HORIZONS

Extensively Drug Resistant Tuberculosis(XDR-TB)

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Introduction

Extensively drug-resistant tuberculosis (XDR-TB) was first described in March 2006 following a joint survey of laboratories by the WHO, IUATLD, and CDC. The original definition of XDR-TB was revised at the WHO Global Task Force on XDR-TB, October 2006 (1). WHO in February, 2008, showed that the number of cases has reached the highest level ever recorded (2).

What is XDR-TB?

In 2000, the Stop TB Partnership's Green Light Committee was created to increase access to second line drugs worldwide while ensuring their proper use to prevent increased drug resistance. While assisting MDR TB treatment programs worldwide, and ensuring the proper use of second line drugs in resource limited countries the committee encountered reports of multiple cases of TB with resistance to virtually all second line drugs (3). This led to the emergence of a new terminology in relation to the drug resistant tuberculosis, known as extensively drug resistant tuberculosis (XDR-TB). XDR-TB was defined by US CDC and WHO as tuberculosis caused by M. tuberculosis that was resistant not only to isoniazid and rifampicin (MDR-TB) but also to at least three of the six classes of second-line anti-TB drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and para-aminosalycilic acid) (4). WHO - XDR-TB Task Force Committee gave a much-accepted definition of XDR-TB which defines it as "resistance to at least rifampicin and isoniazid among the first line-anti tubercular drugs in addition to resistance to any fluroquinolones i.e. ofloxacin, ciprofloxacin and levofloxacin, and at least one of three injectable second line anti tubercular drugs i.e. amikacin, kanamycin and capreomycin (1).

Magnitude of the Problem

Prevalence of XDR-tuberculosis cases is notably high in eastern Europe, sub-Saharan Africa and Asia (5). In one study the prevalence of XDR-TB among all MDR-TB patients was 6.6% overall worldwide,6.5% in industrialized countries, 13.6% in Russia and Eastern Europe, 1.5% in Asia, 0.6% in Africa and Middle East, 15.4% in Republic of Korea. As of June 2008, a total of 49 countries worldwide reported to the World Health Organization (WHO) at least one case of extensively drug-resistant tuberculosis (6).

Mechanism of resistance in XDR-TB (7)

The basis of tuberculosis drug resistance is the selection of bacterial mutants with innate resistance to chemotherapy.Acquired and amplified drug resistance is the primary means by which tuberculosis drug-resistant strains have been generated.However, the key determinant that has led to the exponential rise in XDR-tuberculosis cases is likely to have been transmitted resistance.

1. Conversion of wildtype pan-susceptible strains to drug resistant strains during treatment (acquired resistance)
2. Increasing development of resistance in drug-resistant strains because of inappropriate chemotherapy (amplified resistance)
3. Transmission of drug-resistant cases (transmitted resistance)

Posible Reasons For XDR-TB (8)

1. Erratic use of second line drugs moreover poor quality drugs
2. Lack of experience and skill to manage drug resistant TB
3. Use of poor quality second line drugs
4. Little or no access to reliable laboratory for drug susceptibility testing against Ist &2nd line drugs
5. Factors linked to poor control practices

Ray of Hope in the Management

It has been considered as untreatable or death sentence in both developed and developing countries. Countries such as former Soviet Union, XDR-TB cases are common among drug resistant cases and have been linked to very poor treatment outcomes (9). Observations among XDR-TB patients coinfected with the human immunodeficiency virus (HIV) in South Africa reveals that XDR-TB has been fatal in virtually all cases (10). But evidence has also come from studies of mostly HIV-seronegative patients in Europe, the United States, and Korea, where extensively drug-resistant tuberculosis was associated with much higher failure and mortality rates than multidrug-resistant tuberculosis (11-13). But recent report from Peru reveals a new and brighter perspective: even in developing countries, extensively drug-resistant tuberculosis may be cured in the majority of cases when management is aggressive and appropriate (14). XDR

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tuberculosis requires individualised treatment given the inability of standardised regimens to accurately address both first-line and second-line treatment resistance. Individualised regimens are also the only reliable means by which the amplification of drug resistance may be avoided (15). Duration of treatment for XDR tuberculosis has not been firmly established and is often based on individual clinical presentations(16). Treatment of XDR tuberculosis should include agents that the strain of M tuberculosis has proven to be susceptible to. Any first-line agent to which the isolate has shown to be susceptible and any appropriate second-line drugs should be used to achieve a regimen with a minimum of four to five effective medications. Surgical treatment should also be considered if clinically significant parenchymal lung disease is localised and high-grade resistance is present (17).New antituberculosis drugs with novel mechanisms of action are necessary if XDR-TB is to be successfully treated. Future treatment also requires development of drugs with minimal adverse events. Ideally, such agents would not have pharmacological interactions with antiretroviral drugs commonly used to treat HIV. Promising new compounds with high potency against M tuberculosis include a diarylquinoline compound (R207910, also called TMC207) and two nitroimidazole compounds (PA-824 and OPC-67683) (18-19). Moreover, tuberculosis vaccines are currently being tested which might serve as immunotherapeutic agents to accompany tuberculosis drug regimens (20).

Prevention of XDR-TB (21)

WHO Global XDR-TB Task Force Recommendations

- Improve global tuberculosis control by enhancing the testing and care of HIV-infected populations.
- Develop program management and treatment guidelines of XDR tuberculosis in high and low HIV prevalence settings.
- Strengthen laboratory diagnostic services to ensure rapid and accurate drug-susceptibility testing.
- Reducing transmission in health-care settings and other high-risk areas to improve infection control.
- Increase disease surveillance efforts to accurately assess epidemiological trends.
- Enhance educational advocacy and research funding to encourage of new drugs and diagnostics

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