Primary anti-tuberculous drugs resistance of pulmonary tuberculosis in Southwestern Saudi Arabia

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KEYWORDS
Primary resistance; Pulmonary tuberculosis; Anti-tuberculosis drugs; Multi-drug resistance

Summary The emergence of drug-resistant tuberculosis (TB) is an increasing problem which adversely affects patient care and public health. This study aimed to determine the rates and patterns of primary anti-TB drugs resistance in Najran, Southwestern Saudi Arabia. The study included 80 smear-positive new pulmonary TB patients. Sputum samples were cultured on Lowenstein–Jensen and Middle-Brook 7H10 media. Mycobacterium 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. The most common 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-tuberculosis 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 continuous history of causing worldwide morbidity and mortality.

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The World Health Organization (WHO) estimated the global burden of tuberculosis in 2009 to be 9.4 million incident patients, 14 million prevalent cases and 2.4 million deaths [1]. Saudi Arabia has a moderate TB infection rate compared with other developing countries. A recent Saudi study [2] evaluating changes TB incidence rates in 13 provinces found that the TB incidence rates were 11.8–12.1 per 100,000 individuals between 2005 and 2009. The investigators reported that the
yearly TB incidence rate was significantly increasing among Saudis in Najran (21.3%) and Riyadh (8.5%) and significantly decreasing in non-Saudis in Baha (23.1%), Hail (17.4%) and the eastern region of Saudi Arabia (22.6%).

The emergence of drug-resistant *Mycobacterium tuberculosis* strains has proven to be a difficult problem and is one of the greatest public health threats worldwide. Multidrug-resistant TB (MDR-TB) is defined as having resistance to at least isoniazid (INH) and rifampicin (RIF), the 2 principal first-line anti-TB drugs. MDR-TB poses an important threat to TB control because it reduces the response to standard short-course chemotherapy with first-line anti-TB drugs, leads to higher mortality and treatment failure rates, and increases the period of disease transmissibility [3,4]. 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, which result from financial constraints in a number of developing countries [5,6]. Approximately 250,000 TB patients identified in 2009 had multidrug resistant TB (MDR-TB), and 440,000 MDR-TB cases were identified in 2008 [7]. The prevalence of single-drug-resistant TB or MDR-TB in the Kingdom of Saudi Arabia is largely unknown because only a few studies confined to large centers have been completed [8–13]. Unfortunately, there are no previous reports on *M. tuberculosis* susceptibility in Najran, which is located in southwestern Saudi Arabia. The prompt detection of anti-TB drug resistance is essential for controlling the development and spread of MDR-TB because detection facilitates the appropriate and timely delivery of anti-TB therapy, reduces the overall cost of treatment, minimizes the risk of developing further resistance and limits the spread of drug-resistant *M. tuberculosis* [14].

This study aimed to determine the rates and patterns of primary anti-TB drug resistance in Najran, southwestern Saudi Arabia. It is our intention that these data can not only be used locally but also in conjunction with related studies from other regions of the Kingdom and worldwide to highlight the extent of the problem in the community and to help in planning and implementing successful treatment programs.

**Materials and methods**

A total of 80 smear-positive, newly diagnosed pulmonary TB patients from the Chest and Fever Hospital and King Khalid Hospital in Najran were included in this study. The patients were identified between March 2009 and August 2011. New TB cases were defined as TB patients who had never been treated with anti-tuberculous drugs or had received the drugs for less than 1 month [1].

Three consecutive sputum samples were collected from each patient and were sent to the microbiology department of the Najran University College of Medicine for further processing.

Each specimen was processed with the N-Acetyl-L-Cysteine sodium hydroxide (NALC-NaOH) method and cultivated on Lowenstein–Jensen (L–J) (BioMerieux, Marcy l’Etoile, France) and Middle-Brook 7H10 (Difco Laboratories, Detroit, USA) media as described by Kent and Kubica [15]. The cultures were incubated at 37°C for up to 2 months. The 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 [15].

All of the *M. tuberculosis* isolates were tested for susceptibility to INH, RIF, streptomycin (SPM) and ethambutol (EMB) with 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. An *M. tuberculosis* isolate was considered drug-resistant if the number of colonies on the drug-containing media was 1% or more of the colonies on the drug-free media [15].

**Results**

Sixty-eight of the 80 cases in this study exhibited sputum cultures that were positive for *M. tuberculosis*. Contamination occurred in 4 cases, non-tuberculous mycobacteria were present in 3 cases, and 5 cases did not exhibit mycobacterial growth. Forty-two (61.8%) of the 68 *M. tuberculosis* isolates were sensitive to all 4 drugs, and 26 (38.2%) isolates were resistant to one or more drugs. The colonies were primarily resistant to INH (33.8%) followed by RIF (23.5%), SPM (13.2%) and EMB (2.9%) (Table 1).

The resistance patterns of the *M. tuberculosis* isolates are presented in Table 2. Eight (11.8%) of
the 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 isolates were found in 14 (20.6%) cases.

Discussion

The observed overall drug resistance rate of 38.2% is higher than that reported in previous Saudi studies, which found values ranging from 8.7% to 30% [8–13]. Schiott et al. [16] reported a 43.7% resistance rate after investigating patients in Jazan. The investigators attributed this finding to Jazan’s proximity to Yemen, which reportedly has one of the highest rates of active TB among Arab countries. Workers moving across the border might be the cause for the high resistance rate. Najran is also very close to Yemen geographically, and this resistance rate represents a highly alarming situation. The Global Project on Anti-tuberculous Drug Resistance Surveillance (GPADRS) investigated the prevalence of TB in 83 countries from 2002 to 2007 [17] and found that the median prevalence of primary resistance to any drug was 11.1% and that resistance values ranged from 0% in Iceland to 56.3% in Azerbaijan. The 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 implementing control measures and planning successful treatment programs. Resistance to INH as a single drug occurred most frequently (5.9%) in our study. Reports from different regions in Saudi Arabia have shown INH resistance rates of 4.4–19.4% in Riyadh [8,9], 10.3–28.7% in Jeddah [10,11], 9.5–17% in Dammam [12,13], 6.5% in Taif [18] and 40.8% in Jazan [16]. The GPADRS report [17] found that the prevalence of INH resistance ranged from 0% in Iceland to 42.4% in Uzbekistan, reaching 4.7% in Oman, 9% in Jordan and 3.9% in Yemen. INH resistance is important because INH is a potent bactericidal drug that is an important component of the short course anti-TB regimen. According to the WHO guidelines [19], the suspicion or knowledge of high levels of isoniazid resistance dictates that new TB patients receive isoniazid, rifampicin and ethambutol as an acceptable alternative therapy to isoniazid and rifampicin in the continuation phase. In light of these guidelines, our finding of high INH resistance is of considerable concern in deciding the treatment regimen for new TB patients in Najran.

Rifampicin is the most potent first-line anti-tuberculous drug and an important component of treatment regimens. Within the last few years, the WHO has recommended discontinuing the 6-month isoniazid and ethambutol regimen given during the continuation phase in favor of treatment with isoniazid and rifampicin for 4 months [20]. This approach will reduce the number of relapses and failures and conserve patient and national program resources. The RIF resistance rate (2.9%) was lower in this study than other Saudi studies, which have found 3.7–9.7% resistance in Riyadh [8,9], 5.1–23.4% resistance in Jeddah [10,11], 2.9–17% resistance in Dammam [12,13], 15.3% resistance in Taif [18] and 20.4% resistance in Jazan [16]. The prevalence of

<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>

Table 1 Susceptibility patterns of the 68 M. tuberculosis isolates to 4 anti-tuberculosis drugs.

Table 2 Resistance patterns of drug-resistant M. tuberculosis isolates to 4 anti-tuberculosis drugs.

<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</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>(11.8)</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</td>
</tr>
<tr>
<td></td>
<td>INH + SPM</td>
<td>4 (5.9)</td>
<td>(20.6)</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>14 (20.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a INH, isoniazid; RIF, rifampicin; SPM, streptomycin; EMB, ethambutol.
RIF resistance varied from 0.5% in Iceland to 22.7% in Azerbaijan in the GPADRS study [17], reaching 1.3%, 2.9% and 11.7% in Oman, Yemen and Jordan, respectively.

The SPM and EMB resistance rates found in this study were lower than the SPM and EMB resistance rates reported in other Saudi studies [8–13].

In addition to the high overall drug resistance rate identified in this study, another important observation was the significant number of patients (18, 26.5%) with primary resistance to more than one drug. The data revealed that 20.6% of patients in this study exhibited resistance to two drugs, 4.4% of patients exhibited resistance to 3 drugs, and 1.5% of patients exhibited resistance to 4 drugs. A previous report from Saudi Arabia [21] showed that 3.7% of all patients had resistance to at least three drugs, 3.6% of patients had resistance to at least two drugs, and 6.8% of patients had resistance to only one drug. TB that is resistant to two or more drugs is difficult to treat and often results in treatment failure. This resistance should be considered in prevention plans and when determining treatment protocols in Najran.

The presence of MDR-TB is of considerable public health concern in any community because of both its mortality rate and low therapeutic response and the implications for speedy and energetic contact tracing and the management of exposed contacts [6]. The MDR-TB rate identified in this study (20.6%) is comparable to that (20.9%) reported in a previous study [16] that investigated the southern region of the country. Other Saudi studies have identified MDR-TB rates ranging from 2.7% to 19.4% [8–13]. The median prevalence of MDR-TB in new TB cases was 1.6% in the GPADRS study [17], ranging from 0% in 8 countries with low TB prevalence to 19.4% in Moldova and 22.3% in Azerbaijan. This report identified the MDR-TB rates in Oman, Jordan and Yemen as 2%, 13% and 15%, respectively.

The prevalence of anti-tuberculous drug resistance in previously untreated cases (primary resistance) is considered a good epidemiological indicator of the quality of the TB treatment program. Therefore, a high level of primary resistance indicates the transmission of drug-resistant TB in the community and a poorly performing TB program [22]. The Saudi Ministry of Health established the National Tuberculosis Control Committee to develop the directly observed therapy (DOT) program that has been applied in the Kingdom since 1999. However, Saudi Arabia’s success rate (65%) is comparatively less than the WHO target of 85%, with drug resistance, non-compliance and over-the-counter access to anti-TB treatments contributing to the low success rate [23].

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

Conclusion

This study showed that the primary resistance rate to four first-line anti-tuberculous drugs and MDR-TB rate in Najran are distressingly high. Further studies are necessary to monitor the M. tuberculosis resistance pattern continuously, further delineate risk factors and formulate plans for preventing the dissemination of drug-resistant isolates, particularly MDR isolates, to the general population.

Conflict of interest statement

Funding: No funding sources.
Competing interests: None declared.
Ethical approval: Not required

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