MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS

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The development of antitubercutosis treatment is characterized by increasing knolwedge about principles of treatment, accompanied by neglect of that knowledge about principlee of treatment, accompained by neglect of that knowledge by large segments of the medical community.[1] Historically the problem of drug resistance tuberculosis was recognised in 1946 immediately following the introduction of streptomycin.[2] The most recent chapter in complacency over well established principles has resulted in the emergence of Multi Drug Resistant strains of Mycobacteria tuberculosis resistant to both Isoniazid and Rifampicin, the two most important antituberculous drugs.

DEFINITIONS

Drug Resistance: It is the temporary or permanent capacity of the organisms and their progeny to remain viable or to multiply in the presence of the concentration of the drug that would normally destroy or inhibit the growth of other cells.[9]

Primary resistance: In patients who have never received prior tuberculosis chemotherapy, the bacterial resistance is called primary resistance.

Acquired resistance or secondary resistnce: In patients with some records of previous treatment, the bacterial resistance is called acquired resistance. It usually results of non-adherence to the recommended regimen or faulty prescribing.

Initial resistance: It is the presence of drug resistance to one or more antituberculosis drugs in a new tuberculosis patient who presents to a treatment centre, and it is doubtful that patient really has not received prior treatment. This category include those patients with primary resistance as well as those with undisclosed acquired resistance who either do not remember prior treatment, refuse to divulge the information on past treatment, or were not appropriately asked about treatment history.

Multi Drug-Resistance: It is the resistance to more than one antituberculosis drug. Miultidrug resistance (MDR) is defined as resistance to atleast both Isoniazid and Rifampicin.[4] This type of resistance can occur both as primary and secondary resistance.

Chronic Patient: Patient who has failed a long, often irregular,

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course or courses of therapy. Chronic Patient is defined as a patient who remains smear-positive after completing a WHO Retreatment Regimen under supervision. Such patients are likely to have acquired resistance to one or more antituberculous drugs.

CLINICAL SIGNIFICANCE OF DRUG RESISTANSE

The presence of drug resistant ogarnism at the start of therapy increases the risk of treatment failure many folds.[5]-[6] Initial resistant to single drug such as Isoniazid or Streptomycin could be treated successfully with six month of short course chemotherapy.[5] The resistance to Rifampicin is a serious problem. The success rate is much lower among patients with organism resistant to rifampicin and isoniazid. About 70-90 percent patients with isoniazid and rifampicin resistant bacilli did not respond or relapsed to treatment with short course chemotherapy.[5,6] Emergence of acquired resistance in a patient receiving chemotherapy is serious and one of the frequent reasons of treatment failure.

PREVALENCE OF DRUG RESISTANT TUBERCULOSIS IN INDIA

There has been paucity of reports, much of the drug resistance has been presumed clinically. The available literature indicates that primary/initial drug resistance.[7-9] Initial Multidrug resistance is probably very low. MDR-tuberculosis is more common in previously treated patients. Acquired resistance to Rifampicin (33-35%) and Isoniazid (50-55%) is substantial.[7-9] Strains resistant to Rifampicin were usually resistant to Isoniazid, where as converse was not necessarily true.[7]

HOW IS DRUG RESISTANT TUBERCUULOSIS PRODUCED?

Development of drug resistant tuberculosis is the result of human error in any of the following:

I Prescribing: Administration of initial regimen inadequate in number of drugs or duration or both, addition of single drug to a failing regimen and failure to identify pre existing or acquired drug resistance, lead to the selection of resistant bacilli.

II Drug Supply: This include financial difficulty in buying all the drugs prescribed, frequent or pro longed shortages of anti tubercuosis drugs in free TB clinics due to poor management and/or financial constraints and use of drugs of unproven bioavailability.

III Case Management: The risk to successive monotherapies multi plies if the treatment is not directly observed, especially during the initial phase. The patient's Lack of Knowledge and inadequate explanation before starting treatment, is frequently associated with de fault of treatment.

DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS

When a patient of tuberculosis on TB treatment fails to respond or deteriorates, one should need to consider: Was the initial diagnosis of tuberculosis corect? Is the patient taking drugs regularly and in adequate dosages? Is the drug resistance a probability? Is there some new disease that has occurred. At time review of diagnosis of tuberculosis may be necessary if initial diagnosis was not based on positive sputum smear. Any evidence of new disease in terms of symptoms, signs or abnormalities in (investigations should be considered. At this stage sputum should be examined for AFB and fresh chest x-ray should be done. If the diagnosis is not in doubt, the patient has been fully compliant with treatment and no new disease is present, then drug resistant should be suspected. Unless the sputum is positive for AFB, one cannot diagnose multidrug resistant tuberculosis. For example, a patient will have a destroyed lung all throughout his life unless such a patient is sputum positive inspite of treatment, one cannot consider such a patient a suspected case of drug resistance.

To confirm the resistance it is desirable to have sputum culture for **Myoobacteria** and drug sensitivity are available. At such time resistance can be assumed on the basis of clinical criteria: failure or relapse after 2 course of chemotherapy, atleast one of which was directly observed.[10] The 'chronic cases' are likely to be due to MDR bacilli.

MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS

Treatment of drug resistant tuberculosis is frustrating than drug susceptible tuberculosis. The treatment required to be individually tailored. Most experienced clinicians, recommend minimum of three or four and possible as many as six or seven drugs.[11-16] The regimen should include atleast three drugs for which the patient's organism have proven invitro susceptibility and preferably that have not been used to treat the patient before.[12-16] Decision regadring optimal drug selection for the treatment of *drug* resistant-TB are best made with the assesment of treatment history and with the aid of drug susceptibility testing. Some times problem may arise if different susceptibility patterns are found at diffeenrt times in the treatment course; two different sensitivity reports are obtained from two different laboratories; the sensitivity reports does not correlate with clinical findings or clinical judgement of what the patient is resistant to. In such circumstances it is appropriate to assume the worst combination of resistance has been found. In

addition the expeienrce and quality of the microbiology laboratory must be considered in accepting the result. Drug susceptibility test should not be used in isolation to clinical response to treatment. If the results of drug susceptibility will not be available for two to four months, it might be prudent to add several new drugs. Therefore, it is crucial to elicit a proper history of previous treatment. Meticulous study of records of therapy provide good premium. In the group of tuberculosis patients previously treated with one or several courses of chemotherapy and who remain sputum positive (by smear and/or culture), three subpopulations can be observed: (1) patients excreting bacilli still susceptible to all antitubreculosis drugs; (2) patients excreting bacilli resistant to at least isoniazid, but still susceptible to rifampicin; (3) patients excreting bacilli resistant to at least, isoniazid and rifampicin.

The respective proportion of the three subpopulations varies according to the chemotherapy applied in the community during the past years, it varies also with the number of courses of chemotherapy received by the patients. In patients who have failed after the first course of chemotherapy (WHO recommended regimens or any other), the proportion of patients excreting bacilli still susceptible to all drugs is usually higher than the proportion of the two other subpopulations. For this reason, the standard WHO retreatment regimen of 8 months (using 5 drugs for the first 2 months, then 4 drugs for the third month, and then 3 drugs for the remaining 5 months of treatment, i.e. 2SH'RZE/1HRZE/5HRE) given under direct observation, can cure the majority of patients- those having still susceptible bacilli, and those having bacilli resistant to isoniazid and/or streptomycin, but still susceptible to rifampicin. In patients who have failed after two courses chemotherapy (the second being the fully supervised standard WHO retreatment regimen), the proportion of patients excreting resistant bacilli is up to 80% and the proportion of patients with MDR tuberculosis can be as much as 50 percent. For this reason, a second application of the standard WHO retreatment regimen is likely to fail.

CROSS RESISTANCE

Cross resistance is of great practical and clinical importance. It will determine the use and sequence of administration of antituberculosis drugs especially in retreatment regimens of drug resistant cases. Cross resistance is described under two broad categories : (1) Synthetic antituberculous drugs (Isoniazid, Pyrazinamide, Ethionamide, and Thiacetazone) and (2) Aminoglycoside and Peptide antibiotics (Streptomycin, Kanamycin, Amikacin and Capreo-

mycin). There is existence literature available on Ethionamide and Thiacetazone. These two drugs appear to be influenced by the manner in which resistance to the individual drugs is developed; For example, natural resistance to thiacetazone does not involve resistance to ethionamide, and reciprocally, natural resistance to ethionamide does not imply thiacetazone resistance. On the other hand, acquired resistance to one drug often involved cross resistance to other drug. A further complication is seen when resistance is developed in combination therapy with Isoniazid and thiacetazone. In this situation acquired resistance to thiacetazone need not always follow acquired resistance to ethionamide. Ethionamide and prothoinamide should be considered as the same drug. Ethionamide induces complete cross-resistance with prothionamide. No cross resistance is seen between Isoniazid and Pyrazinamide although they are structurally similar.

Although Kanamycin has chemical similarities to streptomycin, it is effective against streptomycin resistant organism. Kanamycin resistant organisms, however are resistant to streptomycin. Resistance to Kanamycin induces a complete cross resistance with Amikacin. Resistance to Kanamycin-amikacin induces also resistance to Streptomycin. Though Capreomycin is often grouped with the aminoglycosides, it Js structurally unrelated and therefore exhibits no cross resistance. As expected strains resistant to streptomycin, Kanamycin, amikacin are still susceptible to caperomycin. Ofloxoacin, ciprofloxacin and sparfloaxcin induce complete cross resistance for all fluoroquinlones. Two third strains resistant to rifampicin were also resistant to rifabutin.[17]

SUGGESTED TREATMENT REGIMENS FOR SPECIFIC DRUG RESISTANCE PATTERNS

The aim is to provide the reader with examples of the application of general guidelines, not rigid protocols. Indeed, the key to successful treatment of MDR TB is individualization of therapy and the ability to adapt treatment strategy m response to changing clinical situations. No treatment regimen will be successful unless the patient actually receives the medications. For this reason, essentially all patients with MDR TB are best treated by means of some type of directly observed therapy (DOT) Program to ensure compliance.

Situation A : Drug senstivity results are not available before starting the new treatment: In this situation, after a failure of the WHO standard retreatment regimen, a “third tine” regimen should be prescribed containing :

— at least 3 drugs never used : kanamycin, ethionamide, ofloxacin — and pyrazinamide.

After bacteriological conversion (usually after three to four months), if the initial susceptibility test results cannot be obtained, the continuation phase during 18 months should employ the two drugs best tolerated and more usually more active: ethionamide and ofloxacin.

Situation B: Susceptibility test results are available.

I Resistanre to isoniazid, but rifampicin still active: (a) Resistance to Isoniazid alone or in combination with resistance to streptomycin (and/or with thioacetazone: It may be simplest to use the WHO standard reteartment regimen during the first three months (2SERHZ/11ERHZ), thoough isoniazid and and streptomycin are redundant and could be omitted. After smear conversion, use rifampicin and ethambutol until the end of the ninth month. **(b) Resistance to Isoniazid and ethambutol (with or without resistance to streptomycin :** Use rifampicin and ethionamide or Ofloxacin for nine months at least with pyrazinamide and one aminoglycoside (kanamycin or amikacin if resistance to streptomycin; capreomycin if resistance to streptomycin and kanamycin) during the initial phase until smear conversion.

II Resistance to at least isoniazid and rifampicin- (a) Resistance to to isoniazid and rifampicin (with or without resistance to streptomycin : A five-drug regimen is mandatory. During the initial phase, use ethionamide plus ofloxacin plus another bacteriostatic durg (ethambutol if possible) with pyrazinamide and an aminoglycoside available for a minimum of 3 months, or until smear conversion. During the continuation phase, use ethionamide plus ofloxacin plus another bacteriostatic drug for at least 18 months after smear conversion.

(b) Resistance to isoniazid, rifampicin, ethambutol (with or without resistance to streptomycin: During the initial phase, use ethionamide plus ofloxacin plus another bacteriostatic drug (cycloserine or PAS) with pyrazinamide and an aminoglycoside available for a minimum of 3 months or until smear conversion. During the continuation phase, use ethionamide plus ofloxacin plus cycloserine (or PAS) for at least 18 months after smear conversion.

Usually, reliable information on susceptibility of **M.tuberculosis** to pyrazinamide is not available. But if the resistance to pyrazinamide is duly proven and compatible with clinical data, pyrazinamide should be stopped and cycloserine or PAS may be included in the regimen.
MONITORING TREATMENT

Improvement fin the results of bacteriologic tests of sputum is the main maker of response, but decreased fever, cough, sputum, and weight loss are important indirect indicators. Improvement on the chest x-ray may lag behind other changes. Therefore, sputum smear AFB should be examined every month. The overall cure rate among patients with MOR tuberculosis is about 50%.[15] Experience indicates that if chemotherapy is to achieve sputum conversion, it will do so within five months in most patients.[11] If sputum conversion does no occur or the patient relapses, further acquired resistance to the agents being used will appear. Hence, If chemotherapy is not successful the potential benefit of surgery should be considered.

THE ROLE OF SURGERY

Surgery is indicated in patients with poor response to medical therapy with disease sufficiently localized to permit resection of the bulk of involved lung. The goal of surgery must be to removes much diseased lung as possible, particularly cavities, while not causing crippling respiratory impairment, Selection of surgical candidates and timing of adjunctive surgery must be performed o-n a patient by patient basis.

PREVENTION OF DRUUG RESISTANT TUBERCULOSIS

Drug resistant tuberculosis is a man made problem and is thus amenable to corrective action.[1] The cost of treatment for multidrug-resistant disease is prohibitive and only hope of overcoming it is prevention. Adequate initial chemotherapy is most important in prevention. Fortunately effective drugs are available. Unfortunately increasing number of patients are not completing therapy and have either ongoing or recurrent disease.[18,91] The best prevention is to give each new case of Sputum Positive Pulmonayr Tuberculosis case an effective regimen of Short Sourse Chemotherapy with four drugs (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) during atleast the first two months, given under Direct Supervision

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