EDUCATIONAL COMMENTARY – TUBERCULOSIS: DRUG RESISTANCE AND RECENT TRENDS

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Learning Outcomes

Upon completion of this exercise, participants will be able to:

- discuss the impact of the AIDS pandemic on the incidence of tuberculosis.
- explain why tuberculosis must be treated with more than one antimicrobial drug.
- define “multidrug-resistant tuberculosis” (MDR-TB) and “extensively drug-resistant tuberculosis” (XDR-TB).
- compare and contrast recent trends in tuberculosis worldwide with recent trends in the United States.

Tuberculosis in humans is caused by members of the group *Mycobacterium tuberculosis* complex. Microbiologists use the term “complex” to describe a group of two or more species whose distinction is complicated and medically insignificant. Thus, *M. tuberculosis* complex consists of four species: *Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium bovis BCG* (bacille Calmette-Guérin), and *Mycobacterium africanum*. Of these four species, *M. tuberculosis* causes most cases of tuberculosis, especially in developed countries.

Worldwide, about one out of every three persons is infected with *M. tuberculosis* complex. However, individuals with a healthy immune system have only an approximate 10% lifetime risk of developing tuberculosis. Today, the greatest risk factor for developing active tuberculosis is infection with the HIV virus. Persons who are infected with both *M. tuberculosis* complex and HIV have a 10% to 15% annual risk of developing tuberculosis, and they are more apt to develop rapidly progressive pulmonary disease than a subclinical infection. Other factors that weaken the immune system, such as advancing age and underlying medical conditions, as well as heavy exposure to the bacteria, also increase the risk of developing disease. Tuberculosis is most prevalent in areas where people live in crowded conditions and lack access to good medical care. In developed countries, segments of the population most at risk are prison inmates, alcoholics, drug abusers, homeless persons, the urban poor, and contacts of persons with tuberculosis.

Drug Therapy and Resistance

Persons who have a positive purified protein derivative (PPD) skin test for tuberculosis but do not have active disease are treated with a prophylactic course of isoniazid. However, individuals with active
tuberculosis must be treated with two or three antibiotics. Uncomplicated tuberculosis is commonly treated with isoniazid and rifampin for nine months. Alternatively, therapy can be reduced to six months if pyrazinamide is added to the regimen during the first two months of treatment.

The generally accepted theory that explains why tuberculosis must be treated with multiple drugs is termed the "special populations hypothesis." Proposed by Mitchison in 1979, this theory postulates that *M. tuberculosis* complex infection consists of four subpopulations:

1. Continuously growing bacilli that are susceptible to isoniazid, rifampin, and streptomycin
2. Bacilli growing in short bursts that may be susceptible to rifampin but not isoniazid
3. Bacilli in caseous lung lesions (that is, areas of necrotic tissue with a characteristic cheeselike appearance) susceptible to pyrazinamide
4. Dormant bacilli that may be sensitive to nitroimidazoles such as metronidazole

Inadequate treatment of any of these special populations can lead to antibiotic resistance, especially if the initial population of *M. tuberculosis* complex is large. Also, if more than 1% of the tubercle bacilli are resistant to a particular drug, that drug is unlikely to cure the infection, and a drug-resistant population of mycobacteria may ensue. If resistance develops to at least isoniazid and rifampin, the organism is termed multidrug-resistant TB (MDR-TB). If, in addition to isoniazid and rifampin, resistance also develops to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, or amikacin), the organism is termed extensively drug-resistant TB (XDR-TB).

MDR-TB and XDR-TB often begin as cases of tuberculosis susceptible to the normal first-line drugs. Then, due to improper use of antibiotics, resistance develops. This can happen if the wrong drug or the wrong dose is prescribed, if patients do not complete the full course of treatment, or if the drugs are of poor quality. Another mode of infection with MDR-TB or XDR-TB is by direct exposure to someone who has the disease. To detect resistance, antimicrobial susceptibility testing should be performed on the first isolate from all patients. Susceptibility testing should be repeated after three months of therapy if the organism still grows in culture.

Whether MDR-TB or XDR-TB can be successfully treated depends on the extent of drug resistance, the severity of the disease, and the integrity of the patient’s immune system. Cases of MDR-TB are often treated successfully because they are susceptible to at least some secondary drugs. In contrast, currently only about 30% of cases of XDR-TB are successfully treated.
EDUCATIONAL COMMENTARY – TUBERCULOSIS: DRUG RESISTANCE AND RECENT TRENDS (cont.)

A new treatment proposed by Hugonnet and colleagues has shown promise for treating both XDR-TB and routine TB cases. This treatment, which uses a combination of meropenem and clavulanate, has inhibited growth of both routine TB and XDR-TB strains in culture media. Clinical trials are now being planned in South Korea and South Africa to test the drug combination in a small number of patients with TB.

Trends in Tuberculosis
As a result of the AIDS pandemic and the emergence of drug resistance, cases of tuberculosis have increased globally since the 1980s. The World Health Organization (WHO) estimates that nearly half a million cases of MDR-TB occurred in 2004, and that, in some places, as many as 19% of the MDR-TB cases were in fact XDR-TB. Despite this, the overall incidence of XDR-TB is very rare, even in places with high rates of HIV infection.

In contrast to the rising rate of TB cases globally, both the number and the rate of TB cases in the United States has declined in recent years. The Centers for Disease Control and Prevention (CDC) reported that in 2008, 12,904 U.S. cases of TB occurred, a rate of 4.2 cases per 100,000 persons. Compared with statistics from 2007, this is a decline of 2.9% in the number of cases and a decline of 3.8% in the rate. Moreover, the number of deaths from TB declined from 1202 in 1996 to 644 in 2006, a decrease of 46%. Also, the number and percentage of MDR-TB cases in the United States declined from 407 (2.5%) in 1993 to 86 (1.0%) in 2008. Among persons born in the United States, the incidence of MDR-TB has remained at or below 1.0% since 1997. However, the proportion of the total number of primary MDR-TB cases occurring in foreign-born persons has increased from 25.3% (103 of 407 cases) in 1993 to 76.7% (66 of 86 cases) in 2008. The improvement in the number of TB cases in the United States is attributed largely to the availability of antiretroviral drugs to treat HIV infection.

Conclusion
Despite the encouraging trends in the United States in recent years, tuberculosis is still a devastating disease, especially in persons who are also infected with HIV. It is more prevalent in areas of the world where the rate of infection with HIV is high and access to good medical care is difficult or impossible. Further, drug-resistant TB strains are far more prevalent in areas that lack adequate treatment for HIV and TB. In an effort to educate the public about the threat of TB and the link between TB and HIV infection, both the WHO and the CDC maintain sections devoted to TB on their Web sites. This information is available at www.who.int/tb and www.cdc.gov/tb.
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