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Research Article

Mycobacterium tuberculosis drug resistance and evaluation of the current situation

Mycobacterium tuberculosis ilaç direnci ve güncel durumun değerlendirilmesi

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Abstract

Aim: We aimed to determine the antituberculosis drug susceptibility status in Mycobacterium tuberculosis complex isolates, considering that current drug resistance rates will be an important indicator of the prevalence of primary drug resistance in the future.

Material and Methods: All cases whose culture sample was taken with clinical suspicion of tuberculosis at Samsun Training and Research Hospital in the period between January 2018 and December 2023 and who had a positive result in at least one of the Acid-fast stain (AFS) and culture methods were included in the study.

Results: The average age of the patients was 54.5±18.5 (range: 17-93) and 398 (74.1%) were male. In the study, 77.3% of the samples were sputum and 15.8% were bronchoalveolar lavage. 474 (88.3%) of the isolates were M. tuberculosis complex. 49% of the samples were positive with the AFS method, 96.5% with Mycobacteria Growth Indicator Tube (MGIT), and 84.5% with Löwenstein-Jensen (LJ) medium. The resistance rates in the isolates were 10.6%, 2.8%, 1.1% and 7.0% for isoniazid, rifampicin, ethambutol and streptomycin, respectively. All isolates resistant to rifampicin were also resistant to isoniazid. The rate of multidrug-resistant isolates was found to be 2.8%. The single drug resistance rate was found to be 14.0%. It was determined that the resistance rates before the pandemic were significantly higher than during the pandemic period.

Conclusion: The resistance rates to isoniazid in M. tuberculosis complex isolates were around 10% and that the general resistance rates to primary anti-tuberculosis drugs decreased significantly during the pandemic period.

Keywords: tuberculosis; resistance; pandemic; COVID-19

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Öz

Amaç: Günümüz ilaç direnç oranlarının gelecekte birincil ilaç direncinin yaygınlığının önemli bir göstergesi olacağını göz önünde bulundurarak Mycobacterium tuberculosis kompleks izolatlarında antitüberküloz ilaç duyarlılık durumunu belirlemeyi amaçladık.

Gereç ve Yöntemler: Samsun Eğitim ve Araştırma Hastanesi'nde Ocak 2018-Aralık 2023 tarihleri arasında klinik tüberküloz şüphesiyle kültür örneği alınan, asido-rezistan boyama (ARB) ve kültür yöntemlerinden en az birinde pozitif sonuç veren tüm olgular çalışmaya dahil edildi.

Bulgular: Hastaların yaş ortalaması 54,5±18,5 (aralık: 17-93) olup 398'i (%74,1) erkekti. Çalışmada örneklerin %77,3'ü balgam, %15,8'i ise bronkoalveolar lavajdan oluştu. İzolatların 474'ü (%88,3) M. tuberculosis kompleksi idi. Örneklerin %49'u ARB yöntemiyle, %96,5'i Mycobacteria Growth İndikatör Tüp (MGIT) ve %84,5'i Löwenstein-Jensen (LJ) kültür yöntemiyle pozitifti. İzolatlardaki direnç oranları izoniazid, rifampisin, etambutol ve streptomisin için sırasıyla %10,6, %2,8, %1,1 ve %7,0 idi. Rifampisine dirençli izolatların tamamı aynı zamanda izoniazide de dirençliydi. Çoklu ilaca dirençli izolatların oranı %2,8 olarak belirlendi. Tek ilaca direnç oranı %14,0 olarak belirlendi. Pandemi öncesindeki direnç oranlarının pandemi dönemine göre ciddi oranda yüksek olduğu belirlendi.

Sonuçlar: M. tuberculosis kompleks izolatlarında izoniazid direnç oranlarının %10 civarında olduğu ve pandemi döneminde birincil anti-tüberküloz ilaçlara karşı genel direnç oranlarının önemli ölçüde azaldığı görüldü.

Anahtar Kelimeler: tüberküloz; direnç; pandemi; COVİD-19

Introduction

Tuberculosis (TB) is a historically important disease caused by the Mycobacterium tuberculosis complex, which has caused epidemics in the past. Mycobacterium tuberculosis (MTb) is one of the chronic granulomatous infection agents that can affect all systems in the human body, mostly the lungs. Although its frequency has decreased over time, it has been reported that in recent years there has been an increase in tuberculosis cases caused by bacilli resistant to both isoniazid and rifampicin and therefore known as multidrug-resistant (MDR) (1,2). In some of these cases, the presence of extensively drug-resistant tuberculosis (XDR) clinic, together with additional resistance to fluoroquinolones and linezolid and/or bedaquiline, appears as a reason that increases mortality in patients (3).

Despite the development of modern diagnosis, treatment, and control methods, wars, migrations, inadequacies in the public health infrastructure system, HIV epidemics, inadequacies in patient follow-up, inadequate isolation procedures, delays in diagnosis and treatment, lack of qualified personnel and development of resistance to anti-tuberculosis drugs. Treatment of tuberculosis disease is becoming difficult (4). In endemic regions, different studies are trying to develop diagnosis, prevention, and treatment strategies aimed at preventing transmission through vaccination, diagnosing asymptomatic M. tuberculosis carriers, and improving antimicrobial drug treatment responses (5). The aim of tuberculosis treatment; is to cure the patient, prevent possible complications and mortality, and prevent relapses, contamination, and the spread of resistant isolates. TB treatment, which especially brings with it patient compliance, involves the principle of the combined use of many anti-tuberculosis drugs. The treatment is long-term and the main goal in this process is to reduce the bacterial load and sterilize it with treatment lasting at least six months (6).

In current tuberculosis diagnosis and treatment guidelines, it is recommended to determine first-line drug sensitivity, especially for all cases (7). As the main strategy in the control of resistant strains, it is considered important to know the susceptibility results of the bacteria before treatment to give effective treatment to patients. However, the rate of resistant strains may vary between regions or within the same region over the years (8). Therefore, performing and monitoring drug sensitivity tests regularly has a very beneficial effect on the selection of drugs used in first-line treatment and in preventing the spread of tuberculosis (9). In addition, regional antituberculosis drug resistance rates and epidemiological information obtained about the status of TB disease play an important role in the increasingly global fight against antimicrobial resistance (10).

In our study, we aimed to determine the anti-tuberculosis drug susceptibility status in Mycobacterium tuberculosis complex isolates, considering that current drug resistance rates will be an important indicator of the prevalence of primary drug resistance in the future.

Material and Methods

All cases whose culture sample was taken with clinical suspicion of tuberculosis at Samsun Training and Research Hospital in the period between January 2018 and December 2023 and who had a positive result in at least one of the Acid fast stain (AFS) and culture methods were included in the study. The pandemic period is accepted as between March 2020, when the first case was seen in our country, and April 2022, when all pandemic measures were completely removed. More than one result of patients for whom culture samples were requested were not included in the study. This retrospective study was approved by the local ethics committee decision (GOKAEK 2024/3/10). This study was carried out in accordance with the Declaration of Helsinki Principles.

Mycobacterial Culture

After the homogenization and decontamination process was applied to the samples coming to the laboratory using 4% NaOH solution, they were planted in BACTEC MGIT 960 (Becton Dickinson, USA) Mycobacteria growth indicator tube and Löwenstein-Jensen (LJ) medium (Becton Dickinson, USA) following the manufacturer's recommendations. Then, the preparation was prepared by staining with Ehrlich-Ziehl-Neelsen (EZN). Sterile samples were taken into the study without homogenization and decontamination processes. Direct smear preparations were examined with EZN staining. 0.5 mL of processed clinical samples were added to Mycobacteria Growth Indicator Tube (MGIT) tubes, and the samples were incubated with automated devices until a positive alert was received or for eight weeks. The tubes from which the growth signal was received were evaluated for contamination and positivity by acid-resistant staining. 100 µl of each of the samples detected as acid-resistant in microscopy were dropped into the BD MGIT TB Identification Test (Becton Dickinson, USA) kits, which detect MPT64 antigen. The samples giving positive results at the end of the 15 minutes specified in the kit procedure were tested for Mycobacterium tuberculosis complex (MTC), and the samples giving negative results were tested for tuberculosis. It was evaluated as non-mycobacteria (TDM). The sensitivity of samples with MTC to INH (0.1 µg/mL), RIF (1.0 µg/mL), ETB (5.0 µg/mL), and SM (1.0 µg/mL) antibiotics was determined by BACTEC following the manufacturer's recommendations. It was investigated using the MGIT 960 SIRE kit (Becton Dickinson, USA) system. M. tuberculosis ATCC 27294 (H37Rv) isolate, which is known to be sensitive to the tested drugs, was used in the quality control of the sensitivity tests.

Statistical analysis

The sample size in the study was calculated by power analysis using G-Power (version 3.1.9.6, Franz Faul, Universitat Kiel, Germany). Effect size 0.2; Type 1 error was taken as 0.05 and test power as 0.8, and the total required sample size was determined as at least 321.

All statistical analyses in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Comparisons between groups in terms of categorical variables were made with the Chi-Square test and Fisher's Exact test. The results were evaluated within the 95% confidence interval and p values <0.05 were considered significant. Bonferroni correction was made where necessary.

Results

The average age of the patients was 54.5±18.5 (range: 17-93) and 398 (74.1%) were male. 52.9% of the patients were admitted between April and September (Table 1).

77.3% of the samples were sputum and 15.8% were bronchoalveolar lavage. 474 (88.3%) of the isolates were M. tuberculosis. 49% of the samples were positive with the AFS method, 96.5% with MGIT, and 84.5% with LJ medium. Resistance rates in isolates were 10.6% for isoniazid; rifampicin 2.8%; ethambutol 1.1%; to streptomycin was 7.0%. All isolates resistant to rifampicin were also resistant to isoniazid. The rate of multidrug-resistant isolates was found to be 2.8%. The single drug resistance rate was found to be 14.0% (Table 1).

AFS and culture results by year are shown in Table 2. When the resistance rates were examined, it was determined that the highest resistance rates in all four antituberculosis drugs belonged to 2018. Rifampicin (5.8% vs. 0.6%; p=0.002), ethambutol (2.4% vs. 0%; p=0.039), and streptomycin (9.3% vs. 4.3%; p=0.048). It was determined that the resistance rates before the pandemic were significantly higher than during the pandemic period. Additionally, no resistance was observed to ethambutol during and after the pandemic, and to rifampicin after the pandemic (Table 2).

AFS and culture results and resistance rate distributions according to periods during the year are given in Table 3. Comparisons of AFS, MGIT, and LJ medium results are shown in Table 4. The sensitivity of the AFS method compared to the MGIT was 53.4%; Its sensitivity was found to be 58.7% compared to the LJ medium. Among the samples within the scope of the study, the compatibility of MGIT and LJ media in terms of positive cultures was seen in 80.9% (372/460) of the samples. It was observed that there was no growth in the LJ medium in 72 samples in which growth was detected by MGIT, and there was no growth in the MGIT in 15 samples in which growth was detected in the LJ medium (Table 4).

Table 1. Distributions according to variables.

	n	%
n	537	100
Gender		
Erkek	398	74.1
Kadın	139	25.9
Year		
2018	110	20.5
2019	89	16.5
2020	89	16.5
2021	76	14.2
2022	90	16.8
2023	83	15.5
Period		
April-September	284	52.9
October-March	253	47.1
Sample		
Sputum	415	77.3
Bronchoalveolar lavage	85	15.8
Pleural fluid	18	3.4
Wound	10	1.9
Urine	4	0.7
fasting gastric fluid	4	0.7
Cerebrospinal fluid	1	0.2
Type		
Mycobacterium tuberculosis complex	474	88.3
Non-tuberculous Mycobacterium	63	11.7
AFS		
Negative	274	51.0
Positive	263	49.0
1+	36	6.7
2+	89	16.6
3+	62	11.5
4+	76	14.2
MGIT		
Negative	17	3.5
Positive	472	96.5
LJ		
Negative	74	15.5
Positive	404	84.5
1+	165	34.6
2+	69	14.4
3+	69	14.4
4+	101	21.1
Resistance rates		
Isoniazid	49	10.6
Rifampicin	13	2.8
Ethambutol	5	1.1
Streptomycin	32	7.0
Single drug resistance	65	14.0
Multidrug resistance	13	2.8

AFS: Acid fast stain, MGIT: Mycobacteria Growth Indicator Tube, LJ: Löwenstein Jensen

Considering the drug resistance of the strains growing in the LJ culture, Isoniacid was the most resistant anti-tuberculous drug. Resistance rates of isolates according to AFS and LJ results are shown in Table 5.

Discussion

As in all other infection cases, the increase in resistance rates in tuberculosis cases causes difficulties in treatment management and increases the possibility of morbidity and complications in patients (11-14). In this study, the current status of the resistance pattern in tuberculosis isolates is shown.

It has been stated that men may be at higher risk in terms of clinical and prognosis in tuberculosis cases (15). In our study, it was determined that 74.1% of the patients with positive tuberculosis cultures were male. This finding shows that there is a male predominance in ¾ of the cases. This may be related to the fact that men constitute the population working in crowded environments.

In our study, 88.3% of the isolates were found to be M. tuberculosis complex. This finding shows that non-tuberculous mycobacteria grow in approximately 10% of tuberculosis cultures that show growth and that these factors play an important role in suspected tuberculosis cases.

In our study, it was found that 52.9% of the patients applied between April and September. Additionally, no significant difference was detected in terms of culture and resistance rate distributions between periods. While the number of cases is expected to increase in cold months, this finding shows that the distribution of cases is similar in hot and cold months.

Alışkan et al. (16) reported that the sensitivity of the AFS method was 50% and the sensitivity of the LJ was 80% when the MGIT method was taken as a reference. Cases with positive results in at least one of the AFS or culture methods were included in our study. Accordingly, 49% of the samples were positive with the AFS method, 96.5% with MGIT medium, and 84.5% with LJ medium. The study also found that the sensitivity of the AFS method compared to the MGIT medium was 53.4%; Its sensitivity was found to be 58.7% compared to the LJ medium. These findings show that MGIT medium has a much better performance than LJ medium and AFS in detecting the agent, and AFS can detect approximately half of these cases. Among the samples within the scope of the study (ignoring and not including culture-negative ones), the compatibility of MGIT and LJ media was observed in 80.9%

Table 2. AFS, culture and sensitivity test results by years.

	AFS, positive		MGIT positive		LJ positive			
	n	%	n	%	n	%		
2018	62	56.4	99	93.4	62	91.6		
2019	41	46.1	83	97.6	41	85.7		
2020	47	52.8	74	96.1	47	82.7		
2021	40	52.6	67	94.4	40	84.1		
2022	33	36.7	67	98.5	33	77.9		
2023	40	48.2	82	100	40	81.3		
p-value	0.105		0.145		0.205			
	Isoniazid resistant		Rifampicin resistant (MDR)		Ethambutol resistant		Streptomycin resistant	
	n	%	n	%	n	%	n	%
2018	15	14.6	8	7.8	3	2.9	12	11.8
2019	7	8.1	3	3.5	1	1.2	5	5.68
2020	8	10.3	1	1.4	1	1.2	3	3.8
2021	7	10.6	0	0.0	0	0	4	8.6
2022	9	12.5	1	1.4	0	0	6	6.7
2023	3	5.1	0	0	0	0	2	3.6
p-value	0.487		0.014		0.374		0.28	
Before the pandemic1	25	12.1	12	5.8	5	2.4	19	9.3
Pandemic2	14	9	1	0.6	0	0	7	4.3
Post pandemic3	10	9.8	0	0	0	0	6	6.2
p-value1-2	0.199		0.005		0.039		0.048	
p-value1,2,3	0.601		0.002		0.045		0.203	

AFS: Acid fast stain, MGIT: Mycobacteria Growth Indicator Tube, LJ: Löwenstein Jensen

Table 3. AFS, culture and sensitivity test results according to periods

	AFS, positive		MGIT positive		LJ positive			
	n	%	n	%	n	%		
April-September	126	44.4	253	97.7	207	83.1		
October-March	137	54.2	219	95.2	197	86.0		
	0.024		0.137		0.382			
	Isoniazid resistant		Rifampicin resistant (MDR)		Ethambutol resistant		Streptomycin resistant	
	n	%	N	%	n	%	n	%
April-September	24	9.7	7	2.8	3	1.2	14	5.8
October-March	25	11.5	6	2.8	2	0.9	18	8.3
p-value	0.528		0.964		>0.999		0.291	

AFS: Acid fast stain, MGIT: Mycobacteria Growth Indicator Tube, LJ: Löwenstein Jensen

of the samples. In addition, it was observed that there was no growth in the LJ medium in 72 samples in which growth was detected by MGIT, and there was no growth in the MGIT medium in 15 samples in which growth was detected in the LJ medium. These findings show that many cases may be missed if only one of the culture methods is used.

Dundar et al. (17) in their study in 2008, found the rate of single-drug resistance in tuberculosis cases to be 21% and the rate of multi-drug resistance to be 5%. Alışkan et al. (16) reported sensitivity rates to primary tuberculosis drugs between 0.5-3.2% in their study in 2013. Tanrıverdi Çaycı et al. (18) in their study in 2017, found the resistance rate to Streptomycin to be 14.1%, and the resistance rates to other primary anti-tuberculosis drugs to be between 2.3-3.8%. Terzi et al. (19) in their study in 2017, found the single drug resistance rate to be 14.8%; They reported the multi-resistance rate as 4.1%. In our study, resistance rates in isolates were 10.6% for isoniazid; rifampicin 2.8%; ethambutol 1.1%; and streptomycin was found to be 7.0%. All isolates that were resistant to rifampicin were also found to be resistant to isoniazid, and therefore the rate of multidrug-resistant isolates was found to be 2.8%. The single drug resistance rate was found to be 14%. These findings show that the resistance rates to isoniazid and streptomycin in mycobacteria are higher and are around 10%, and the resistance rates are generally similar to other studies conducted in our country.

Table 4. Comparisons between AFS, MGIT and LJ methods results.

		MGIT				
		Negative		Positive		Total
		n	%	n	%	N
AFS	Negative	14	82.4	220	46.6	234
	Positive	3	17.6	252	53.4	255
	Total	17	100	472	100	489
		LJ				
		Negative		Positive		Total
		n	%	n	%	n
AFS	Negative	69	93.2	167	41.3	236
	Positive	5	6.8	237	58.7	242
	Total	74	100	404	100	478
		MIGIT				
		Negative		Positive		Total
		n	%	n	%	n
LJ	Negative	1	6.3	72	16.2	73
	Positive	15	93.7	372	83.8	387
	Total	16	100	444	100	460

AFS: Acid fast stain, MGIT: Mycobacteria Growth Indicator Tube, LJ: Löwenstein Jensen

Table 5. Resistance rates of isolates according to AFS and LJ results.

	Total	Isoniazid resistant		Rifampicin resistant (MDR)		Etham-butol resistant		Strepto-mycin resistant	
AFS	n	n	%	n	%	n	%	n	%
Negative	218	20	9.2	4	1.8	3	1.4	10	4.7
1+	34	3	8.8	1	2.9	0	0	3	8.8
2+	80	9	11.3	6	7.5	2	2.5	10	12.7
3+	58	7	12.1	1	1.7	0	0	3	5.3
4+	74	10	13.5	1	1.4	0	0	6	8.3
Total	464	49		13		5		32	
LJ	n	n	%	n	%	n	%	n	%
Negative	54	3	5.6	1	1.9	2	3.8	4	7.5
1+	154	14	9.1	2	1.3	1	0.7	7	4.6
2+	64	11	17.2	4	6.3	0	0	6	9.5
3+	68	10	14.7	4	5.9	1	1.5	9	13.2
4+	98	8	8.2	2	2	1	1.1	5	5.3
Total	438	46	10.5	13	3	5	1.2	31	7.2

AFS: Acid fast stain, MGIT: Mycobacteria Growth Indicator Tube, LJ: Löwenstein Jensen

It was determined that there was a significant increase in antibiotic resistance rates in many bacterial factors in general during the pandemic period, and it was stated that this was associated with the intense use of broad-spectrum antibiotics due to the Coronavirus-2019 (COVID-19) pandemic (20,21). It has been reported that resistance rates in tuberculosis strains generally increased during the COVID-19 pandemic (22). However, in our study, only primary antituberculosis drugs were evaluated and it was observed that the resistance rate of the isolates decreased during the pandemic period. Alao et al. (23) reported in their study in 2022 that, similar to our study, the rifampicin resistance rate in tuberculosis isolates decreased from 9.5% before the COVID-19 pandemic to 2.5% during the pandemic, and that the resistance rate in tuberculosis cases decreased significantly during the pandemic. Interestingly, in our study, it was found that the highest resistance rates for all four anti-tuberculosis drugs belonged to 2018, and resistance rates decreased especially in the years after 2019. The study also found that resistance rates to rifampicin (5.8% vs. 0.6%), ethambutol (2.4% vs. 0%), and streptomycin (9.3% vs. 4.3%) were significantly higher before the pandemic than during the pandemic period. In addition, no resistance was observed to ethambutol during and after the pandemic, and to rifampicin after the pandemic. The decrease in these resistance rates may be related to the social measures taken due to the COVID-19 pandemic, which was effective all over the world between 2020 and 2022. During the pandemic period, situations such as the spread of resistant tuberculosis cases or the acquisition of resistance of strains occurred due to various measures taken such as social distancing, hygiene, curfews, reduced and diluted working hours in schools and workplaces, reduction or postponement of procedures such as routine outpatient clinics, services, and surgeries in hospitals. may be restricted. Since primary anti-tuberculosis drugs are different from the antibiotics commonly used in other infections and COVID-19, the increase in resistance seen in different infectious agents throughout the world during the pandemic may not have been seen in tuberculosis causative strains. However, there are also publications showing that the sensitivity to antibiotics in bacterial infection agents in the post-COVID-19 period has increased significantly compared to the pre-COVID-19 period (24). We believe that more detailed studies are needed on this subject.

Since our study focused specifically on the temporal change of resistance patterns, cases that were positive in at least one of the AFS and culture methods were evaluated, and therefore, one of the limitations is that specificity values could not be determined. Additionally, the low number of ethambutol-resistant isolates in the study may have reduced the significance level of the statistical analysis in terms of comparison between the pre-pandemic and the pandemic period.

Conclusion

Our study is one of the rare studies that examine the relationship between the resistance to primary antituberculosis drugs and the pandemic period in tuberculosis cases. The findings obtained from our study showed that the resistance rates to isoniazid in M. tuberculosis complex isolates were around 10% and that the general resistance rates to primary anti-tuberculosis drugs decreased significantly during the pandemic period.

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Disclosure statement

The authors declare that they have no conflict of interest

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