Primary Anti-Tuberculous Drugs Resistance of Pulmonary Tuberculosis in Southwestern Saudi Arabia

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ABSTRACT

The emergence of drug-resistant tuberculosis (TB) is an increasing problem which adversely affects patient care and public health. This work aims to determine the rates and patterns anti-TB drug resistance in Najran, Southwestern Saudi Arabia. The study included 80 smear-positive new pulmonary TB patients. Sputum samples were cultured on Lowenstein-Jenseen and Middle-Brook 7H10 media. M. tuberculosis susceptibility testing was done by the conventional agar proportion method for isoniazide (INH), rifampicin (RIF), streptomycin (SPM) and ethambutol (EMB). Out of the 68 M. tuberculosis isolates, 42 (61.8%) were sensitive to all 4 drugs and 26 (38.2%) were resistant to one or more drugs. Highest resistance was found to INH (33.8%), followed by RIF (23.5%), SPM (13.2%) and EMB (2.9%). Eight (11.8%) isolates were resistant to one drug, 14 (20.6%) were resistant to 2 drugs, 3 (4.4%) were resistant to 3 drugs and one (1.5%) was resistant to 4 drugs. Multi-drug resistant (MDR) isolates were found in 14 (20.6%) cases. In conclusion, the primary resistance rate to four first-line anti-tuberculous drugs and MDR-TB rate are worryingly high, representing an alarming situation in Najran. Further studies are necessary for continuous surveillance of M. tuberculosis resistance patterns.

INTRODUCTION

Tuberculosis (TB) has a long and continuing history of causing worldwide morbidity and mortality. The World Health Organization estimated the global burden of tuberculosis disease in 2009 as 9.4 million incident patients, 14 million prevalent cases and 2.38 million deaths(1). The emergence of Mycobacterium tuberculosis strains resistant to anti-tuberculosis drugs is a difficult problem to solve and is one of the greatest threats to public health worldwide. The emergence of multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampin (RIF), the 2 principal first-line anti-TB drugs, poses an important threat to TB control as MDR-TB reduces response to standard short-course chemotherapy with first-line anti-TB drugs, leads to higher mortality and treatment failure rates, and increases periods of transmissibility of the disease(2-3). The underlying causes of MDR-TB have been suggested to be incorrect treatment, poor compliance and erratic drug ingestion, poor drug absorption or frequent or prolonged shortages of anti-TB drugs due to financial constraints in some developing countries(4-5). Among TB patients notified in 2009, an estimated 250000 had multi-drug resistant TB (MDR-TB), while they were 440000 cases in 2008(6). The prevalence of single-drug resistant TB (SDR-TB) or MDR-TB in the Kingdom of Saudi Arabia is largely unknown, except for a few studies confined to large centers(7-12). Unfortunately, there are no previous reports on M. tuberculosis susceptibility from Najran, southwestern Saudi Arabia.

Prompt detection of anti-TB drug resistance is essential for controlling the development and spread of MDR-TB as it facilitates the appropriate and timely delivery of anti-TB therapy, reduces overall cost of treatment, minimizes the risk of further resistance development and limits the spread of drug-resistant M. tuberculosis(13). This work aims to determine the rates and patterns anti-TB drug resistance in Najran, Southwestern Saudi Arabia. It is our intention that these data could then be used locally, in conjunction with related studies from other regions of the Kingdom and worldwide to reflect the extent of the problem in the community.

MATERIALS & METHODS

A total of 80 smear-positive new pulmonary TB patients from Chest and King Khalid Hospitals in Najran were included in this study between March, 2009 and August, 2011. New TB cases were defined as patients with TB who have never been treated with anti-tuberculous drugs or have received them for less than 1 month(14). Three consecutive sputum samples were collected from each patient and sent to the
Microbiology Department, College of Medicine, Najran University for further processing.

Each specimen was processed by N-Acetyl-L-Cystein sodium hydroxide (NALC-NaOH) method and cultivated on Lowenstein-Jenseen; L-J (BioMerieux, France) and Middle-Brook 7H10 (Difco Laboratories, USA) media as described by Kent and Kubica\textsuperscript{(14)}. Cultures were incubated at 37°C for up to 2 months. Suspected colonies were identified by Kinyoun-stained smears, niacin accumulation, using niacin TB test strips (Difco Laboratories), nitrate reduction, using nitrate test strips (Difco Laboratories) and heat stable catalase tests\textsuperscript{(14)}.

All \textit{M. tuberculosis} isolates were subjected to susceptibility testing for INH, RIF, streptomycin (SPM) and ethambutol (EMB) by the conventional proportion method on antibiotic-free and antibiotic-incorporated Middle-Brook 7H10 agar plates containing OADC (oleic acid-albumin-dextrose-catalase) enrichment. The critical drug concentrations were 0.2, 1.0, 2.0 and 5.0 µg/ml for INH, RIF, SPM and EMB respectively. \textit{M. tuberculosis} isolate was considered drug-resistant if the number of colonies on drug-containing media is 1% or more of the colonies on drug-free media\textsuperscript{(14)}.

**RESULTS**

In this study, culture for \textit{M. tuberculosis} was positive in 68 of the 80 cases, while contamination was in 4 cases, non-tuberculous mycobacteria in 3 cases and no growth of mycobacteria in 5 cases. Out of the 68 \textit{M. tuberculosis} isolates, 42 (61.8%) were sensitive to all 4 drugs and 26 (38.2%) were resistant to one or more drugs. Highest resistance was found to INH (33.8%), followed by RIF (23.5%), SPM (13.2%) and EMB; 2.9% (table 1).

<table>
<thead>
<tr>
<th>Name of drugs</th>
<th>Sensitive isolates No. (%)</th>
<th>Resistant isolates No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazide</td>
<td>45 (66.2)</td>
<td>23 (33.8)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>52 (76.5)</td>
<td>16 (23.5)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>59 (86.8)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>66 (97.1)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Sensitive to all drugs</td>
<td>42 (61.8)</td>
<td>-</td>
</tr>
<tr>
<td>Resistant to all drugs</td>
<td>-</td>
<td>26 (38.2)</td>
</tr>
</tbody>
</table>

The resistance patterns of \textit{M. tuberculosis} isolates are presented in table (2). Eight (11.8%) isolates were resistant to one drug, 14 (20.6%) were resistant to 2 drugs, 3 (4.4%) were resistant to 3 drugs and one (1.5%) was resistant to 4 drugs. MDR was found in 14 (20.6%) cases.

<table>
<thead>
<tr>
<th>Number of drugs</th>
<th>Name of drugs</th>
<th>Resistant isolates No. (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One drug</td>
<td>INH</td>
<td>4 (5.9)</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPM</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Two drugs</td>
<td>INH+RIF</td>
<td>10 (14.7)</td>
<td>14 (20.6)</td>
</tr>
<tr>
<td></td>
<td>INH+SPM</td>
<td>4 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Three drugs</td>
<td>INH+RIF+SPM</td>
<td>3 (4.4)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Four drugs</td>
<td>INH+RIF+SPM+EMB</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>MDR</td>
<td></td>
<td>14 (20.6)</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

In this study, the overall drug resistance rate of 38.2% is higher than that reported in previous Saudi studies with values ranging from 8.7% to 30%\textsuperscript{(7-12)}. Higher resistance rate of 43.7% was reported in the study of Schiott et al\textsuperscript{(15)} in Jazan in the south west of the country. The investigators attributed this to the fact that Jazan is very close to Yemen, which has been reported to have one of the highest rates of active TB among Arab countries, and the workers moving across the border might be the cause for their high resistance rate.
Geographically, Najran is also very close to Yemen, and this resistance rate is a highly alarming situation. According to the Global Project on Anti-tuberculous Drug Resistance Surveillance (GPADRS) in 83 countries during 2002 to 2007\(^{\text{[16]}}\), the median prevalence of primary resistance to any drug was 11.1% with values ranging from 0% in Iceland to 56.3% in Azerbaijan. In this report, data from Arab countries showed primary resistance rates of 10% in Oman, 35% in Jordan and 49% in Yemen.

The rate of resistance to anti-tuberculous agents is an important parameter for control measures and success of treatment programs. In this study, resistance to INH as a single drug was the most common (5.9%). Reports from different regions in Saudi Arabia showed INH-resistance of 4.4% to 19.4% in Riyadh\(^{[7,8]}\), 10.3% to 28.7% in Jeddah\(^{[9,10]}\), 9.5% to 17% in Dammam\(^{[11-12]}\), 6.5% in Taif\(^{[17]}\), and 40.8% in Jazan\(^{[18]}\). In the GPADRS report\(^{[16]}\), the prevalence of INH-resistance ranged from 0% in Iceland to 42.4% in Uzbekistan, while it was 4.7% in Oman, 9% in Jordan and 3.9% in Yemen. INH-resistance is important, because it is a potent bactericidal drug, and is an important component of short course anti-TB regimen. According to the Centers for Disease Control and Prevention (CDC), when INH-resistance rates are >4%, quadruple empiric therapy with INH, RIF, pyrazinamide (PZA) and EMB or SPM is indicated\(^{[18]}\). In the light of our findings and as per CDC guidelines, the initial treatment of pulmonary TB with the 4-drugs regimen should be maintained as INH-resistance is higher than the cut off value of 4%.

Rifampicin is a potent bactericidal and sterilizing drug which acts on dormant and persistor bacilli on short exposure and RIF-resistance may lead to the failure of directly observed treatment short-course (DOTS) program\(^{[19]}\). RIF-resistance in this study (2.9%) is lower than that reported in other Saudi studies, accounting for 3.7% to 9.7% in Riyadh\(^{[7,8]}\), 5.1% to 23.4% in Jeddah\(^{[9,10]}\), 2.9% to 17% in Dammam\(^{[11-12]}\), 15.3% in Taif\(^{[17]}\), and 20.4% in Jazan\(^{[18]}\). In the GPADRS study\(^{[16]}\), the prevalence of RIF-resistance ranged from 0.5% in Iceland to 22.7% in Azerbaijan, whereas it was 1.3%, 2.9% and 11.7% in Oman, Yemen and Jordan respectively.

In this study the SPM- and EMB-resistance rates were lower than the resistance rates reported in other Saudi studies\(^{[7,12]}\).

Besides the high overall drug-resistance rate, another important observation in this study was a significant number of patients (18; 26.5%) with primary resistance to more than one drug, including 20.6% of patients with resistance to two drugs, 4.4% of patients to 3 drugs and 1.5% of patients to 4 drugs. Previous report from Saudi Arabia\(^{[20]}\) showed that 3.7% of all patients had resistance to at least three drugs, 3.6% had resistance to at least two drugs and 6.8% had resistance to one drug only. Resistances against two or more drugs are difficult to treat and often result in treatment failure.

The problem of MDR-TB in any community is of considerable public health concern, not only because of its mortality and low therapeutic response but also because of the implications for a speedy and energetic contact tracing and management of exposed contacts\(^{[5]}\). The rate of MDR-TB in this study (20.6%) was comparable to that (20.9%) reported in a previous study\(^{[15]}\) in the southwestern region of the country. Other Saudi studies showed MDR-TB rates ranging from 2.7% to 19.4%\(^{[7,12]}\). In the GPADRS study\(^{[16]}\), the median prevalence of MDR-TB in new TB cases was 1.6%, ranging from 0% in 8 countries with low TB prevalence to 19.4% in Moldova and 22.3% in Azerbaijan. In this report, the MDR-TB rates were 2% in Oman, 13% in Jordan and 15% in Yemen.

Anti-tuberculous drug resistance in never treated cases (primary resistance) is considered a good epidemiological indicator of long term surveillance of the quality of treatment performed by the TB program. Therefore, a high level of primary resistance indicates poor performance of the TB program by allowing transmission of resistant TB in the community\(^{[21]}\). The Saudi Ministry of Health has established the National Tuberculosis Control Committee to put forward the DOTS program that is applicable to the Kingdom since 1999. However, Saudi Arabia’s success rate (65%) is comparatively below the WHO target of 85% with drug resistance, non-compliance and over the counter access to anti-TB treatment being contributing factors\(^{[22]}\).

This study had some limitations. First, the small number of cases and lack of demographic data restricted our ability to describe characteristics of patient sub-strata. Second, the study did not include previously treated TB cases to determine the secondary resistance rates at the same time. Finally, the study included only pulmonary \textit{M. tuberculosis} isolates.
CONCLUSION

The results of this study showed that the primary resistance rate to four first-line anti-tuberculous drugs and MDR-TB rate are worryingly high, representing an alarming situation in Najran. Further studies are necessary for continuous surveillance of resistance pattern of M. tuberculosis to further delineate the risk factors and to formulate the plans for preventing the dissemination of resistant isolates, in particular MDR-isolates to the general population.

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REFERENCES


المختصر العربي

د/ أحمد مراد سعد، و/ جبران مرعي القحطاني
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إن ظهور السل المقاوم للأدوية هو المشكلة المتزائدة التي تؤثر سلبًا على رعاية المرضى والصحة العامة. يهدف هذا العمل إلى تحديد معدلات وأنماط مقاومة الأدوية المضادة للسل في نجران، جنوب غرب المملكة العربية السعودية. شملت الدراسة 80 مريض بالسل وتم جمع عينات البصاق وتم عمل اختبار حساسية معزولات المنغوفطة التلقائية لكل من أيزونيازيد، ريفاميسين، ستروتوميسين و إيثاميتوتول. أسفرت نتائج البحث على وجود 26 معزولًا مقاومة لأدوية السل و44 معزولًا حساسة لكل الأدوية. كانت أعلى مقاومة لدواء الأيزونيازيد (33.8%) وليبيا اثاميتوتول (32.9%) و ريفاميسين (23.3%) و ستروتوميسين (13.5%). تم فصل 14 معزولًا مقاومة للفعاقير المتعدد. من هذا البحث تم استنتاج أن معدل المقاومة الأولية إلى أربعة عفاقير من الخط الأول ضد السل و معدل السل المقاوم للأدوية مرتفعة بشكل يدعو إلى التقلق وهو ما يمثل حالة مثيرة للمقلق في نجران. ونوصي بمزيد من الدراسات اللازمة لدراسة مستمرة لأمراض مقاومة السل.