Susceptibility Pattern and Epidemiology of *Mycobacterium tuberculosis* in United Emirati Hospital

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Abstract: *Objective*: Human tuberculosis (TB) has re-emerged at an alarming rate as one of the deadliest contagious diseases; not only in the developing world, but also in the developed countries. Its re-emergence indicates failure to control its transmission. What causes part of the alarm is the growing number of isolates displaying resistance to the first line drugs used in its control. The very high volume of travel to the United Arab Emirates (UAE) is yet another reason for concern over the spread of the disease. This study reports on the pattern of multiple drug (MDR) resistance exhibited by *Mycobacterium tuberculosis* (MTB) isolates from a major hospital in the UAE.

Methods: All pulmonary and extrapulmonary tuberculosis patients with positive culture results from January 2001 to December 2008 were included in the study. Cultures were performed at the mycobacteriology laboratory of the Emirati Hospital, Abu Dhabi, UAE, using the conventional Lewes-Johnson media. *M. tuberculosis* was isolated by standard procedures. *M. tuberculosis* complex was identified by conventional biochemical tests. Anti-mycobacterial sensitivity testing was done by the disk method as described by Wayne & Krasnow.

Results: From 2002 to 2008, 43 nonrepetitive culture-positive cases were identified. The resistance rates of *M. tuberculosis* to tested first-line agents were as follows: isoniazid, 34.5%; pyrazinamide, 34.8%; rifampin, 32.5%; streptomycin, 25.6%; and ethambutol, 20.9%. The resistance rate to isoniazid, rifampin and pyrazinamide was 7%; to isoniazid, rifampin and streptomycin was 2.3%; and to isoniazid, rifampin, streptomycin and pyrazinamide was 2.3%. The resistance rate to all the five agents together was 4.6%.

Conclusion: This study is the first in the UAE to report such high levels of resistance to anti-TB drugs; 27.7% for anti-tuberculosis Drugs such as isoniazid and pyrazinamide are of great significance to achieve proper treatment in *M. tuberculosis* infections in future. Indeed, isoniazid and rifampicin are important components of any regimen for the treatment of drug susceptible TB.

Keywords: MDR, United Arab Emirates, tuberculosis, resistance.

INTRODUCTION

Human tuberculosis (TB) continues to be the deadliest contagious infectious disease. It is estimated that one third of the world population is infected with the aerobic pathogenic bacterium, *Mycobacterium tuberculosis*, which usually establishes its infection in the lungs. TB is transmitted mainly by inhalation of infectious droplets produced during coughing, sneezing, laughing or shouting, by persons with pulmonary or laryngeal disease. The TB bacilli invade the body through mucous membrane and/or damaged skin [1].

The impact of tuberculosis (TB) on global health has grasped the international attention after the increase in the number of cases worldwide, including the developed countries [2]. There are approximately 10 million new cases and three million deaths annually throughout the world. More than 90% of the cases occur in developing countries. In 1993, TB was declared by the WHO as a global public health emergency [1].

The number of cases of tuberculosis showed an initial decline in the United States from 84,304 in 1953 to 22,201 in 1985. The number of reported cases of tuberculosis in the United States increased in 1992 by 18% [3]. The reversal of the downward trend was due to multiple factors, including the AIDS epidemic and the emergence of drug resistance.

Treatment consists of a combination from the six essential anti-TB drugs, namely; isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thioacetazone. Strains of *M. tuberculosis* resistant to chemotherapeutic agents have been recovered with increasing frequency [2].

Control measures and program implementation had several obstacles that limited their targeted achievements [4]. Complicating the matters more, the resurgence of TB in many areas was also associated with increasing rates of drug resistant *Mycobacterium tuberculosis (M. tuberculosis)*. Multidrug-resistant tuberculosis (MDR-TB) is associated with higher rates of failure and death than in drug-susceptible TB [3] and it is more difficult and expensive to treat [2]. A survey on global anti-TB drug resistance was conducted by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease

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(IUATLD); the released report indicated that the data obtained represent all geographical areas of the world except the Eastern Mediterranean Region [5]. United Arab emirates (UAE) is one of the countries in this region. It receives millions of visitors a year for commerce and work purposes. No information was reported on the pattern of MDR resistance. Thus, we undertook this study to evaluate the prevalence and trends of resistance of *M. tuberculosis* in a major hospital in the United Arab Emirates.

MATERIALS AND METHODS

All pulmonary and extrapulmonary tuberculosis patients with positive culture results from January 2001 to December 2008 were included in the study. The medical records were reviewed for the age, sex, nationality, and the site of the culture. Cultures were performed at the mycobacteriology laboratory of the Emirati Hospital, Abu Dhabi, UAE, using the conventional Lowwenstein-Johnson media [6]. *M. tuberculosis* was isolated by standard procedures [6]. *M. tuberculosis* complex was identified by conventional biochemical tests. Anti-mycobacterial sensitivity testing was done by the disk method as described by Wayne & Krasnow [7]. Although this is a retrospective study, quality control was usually performed during susceptibility testing using the reference strain provided by the College of American Pathologists. The concentrations of the drugs used were as follows: isoniazid, 1 µg/mL and 5 µg/mL; rifampin, 5 µg/mL; streptomycin, 10 µg/mL; and ethambutol, 25 µg/mL. The tested isolate was considered resistant if the proportion of the tested isolate was > 1% of the control population. Drug-resistant tuberculosis was calculated for single first-line agents. Multidrug-

resistant *M. tuberculosis* (MDR-TB) was defined as resistance to two or more first-line drugs.

RESULT

From 2002 to 2008, a total of 37 distinct positive culture findings for *M. tuberculosis* were identified. The annual incidence rates per 100,000 outpatient population are shown in Fig. (**1**) and Table **1**. The incidence in 2002 was 0.64/100,000, increased to 1.22/100,000 in 2004 and reached 1.29/100,000 in 2008. An increasing trend in incidence rates of culture-positive tuberculosis was observed during the study period. This was not stastistically significant (P=0.064).

Of the total patients, there were 33 Emirati (76.7%), and the remaining 10 patients (23.3%) were non-Emirati. Of the total patients, 34 were male (79%) and 9 were female (21%). The isolates were obtained from pulmonary specimens (n= 30, 69.7%) and the extrapulmonary sites (n= 13, 30.3%). The majority of the extrapulmoary isolates were obtained from abscesses.

Resistance to Single Antituberculsis Medication

The resistance rate of *M. tuberculosis* to any single drug was 23% (n=10) (Table **1**). The resistance rate of *M. tuberculosis* to the tested first-line agents were as follows: Isoniazid, 34.8%; ethambutol, 20.9% (n=9); streptomycin, 25.6 (n=11); rifampin, 32.5% (n=14); and pyrazinamide, 34.8% (n=15). The rates are shown in Table **2**. There was no statistical difference in the rate of resistance between Emirati and non-Emirati patients. In addition, there was no differ-
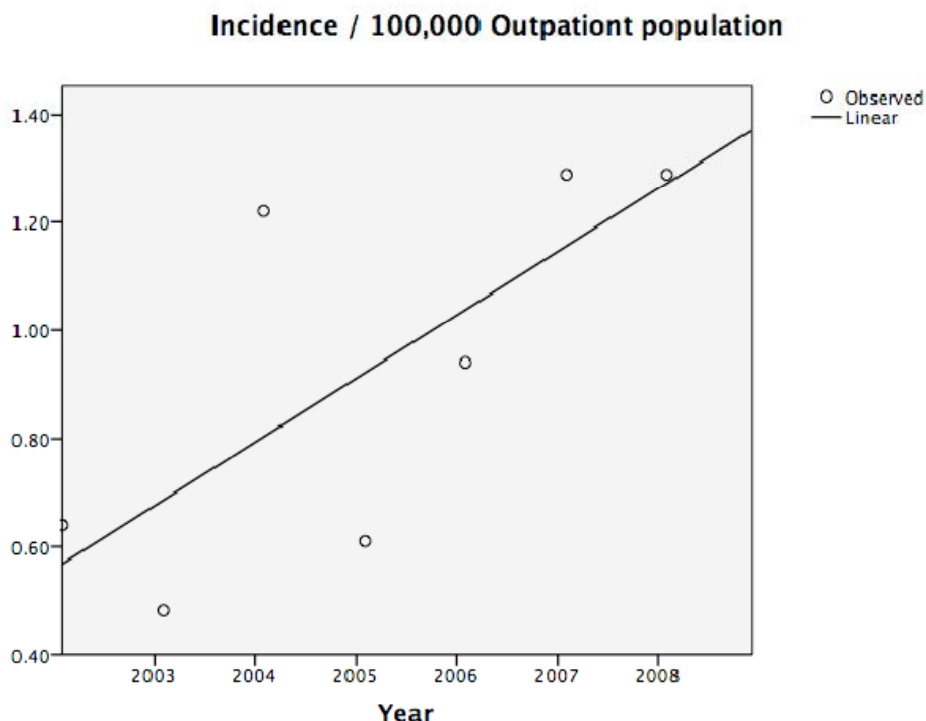

Fig. (1). Line graph showing the annual incidence of culture-positive tuberculosis from 2002 to 2008.

ence in the rate of resistance between pulmonary and extrapulmonary isolates.

Table 1.   **Incidence / 100,000 Outpatient Population of *M. tuberculosis***

Year	Incidence/ 100,000 Outpatient
2002	0.64
2003	0.48
2004	1.22
2005	0.61
2006	0.94
2007	1.29
2008	1.29

Table 2.   **Rates of Resistance of *M. tuberculosis* to Single First-Line Medications**

Antituberculosis Drugs	Resistance Rate, % (No.of Cases)
Isoniazid	34.8(15)
Pyrazinamide	34.8(15)
Rifampin	32.5(14)
Streptomycin	25.6(11)
Ethambutol	20.9(9)
Any First-Line Drug	27.7(10)

MDR-TB

MDR-TB was defined as resistance to two or more first-line agents. The rates of MDR-TB are shown in Table **3**. The resistance rate for any combination of MDR was 16.2% (n=7). The resistance rate to isoniazid , rifampin and pyrazinamide was 7%(n=3), to isoniazid , rifampin and streptomycin was 2.3%(n=1), and to isoniazid, rifampin, streptomycin and pyrazinamide was 2.3%(n=1). The resistance rate to all the five agents together was 4.6%(n=2).

DISCUSSION

Tuberculosis continues to be a major concern for healthcare workers throughout the world. The numbers of tubercu-

losis cases have declined steadily in western and central Europe, North and South America, and the Middle East, and have increased in countries of the former Soviet Union and in sub-Saharan Africa [8]. In the United States, there were a total of 14,871 tuberculosis cases (5.1/100,000 population) during 2003, representing a 1.9% decline in the rate from 2002 [9]; however, tuberculosis rates have increased in certain states in the United States [9].

The incidence of smear-positive tuberculosis in Saudi Arabia was estimated to be 20 per 100,000 populations [10]. The incidence of smear-positive tuberculosis in The United Arab emirates was estimated to be 20 per 100,000 populations [10]. The incidence rates of culture-positive tuberculosis in our study per 100,000 populations were 0.64 in 2002, 1.22 in 2004, and 1.29 in 2008. Thus, the incidence of tuberculosis in the current study showed an increasing linear trend over the study period from 2002 to 2008; however it was not statistically significant (p=0.064).

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 [10] and 10% in 1997 [11]. In the United States, isoniazid resistance was the most prevalent and accounted for 8% [12]. Isoniazid resistance has ranged from 0% in New Caledonia to 7.9% in Mozambique [12], and is 10% in India [13]. In Saudi Arabia, isoniazed resistance was the most prevalent and it varied from one part of the country to another. The highest rate (41%) was observed in Gizan [14-16].

In the current study, isoniazid and pyrazinamide resistance was 34.7% each. The second most common resistance pattern in our study was found in rifampin (32.5). A high rate of rifampin resistance was reported from Riyadh-KSA (9%) [17, 18]. In other parts of the world, the prevalence of rifampin resistance was 0% in New Zealand and New Caledonia, 1.7% in the United States, and 1.8% in Mozambique [12].

In our study, the rate of resistance of *M. tuberculosis* to streptomycin was 25.6%. Similarly, in a study from Jeddah-KSA, streptomycin resistance was 22.7% [16]. The rates were 14.5% in Sierra Leone and 6.6% in India.

The resistance rate to ethambutol was 20.9% in our study. This is much higher than other reports worldwide. A high rate of ethambutol resistance was observed in Uganda (2.4%) and Thailand (3%). In a study from India, the rate of ethambutol resistance was 6.6%.

The rate of MDR-TB in our study was high. The highest rate of resistance was to isoniazid, rifampin and pyrazinamide (7%). The prevalence of MDR-TB among new cases of

Table 3.   **Rates of Resistance of *M. tuberculosis* to two or More First-Line Medications**

Antituberculosis Drugs	Resistance Rate, %(No.of cases)
Isoniazid, rifampin and pyrazinamide	7(3)
Isoniazid, rifampin and streptomycin	2.3(1)
Isoniazid, rifampin, streptomycin and pyrazinamide	2.3(1)
All five agents	4.6(2)

tuberculosis was 44% Gizan-KSA, 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 [11].

The importance of knowing susceptibility results for *M. tuberculosis* became more significant especially in our region of the world, because of the increase in resistance rates, high travel activity of hosts and the limited available agents. Appreciating the importance of documenting the susceptibility findings of *M. tuberculosis*, the WHO has inaugurated a worldwide program for surveillance [6].

Multi-drug-resistant *M. tuberculosis* (MDR-TB) as defined by Centers for Diseases Control and Prevention, the World Health Organization, and the International Union against Tuberculosis and Lung Disease is resistance to at least isoniazid and rifampin with or without resistance to other agents [9-10]. First-line agents are isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. We have adopted the definitions recommended by WHO and IUATLD for anti-TB drug resistance surveillance [11].

We are well aware of the limitations of meta-analysis as an evidence-based approach in the field of infectious diseases [12]. It was indicated that there was only one report on *M. tuberculosis* susceptibility from Saudi Arabia [13]. In fact, Al-Jama *et al*. [19] also reported on the susceptibility of isolates of *M. tuberculosis* from the Eastern province in 1999.

This study is the first in the UAE to report such high levels of resistance to anti TB drugs; 21% for Anti tuberculosis Drugs such as isoniazid and pyrazinamide are of great significance to achieve proper treatment in *M. tuberculosis* infections in future. Indeed, isoniazid and rifampicin are important components of any regimen for the treatment of drug susceptible TB. Resistance to those two agents, by definition, indicates MDR-TB [20]. This definition marks the threshold for grave consequences of resistance to those agents in TB treatment [21].

In conclusion, in this study we examined the pattern and incidence of resistance of tuberculosis to first-line agents over time. The resistance rate to isoniazid and pyrazinamide showed a significant decline over the study period, whereas the resistance rate of ethambutol remained low and stable. Further studies and continued surveillance of the resistance pattern of *M. tuberculosis* is needed to further delineate the risk factors and to formulate the plans for the future management of tuberculosis.

ABBREVIATION

MDR-TB   =   Multidrug-resistance *Mycobacterium tuberculosis*

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