

Emerging Infectious Disease (4): Drug-Resistant Tuberculosis

Chi-Fang You, MD; Han-Ping Ma, MD; Tzong-Luen Wang, MD, PhD;
Aming Chor-Min Lin, MD

Abstract

Before the discovery of specific antibiotics for the treatment of tuberculosis, there was no cure. Mortality of those pulmonary diseases was about 50%. The first specific anti-tuberculosis drug, streptomycin was discovered in the USA during 1944 and the various drug regimens were developed in 1980s. The mortality fell to less 5% and there was a 98% chance of cure. However, inadequate treatment or improper use of the anti-tuberculosis medications resulted in drug-resistant tuberculosis. Multidrug-resistant tuberculosis (MDR-TB) is resistant to two or more of the primary drugs used for the treatment of tuberculosis. The most common primary drugs used for treatment tuberculosis are isoniazid and rifampicin. MDR-TB is not only more difficult to treat than drug-susceptible strains of TB but complex and expensive. The best way is treatment of tuberculosis with directly observed therapy system (DOTS). Along with the proper prescription of drugs, we believe that DOT monitoring will greatly reduce drug resistant TB. (*Ann Disaster Med.* 2005;3 Suppl 2:S67-S72)

Key words: Tuberculosis; Drug Resistant; MDR-TB

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis spreads through the air when a person sneezes, coughs, or breathes. TB primarily attacks the respiratory system, although it can attack other organs as well. The symptoms of TB include fever, night sweats, weight loss, chest pain, and coughing.

Multidrug-resistant tuberculosis (MDR-TB) is resistant to two or more of the primary drugs used for the treatment of tuberculosis. This special kind of TB has developed because

people infected with TB have not taken their drugs correctly or for an indicated period. The two drugs most common used to treat TB are Isoniazid and Rifampin. In 2003, the CDC reported that 7.7 percent of tuberculosis cases in the U.S. were resistant to isoniazid, the first line drug used to treat TB. The CDC also reported that 1.3 percent of tuberculosis cases in the U.S. were resistant to both isoniazid and rifampin, the drug most commonly used with isoniazid.¹

The World Health Organization estimates that up to 50 million persons worldwide may be infected with drug resistant strains of TB.

From Department of Emergency Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
Address for reprints: Dr. Aming Chor-Min Lin, Department of Emergency Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, No 95, Wen Chang Road, Taipei, Taiwan
Received: Feb 10 2005. Revised: Feb 20 2005. Accepted: Mar 10 2005.
TEL: 886-2-28389425 FAX: 886-2-28353547 E-mail: M002087@ms.skh.org.tw

Also, 300,000 new cases of MDR-TB are diagnosed around the world each year.² Without early detection and treatment, MDR-TB is untreatable and, in most cases, fatal.

Pathophysiology

TB is treated with antibiotics, which must be specific and only kill a certain kind of cell, or else they would hurt the human cells too, and that would make them dangerous. Antibiotics must be used wisely. If antibiotics are used incorrectly, bacteria can change in an effort to resist the drugs that can kill them. Bacteria can become resistant. Dr. Cranston demonstrated that there is selective pressure for resistance to occur whenever antibiotics are used. More and more organisms develop resistance to more and more drugs.³

Once bacteria have become resistant to a certain antibiotic, it will no longer work to kill them. If you keep treating these resistant bacteria with the same drugs after they become resistant, they will just keep on growing. But, if you use another drug to which they are not resistant, then they can be killed. This is why tuberculosis is suggested to treat with more than one type of drug at a time. Even if some of the bacteria in the patient are resistant to one or two drugs, the third should make sure that they are all killed. Antibiotic resistance is now a major public health issue.

Antibiotic resistance results from gene action. Bacteria acquired genes conferring resistance in any of three ways: (1) *spontaneous DNA mutation*: bacterial DNA may mutate spontaneously. Drug-resistant tuberculosis arises this way. (2) *transformation*: one bacterium may take up DNA from another bacterium. Pencillin-resistant gonorrhea results

from transformation. (3) *plasmid*: a small circle of DNA, that can flit from one type of bacterium to another. A single plasmid can provide a slew of different resistances.

Resistance to one or several forms of treatment occurs when the bacteria develops the ability to withstand antibiotic attack and relay that ability to their progeny. Since bacteria inherits this capacity to resist the effects of the various treatments, resistance can spread from one person to another. However, the problem of anti-tuberculous drug resistance results from treatment often because of: (1) an irregular drug supply, (2) inappropriate regimens, and (3) poor patient compliance.

Epidemiology and Prevalence

In recent years, the worldwide situation of tuberculosis has changed considerably. From 1990 through 1997, many outbreaks of multidrug-resistant tuberculosis have been reported. Today, one in seven new TB cases is resistant to the two drugs most commonly used to treat it (isoniazid and rifampin), and 5 percent of these patients die.³

In 1994, the Global Tuberculosis Program of the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) initiated the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. WHO conducted a survey in 35 countries involving about 50,000 tuberculosis cases to evaluate the incidence of drug resistance from 1994 to 1997.

The study defined two types of tuberculosis drug resistance: "acquired drug resistance" and "primary drug resistance." (1) *Acquired drug resistant tuberculosis* was defined as patients who had a history of drug susceptible

tuberculosis, which later was confirmed to have changed to drug resistant tuberculosis. (2) *Primary drug resistant tuberculosis* was defined as patients who contracted their drug resistant tuberculosis as their initial presenting tuberculosis diagnosis.^{4,5} The former is more common. Multidrug resistance was defined as resistance to at least isoniazid and rifampin. And four drugs resistance was defines as resistant to isoniazid, rifampin, ethambutol, and pyrazinamide.

The results showed that 36% of cases were resistant to at least one drug, 13% were resistant to MDR, and 4% were resistant to four drugs in acquired drug resistant TB group. In primary drug resistant TB groups, 10% had resistance to at least one drug, 1% had MDR, and only 0.2% had resistance to four drugs. The overall resistant rate to any drug, MDR, and four drugs were 13%, 2%, and 0.6%, respectively. The results were summarized in Table 1.

Prevention the spread of drug resistant strains will be unsuccessful if urgent action is not taken to persuade health authorities and doctors to follow recommended treatments. By contrast, countries that have used the recommended treatment strategies tend to have lower rates of resistance. "We only see significant drug resistance in countries without good control

programs," said Dr Marcos Espinal, an epidemiologist and head of the report's team of authors.⁹

A previous report indicated the five countries with the highest incidence of tuberculosis worldwide were India, China, Indonesia, Bangladesh, and Pakistan. A high rate of resistance to one or more drugs was found in new tuberculosis cases in Estonia, with 37% of all strains resistant to any drug and 14% multidrug resistant. The prevalence of resistance in Estonia had grown substantially, both in new cases and previous treated cases.⁶

New data and study also showed tuberculosis patients in parts of Eastern Europe and Central Asia are 10 times more likely to have multidrug-resistant TB (MDR-TB) than in the rest of the world. Six out of the top ten global hotspots are: Estonia, Kazakhstan, Latvia, Lithuania, parts of the Russian Federation and Uzbekistan, with drug resistance in new patients as high as 14%.⁷

MDR-TB also appears in association with HIV infection and AIDS. HIV itself does not increase the chance of drug resistance but accelerate the progression of TB infection into active TB disease. MDR-TB can cause death within a few weeks in persons with HIV/AIDS. However, it was not until the early 1990s when

Table 1. WHO-IUATLD global TB drug resistance study: 1994 - 1997

Acquired resistance	Any drug	36%
	MDR	13%
	Four drugs	4%
Primary resistance	Any drug	10%
	MDR	1%
	Four drugs	0.2%
Overall	Any drug	13%
	MDR	2%
	Four drugs	0.6%

outbreaks of multidrug-resistant tuberculosis were reported in patients with human immunodeficiency virus (HIV) infection in the United States and Europe, that the problem received international attention.⁸

Since HIV-infected individuals have an extraordinarily high risk of both reactivation of *Mycobacterium tuberculosis* infection, as well as rapid progression of recently acquired tuberculous infection, the global HIV pandemic is amplifying the incidence of tuberculosis. Highest prevalence of MDR-TB coincides with one of the world's fastest growing HIV infection rates in Eastern Europe and Central Asia. People whose immune systems are compromised with HIV are more susceptible to contracting all forms of TB." With people's immune systems compromised, MDR-TB has a perfect opportunity to spread rapidly and kill," said WHO Assistant Director-General of HIV/AIDS, TB and Malaria, Dr Jack Chow.

Management and Prevention

The principle modern treatment of tuberculosis

The two drugs, isoniazid which kills the great bulk of bacteria, rapidly rendering the patient non-infectious within days of starting treatment and rifampin eliminates the persisting bacteria allowing treatment time to be shortened are by

far the most important for treatment TB. Treatment with these two drugs alone for nine months will provide cure in 95% of cases. However patients should not be started on two drugs alone in case resistance is present in one of them.¹⁰

MDR-TB patients should be started on isoniazid and rifampicin plus at least one drug. These drugs are pyrazinamide, ethambutol, streptomycin. The addition of pyrazinamide for the first two months allows treatment to be given for six months. Because the emergence more drug resistant cases developed worldwide, the current recommendation is to give isoniazid and rifampicin plus pyrazinamide and ethambutol for treatment TB, especially for immunocompromised patient. Table 2 shows the drugs available for the treatment of tuberculosis.

Treatment of the multi-drug resistant patient

The treatment of multi-drug resistant tuberculosis is specialized, complex and expensive. If drug resistance is suspected, the patient should then be put on at least three drugs and preferably four to which they have not had previous exposure. The danger of adding a single drug to a regimen already being given will therefore be avoided. The most important principles are

Table 2. Drugs available for the treatment of tuberculosis

First line drugs	Isoniazid 、 Rifampicin
	Pyrazinamide 、 Ethambutol 、 Streptomycin
Secondary line drugs	Ethionamide 、 Cycloserine 、 Capreomycin
	Amikacyn 、 Kanamycin 、 PAS
	Thiocetazone
	Ofloxacin 、 Ciprofloxacin 、 Sparfloxacin
	Clarithromycin
	Clofazimin 、 Amoxycillin & Clavulanic acid

(1) never add a single drug to a failing regimen; and (2) always maintain at least two active drugs.

The World Health Organization has established guidelines for the treatment of tuberculosis with directly observed therapy supervised (DOTS). DOT is a system of treatment in which the patient is administered his or her medication by a nurse or health worker and observed taking the medication. Directly observed therapy (DOTS) can rapidly reduce the transmission and incidence of the drug resistant form of the disease.¹¹

In the Texas study, 407 patients from 1980 to 1986 were allowed to take their medication on their own and, 581 patients from 1986 to the end of 1992 were closely followed, with nurses observing them take their pills. The relapse rate fell from 20.9 to 5.5 percent. The conclusion was resistance of the treatment for TB can be slowed if patients take medications correctly.

Another way to prevent development of MDR-TB is that the clinician must be aware of risk factor which may raise the possibility of drug resistant tuberculosis. Table 3 shows the risk factors.¹⁴

Sometimes treatment of tuberculosis with DOTS was failed, the WHO suggested second- and third-line recommendations for managing tuberculosis. The second-line regimen is treatment with 5 drugs (streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide) for 3 months in the initial phase. In the continuation

phase, treat with 3 drugs (isoniazid, rifampin, and ethambutol) for 5 months. The third-line regimen is treatment with 3 drugs (kanamycin, ethionamide, and ofloxacin) never used and pyrazinamide for 3 months in the initial phase. In the continuation phase, the two drugs best tolerated (usually ethionamide, and ofloxacin) were used for 18 months.¹²

The Population and Public Health branch, Health Canada has developed guidelines to prevent the transmission of tuberculosis in Canadian. The guidelines recommend establishing an effective infection control program aiming at:¹³

- Early detection of TB and prompt isolation and treatment of patients.
- Educating health care workers about TB.
- Screening health care workers for TB.
- Implementing effective work practices including wearing proper respiratory protection.
- Preventing the spread of infectious droplets into the air by using appropriate exhaust ventilation,
- Controlling the direction of air flow to prevent air contamination adjacent to the infectious source.
- Diluting the air through general ventilation.
- Cleaning the air through air filtration.

Conclusion

Drug resistant tuberculosis is increasing. Its treatment is costly and lengthy. Development of new drugs is very costly and not seen as a

Table 3. Risk factors of development of MDR-TB

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1. Previous treatment for tuberculosis especially if prolonged.
 2. Contact with another patient known to have drug resistant disease.
 3. Immigration from an area with a high incidence of drug resistance.
 4. HIV seropositivity.
 5. Substance abuse.
 6. Homelessness.
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priority in the market orientated economics of the pharmaceutical industry. Prevention of drug resistance by directly observation must be the first priority.

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