>11878</td>
<td>48</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td>Manipur</td>
<td>25 (100)</td>
<td>9</td>
<td>8</td>
<td>382</td>
<td>98%</td>
<td>1357</td>
<td>216</td>
<td>339</td>
<td>54</td>
<td>87%</td>
<td>86%</td>
</tr>
<tr>
<td>Mizoram</td>
<td>9 (100)</td>
<td>8</td>
<td>8</td>
<td>262</td>
<td>109%</td>
<td>617</td>
<td>263</td>
<td>219</td>
<td>93</td>
<td>88%</td>
<td>86%</td>
</tr>
<tr>
<td>Nagaland</td>
<td>19 (84)</td>
<td>8</td>
<td>7</td>
<td>238</td>
<td>7754%</td>
<td>476</td>
<td>101</td>
<td>179</td>
<td>39</td>
<td>87%</td>
<td>86%</td>
</tr>
<tr>
<td>Orissa</td>
<td>218 (58)</td>
<td>30</td>
<td>19</td>
<td>3859</td>
<td>99%</td>
<td>6058</td>
<td>131</td>
<td>2839</td>
<td>72</td>
<td>88%</td>
<td>84%</td>
</tr>
<tr>
<td>Punjab</td>
<td>154 (61)</td>
<td>17</td>
<td>9</td>
<td>2528</td>
<td>8804%</td>
<td>4214</td>
<td>110</td>
<td>1533</td>
<td>40</td>
<td>88%</td>
<td>89%</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>594 (100)</td>
<td>32</td>
<td>32</td>
<td>17534</td>
<td>93%</td>
<td>25991</td>
<td>175</td>
<td>10200</td>
<td>69</td>
<td>90%</td>
<td>87%</td>
</tr>
<tr>
<td>Sikkim</td>
<td>6 (100)</td>
<td>4</td>
<td>4</td>
<td>157</td>
<td>94%</td>
<td>366</td>
<td>256</td>
<td>98</td>
<td>69</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>634 (100)</td>
<td>29</td>
<td>29</td>
<td>12754</td>
<td>97%</td>
<td>22562</td>
<td>142</td>
<td>8775</td>
<td>55</td>
<td>91%</td>
<td>86%</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>782 (45)</td>
<td>70</td>
<td>28</td>
<td>15355</td>
<td>88.66%</td>
<td>22472</td>
<td>119</td>
<td>9758</td>
<td>51</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td>Uttarakhand</td>
<td>20 (233)</td>
<td>13</td>
<td>2</td>
<td>400</td>
<td>95%</td>
<td>606</td>
<td>123</td>
<td>217</td>
<td>44</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td>West Bengal</td>
<td>812 (98)</td>
<td>19</td>
<td>18</td>
<td>13904</td>
<td>94%</td>
<td>24098</td>
<td>119</td>
<td>10426</td>
<td>51</td>
<td>89%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7442 (70)</strong></td>
<td><strong>580</strong></td>
<td><strong>388</strong></td>
<td><strong>158794</strong></td>
<td><strong>93%</strong></td>
<td><strong>245678</strong></td>
<td><strong>135</strong></td>
<td><strong>98034</strong></td>
<td><strong>54</strong></td>
<td><strong>89%</strong></td>
<td><strong>86%</strong></td>
</tr>
</tbody>
</table>

$\dagger$ Smear conversion rate not expected for states that began implementing RNTCP during 3rd quarter 2003.

$\ddagger$ Cure rate and success rate data are not expected for states that began implementing RNTCP after 3rd quarter of 2002.
high HIV prevalence states of Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh, Manipur & Nagaland. At present, 230 Voluntary Counselling and Testing Centres (VCTCs) are functional in these states and as a result of referrals, around 7,000 HIV+ individuals were put on DOTS. TB/HIV coordination activities are being expanded to 8 other states in the near future.

RNTCP—WHO Joint Monitoring Mission

A review of the RNTCP was conducted from 15 to 26 September 2003 by a team of 20 national and 22 international tuberculosis experts. The team made field visits to 5 states (viz. Maharashtra, Orissa, Rajasthan, Tamil Nadu, and Uttar Pradesh). The team reviewed the programme at central level, visited more than 70 health facilities in 20 districts, interviewed administrators, health staff, TB patients, community members, and reviewed the records of more than 10,000 patients.

The key findings of the mission highlight: i) rapid expansion of DOTS and 5 fold increase from 1.35 million in the year 2000 to 7.40 million at the time of review, ii) RNTCP as highly economical, costing less than Rs.2 per capita, iii) good infrastructure and management system for TB control, iv) increased detection and cure rates, and v) overall excellent reporting and recording system.

Joint monitoring mission also pointed out the areas that need strengthening. These are: i) Strengthening of staff position at central and state level, ii) Strengthening of managerial capacity for planning, implementation, supervision, monitoring and financial management at state level iii) setting up of efficient system for flow of funds from state to the districts, iv) ensuring sufficient buffer stock of the drugs, v) greater involvement of private sector, and vi) filling up the vacancies of contractual staff.

There has been continuous progress in the case detection and cure rates. RNTCP is progressing well and every effort is being made at the central, state and district levels to keep up the performance of the programme by all those involved in RNTCP. However, there are several challenges that need to be addressed through the joint efforts of staff at all levels of implementation. Involvement of all sectors in service delivery is a must and programme is making all efforts in this direction.
A US study published in the journal *Cancer* has reported that people who avoid the sun may be at an increased risk of developing cancer of the breast, prostate, lung, colon, ovaries and pancreas. Scientists from the National Cancer Institute have found that the chances of dying from many of these cancers were reduced by 10 to 27% for people who live in the sunniest areas. According to Dr. Michael F. Hilick of Boston University Medical Centre, ultra violet light can have powerful health benefits. He has concluded that brief exposure to sunshine or artificially produced UV light produced by indoor tanning beds can help to ward off a host of debilitating and sometimes deadly diseases, including osteoporosis, hypertension, diabetes, multiple sclerosis, rheumatoid arthritis, depression and cancers of colon, prostate and the breast. According to Dr. Holicks’s studies, exposing people with high blood pressure to UV rays in a tanning saloon lowers their blood pressure. He also found that increasing vitamin D intake improved the heart’s pumping ability and reduced cardiac strain. Dr. Gordon Ainsleigh also advocates UV exposure because “its benefits for immune system stimulation and cancer suppression far outweigh any risk”. “American Cancer Society statistics show that sun inhibited internal cancers kill at more than 100 times greater frequency than do sun promoted skin cancers, so increasing sun exposure will save many lives”.

The first international treaty against smoking, including an advertising ban, has been approved by more than 190 countries. The World Health Assembly, the annual meeting of the World Health Organisation’s 192 countries, unanimously adopted the Framework Convention on Tobacco Control (FCTC) that commits them to fighting the “devastating consequences of tobacco consumption and exposure”. “Today, we are acting to save billions of lives and protect people’s health for generations to come. This is an historic moment,” said WHO Director General Gro Harlem Brundtland.

The pact, which was agreed to by member states in March, 2003 after three years of negotiations, requires countries to ban or set tough restrictions on tobacco advertising, sponsorship and promotion within five years. It also lays down guidelines on health warning on cigarette packets, recommends tax increases on tobacco products and calls for a crackdown on cigarette smuggling, amongst other measures. The UN health agency says 4.9 million people die each year from cancer, cardiovascular disease and other conditions linked to smoking and that the toll is likely to exceed 10 million by 2020, with 70 per cent of the victims in developing world. “The spread of the tobacco epidemic is a global problem with serious consequences for public health that calls for an effective, appropriate and comprehensive international response,” the treaty declares. The chairman of the pact’s drafting committee, ambassador Luz Seixas de Correa of Brazil, told a news conference it would probably take around a year to achieve the 40 ratifications the pact needs to come into force.

K.K. Chopra
Alkaline Phosphatase in Pleural Effusions


Pleural effusion is a common clinical presentation in several diseases. Various parameters from pleural fluid have been studied to identify the cause. The diagnostic value of these parameters varies. This study was carried out to evaluate the value of alkaline phosphatase concentration in the pleural effusion as a diagnostic tool. One hundred and one patients with pleural effusion admitted over a period of two years were studied. The diagnosis was confirmed by pleural biopsy and cytology for malignant cells. Pleural fluid alkaline phosphatase levels of more than 75 mg/dl are usually transudative but do not differentiate tubercular pleural effusions from other exudative conditions.

Urinary Neopterin Measurement as a Noninvasive Diagnostic Method in Pulmonary Tuberculosis


To investigate the usefulness of neopterin in pulmonary tuberculosis (PTB) as a rapid diagnostic tool, neopterin concentrations in bronchoalveolar lavage fluid (BAL), serum and urine were measured in patients with PTB, with lung cancer and with pneumonia and in a healthy control group. In the BAL serum and urine of PTB patients, levels of neopterin were significantly higher than all the other groups (P<0.0001). Compared with the lung cancer group, PTB patients had higher neopterin in BAL and urine (P<0.05). The PTB group had higher levels not only in BAL and urine, but also in serum, than the pneumonia group (P = 0.05). In the PTB group, patients with moderately advanced PTB, according to radiographic extent had higher levels of urine neopterin than patients with minimal disease (P = 0.1). Neopterin levels in BAL, serum and, particularly in urine, may reflect PTB activity before exact diagnosis of the disease by culture results, and correlate with radiological extent.

Clinical and Radiographic features of Pulmonary Tuberculosis in Non-AIDS Immunosuppressed Patients


To determine the clinical and radiographic presentation of pulmonary tuberculosis in non-AIDS immunocompromised patients (ICP), a retrospective review of medical records of 143 patients (63 immunocompromised and 80 immunocompetent) with pulmonary tuberculosis from 1992 to 2001 was done. In ICPs, fever was more frequently observed (84.1% vs. 40%, P = 0.0000002), tuberculosis was more frequently disseminated (23.8% vs. 3.8%, P = 0.0008), and lung infiltrations were more often lobular or segmental consolidation (20.6% vs. 3.8%, P = 0.0008) and miliary lesions (17.5% vs. 3.8%, P = 0.14) than in the control patients. Hilar and/or mediastinal adenopathy was also more frequently documented in ICPs (14.3% vs. 2.5%, P = 0.01)

Effect of inhalation of Salbutamol, Beclomethasone dipropionate and Ipratropium bromide on mucociliary clearance in chronic stable bronchial asthma


The aim of the study was to investigate the effect of salbutamol, ipratropium bromide and
beclomethasone on mucociliary clearance in patients with chronic stable asthma and to compare the efficacy of these drugs on mucociliary clearance. Ten patients with chronic stable asthma were enrolled in the study, but two patients did not complete the study. Patients with bronchial asthma were chosen on clinical grounds. \(^{99m}\text{TC} \) phytate radioaerosol, generated through a nebulizer, was given to each patient on four days. After each administration the radioactivity over the thorax was constantly measured in sequential frame mode for 120 min. Radioactivity in the thorax was also measured after 24h. A base-line pulmonary function test with reversibility was obtained. Salbutamol, ipratropium bromide, beclomethasone dipropionate and placebo inhalation were given randomly to each patients on four days. The mean age of patients \((n=8)\) was 36±9.3 years and mean duration of symptoms was 5 years. There was no visual impression that mucociliary clearance was enhanced with any of the drugs. The time activity curves did not show any visually recognisable change in the slope. In only one patient the curve tended to show a steeper slope with ipratropium inhalation. In the rest of the patients the curves showed no difference at all with medication when compared with placebo. All the quantitative indices analyzed by two-way ANOVA at the end of one and two hours were comparable for the three test drugs and placebo. None of the three test drugs demonstrated statistically significant mucociliary clearance effect compared with placebo. However, the temporal difference in airways clearance efficiency (ACE) was significant with Beclomethasone and Ipratropium bromide.

**Predominant location of pulmonary parenchymal lesions of tuberculosis primary complex in infants**


It is useful to know the distribution of pulmonary lesions in the diagnosis of tuberculosis on radiological examination. The aim of this study was to investigate if there is a predominant lung segment or lobe for tuberculosis lesions in infants using contrast enhanced CT. They studied 57 infants (40 boys, 17 girls) who were diagnosed as tuberculosis by isolation of *Mycobacterium tuberculosis* or combination of family contact, radiographic findings suggesting tuberculosis and positive reaction of 5 mm or more induration of PPD tuberculin. All the infants had lesions in mediastinal and/or hilar lymph-nodes, and 54 out of 57 infants had parenchymal lesions as well. In the study of the segmental predominance of tuberculosis lesions, each infant had a share of 100 points. If an infant had a single focus, all the points were distributed to the corresponding segment. If he or she had multiple foci, the 100 points were equally divided into affected lung segments. There was no significant difference between right (3385 points/10 segments) and left (2005 points/8 segments) lungs. The points in upper lobes (2224 points/ 5 segments) were significantly higher than the combined points of middle and lingual (896 points/ 4 segments) and lower (2270/9 segments) lobes \((p<0.05)\). The points in posterior lung segment (2839 points/7 segments) were significantly higher than the combined points of middle (436 points/ 3 segments) and anterior (2115 points/8 segments) lung segments \((p<0.05)\). These results suggest that upper lobes and posterior segments are predominant parenchymal regions of tuberculosis among infants less than one year old, although tuberculosis lesions may be located in any lung segment.

A new method of sputum pre-treatment for PCR preparation


A rapid sputum processing method developed for PCR is described. As the protocol prepared for commercial kit is too brief, PCR inhibitor is not completely removed for sputum. A new semi-alkaline protease method to dissolve sputum has been developed. In this method, lysis agent used is semi-alkaline protease added to equivalent volume of sputum. The mixture is centrifuged for 5 minutes and kept overnight in refrigerator. 0.5 to 1 ml of the sample is added to 0.067 PBS or saline and centrifuged at 3000 rpm for 15 minutes. From April
2001 to August 2001, 261 sputum samples were treated with this new method. Twenty one cases (8.0%) were PCR positive and all the results perfectly coincided with the results of the conventional culture method.

**Evaluation of diagnostic value of two major secreted proteins of Mycobacterium Tuberculosis**


Two secreted antigens of *Mycobacterium tuberculosis*, namely the antigen 85 complex (30/31) and 38kDa antigens, were purified from the whole culture filtrate by using two dimensional preparative electrophoresis and anion exchange chromatography, respectively. Individual components of the antigen 85 complex namely, antigen 85A, 85B, and 85C, were separated using hydrophobic interaction chromatography. The humoral antibody activity to these antigens in sputum positive cases of active pulmonary tuberculosis and normal healthy volunteers was determined by enzyme linked immunosorbent assay (ELISA) and immunoblot. Recombinant 38 kDa and antigen 6 were used as reference antigens for the assay. None of the healthy volunteers reacted with the 38 kDa antigen, while 52% of the TB sera reacted with it. Of the three components of the antigen 85 complex, 85B gave the highest positivity of 40 per cent. The results of combination of 38 kDa with antigen 6 offered better results with 76% positivity.

**Screening of malignant pleural effusion by discriminant analysis**


To assess the value of discriminant analysis as a method of optimizing the discriminant power of routine parameters in differentiating between malignant and non-malignant pleural effusions, a retrospective review of the medical records of 245 patients with exudative pleural effusion was done. The most powerful predictor of the malignant aetiology of pleural effusion was a function that consisted of seven variables: age (years); effusion volume (coded as up to one third = 1, up to two thirds = 2, massive = 3); sedimentation rate (mm/h); monocyte count in the peripheral blood (cells mm⁻³); bloodstained exudates (coded as yes = 1, no = 2); and glucose (mg/dL) and iron (µ g/dL) concentration in pleural fluid. This function showed a sensitivity of 77%, specificity of 85%, positive predictive value (PPV) of 76%, negative predictive value (NPV) of 86%, and was able to give an 82% rate of correct classification. In patients aged 50 years or younger, the NPV ranged between 91% and 98%, whereas in those older than 60 years, the PPV was 89%.

**A cluster of tuberculosis associated with use of a marijuana water pipe**


New cases of pulmonary tuberculosis (TB) were noted in a cluster of young Caucasian males, an unusual ethnic group for this disease in Queensland, Australia. It was noted that marijuana water pipe (‘bong’) smoking was common amongst cases and contacts. Objective was to investigate whether shared use of a marijuana water pipe was associated with transmission of TB. All contacts were identified and screened according to standard protocols. Cases were asked to list contacts with whom they had shared a marijuana water pipe. Five cases of open pulmonary TB were identified clinically and on sputum culture, and all isolates of *Mycobacterium tuberculosis* were identical on typing. Of 149 contacts identified, 114 (77%) completed screening, and 57 (50%) had significant tuberculin skin test (TST) reactions on follow-up. Of 45 contacts who had shared a marijuana water pipe with a case, 29 (64%) had a significant TST reaction. Sharing a marijuana water pipe with a case of pulmonary TB was associated with transmission of TB (OR 2.22, 95% CI 0.96-5.17), although the most important risk factor for acquiring TB infection in the clusters was close household contact with a case (OR 4.91, 95% CI 1.13-20.70).
Routine use of Gen-Probe Amplified Mycobacterium Tuberculosis Direct (MTD) Test for detection of Mycobacterium tuberculosis with smear-positive and smear-negative specimens


Nucleic acid amplification tests, such as the Amplified Mycobacterium Tuberculosis Direct (MTD) Test, may improve early diagnosis of tuberculosis when used in combination with acid-fast bacilli smear examination. Objective of the study was to evaluate the routine use of MTD in respiratory and non-respiratory samples, to investigate the improvement of MTD specificity and positive predictive value by defining an equivocal zone for result interpretation. MTD was performed according to the instructions supplied by the manufacturer. An equivocal zone was included for interpretation of results. Discordant results with culture were resolved by incorporating clinical data and multiple specimen analysis. The overall sensitivities, specifications, and positive and negative predictive values for respiratory specimens (n=3308) were 90.9, 99.9, 99.1 and 99.2% respectively. With extra-pulmonary specimens (n=1350), those values were 67.4, 99.9, 98.2 and 97.9% respectively. By implementing an equivocal zone, the specificity and positive predictive value of MTD were improved (from 99.1% and 88.6% to 99.9% and 98.9% respectively) without significantly altering other performance characteristics. Amplification assays cannot yet replace the conventional diagnostic techniques. Nevertheless, MTD is a reliable method for the direct detection of *M. tuberculosis* in clinical specimens. The number of false-positive results can be limited by defining an equivocal zone.

A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting


A randomised, controlled clinical trial of the effectiveness of a family-based programme of directly observed treatment (DOT) for tuberculosis was done. TB patients seen in Victoria, Australia, were randomly allocated to DOT observed by a family member (FDOT), or to standard supervised but non-observed therapy (ST). The outcome measure was compliance, measured by blinded testing of Isoniazid levels in urine. Of 173 patients, 87 were allocated to FDOT and 86 to ST. Only 58% in the FDOT group were able to receive FDOT, the major reason being living alone and not having a family member to observe treatment. The rate of non-compliance was 24% (41/173), with no significant difference between FDOT (22/87) and ST (19/86). No clinical or socio-demographic variable predicted compliance. Benefit of FDOT in an urban, industrialised country setting could not be demonstrated. FDOT may be more appropriate in developing countries, where extended family support is often available and burden of TB is much higher. Poor compliance and difficulty in predicting non-compliance shown in this study highlights the need for DOT for all TB patients.

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