

## TUBERCULOSIS: CURRENT TRENDS IN DIAGNOSIS AND TREATMENT

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### ABSTRACT

Among communicable diseases, tuberculosis (TB) is the second leading cause of death worldwide, killing nearly 2 million people each year. It is estimated that about one-third of the world population are infected with TB (2 billion people) and about 10% of this figure will progress to disease state. Most cases are in the less-developed countries of the world. Tuberculosis incidence has been on the increase in Africa, mainly as a result of the burden of HIV infection. Definitive diagnosis of tuberculosis remains based on culture for *Mycobacterium tuberculosis*, but rapid diagnosis of infectious tuberculosis by simple sputum smear for acid fast bacilli remains an important tool, as more rapid molecular techniques are being developed. Treatment with several drugs for 6 months or more can cure more than 95% of patients. Direct observation of treatment, a component of the recommended five-element DOTS strategy, is judged to be the standard of care by most authorities. Currently only a third of cases worldwide are treated using this approach. There may be need to modify the treatment modalities especially with the choice of drugs and duration of therapy when TB infection occurs in special situation like pregnancy, liver disease, renal failure or even in coexistence with HIV/AIDS or the drug resistant state.

**Key Words:** Tuberculosis, current approaches, diagnosis, treatment, special situations.

### INTRODUCTION

About one-third of the world's population (2 billion people) is believed to be infected with one of the species of *Mycobacterium tuberculosis* complex, the aetiologic agent in tuberculosis (TB)<sup>1</sup>. Most cases of TB result from *M.tuberculosis* infection, while *M.bovis* and *M.africanum* are less common. Poverty and social deprivation are the commonest factors associated with high prevalence of TB<sup>1</sup>. About 10% of those infected eventually develop clinical disease. Tuberculosis is the second commonest cause of death from infectious diseases globally, after HIV/AIDS<sup>1</sup>. There were an estimated 8-9 million new cases of tuberculosis in 2000 alone, fewer than half of which were reported. Three to four million cases were sputum-smear positive, the most infectious form of the disease. Most cases (5-6 million) are in people aged 15-49 years, the economic backbone of all societies<sup>1</sup>.

Sub-Saharan Africa has the highest incidence rate (290 per 100,000 population), but some countries in the Asian continent have the highest prevalence rates: India, China, Indonesia, Bangladesh and Pakistan together account for more than half the global burden of TB<sup>2</sup>. Tuberculosis rates have been on the increase in developing countries of the world due to crowded housing, poor sanitation and more importantly due to resistance to therapy and upsurge

in HIV/AIDS cases. HIV infection accounts for much of the recent increase in the global tuberculosis burden Worldwide. An estimated 11% of new adult tuberculosis cases reported in 2000 were infected with HIV, with wide variations among regions: 38% in sub-Saharan Africa, and 14% in developed countries<sup>3</sup>.

This review attempts to highlight the current approaches to the diagnosis and treatment (even in special situations) of TB in both developing and developed countries of the world.

### CLINICAL MANIFESTATIONS

Tuberculosis has varied manifestations and can affect all organs and systems in the body. Pulmonary TB is the most common clinical presentation of tuberculosis, accounting for 74% of all cases<sup>4,5</sup>. Extra-pulmonary tuberculosis accounts for about 20% of disease in HIV-seronegative people but is said to be more common in HIV-seropositive individuals<sup>5</sup>. Among people not infected with HIV, extra-pulmonary disease, particularly with lymphatic involvement, is common in women and young children<sup>6</sup>.

Patients with persistent chronic cough (lasting longer than 2 weeks) with or without associated fever, night sweats, weight loss, shortness of breath, haemoptysis, and chest pain should be assessed for tuberculosis<sup>4,5</sup>. In children, important diagnostic clues may be a history of previous exposure to an individual with tuberculosis or evidence of

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tuberculous infection (e.g., a positive tuberculin skin test)<sup>5</sup>.

The most serious clinical manifestation of tuberculosis results from involvement of the central nervous system. Such involvement can include inflammation of the meninges (TB Meningitis), as well as space-occupying lesions (tuberculomas) of the brain. Children under 5 years of age and HIV-infected individuals are at increased risk of neurological involvement.

The skeletal manifestations with involvement of any bone or joint are commonly encountered. The spine (Pott's disease) is the most common bony structure involved with the thoracic spine being most commonly affected.

Abdominal TB may manifest with few weeks of vague ill health. The problem may be mainly loss of weight. Diarrhoea, malabsorption and occasionally intestinal obstruction may be a feature. There may or may not be a previous history of ingesting unpasteurised milk. Exudative ascites may develop acutely or insidiously which in women may be mistaken for pregnancy since it is often associated with amenorrhoea. Hepatosplenomegaly may be present. Lymphocytosis, detected in peritoneal fluid may be suggestive while positive culture of peritoneal biopsy specimen is diagnostic. A negative culture may not completely rule out the diagnosis.

Tuberculous pleural effusion is exudative and is usually associated with loss of weight. It tends to re-accumulate if not identified early and treated appropriately. It may sometimes be haemorrhagic. The above features tend to confuse it with malignant effusion. Cytological examination and culture of pleural aspirate and pleural biopsy specimen tend to distinguish one from the other. Use of LDH levels and relationship between pleural fluid LDH and serum LDH in such patients mostly serve to confirm that they are exudates.

Genitourinary tuberculosis, (in male and female) occurs less commonly than the aforementioned types and is difficult to distinguish from other infections of the genitourinary tract. It may manifest in men as prostatitis or prostatic enlargement, epididymitis, orchitis or it can also present as a painless scrotal mass. In women, genitourinary tuberculosis is an important cause of infertility most especially in developing countries of the world.

The manifestations of TB can also be wide spread as in disseminated tuberculosis in which many organs are involved simultaneously. This may result from a primary progressive disease or a reactivation of a previous latent infection. The clinical manifestation of pulmonary involvement is a miliary (millet seed) pattern rather than an infiltrate in most cases, but not all patients with disseminated disease have pulmonary involvement.

## DIAGNOSIS

The approach to the diagnosis of tuberculosis varies according to the local setting, which is dependent upon available resources in terms of diagnostic equipment and consumables and trained manpower.

Tests for the diagnosis of tuberculosis are of various types which vary in sensitivity, specificity, speed, and cost. Some are simple and make use of readily available equipment while some are complex requiring complex equipment which are expensive and may only be found in reference laboratories.

### 1. BIOLOGICAL DIAGNOSTIC TESTS

The sputum smear has been in use in the diagnosis of TB, since the time of Robert Koch in 1882. It is an inexpensive test that can be carried out rapidly in most places; fluorochrome, Ziehl-Neelsen, and Kinyoun staining methods can all be used. The International Union Against Tuberculosis and Lung Disease (IUATLD) and World Health Organisation (WHO) recommend the Ziehl-Neelsen method under most circumstances<sup>5</sup>.

The significance of the sputum smear examination lies in the fact that, although it is reported to be positive in only 50–80% of individuals with culture-confirmed pulmonary tuberculosis, cases with organisms on the smear are more infectious than smear negative cases and are associated with higher case-fatality rates. However, in countries with a high prevalence of tuberculosis, a positive direct smear is due to *M tuberculosis* in more than 95% of patients suspected of having tuberculosis<sup>7</sup> making routine cultures unnecessary for disease management.

Culture is of beneficial usage in infections with nontuberculous mycobacteria (NTM), particularly in HIV-infected patients, since the organism tends to be present in much lower concentration and is therefore rarely seen on a direct sputum smear<sup>7</sup>. The use of sputum culture has also been in practice. Though the organisms are slow growing and can take 6 weeks or longer to grow on solid culture media (e.g., the egg-based Lowenstein-Jensen medium or the agar-based Middlebrook 7H10 or 7H11), growth can now occur within 7–21 days with the recently introduced liquid culture media<sup>8</sup>. The newly automated systems developed are the MB/BacT (Biomérieux), BACTEC 9000 (Becton Dickinson) among others for culture with rapid efficacy of detection than the old conventional methods of culture<sup>8</sup>. It has been suggested that while waiting for the more sensitive techniques especially with the advent of HIV/AIDS, reliance could still be placed on culture on solid medium, where available. In Nigeria or in its absence, concentrated sputum smear techniques should always be carried out to improve diagnostic yield<sup>9</sup>.

Other rapid identification methods of *M.tuberculosis* complex have also been identified. These include probe detection methods such as Accuprobe (Gen-Probe Inc) targeting ribosomal RNA; which can identify *M.tuberculosis avium* complex, *M.intracellulare*, *M.gordonae* and *M.kansasii*<sup>10</sup>. These methods, though robust are reported to be rapid and simple to perform, giving results in 1-2 hours with accuracy estimated to be above 90%<sup>10</sup>. They are alternative approaches to distinguish the *M.tuberculosis* complex and non-tuberculous mycobacteria of much significance in this era of the HIV/AIDS pandemic<sup>11</sup>.

Other more recent rapid identification tests include the use of Polymerase Chain Reaction (PCR) by reverse hybridisation; restriction enzyme analysis and gene sequencing which are now available in some centres. The use of PCR in the identification of drug resistance is gaining more acceptance<sup>12</sup>. Use of immunoassays for mycobacterial antigens in liquid mycobacterial cultures and serological studies for antibodies against mycobacterial antigens have been shown to be as sensitive as sputum smear but are hampered by the complexity of the antigenic profile and cross reactions with other mycobacteria<sup>13</sup>. They have greater application in children and in extra pulmonary tuberculosis. Additional promising techniques are the identification of species-specific mycolic acid by high performance liquid chromatography or tuberculostearic acid by gas liquid chromatography<sup>13</sup>. They are capable of rapidly identifying the mycobacteria by their characteristic lipids. Their use is however, limited to reference laboratories with sufficient instrumentation and capable manpower.

## 2. IMAGING

The chest radiographic findings suggesting tuberculosis are widely known. These include the characteristic upper-lobe infiltrates, cavitory infiltrates, and hilar or paratracheal adenopathy. In many patients with primary progressive disease and those with HIV infection, radiographic findings are subtler and may show lower-lobe infiltrates or a miliary pattern. HIV-infected patients, particularly those late in the course of HIV infection, generally experience greater weight loss and fever but are less likely to have cavitory disease and positive smears for acid-fast bacilli compared to those not infected with HIV. In one study, 8% of HIV-infected patients with pulmonary tuberculosis had been shown to have normal chest radiographs<sup>14</sup>.

In addition, ultrasonography, CT scan or MRI can be used where available to localise extra-pulmonary disease.

## TREATMENT

The main objectives of treatment are to ensure cure

without relapse, to prevent death, to stop transmission, and to prevent the emergence of drug resistant cases. It is a widely acknowledged fact that treatment of active tuberculosis with a single drug should never be attempted, and a single drug should never be added to a failing regimen<sup>15</sup>. All recommended treatment regimens have two phases (initiation and continuation) on the basis of extensive evidence derived from some controlled clinical trials<sup>16</sup>.

The initial intensive phase is designed to kill actively growing and semi-dormant bacilli. This action shortens the duration of infectivity with rapid smear and culture conversion after 2-3 months of treatment, in most cases (80-90%). At least two bactericidal drugs, isoniazid and rifampicin, are necessary in the initiation phase. Pyrazinamide, give in the initial intensive phase allows the duration of treatment to be reduced from 9 to 6 months, but has been shown to offer no extra benefit if given past the second month to patients with drug susceptible tuberculosis. The addition of ethambutol is of benefit where initial drug resistance is suspected or where the burden of organisms is high.

Several studies have shown that reliable prediction of which patients will take all prescribed medication by themselves is not possible<sup>17</sup>; thus only direct observation can ensure that all drugs are taken. Directly observed treatment, in which a trained observer personally observes each dose of medication being taken by the patient, can ensure high rates of treatment completion, reduce development of acquired drug resistance, and prevent relapse<sup>17</sup>. This form of treatment observed by trained individuals is the standard of practice in most countries and is a component of the five-point DOTS strategy recommended by WHO and IUATLD<sup>4,5,15</sup>. It is of importance that the initial phase of regimen including rifampicin should always be directly observed to ensure adherence and prevent emergence of resistance to rifampicin. The continuation phase aims to eliminate most residual bacilli and reduces numbers of failures and relapses. At the start of the continuation phase, fewer drugs are needed since there are low numbers of bacilli and less chance that drug-resistant mutants will be selected.

The standard treatment regimens recommended by WHO and some other global bodies are numerous and sometimes varied. For each patient, the recommended regimen depends on the treatment category, which is based on severity of disease and history of previous treatment with anti-TB medications. For some forms of TB, such as tuberculous meningitis, disseminated tuberculosis, and spinal tuberculosis with neurological involvement, a 7-10 month continuation phase with isoniazid and rifampicin is often recommended<sup>4</sup>. There are slight differences in the recommendations

of the US Centre for Disease Control and Prevention and the American Thoracic Society (CDC/ATS), the UK Joint Tuberculosis Committee of the British Thoracic Society (BTS), WHO and IUATLD<sup>4,5,15,16</sup>. WHO, IUATLD, and the BTS do not recommend twice-weekly dosing, although this is recommended in the USA. The 8-month regimen [2 months of Isoniazid (H) Rifampicin (R) Pyrazinamide (Z) Ethambutol (E)/6 months of HE] is not recommended in the USA or the UK. The UK and US guidelines recommend use of the same 6-month rifampicin-based regimens for both smear-positive and smear-negative pulmonary tuberculosis<sup>15,16</sup>.

## MANAGEMENT OF TB IN SPECIAL SITUATIONS

### 1. EXTRAPULMONARY TUBERCULOSIS

In most cases of extra-pulmonary tuberculosis there are fewer organisms present in contrast to the pulmonary forms. But in general, regimens used for pulmonary tuberculosis are effective in the treatment of extra-pulmonary tuberculosis<sup>18</sup>.

WHO recommends classification of the extra-pulmonary TB into severe and non-severe categories? Severe forms include meningeal and central nervous system tuberculosis, spinal tuberculosis, abdominal tuberculosis, bilateral pleural effusion, pericardial effusion, and bone and joint tuberculosis involving more than one site. Two months of HRZE or 2 months of HRZ and Streptomycin (S) in the initiation phase and 4 months of H and R in the continuation phase are recommended for such cases<sup>4</sup>.

Other organisations like BTS, IUATLD, CDC/ATS agree that some forms of disease, such as meningitis, may benefit from a longer treatment course<sup>4,15,16</sup>. Additional therapy with steroids can be used for patients with large pleural effusions, pericardial disease, and meningitis, particularly with neurological impairment, since these agents have been shown to decrease morbidity and mortality in many of such cases<sup>19,20</sup>.

### 2. PREGNANCY AND BREASTFEEDING

It is not uncommon to encounter cases of TB in pregnant women or breast-feeding mothers.

Isoniazid, rifampicin, pyrazinamide, and ethambutol are not teratogenic, and can be used in their management<sup>21</sup>. Their recommendation is supported by WHO. In the USA, pyrazinamide is not recommended for use during pregnancy except when alternative drugs are not available or are less effective<sup>15</sup>. The main argument here is that active tuberculosis in pregnancy must be treated, because untreated disease will harm the mother and the foetus more than standard drugs would. The use of a regimen of 2ERZH/6H and Thiacetazone (T) by Dosumu on 30 pregnant women recruited in the first

trimester of their pregnancy at Iwo, Nigeria was found to be good, effective and characterised by minor side effects. No teratogenic effects were noted in their babies one year after delivery<sup>22</sup>. However, some of the secondary (reserve) drugs such, as Capreomycin, Ciprofloxacin, Cycloserine, Kanamycin, etc may be more toxic. The risks and benefits of these drugs must be assessed for each woman separately, and in some instances treatment with the reserve drug if needed, should be deferred<sup>15</sup>. Most anti-tuberculosis drugs can be used during breast-feeding<sup>23</sup>. But no data are yet available for ethionamide usage. Data are lacking on amikacin and capreomycin, though they are likely to be safe given their structural similarity to streptomycin and kanamycin which are considered safe<sup>24</sup>.

### 3. LIVER DISEASE

The use of anti TB drugs can be a double-edged sword in patients with liver disease. All the major TB medications are associated with liver toxicity. Hepatic function monitoring is mandatory during treatment.

Drug-induced hepatitis can be fatal<sup>24</sup>. WHO recommends that pyrazinamide should not be used in patients with known chronic liver disease<sup>24</sup>. In decompensated liver disease, a regimen without rifampicin appears to be safer<sup>4</sup>. Streptomycin, ethambutol, and a reserve drug such as a fluoroquinolone can be used if treatment is necessary in patients with fulminant liver disease with strict care and monitoring<sup>15</sup>.

### 4. RENAL FAILURE

Normal doses of isoniazid, rifampicin, and pyrazinamide can be given in renal failure, since these drugs are eliminated almost entirely by biliary excretion or are metabolised into non-toxic compounds<sup>25</sup>. In severe renal failure, patients receiving isoniazid should also receive pyridoxine to prevent peripheral neuropathy. Ethambutol can accumulate and cause optic neuropathy<sup>25</sup>, and streptomycin use is better avoided.

Individuals on haemodialysis should receive their treatment by direct observation after dialysis. This is because several of the drugs are eliminated during dialysis<sup>26,27</sup>.

### 5. HIV-INFECTED PATIENTS

Involvement of a specialist is needed in the management of TB in HIV-positive cases, because extreme care is needed in regimen formulation to avoid potentially hazardous drug interactions and the difficulty associated with managing TB due to atypical mycobacteria. Recommended treatment regimens are similar for HIV-infected and HIV-negative tuberculosis patients. However, thiacetazone should never be used, because it is associated with an

increased risk of severe and in some cases fatal skin reactions in HIV-infected individuals<sup>28,29</sup>.

It has also been shown that response to treatment and survival are better in HIV-infected patients if treated with short-course treatment including rifampicin than with other regimens that do not include rifampicin<sup>28,30</sup>. Therefore, all attempts should be made to use directly observed rifampicin-based regimens. The clinical, radiographic, and microbiological responses to short-course treatment are similar irrespective of HIV status, although death during anti-tuberculosis treatment is much more common in HIV-infected individuals<sup>31,32</sup>. Concrete evidence is pointing to the fact that direct observation of treatment is even more important for HIV-infected patients, and it is considered the standard of care for them.

Several antiretroviral drugs (i.e., most protease inhibitors and non-nucleoside reverse transcriptase inhibitors except efavirenz) should not be used with rifampicin. Rifabutin has similar activity against *M tuberculosis* as rifampicin, and has less effect on the pharmacokinetics of some antiretroviral drugs. It is recommended in the USA as an equivalent alternative agent for HIV-infected patients receiving certain antiretroviral drugs.

Paradoxical worsening of tuberculosis (defined as increased fever, worsening of pulmonary infiltrates, or new clinical manifestations of disease) can occur in patients on effective treatment. This is reported in both HIV-seronegative and HIV-seropositive patients, but is said to be more common in the latter<sup>33</sup>. The underlying pathophysiology of paradoxical worsening is still unclear, but it probably involves increased recognition of mycobacterial antigens resulting from improved immune function associated with an effective treatment<sup>34</sup>. Antiretroviral therapy reconstitutes CD4<sup>+</sup> lymphocyte number and immune function. The other problems such patient may have include failure to absorb the drug due to diarrhoea which increase treatment failure and drug-drug interaction which may compromise drug levels and lead to resistance.

## 6. DRUG-RESISTANT CASES

This is one of the difficult aspects in TB management globally. This is because the treatment of patients whose organisms are resistant to standard drugs or who do not tolerate them is difficult. The formulation of a regimen for suspected or confirmed drug-resistant disease involves several important principles that must be followed. The initial regimen should include at least three drugs to which the bacilli are likely to be fully susceptible<sup>4</sup>, and the regimen most likely to be effective should be prescribed. Second-line drugs should be given daily under direct observation. Bacteriological results (smear and, if possible, culture) should be monitored<sup>4,35</sup>. If susceptibility test results are

available, a regimen can be chosen, based on the drugs to which the strain of *M tuberculosis* is susceptible.

Most authorities (WHO, BTS, IUATLD) recommend three or four oral drugs plus one injectable drug (such as capreomycin, amikacin, or kanamycin) to which the isolate is susceptible for 3–6 months, and then at least three effective oral drugs for 15–18 months, or for a total of 12–18 months after culture conversion to negative<sup>4</sup>. It is essential to obtain an accurate susceptibility profile in patients for whom a standard regimen with first-line drugs fails, particularly if the treatment was given under direct observation<sup>4</sup>. If drug susceptibility testing is not available, standard re-treatment regimens can be used<sup>4</sup>. Decisions must take into account the regimens the patient has received before, and whether the previous regimens were fully administered under direct observation and for how long. Longer use of injectable drugs is associated with improved outcomes<sup>35</sup>, but long-term administration is commonly complicated by ototoxicity, nephrotoxicity, and some local adverse reactions<sup>35,36</sup>.

## 7. LATENT TUBERCULOSIS INFECTION

Treatment of latent infection involves the use of daily administration of isoniazid for 6–12 months. Such treatment is reported to be 60–90% effective in reducing the risk of progression from tuberculous infection to disease<sup>37</sup>. HIV infected, tuberculin-positive individuals can benefit greatly from treatment of latent tuberculosis infection. Contacts of active cases (especially children), recent converters to tuberculin skin test positivity, and selected individuals at high risk of disease can also benefit<sup>37</sup>. Some recent clinical trials have shown that drug combinations, particularly rifampicin and pyrazinamide for 2–3 months, can be as effective as 12 months of isoniazid though not as safe<sup>38</sup>. In the HIV infected individuals, treatment of latent tuberculous infection, though it may not offer protection in areas of high transmission for more than 2–3 years beyond the end of treatment, at least offers a short prolongation of life<sup>39</sup>.

## CONCLUSION

There has been some considerable progress in the development of new diagnostic tools for TB and newly designed clinical trials are looking for the most effective treatment regimens especially in the face of the growing pandemic of HIV/AIDS.

The mainstay of diagnosis remains the sputum smear and culture. Though, there are no new first-line drugs discovered for several decades, there were improvements in the area of treatment combinations and strategies such as the use of DOTS. The impact of HIV infection on the burden of tuberculosis, most especially in the deprived parts of the globe will be difficult to reverse without more effective HIV

prevention and more widely available antiretroviral therapy in the less-developed countries. Further progress will require continued rigorous and dedicated application of current technology and will be greatly facilitated by the discovery and widespread application of new diagnostic techniques, and treatment strategies.

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