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Original Article

Antibiotic sensitivity of *Mycobacterium tuberculosis* isolates; a retrospective study from a Saudi tertiary hospital

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الملخص

أهداف البحث: هدفت هذه الدراسة إلى فحص حساسية المضادات الحيوية لعزل المتفطّرة السلية ومقاومتها للعقاقير. قمنا أيضا بتقييم العلاقة بين الخصائص الديموغرافية وقابلية العلاج بعقاقير السل.

طرق البحث: أجريت الدراسة بأثر رجعي لتحليل حساسية المضادات الحيوية لعزليات المتفطرة السلية ومقاومتها للعقاقير المضادة للسل من الصف الأول. خلال الفترة ٢٠٠٨-٢٠١٣، تمت مراجعة السجلات الطبية لـ ١٩١ مريضا من جناح السل وقسم المرضى الخارجيين في مستشفى ثالثي في شرق المملكة العربية السعودية.

النتائج: قمنا بتصنيف العينة إلى فئتين: السل خارج الرئوي والسل الرئوي. في مرض السل الرئوي، تم فحص عينات وكان ٣٦.٥٪ منها من سوائل الجسم، و٢٩.٢٪ من زراعة الأنسجة و٥.٢٪ من خراجات الجسم. في السل الرئوي، شكلت عينات البلغم أعلى نسبة من العينات (٢٨.٦٪)، وتليها نضح الشعب الهوائية (١٣.٢٪)، والسائل الجنبي (٥.٧ ٪). أظهرت العزلات السريرية لدى النساء مقاومة أعلى للإيثامبوتول مقارنة بالعزلات الذكورية. كما أظهر عقار أيزونيازيد أعلى نمط مقاومة بين جميع المضادات الحيوية التي تم اختبارها (١٧٪). وفي الوقت نفسه، كانت لمزارع الأنسجة مقاومة أعلى للأيزونيازيد مقارنة مع العينات الأخرى.

الاستنتاجات: المقاومة لعقاقير السل من الصف الأول أعلى في عزلات السل خارج الرئة من العزلات الرئوية. وكان ما يقرب من ربع جميع السلالات السريرية لمرض المتفطرة السلية مقاومة للمضادات الحيوية التي تم اختبارها بطرق مقاومة متعددة أو مقاومة أحادية. كما كانت النساء أكثر مقاومة لعقار إيثامبوتول مقارنة بالرجال. وفي الوقت نفسه، أظهر السل الرئوي، وتحديدا زراعة الأنسجة، مقاومة أكبر للإيزونيازيد مقارنة بالعينات السريرية الأخرى.

الكلمات المفتاحية: المضادات الحيوية؛ الفطرية السلية؛ رئوي؛ خارج الرئة؛ السل

Abstract

Objectives: This study aims to examine the antibiotic sensitivity of *Mycobacterium tuberculosis* isolates and its drug resistance. We also evaluated the relationship between demographic characteristics and tuberculosis (TB) drug susceptibilities.

Methods: A retrospective study was conducted to analyse the antibiotic sensitivity of *M. tuberculosis* isolates and its resistance to first-line anti-TB drugs. During the period 2008–2013, the medical records of 191 patients from the TB ward and the Out-Patient Department in an Eastern KSA tertiary hospital were reviewed.

Results: We classified the specimens into two categories: extra-pulmonary and pulmonary TB. Among the extra-pulmonary TB specimens, 36.5% were from body fluids, 29.2% from tissue cultures and 5.2% from body abscesses. In case of pulmonary TB, sputum samples accounted for the highest proportion of the specimens (28.6%), followed by bronchial aspirates and pleural fluid (13.2% and 5.7%, respectively). Clinical isolates from women showed higher resistance to ethambutol compared to those from men. Isoniazid showed the highest resistance pattern among all antibiotics tested (17%). Meanwhile, tissue cultures had higher resistance to Isoniazid antibiotic compared to the other specimens.

Conclusion: Resistance to first-line TB drugs is higher in extra-pulmonary TB isolates than pulmonary isolates. Nearly one-fourth of all *M. tuberculosis* clinical strains were resistant to the antibiotics tested in mono-resistant or multi-resistant manners. Women had greater resistance to TB drug ethambutol as compared to men. Meanwhile, extra-pulmonary TB specimens, specifically

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that from tissue cultures, showed greater resistance to Isoniazid than other clinical specimens.

Keywords: Antibiotics; Extra-pulmonary; *Mycobacterium tuberculosis*; Pulmonary; Tuberculosis (TB)

Introduction

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) which spreads into the lymphatic system, brain, spine, and lungs. It is estimated that nearly 25% of the global population is infected with this bacterium.[1] Several countries have been recorded as endemic areas of TB and these include Bangladesh, Indonesia, China, Philippines, India, Pakistan, and Nigeria.[2] In spite of the high TB rates, it is a treatable disease. TB treatment utilizes four anti-TB drugs (ethambutol, isoniazid, rifampin, and streptomycin), coupled with close support from health care professionals, and treatment adherence.

From 2008 to 2018, 58 million people were saved through TB medication treatment.[2] Currently, several TB antibiotics including rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin, are administered to patients based on drug potency.[3] Notwithstanding the improvements in TB treatment regimens due to the potency of TB drugs,[4] it remains one of the most critical public health issues owing to the rapidly increasing antibiotic resistance.[5] Antibiotic resistance is associated with inappropriate treatment regimens, patient non-compliance, incorrect prescriptions by physicians, poor drug quality, and the premature cessation of treatment by patients.[6,7]

In KSA, higher TB incidence and TB drug resistance remain despite extensive government campaigns to eradicate this disease.[8] Several reasons contributing to this situation include an increase in expatriate workers coming from TB-endemic regions such as countries in Asia and Africa.[9] Furthermore, KSA is a pilgrimage centre to the Two Holy Mosques (in Makkah and Al-Madinah). The millions of pilgrims who arrive annually from regions stricken with high TB occurrence, hamper efforts to decrease the incidence of this infectious disease.[10] Increasingly, TB drug-resistant cases are reported in KSA because of patient non-compliance and interruption in drug regimens. These further hinder the government's goal to eradicate TB.[11] This growing health concern highlights the importance of implementing effective disease control measures, revision of disease transmission dynamics, and the development of proper diagnostics and logistics. Despite some empirical data pertaining to drug resistance in the country,[9,11] there is still a limited understanding of antibiotic sensitivity and resistance of *M. tuberculosis*. Information regarding TB drug-resistance is scarce; very few studies have examined TB drug sensitivity and associated clinical factors.[9,11] Therefore, this study aims to investigate the antibiotic susceptibility of *M. tuberculosis* isolates to the first-line anti-TB regimen using a retrospective approach. It also assesses the association between demographic characteristics and TB susceptibility in the Eastern Province of KSA. The findings presented herein could aid in increasing the understanding of the extent of TB resistance and suggest more appropriate therapeutic and preventative procedures to control the disease.

Materials and Methods

Design

Retrospective analysis was used to analyse the antibiotic sensitivity of *M. tuberculosis* isolates to the first-line treatment regimen for TB disease – ethambutol, isoniazid, streptomycin, and rifampin.

Data and inclusion criteria

This retrospective analysis studied patient records, from 2008 to 2013, at the tuberculosis ward/OPD of a single tertiary hospital (King Fahd University Hospital, Alkhobar) in Eastern KSA. Ethical approval was obtained from the hospital Clinical Laboratories Directorate and confidentiality was ensured by using only code numbers to identify patients. Laboratory-confirmed TB patients who had test results on the antibiogram pattern of their *M. tuberculosis* isolates were included in the study. A record-based study for TB patients from the Eastern Province of KSA the period (2008–2013) was conducted and resistance to the first-line TB antibiotics (ethambutol, isoniazid, rifampin, and streptomycin) was determined.

Data analysis

SPSS version 24 software was utilized for data analysis. Descriptive statistics such as frequency, percentage, mean, and standard deviation were used to determine the respondents' demographic characteristics. ANOVA was used to determine the differences in specimen type to culture-positive TB drug sensitivity and TB drug resistance. t-test was used to compare the culture-positive TB drug sensitivity and TB drug resistance between genders. Pearson product–moment correlation was used to examine the relationship between age, TB drug effectiveness, and TB drug resistance. A p-value of less than 0.05 was considered significant.

Results

The respondents' characteristics are shown in Table 1. The results showed that the majority of clinical isolates were from females (52.4%). The specimen could be classified based on their origins: extra-pulmonary TB (52.3%) and pulmonary TB (47.6%). In extra-pulmonary TB, body fluids such as cerebrospinal fluid and mid-stream catch urine clinical specimens (24.1%) were also examined. Among the other specimens, 20.4% were from tissue biopsies and swabs and 5.2% were from body abscesses. Regarding the specimens of pulmonary origin, sputum specimens accounted for the highest percentage (28.6%), followed by

Table 1: Patient demographic characteristics. 2008–2013 (Number of samples = 191).

Gender	Frequency	Percentage (%)
Male	89	46.6
Female	102	53.4
Specimen type		
Extra-pulmonary TB (52.4%)		
Body fluids	46	24.1
Tissue swabs & biopsies	39	20.4
Body abscess	15	7.9
Pulmonary TB (47.6%)		
Sputum	55	28.6
Bronchial wash & aspirates	25	13.2
Pleural fluid	11	5.7
	Mean	SD
Age	35.49	15.69

bronchial aspirates and pleural fluid (13.2% and 5.7%, respectively).

Figure 1A illustrates the prevalence of antibiotic resistance among *M. tuberculosis* strains included in the study. Overall, 73% of all TB isolates were sensitive to first-line anti-tuberculosis drugs whereas 27% of the isolates showed resistance to at least one of the drugs. Of the 27% that showed resistance (Figure 1B), 62% of them were resistant to only one antibiotic (mono-resistant) and 38% of the resistant strains were multi-resistant (resistant to more than one antibiotic).

Table 2 and Figure 2 show the susceptibility to all the tested antibiotics along with any resistance to TB drugs from 2008 to 2013. For ethambutol, the majority of the clinical isolates (89%) were sensitive; ~10% were fully resistant while only 1% of the isolates showed heteroresistance. As for isoniazid, most of the clinical isolates (82%) were susceptible to the highest resistance

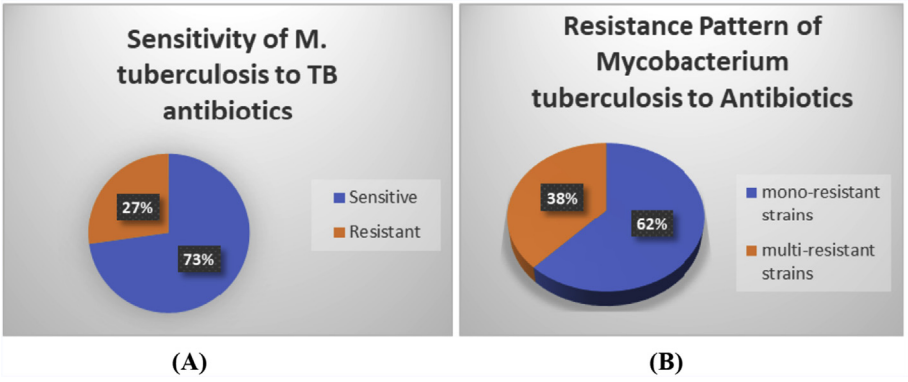

Figure 1: The overall sensitivity of clinical *M. tuberculosis* isolates to antibiotics (A), and pattern of resistance of resistant clinical isolates (B).

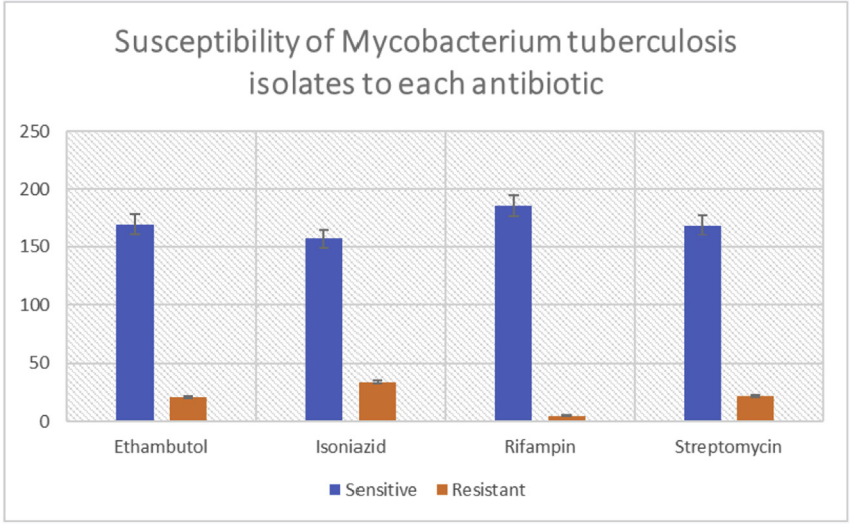

Figure 2: Sensitivity and resistance of TB clinical isolate to each antibiotic studied.

Table 2: Susceptibility of *M. tuberculosis* to antibiotics; 2008–2013 (N = 191).

Drug	Frequency	Percentage (%)
Ethambutol		
Resistant	19	9.9
Susceptible	170	89.0
Hetero-resistant	2	1.0
Isoniazid		
Resistant	34	17.8
Susceptible	157	82.2
Hetero-resistant	–	–
Rifampin		
Resistant	4	2.1
Susceptible	186	97.4
Hetero-resistant	1	0.5
Streptomycin		
Resistant	21	11.0
Susceptible	169	88.5
Hetero-resistant	1	0.5

pattern observed among all antibiotics tested (17%). The second-highest resistance rate of TB isolates was associated with the antibiotic streptomycin (11.5%). Of the single antibiotics resistance tests, *M. tuberculosis* in the specimens displayed the highest sensitivity to rifampin (97.4%). The resistance to rifampin was also the lowest (~2%).

Table 3 shows the association between demographic profiles to the culture-positive drug-sensitive TB and drug-resistant TB isolates from the years 2008–2013 (N = 191). Female patients (mean = 1.54; SD = 0.50) had a higher resistance to ethambutol than males (mean = 1.54; SD = 0.51; t -0.557; p = 0.05). Meanwhile, *M. tuberculosis* from tissue swabs and biopsies had higher resistance to isoniazid compared to other specimen types (F = 0.191; p = 0.05). Apart from the above, the data did not show any other statistically significant correlations between the pattern of *M. tuberculosis* sensitivity, age, and the patients' gender or types of clinical specimens.

Discussion

This is a retrospective study investigating the susceptibility of *M. tuberculosis* to the anti-TB drugs. The associations between demographic profiles, culture-positivity of clinical specimens, and antibiotic sensitivity were shown. The findings revealed that resistance to TB drugs was higher in extra-pulmonary TB isolates than pulmonary isolates. This is in concordance with recent studies.[12,13] In this study, the proportion of confirmed extra-pulmonary cases is high (52.3%) compared to other available national or international data. A previous survey conducted in KSA showed that the rate of the recorded occurrence of extra-pulmonary TB isolates reached between 25% and 31%.[14] This is greater than that in European countries.[15] However, caution was advised in interpreting these previous findings because the technique used, smear microscopy, not sensitive enough and failed to identify 43% of TB patients.[2,16] Moreover, smear microscopy cannot differentiate drug-susceptible from drug-resistant strains.[2] Thus, treatment is frequently given empirically using clinical criteria, leading to wrong patient diagnosis, excessive expenses, toxicities, late response, and poor treatment outcomes.[16] Nevertheless, patients with extra-pulmonary manifestations need specialized clinical investigations; the diagnosis is usually based upon clinical, radiographic or histopathological findings, rather than bacteriologic evidence. Therefore, further studies are warranted. These findings highlight the susceptibility of *M. tuberculosis* to all the test drugs along with TB drug resistance. The findings revealed that almost all of the clinical isolates were resistant to TB drugs (ethambutol, isoniazid, rifampin, and streptomycin). This is worth noting since resistance to TB drugs usually results from non-compliance to medication because of poor TB management.[17] This observation is similar to studies in India,[18] Brazil,[19] and Canada.[20] According to these previous studies, drug resistance is due to poor compliance, improper prescriptions, suboptimal dosage, and drug storage and quality. These significantly contribute to the emergence of drug resistance.[19] Caution is however needed in the interpretation of these findings as this

Table 3: Association between demographic profile with the culture-positivity and drug sensitivity of TB isolates collected from years 2008–2013 (N = 191).

Demographic characteristics	Statistical test (p-value)				
	Frequency (%)	Ethambutol	Isoniazid	Rifampin	Streptomycin
Gender					
Male	46.6	-0.557^{a}(0.05)*	-0.437^{a} (663)	0.882^{a} (0.379)	-1.467^{a} (0.144)
Female	53.4				
Age		r = 0.018^{b} (0.805)	-1.101^{b} (0.163)	-0.063^{b} (0.383)	-0.075^{b} (0.303)
Specimen type					
Tissue swabs and cultures		F = 0.238^{c} (0.626)	F = 0.191^{c} (0.05)*	F = 0.238^{c} (0.626)	F = 0.238^{c} (0.465)
Body fluid secretion		F = 2.596^{c} (0.054)	F = 0.707^{c} (0.549)	F = 1.894^{c} (0.132)	F = 1.466^{c} (0.225)
Sputum		F = 0.213^{c} (0.074)	F = 0.431^{c} (0.360)	F = 0.238^{c} (0.565)	F = 0.238^{c} (0.112)
Body abscess		F = 0.463^{c} (0.833)	F = 0.321^{c} (0.379)	F = 0.187^{c} (0.816)	F = 0.146^{c} (0.638)

Note: T test[a], Pearson-r correlation[b], Anova[c].
*Statistically significant at 0.05 level.

study does not discuss the reasons for the higher resistance of TB drugs among clinical isolates. Nevertheless, training and patient education on how to avoid TB drug resistance could effectively alleviate the problem.

According to data generated in this study, the prevalence of *M. tuberculosis* resistance to first-line anti-TB drugs (ethambutol, isoniazid, rifampin, and streptomycin) is estimated to be 27% among all isolated strains. Among all clinical isolates of the organism, multi-drug resistant strains represent about 10.3%. Based on a limited number of studies previously conducted in KSA, it was estimated that the proportion of drug-resistant *M. tuberculosis* ranged between 14% and 29% in different geographical regions of the country.[8] Isoniazid and rifampin are two principle antibiotics of the anti-TB regimen. In this study, the resistance to these drugs was 17.8% and 2.6%, respectively. These figures contradict previous reports[21] implying that the epidemiology and resistance pattern of *M. tuberculosis* vary greatly from one region to another within the country.

Female clinical isolates had higher resistance to ethambutol compared to male clinical isolates. This is congruent with previous studies that identified a higher prevalence of acquired resistance to ethambutol among female patients.[22,23] A study conducted in South Africa found that women were 38% more likely to experience TB drug-resistance than men.[24] Likewise, another study from India noted that females were more vulnerable to TB than males between the ages of 18–29 years.[25] In an analysis by Liu et al., researchers noted that although TB patients had different drug resistance risks because of differences in access to health care services, females were more likely to have TB resistance than males.[26] There is no clear explanation for this scenario. This might be because women tend to be primary caregivers in a family and may thus devote more time to caring for TB-resistant drug patients than men.[26] In addition, male and female patients might have different care levels and providers might be unwilling to refer female patients with less complex infections to health care settings.[17] According to Surkova et al., during their initial reproductive years, women might have higher infection rates of TB.[27] Ascertaining TB-resistant drug risk in the different genders could provide valuable insight into direct measures and improved TB treatment management.

Limitations

Several limitations need to be considered in the interpretation of this study. The study used secondary data from a tertiary hospital which limits the generalization. The use of the retrospective study methodology cannot determine the causes of TB. Other risk factors affecting TB susceptibility and resistance were also not measured. The data was collected from 2008 to 2013. The lack of recent reliable data limits the analysis scope and sample size. Therefore, further research into the latest TB trend is warranted in the Eastern Province of KSA.

Conclusion

The increase in TB drug resistance rates is creating challenges and fear across the globe with regards to the control of TB. In this study, resistance to TB drugs was higher in extra-pulmonary TB isolates than pulmonary isolates; 27% of the clinical isolates were resistant to at least one of the TB drugs (ethambutol, isoniazid, rifampin, and streptomycin). *M. tuberculosis* isolated from female patients had greater resistance to ethambutol compared to that from male patients. Meanwhile, extra-pulmonary TB tissue cultures had greater resistance to isoniazid than other specimen types.

Recommendations

There has been a rise in antibiotic resistance in KSA hospitals, as well as worldwide, due to the increased use of antibiotics**.** There is thus a need for a more rational approach to using antibiotics based on microbial prevalence and antibiotic susceptibility. The results of this retrospective record-based study illustrate the significance of national efforts to the improvement of treatment and control of drug-resistant TB in the country by executing evidence-based actions monitoring TB treatment and diagnosis. Since women are more likely to experience resistance to TB drugs, increasing efforts to develop gender-dependent protocols from diagnosis to TB treatment, will contribute to the prevention of drug resistance. Further investigation using a representative survey of drug-resistance among all culture-positive TB-resistant and susceptible patients in the country, with a follow-up of their treatment outcomes, is recommended.

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Conflict of interest

There is no conflict of interest.

Ethical approval

This study was directed after receiving approval from the Ethics Review Committee of the University hospital institution.

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