Bull. Pharm. Sci., Assiut University, Vol. 33, Part 2, December 2010, pp. 235-240.

REVIEW

DRUG RESISTANCE OF *MYCOBACTERIUM TUBERCULOSIS*

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تمت مراجعة مقاومة الأدوية المضادة للدرن من حيث الإنتشار واتجاهات المقاومة في المملكة العربية السعودية وبعض البلدان الأخرى. ظهر أن مقاومة بكتيريا الدرن للأدوية المضادة قد نحى مناح متباينة حسب التباين الجغرافي بين الدول تراوح بين صفر و١٨%. وفي المملكة العربية السعودية تبين كذلك أن هذا النوع من المقاومة يتفاوت من منطقة إلى أخرى. وقد ارتبط هذا التباين في مقاومة بكتيريا الدرن في المملكة العربية السعودية بوقت ومكان كل دراسة، كما أثر فيه كذلك عدد المرضى غير السعوديين في كل دراسة منها. لقد عرّفت مقاومة بكتيريا الدرن المتعددة لأدوية الدرن بواسطة مركز التحكم بالأمراض، ومنظمة الصحة العالمية، والإتحاد الدولي لمقاومة الدرن وأمراض الرئة، على أنه المقاومة للريفامبين والأيزونيازايد على الأقل دون مقاومة مضادات الدرن الأخرى.

The prevalence and trends of drug resistance of Mycobacterium tuberculosis at the Kingdom of Saudi Arabia and other countries were reviewed. Drug resistance incidence of M. tuberculosis showed marked geographic variation from one country to the other ranged from 0 to 18%. In Saudi Arabia, the pattern of resistance of M. tuberculosis also showed marked regional variation. The variability in the resistance rates of tuberculosis is dependent on the time and location of the study as well as on the contribution of non-Saudi patients to each study. Multidrug-resistant M. tuberculosis (MDR-TB) was defined by Centers for Diseases Control and Prevention (CDC), the World Health Organization (WHO), and the International Union against Tuberculosis and Lung Disease as resistance to at least isoniazid and rifampicin with or without resistance to other agents.

INTRODUCTION

Mycobacterium tuberculosis (TB) is a major cause of morbidity and mortality throughout the world. Tuberculosis continues to be a major concern for health-care workers throughout the world. A drug-resistant strain of TB is defined as one differing from the tight distribution of wild strains that have not come into contact with the drug concerned.

Until 50 years ago, there was no medicine to cure TB. Drugs used to treat tuberculosis are classified into first-line and second-line agents. First-line essential anti-tuberculosis agents are the most effective, and are a necessary component of any short-course therapeutic regimen. The drugs in this category are isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin. Second-line anti-tuberculosis drugs are clinically much less effective than first-line agents and elicit severe reactions much more frequently. These drugs include para-aminosalicylic acid (PAS), ethionamide, cycloserine, amikacin and capreomycin. New drugs, which are yet to be assigned to the above categories, include rifapentine, levofloxacin, gatifloxacin and moxifloxacin. Recently there has been much development in the molecular pharmacology of anti-tuberculosis drugs.

Now, strains that are resistant to a single drug have been documented in every country surveyed. What is more, strains of TB resistant to all major anti-TB drugs have emerged. Drug-resistant TB is caused by inconsistent or partial treatment, when patients do not take all their medicines regularly for the required period as they start to feel better, or doctors and health workers prescribe the wrong treatment regimens, and because the drug supply is unreliable. A particularly dangerous form of drug-resistant TB is multidrug-resistant TB (MDR-TB), which is defined as TB bacilli resistant to at least isoniazid and rifampicin,

Received in 24/4/2010 & Accepted in 8/9/2010

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the two most powerful anti-TB drugs. Rates of MDR-TB are high in some countries, especially in the former Soviet Union, and threaten TB control efforts[1].

Alrajhi and Al-Barrak[2] mentioned that annual incidence rates of extrapulmonary tuberculosis have been increased over the last few years in the Kingdom of Saudi Arabia. True rates may even be higher due to incomplete reporting.

The rate of resistance to anti-tuberculosis medications differ between newly diagnosed patients with TB and those who have received treatment. Drug resistance of *M. tuberculosis* also shows marked geographic variation from one country to another and ranges from 0 to 18%[3]. In Saudi Arabia, the pattern of resistance of *M. tuberculosis* also shows marked regional variation[4].

Extreme drug-resistant TB (XDR-TB) is defined as TB with resistance to at least isoniazid and rifampicin, and resistance to a fluroquinolone and a second line injectable agent (i.e. amikacin, kanamycin or capreomycin)[1]. XDR-TB is more expensive and difficult to treat than MDR-TB, and outcomes for patients are much worse[5]; therefore, it is important to understand the magnitude and distribution of XDR-TB. Despite limitations in the quality assurance applied to laboratory testing indicated that XDRTB is widespread, with 45 countries having reported at least one case. The high proportion of XDR-TB among MDR-TB, as well as the large overall burden, suggests a significant problem within the countries of the former Soviet Union. Japan and the Republic of Korea have also shown a high proportion of XDR-TB among MDR[1].

What is meant by drug resistance of *Mycobacterium tuberculosis* ?

A drug-resistant strain of *Mycobacterium tuberculosis* is defined as one differing from the tight distribution of wild strains that have not come into contact with the drug concerned. Unlike many bacterial species, there is usually remarkably little variation in the susceptibility of different strains of *Mycobacterium tuberculosis* to the drugs used in first-line treatment[6]. For this reason, it is possible to consider a distribution of the minimal inhibitory concentration (MIC) of "wild" strains that have never come into contact with the drug and, from this distribution, fix a cut-off MIC that distinguishes between those "sensitive" strains that fall within the distribution and those "resistant" strains that have higher MICs, so that they have a chance of, say, <1% of being within the distribution. Since wild strains are so uniform in sensitivity, the resistant strains could only have arisen during the treatment of a patient and are, therefore, capable of growth in patients given the drug concerned in monotherapy. The general adoption of this definition avoided some of the pitfalls in thinking, such as the possibility that there was a difference between "laboratory" and "clinical" resistance. While it is still the best way of defining resistance for rarely used drugs, such as those in use for reserve drug treatment, the occurrence of appreciable proportions of strains with primary resistance amongst pre-treatment strains made it necessary to adopt a discriminant statistical technique, which measures the optimal MIC for discriminating between two groups of strains, one that is probably sensitive (PS) and obtained pre-treatment, and the other that is predominantly resistant (PR) and likely to contain a fairly high proportion of resistant strains. These are the two fundamental ways of defining drug resistance[7&8].

Resistance pattern

I- In the kingdom of Saudi Arabia

In Saudi Arabia, the drug resistance of tuberculosis was studied, where, the resistance rates to isoniazid were varied from region to another in the country. In Riyadh, the resistance rates were ranged from 4.2 to 7.2%[9&10]. Similar rates of resistance of approximately 6% were reported in the Saudi Aramco Medical Services Organization in Dammam[11] and Taif[12]. A higher rate of resistance (10.3 to 28.7%) was found in Jeddah[13-15]. The highest rate of resistance (41%) was reported in Gizan and was attributed to the proximity of Gizan to the Republic of Yemen[16]. However, isoniazid (1 µg/mL) resistance was 12.5% and the resistance to isoniazid (5 µg/mL) was 2.9% in Dammam[16].

Ethambutol resistance in Saudi Arabia has also been variable and was 0% in Dammam[11], approximately 2.4% in Riyadh[11], 1.3 to 6.9% in Jiddah[13], 4% in Taif[12], and Gizan[16]. Recently,

higher resistance rate of ethambutol (7.5%) was reported in Dammam by Al-Tawfiq *et al.*[17].

Whereas, the rate of resistance of *M. tuberculosis* to streptomycin was 6.9%[17] and 8.8%[18] in Dammam and Riyadh, respectively and 15.9% in Taif[12], and 22.7% in Jeddah[13].

Low resistance rate to rifampicin (1.1%) was observed in Dammam[11&17], However, higher rates of rifampicin resistance were recorded in Riyadh (9%) by Shanks *et al.*[19] and Al-Orainey[9], in Jeddah (5.1 to 23.4%) by Zaman[13] and Kinsara[14], in Taif (15.3%) by Jarallah *et al.*[12], and in Gizan by Schiott *et al.*[16].

From January 1989 to December 2003, Al-Tawfiq *et al.*[17] identified 276 nonrepetitive culture-positive cases of *M. tuberculosis* isolated from 236 Saudis (84.6%), and 40 non-Saudis (15.4%). *M. tuberculosis* isolates were obtained from pulmonary specimens (49%) and extrapulmonary sites (51%). The resistance rates of *M. tuberculosis* to tested first-line agents were as follows: isoniazid, 12.5%; ethambutol, 7.5%; streptomycin; 6.9%; and rifampicin, 1.1%. The resistance rate to the combination of isoniazid and streptomycin was 1.8%, the rate to isoniazid and rifampin was 0.7%, and the rate to isoniazid and ethambutol was 2.5%. The resistance rate to the combination of isoniazid, ethambutol, and streptomycin was 0.7%. In conclusion, *M. tuberculosis* resistance to isoniazid showed a decreased rate over the study period from 20 to 5.7%. The rate of multidrug-resistant *M. tuberculosis* remained low.

The rate of ethambutol resistance was higher than previously reported rates from all regions of Saudi Arabia. All susceptibility data from Saudi Arabia, of 3,937 isolates tested against ethambutol, resistance was noted in 2.5% only, the lowest among all first-line agents tested in 6,316 isolates[2]. Ethambutol resistance ranged between 0.5% and 6.9% in various regions. In a report by Kordy *et al.*[20], ethambutol resistance was noted in 1.6% of 764 isolates from a single institute; the majority of the patients were Saudis. The reasons for such high rates of ethambutol resistance in the report by Al-Tawfiq *et al.*[17].

Multidrug-resistant *M. tuberculosis* (MDR-TB) was defined by Centers for Diseases Control and Prevention, the World Health Organization, and the International Union against Tuberculosis and Lung Disease as resistance to at least isoniazid and rifampicin with or without resistance to other agents[21]. The rate of MDR-TB in Saudi Arabia is variable, depending on the date of the study and region of the country. The rate of MDR-TB was low in Dammam, while the highest rate of resistance was 2.5% to both isoniazid and ethambutol[17]. In Riyadh, MDR-TB was ranged between 3.7% from year 1979 to 1982 to 11.8% from year 1986 to 1988[9]. A very high rate of MDR-TB was obtained from the south of the country in Gizan, where the resistance rate reached 44%[16]. In the area near Dhahran, the MDR-TB rate in Dammam was 10.5%[11].

II- In other countries

Treatment of an adult male Arabian oryx (Oryx leucoryx) for bovine tuberculosis was initiated after the animal had reacted positively to an intradermal injection of bovine purified protein derivative. Infection with *Mycobacterium bovis* had been suspected because of the animal's rapid weight loss and a history of tuberculosis in the herd to which it belonged. The administration of ethambutol, isoniazid, and rifampicin through the drinking water resulted in a dramatic improvement of the animal's condition. During the one-year treatment period, blood samples were collected on three occasions. Enzyme-linked immunosorbent assays on blood samples were performed by the University of Otago, New Zealand, by the Central Veterinary Institute in Lelystadt, the Netherlands, and by the Central Veterinary Laboratory in Weybridge, United Kingdom. Additionally, a lymphocyte transformation test was performed on two different occasions at the University of Otago. All tests showed an unusually high reactivity to *M. bovis*. Because the animal was well represented genetically in the herd and was precluded from further breeding because of the disease risk to its mates, it was culled at the end of January 1990, more than a year after the inception of treatment. Necropsy was performed in order to establish the effectiveness of the treatment. It was found that there had been remarkable resolution of a very severe tuberculosis infection, but *M. bovis* was still cultured from a dry, caseous lung lesion and an enlarged mediastinal lymph node[22].

Rapid detection of drug-resistant tuberculosis (TB) has become increasingly

important in the era of pandemic human immunodeficiency virus infection and antibiotic resistance. The identification of the molecular correlates of antibiotic resistance in *Mycobacterium tuberculosis* have engendered the development of DNA-based assays for the identification of drug-resistant TB. This review summarizes the recent discoveries concerning resistance to isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, amikacin, kanamycin and the quinolones[23].

The prevalence of drug resistance of tuberculosis varies from one part of the world to another. In the United States, drug-resistant tuberculosis was detected in 14.2% in 1991[24], and 10% in 1997[25]. In the United States, isoniazid resistant was the most prevalent and accounted for 8% Isoniazid resistance has ranged from 0% in New Caledonia to 7.9% in Mozambique[25], and was 10% in India[26].

A high rate of ethambutol resistance was observed in Uganda (2.4%) and Thailand (3%). Moreover, the rate of ethambutol resistance was 6.6% in India[25].

The resistance rates of *M. tuberculosis* to streptomycin were 14.5% in Sierra Lion[25], and 6.6% in India[26]. Concerning rifampcin resistance in different parts of the world, the prevalence of rifampicin resistance was 0% in New Zealand and New Caledonia, 1.7% in the United States, and 1.8% in Mozambique[25].

The prevalence of MDR-TB among new cases of tuberculosis was 14% in Estonia, 10.8% in Henan Province in China, 9% in Latvia, 9% in Ivanovo Province in Russia, 5% in Iran, and 4.5% in Zhejiang Province in China[25].

Recently, Shi *et al.*[27] reported that One-third of the world's population is infected with *Mycobacterium* (*M.*) *tuberculosis*. Tuberculosis continues to be the most common infectious cause of death and still has a serious impact, medically, socially and financially. Multidrug-resistant tuberculosis (MDR-TB), caused by tubercle bacilli that are resistant to at least isoniazid and rifampicin, is among the most worsen elements of the pandemic of antibiotic resistance because TB patients for whom treatment has failed have a high risk of death.

On the other hand, no MDR-TB was reported in Denmark, New Zealand, Sri Lanka, or among the preliminary data from UR Tanzania. Estonia reported 52.1% MDR-TB among previously treated cases; Baku City, Azerbaijan reported 55.8% and Tashkent, Uzbekistan reported 60.0%. Lebanon reported 62.5% (95% CI, 35.4–84.8); however, only 16 cases were included in the sample. The Russian Federation reported data on retreatment cases in Orel Oblast only. Sixteen settings reported MDR-TB of 25% or higher among previously treated cases[1].

Table 1: Prevalence of non-MDR rifampicin resistance among all TB cases, 2002–2007[1].

Prevalence of non-MDR rifampicin resistance (%)	Number and location of settings
0.0	30 settings
0.1–1.0	47 settings
1.1–3.0	13 settings: • Armenia • Beijing Municipality, China • Donetsk Oblask, Ukraine • Ernakulam District, Kerala State, India • Ethiopia • Guatemala • Lebanon • Paraguay • Republic of Korea • Republic of Moldova • Romania • Shanghai Municipality, China • Tomsk Oblast, Russian Federation
>3.0	3 settings: • Heilongjiang Province, China • Inner Mongolia Autonomous Region, China • Jordan

non-MDR rifampicin resistance = TB with resistance to rifampicin but susceptibility to isoniazid.

In general, absolute numbers of XDR-TB cases were low in Central and Western Europe, the Americas and in the Asian countries that reported data. The proportion of XDR-TB among MDR-TB in these settings varied from 0% in 11 countries to 30.0% in Japan. These countries have a relatively low MDR-TB

burden, so the figure represents few absolute cases. A more significant problem lies in the countries of the former Soviet Union. Of the nine countries that reported, approximately 10% of all MDR-TB cases were XDR, ranging from 4.0% in Armenia to almost 24.0% in Estonia; however, these proportions represent a much larger absolute number of cases. Data recently released from South Africa showed that 996 (5.6%) of 17 615 MDR isolates collected from 2004 to October 2007 were XDR-TB. Proportions varied across provinces, with KwaZulu-Natal reporting 656 (4%) of 4701 MDR-TB cases as XDR-TB. Selection and testing practices varied across the country and over time; however, all isolates correspond to individual cases8. Since 2002, a total of 45 countries have reported at least one case globally. Several other countries are in the process of completing DST[1].

Worldwide capacity to conduct drug resistance surveillance has increased since the initiation of the Global Project, but large gaps still exist. As part of the Global Plan to STOP TB (2006–2015), the Stop TB Partnership's Working Group on MDR-TB has established a set of five specific objectives for MDR-TB control by 2015, two of which provide targets for drug-resistance surveillance. Firstly, by 2015, representative and reliable data should be available on the global magnitude of MDR-TB, trends in high MDR-TB prevalence countries, and the relationship between MDR-TB and HIV/AIDS. Secondly, by 2015, all countries should carry out drug susceptibility testing (DST) for all treated TB patients. In the Eastern European Region, where MDR prevalence is highest, DST should also be done for all new TB patients, while in the Latin American, South-East Asian and Western Pacific Regions, DST should be done for a subset of new TB patients, focused on people at increased risk of MDR-TB[28].

Therefore, most countries are initiating or scaling up the diagnosis and management of drug-resistant TB. Until diagnosis of drug resistance is routine, surveys or surveillance systems will play an important role in determining the magnitude and trends in drug-resistant TB.

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