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Tuberculosis - "Developing Resistance to Existing Therapies"

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Abstract

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that one-third of the population of the world is infected with *Mycobacterium tuberculosis* and that more than 8 million new cases of active TB occur annually. The estimated global annual mortality from TB is close to 2 million people. Although management of TB has faced many challenges in the past, today there are 2 monumental threats to global TB control: the HIV epidemic and the increasing prevalence of drug resistance. Despite all the advances made in the treatment, tuberculosis still remains as one of the main public health problem particularly in the developing countries. Although the phenomenon of drug resistance in *Mycobacterium tuberculosis* was observed as early as 50 year ago, the current threat is due to the emergence of strains resistant to the two most anti TB drugs viz., Isoniazid (H) and Rifampicin (R). A strong TB control programme and continuous surveillance studies employing standardized methodology and rigorous quality control measures will serve as useful parameters in the evaluation of current treatment policies as well as the management of multidrug resistant (MDR) TB cases.

Keywords: Tuberculosis; Antibiotics; Resistance; Drug; Prevention

Introduction

Antibiotics are a true miracle of modern medicine. However, in reference to penicillin, the drug he discovered, Fleming gave warning in 1946 that the public will demand [the drug and]…then will begin an era…of abuses [1-4]. Unfortunately, Fleming's warning was unheeded, so this miracle of antibiotics is now endangered owing to the rapid escalation of antibiotic resistance combined with the equally rapid decline in discovery and development of new antibiotics. This is now considered a global health crisis and the reason is not difficult to understand [5-7].

Anti-tuberculosis drugs are a two-edged sword. While they destroy pathogenic M. tuberculosis, they also select for drug resistant bacteria against which those drugs are then ineffective [3]. The currently prevailing scenarios of drug-resistant tuberculosis (TB) are particularly alarming, and pose a significant threat to the control of the disease globally [1].

The bacteria that cause Tuberculosis can develop resistance to the antimicrobial drugs which is used to cure the disease. This is an example of AMR i.e. ANTIMICROBIAL RESISTANCE. The emergence of drug resistant TB possesses growing threat to National and International biosecurity and to TB control achievements.

The drug resistant TB are classified into -

- **MDR-TB (Multi Drug Resistant TB):** This form of TB occurs when the bacteria that are causing it are resistant to at least Isoniazid and Rifampicin, two of the most effective TB drugs. MDR-TB is also known as *VANKS DISEASE*.
- **XDR-TB (Extensively Drug Resistant TB):** It is defined as strains resistant to at least Rifampicin and Isoniazid in addition to being resistant to one of the Fluoroquinolones as well as resistant to at least one of the second line injectable TB drugs.
- **XXDR-TB (Totally Drug Resistant TB):** TB which is resistant to all the 1st and 2nd line drugs.

According to WHO, India recorded the largest number of TB cases in world in 2014. India accounts for 23% of the global total case of TB. In 2014, an estimated 4,80,000 people worldwide developed MDR-TB. The most recent drug resistance surveillance data issued by WHO Estimates that an average of almost 10% of MDR-TB cases are XDR-TB.

Causes of the Antibiotic Resistance

The reasons why MDR-TB continues to emerge and spread are mismanagement of TB treatment and person to person transmission. Inappropriate or incorrect use of antimicrobial drugs or use of ineffective formulations of drugs can cause drug resistance which can then be transmitted, especially in crowded settings such as prisons and hospitals.

Overuse

The overuse of antibiotics clearly drives the evolution of resistance. Epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacteria strains. In many other countries, antibiotics are unregulated and available over the counter without a prescription. This lack of regulation results in antibiotics that are easily accessible, plentiful, and cheap, which promotes overuse. The ability to purchase such products online has also made them

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accessible in countries where antibiotics are regulated.

Inappropriate prescribing

Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria. Incorrectly, prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy [8-11].

Mechanisms of TB Drug Resistance

Drug resistance to *M. tuberculosis* results from spontaneous and random mutations in the bacterial chromosome that result in reduced susceptibility to specific agents. There is no evidence that acquired genes or plasmids play a role in the emergence of antimicrobial resistance in mycobacteria. These investigators found that deletions of or mutations in the *katG* gene were associated with isoniazid resistance in clinical isolates of *M. tuberculosis*. Three additional genes have been identified as playing a role in isoniazid resistance: *inhA* and *kasA* code for cell wall mycolic acid biosynthetic enzymes and mutations in these genes are found in some resistant isolates. *ahpC* has been associated with some isoniazid resistance, but the role of this gene in isoniazid susceptibility or resistance is still unclear [12-15].

Rifampicin resistance is caused by point mutations or nucleotide deletions or insertions in an 81-base pair region of the *rpoB* gene, which codes for the b-subunit of DNA-dependent RNA polymerase.

The scientific basis of multidrug therapy in the treatment of TB is the need to prevent the emergence of resistant clones under selective drug pressure. In a drug-free environment, mutant organisms evolve in the presence of a majority of drug susceptible organisms. It is only in the presence an antimicrobial agent that selective pressure exists that favors the multiplication of a mutant organism. A patient who begins therapy for pulmonary TB with isoniazid alone will experience an initial response to treatment as the drug kills those organisms that are susceptible to this agent [4].

Ahead of World TB day on March 24, the Union Health Ministry of India has introduced- Bedaquiline into the national TB programme. Bedaquiline is a drug for MDR-TB and is being introduced at six identified tertiary care centers across India. Bedaquiline will be administered to MDR-TB patients with resistance to either all Fluoroquinolones and or all 2nd line injectable and extensive drug resistant TB. This new drug is available in six public hospitals in Delhi, Mumbai, Guwahati and Ahmadabad. But recently it is found that a 16yr old girl of Hinduja Hospital, in Mumbai has shown resistance to this new drug, Bedaquiline also [16-21].

Drug-resistant TB is therefore the product of inappropriate use of anti-TB drugs, either by patients or by clinicians. Some of the common causes of acquired drug resistance are- prescription of inadequate treatment regimen, irregular drug supply, poor drug quality with low bioavailability, and poor compliance.

The Union Health Ministry of India also inducted more than 500 Cartridge based Nucleic Acid Amplification Test (CBNAAT) machines into Revised National TB Control programme. This CBNAAT is fully automated rapid molecular test which detects *Mycobacterium tuberculosis* and Rifampicin drug resistance simultaneously.

According To Revised National TB Control Programme (RNTCP), data shows there is 27,183 patients diagnosed with tuberculosis in Mumbai in 2015.Out of these 3331 have MDR-TB and 552 have XDR-TB.

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Treatment of Drug-Resistant TB

The clinical implications of drug-resistant TB depend on the agents to which an infecting strain is resistant. Isoniazid resistance, for example, can be effectively treated with a standard 4-drug regimen for 2 months, followed by 4 months of rifampin and isoniazid. Rifampin resistance is associated with poorer clinical outcomes and requires an increase in the duration of therapy from 6 months to at least 9 months (and many experts prefer 12 months). Isolated rifampin resistance can be treated with a regimen of isoniazid, pyrazinamide, streptomycin, and ethambutol for 9 months.

The treatment of patients with MDR-TB is much more difficult and relies extensively on second-line drugs, which include fluoroquinolones (moxifloxacin, gatifloxacin, levofloxacin, and ofloxacin), ethionamide, the aminoglycosides kanamycin and amikacin, capreomycin, cycloserine, para-aminosalicylic acid, and clofazimine. Fluoroquinolones such as moxifloxacin and levofloxacin have considerable activity against *M. tuberculosis* and are preferred in the treatment of all MDR-TB cases. Treatment of MDR-TB in developing countries is a particular dilemma because the susceptibility testing and second-line agents are usually insufficient. Most national TB-control programs endorse algorithms for treating patients whose infections fail to respond to treatment that rely on the addition of 1-2 second-line agents to the standard first-line regimen.

A new strategy that uses a standardized regimen of second line drugs (kanamycin, a fluoroquinolone, pyrazinamide, ethambutol, and ethionamide) after the infection fails to respond to the standard retreatment regimen has been recommended recently by the WHO [4].

Principles for the management of multidrug-resistant tuberculosis:

- Start with the standard 4-drug regimen while awaiting the results of drug susceptibility tests.
- Use directly observed therapy.
- If resistance is strongly suspected, add at least 2 agents to which the isolate is likely to be susceptible.
- Single agents should never be added to a failing regimen.
- Perform drug susceptibility testing on all initial isolates and on subsequent isolates when circumstances suggest the emergence of

resistance.

- When resistance is confirmed, use at least 3 drugs known to be active against the isolate.

- Therapy should be taken for at least 24 months and should be continued for at least 18 months after bacteriologic conversion.

- Drug susceptibility testing should be repeated if cultures remain positive after 3 months of therapy.

- The number of cases of Drug Resistant TB is increasing day by day. It is necessary to know about the preventive measures also, to control drug resistant TB.

Some preventive measures are:

- Cure the TB patients around as early as possible.

- Ensure adequate infection control in facilities where patients are treated.

- Ensure the appropriate use of recommended drugs.

- Take all the TB drugs exactly as prescribed.

- No dose should be missed and treatment should not stop early.

- Avoid exposure to known drug resistant TB patients in closed or crowded places, such as Hospitals, Prisons, or Homeless shelters.

Tuberculosis is curable, yet millions continue to suffer and die from this deadly disease every year.

India has the notorious distinction of the highest incidence and number of deaths from TB. India's Revised National Tuberculosis Control Programme (RNTCP) provides free TB testing, medication, and treatment to patients throughout the country. But despite of that the incidence of TB is growing rapidly.

In India, Moradabad, is known locally as "Pital Nagri" or "Brass City" and is famous for its highly skilled artisans producing beautiful brass handicrafts. However, it is also known for its high incidence of TB. Moradabad is one of the TB prone areas. 'Prajnopaya Foundation' and 'Operation ASHA' are working with the Moradabad TB control programme to bring their successful community based TB model to the poor communities in Moradabad.

We, as the Dentist are at high risk of having TB from the patients. Both the Centre for Disease Control and Prevention (CDC) and Occupational Safety and Health Administration (OSHA) recommended that dental practices have protocols in place for protecting themselves from TB exposure.

Preventive Measures for Dentists

- Before treating any patient, it is important to take complete Medical history.

- If a patient is suspected of having TB, and then send them for a medical consult prior to any treatment.

- Elective dental treatment should be deferred until the patients has been declared noninfectious by a physician.

Figure 1: N-95 Respirators facemask. "PREVENTION IS BETTER THAN CURE".

- Providing isolation rooms for persons with or suspected of having TB. Negative-pressure ventilation of isolations rooms.

- Proper ventilation of rooms. Air exhaust directly to outside.

- High efficiency particulate air (HEPA) filtrations.

- Use of personal protective equipment and appropriate respiratory protection is must.

- Have the patients wear a mask.

- Isolation with rubber dams.

- The clinicians should use Respiratory Protection e.g. -Fitted, Disposable N-95 Respirators, facemask. This type of facemask is approved by National Institute for Occupational Safety and Health (NIOSH).

- Minimize the creation of Aerosols during treatment (Figure 1).

Conclusions

Drug resistance is a worldwide problem that threatens to undermine effective control of TB. Prevention of drug resistance depends on appropriate treatment of all patients with TB with combination drug regimens and early detection of resistance followed by tailored treatment with second-line agents. In countries with low levels of MDR-TB, efforts should be concentrated on preventing acquired MDR-TB by endorsing and widely implementing the WHO DOT strategy.

In countries with limited resources, more operational research is needed to define the best cost-effective strategies for individual versus standardized patient management of MDR-TB under national program conditions. The development of better and more rapid diagnostic assays and new classes of anti-TB drugs are urgent priorities for the containment of MDR-TB.

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