

REVIEW ARTICLES

EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (XDR-TB)

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The history of tuberculosis can be traced back to 4000 BC, Egyptian mummies from those times have been shown to bear clear pathological changes related to the disease. Hippocrates at around 460 BC had described a form of consumption disease and termed it as invariably fatal. He had even warned the physicians to attend these patients at the fag end as the result is inevitable and may put a dent to the career of the physician. The actual tubercle was first discovered by Sylvius as stated in the scripture *Opera Medica*, 1679. Benjamin Marten in his article 'A New Theory of Consumption', 1720, first came up with the idea that very tiny living creatures may be responsible for TB and had given an insight to the possibility of human to human spread through direct contact. Finally the discovery of mycobacterium tuberculosis was done by Robert Koch in 1882 by inventing a special staining technique which enabled visualization of the culprit organism. In 1919 after a long 11 years of research French scientist Albert Calmette and his assistant Camille Guerin, a veterinarian came up with a strain of mycobacterium bovis which was not virulent and was able to instill a substantial immune response against mycobacterium tuberculosis. They came up thus with the BCG vaccine and first used it on the human in 1921.¹ Since then the course of the disease and its treatment has come a long way. On the 20th of November 1944 the first successful anti-tubercular chemotherapy was administered using streptomycin. This discovery was followed by the invention of *p*-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962) and rifampin (rifampicin; 1963).

Just when the human kind was breathing the sigh of relieve, the sky again became clouded with the emergence of AIDS in July 27, 1982. This viral disease

caused by HIV which was discovered in 1983 at the same Pasteur Institute of France where BCG vaccine was developed, became infamous for the capability of suppressing human immunity and there by flaring up latent disease. This basic concept had led to the emergence of a new genera of tubercular bacilli which were resistant to at least the two first line drugs INH (Isoniazide) and Rifampicin, earning the title Multi Drug-Resistant TB (MDR-TB). This usually occurs along the course of treatment when the patients fail to complete the full prescribed course of therapy and outbreaks were seen among clusters of HIV infected AIDS patients.^{2,3-7} It is unusual for this form of TB to spread from person to person unless there is obvious immuno-suppression.²

Along the course the capability and power of the tubercle bacilli grew stronger feeding on the host of immunocompromised patients, giving birth to the latest devil of its lineage the XDR-TB. It was first defined in March, 2006 as MDR-TB plus resistance to at least three of the six second-line anti-TB drug groups (Fluoroquinolones, Aminoglycosides, Polypeptides, Thioamides, Cycloserine and para-aminosalicylic acid (PAS)).⁸

Since its formulation the definition of XDR-TB had been under a lot of scrutiny. A number of scientific papers had termed the definition incomplete or inadequate.^{9,10} The basic reason behind this notion was the possibility of these organisms being susceptible to fluoroquinolones or injectable form of drugs such as aminoglycosides and polypeptides, which gives a much better outlook to the whole scenario. As a result, the definition had later on been changed to: MDR-TB plus resistance to fluoroquinolones and at least to one of the second line injectables (kanamycin, amikacin or capreomycin).^{11,12}

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Structurally mycobacterium is different from the common pathogenic bacteria that we encounter. Its cell wall has certain unique structure that had kept it from being stained and for drugs to penetrate. The complexity of its wall has a direct role to the pathophysiological role it plays on the host.¹³ The complex wall is a target for several antitubercular chemotherapeutics used. Isoniazide, thiocetazone, ethionamide and thiocarlide acts by inhibiting mycolic acid synthesis, while ethambutol disrupts the cell wall peptidoglycan formation.¹⁴⁻¹⁹ The cell wall structure of mycobacterium is not known to its detail yet and finding out its complete architecture and identifying its weakness is underway to produce newer drugs that may act on MDR and XDR- TB.²⁰

Till date 45 countries have reported to have XDR-TB.²¹ This was found among 10% of MDR-TB specimens collected from six continents.²² The treatment plan for XDR-TB is one of the major challenges that the physicians are facing now-a-days. In contrast to MDR-TB where most of the second-line drugs including injectable ones are available, treatment options are lacking in XDR-TB and as a result the probability of cure is very low.^{9,23,24} Reports have suggested that these cases may often be untreatable while a report from Kwazulu-Natal Province of South Africa has shown that the fatality is rapid if the cases remain untreated.^{23,25-27} In a recent paper that retrospectively studied the treatment plan of patients suffering from XDR-TB found 48 cases out of 651 specimens tested to have the condition while the rest were MDR-TB.²⁸ These cases were from Lima, Peru between 1999 and 2002, which was before the term was defined and the retrospective study was done in 2008.²⁸ A modified treatment regime consisting of at least five drugs or more to which the subjects were not resistant including a fluoroquinolone and an injectable agent was administered for duration of 18 months for oral agents and 8 months after culture conversion for injectables.²⁸ 60.4% of the patients had survived through out the treatment and deemed to have been cured and none of the XDR-TB cases were found to be co-infected with HIV. To the contrary, the Kwazulu-Natal study was a very gloomy one with a mortality of 52 out of 53 cases and all the 44 who were tested for HIV co-infection were found to be positive.²⁷ This was also true for a number of reports from USA, Europe and Korea where the success rate was far lesser than half.^{9,23,24} One of the major confounding factors may be the HIV co-infection which plays a vital role in the outcome of the cases.

It is standard procedure to send samples for drug susceptibility testing prior to commencement of therapy. A panel of drugs is currently included in the susceptibility test which consists of isoniazide, Rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, cycloserine, capreomycin, ethionamide, ciprofloxacin, para-aminosalicylic acid (PAS), amikacin and levofloxacin.²⁸ The drug panel is in a constant state of change and physicians have the opportunity to request for additional drug-susceptibility testing.²⁹ The process of appropriate nursing care and complete isolation is mandatory along with development of a comprehensive primary health care system for detection and management of such cases while protecting the others from being infected.³⁰

Finally the good news for us is that Bangladesh has not reported any XDR-TB case till date. Though it is essential that we screen all the MDR-TB cases for drug susceptibility to find out where we really stand. An over populated and TB prone country like ours can at any moment be attacked by the deadly form of this disease. If appropriate measures are not instilled right now, by the time we find out the cases it might be too late. The improvement of our environmental and socioeconomic factors along side with our primary health care facility is essential to stay out of danger. A fully equipped TB detection, culture and drug susceptibility testing central laboratory is very much required for Bangladesh.

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