

Comparison of the Mycobacterium Growth Indicator Tube Method and the Method of Proportion for Drug Susceptibility Testing of Mycobacterium Tuberculosis

Mycobacterium Tuberculosis Kökenlerinin İlaç Duyarlılığının Belirlenmesinde Mycobacterium Growth Indicator Tube Sistemi ve Proporsiyon Yönteminin Karşılaştırılması

Ayşe Esin Aktas¹, Nimet Yigit², Ahmet Ayyıldız¹, Ayşe Bastopcu¹

¹Department of Medical Microbiology, Ataturk University Faculty of Medicine, Erzurum, Turkey

²Department of Medical Laboratory, Ataturk University, Health Services Vocational School, Erzurum, Turkey

Abstract

Objective: Tuberculosis is an important public health problem in developed and, especially, developing countries. The incidence of multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB) has increased in recent years. Mycobacterial culture and susceptibility testing must be rapidly concluded for effective treatment and control of the disease. The present study evaluated the reliability of the Mycobacterium Growth Indicator Tube (MGIT) method for testing the susceptibility of *M. tuberculosis* to four first-line antimicrobial drugs by comparing MGIT results to those obtained by the method of proportion (MOP), which served as the reference method.

Materials and Methods: A total of 60 clinical isolates (28 sputum, 7 bronchoalveolar lavage, 7 cerebrospinal fluid, 3 gastric aspirates, 5 urine, 4 pleural fluid and 6 other specimens) of *M. tuberculosis* were tested for susceptibility to streptomycin (SM), isoniazid (INH), ethambutol (EMB) and rifampin (RIF). MOP was carried out according to National Committee for Clinical Laboratory Standards (NCCLS) on Löwenstein-Jensen medium. MGIT susceptibility testing was performed according to the protocol provided by the manufacturer.

Results: Resistance was detected in 18.3% and 16.7% of the isolates for INH, 13.3% and 10.0% for RIF, 16.7% and 11.7% for SM and 6.7% and 8.3% for EMB by MOP and MGIT, respectively.

Conclusion: MOP remains the method of choice, however, the correlation between MOP and MGIT suggested that MGIT can also be used routinely and that it is a reliable method for testing susceptibility of *M. tuberculosis* strains to first-line anti-tuberculosis drugs.

Key Words: MGIT, *M. tuberculosis*, susceptibility

Özet

Amaç: Tuberküloz gelişmiş ve özellikle gelişmekte olan ülkeler için önemli bir halk sağlığı problemidir. Çoklu ilaç direnci gösteren *Mycobacterium tuberculosis* kökenlerinin sayısı son yıllarda artış göstermektedir. Bu hastalığın etkili tedavisi ve kontrol altına alınmasında mikrobiyolojik kültür ve duyarlılık yöntemlerinin hızla sonuçlandırılması zorunludur. Bu çalışmada, *M. tuberculosis* kökenlerinin birinci seçenek anti-tuberküloz ilaçlara karşı duyarlılığı Growth Indicator Tube (MGIT) ve referans metot olarak kabul edilen proporsiyon yöntemi ile araştırılmıştır.

Gereç ve Yöntem: Değişik klinik örneklerden izole edilen 60 *M. tuberculosis* kökeninin (28 balgam, 7 BAL, 7 BOS, 3 açlık mide suyu, 5 idrar, 4 pleval sıvı ve 6 diğer örnekler) dört birinci seçenek anti-tuberküloz ilaç (streptomisin (SM), izoniazid (INH), etambutol (EMB) and rifampisin (RIF)) karşı duyarlılığı araştırıldı. Proporsiyon metodu NCCLS standartlarına göre Löwenstein-Jensen besiyerinde uygulandı. MGIT sistemi ile duyarlılık üretici firma önerileri doğrultusunda çalışıldı.

Bulgular: İki yöntem ile yapılan duyarlılık çalışmasında kökenlerin ilaçlara karşı duyarlılığı iki yöntem (MOP ve MGIT) için sırasıyla; INH direnci %18,3 ve %16,7, RIF direnci %13,3 ve %10,0, SM direnci %16,7 ve %11,7, EMB direnci %6,7 ve %8,3 olarak belirlendi.

Sonuç: Proporsiyon metodu standart yöntem olmakla birlikte, MGIT ve Proporsiyon yöntemi arasında direnç oranları açısından uyum belirlenmiştir. MGIT sistemi *M. tuberculosis* kökenlerinin birinci seçenek anti-tuberküloz ilaçlara karşı duyarlılıklarının belirlenmesinde güvenilir bir yöntemdir ve rutin laboratuarda kullanılabilir.

Anahtar Kelimeler: MGIT, *M. tuberculosis*, duyarlılık

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Correspondence to: Ayşe Esin Aktas, Department of Microbiology and Clinical Microbiology, Ataturk University Faculty of Medicine, 25100, Erzurum, Turkey Phone: +90 442 233 11 11 e-mail: aeaktas@hotmail.com

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Introduction

An ancient disease, tuberculosis remains one of the major causes of disability and death worldwide. The incidence of tuberculosis has been increasing dramatically throughout the world in the last decade. Control of the disease requires rapid identification of patients and prompt implementation of drug therapy. Furthermore, treatment and control of tuberculosis has been increasingly complicated by the emergence of drug resistance [1-3].

Drug-resistant *Mycobacterium tuberculosis* strains represent a serious public health problem. Resistance to the four primary drugs-INH, SM, EMB and RIF-makes tuberculosis difficult to treat. The emergence of MDR-TB within the last decade has posed an exceptionally severe threat and underscores the significance of rapid antimicrobial susceptibility testing of MDR-TB strains to effectively treat patients [4-6].

Among the methods that are used for drug susceptibility testing, MOP is universally accepted as the "gold standard" (NCCLS, 2000) [7]. However, it generally requires 3 to 4 weeks to obtain a final result. The performance standard of a new system should be comparable with that of the BACTEC 460 TB technology, in addition to carrying a low risk of needle punctures and disposal of radioactive waste. Recently, the non-radiometric, fully automated Bactec MGIT 960 system (MGIT) (Becton Dickinson, Sparks, MD) technology has provided a new step forward, as it allows continuous monitoring of positive fluorescence, which is based on bacterial growth. This MGIT system has been proposed as a method for determining susceptibility of *M. tuberculosis* strains to the first-line anti-tuberculosis drugs: INH, RIF, EMB and SM [4-6, 8-10].

In this study, we evaluated, under the routine conditions of a clinical microbiology laboratory, the reliability of the MGIT system for susceptibility testing of 60 clinical *M. tuberculosis* isolates to four first-line anti-tuberculosis agents: INH, RIF, EMB and SM. The results were compared to those obtained by the conventional MOP using Löwenstein-Jensen (LJ) medium, which is proposed as the "gold standard".

Materials and Methods

Strains and Specimens

Sixty strains of *M. tuberculosis* were isolated from various clinical specimens. All specimens were processed following the standard NALC-NaOH method for digestion, decontamination, and concentration. The concentrated sediment was suspended in approximately 2 to 3 mL phosphate buffer (pH 6.8) and mixed thoroughly. A smear was prepared for acid-fast staining, and culture media were inoculated according to the laboratory standard procedure for primary isolation. All clinical isolates were grown on LJ medium slants

and identified as *M. tuberculosis* according to growth rates, pigmentation, properties of colonies, the presence of acid-fast bacilli, nitrate reduction, niacin accumulation and heat stable catalase tests. Sixty isolates were tested by the MOP and MGIT system to determine susceptibility to four first-line anti-tuberculosis agents: INH, RIF, EMB and SM. All procedures in the experimental protocol were approved by the Ethics Committee of Medical Faculty.

Method of Proportion

Each strain was tested for susceptibility to INH, RIF, EMB and SM using MOP on LJ medium. LJ tubes containing an anti-tuberculosis agent and a control (anti-tuberculosis agent-free) were provided by Salubris AŞ, Istanbul. Each of two dilutions (10^{-3} and 10^{-5} of a 10^7 - 10^8 cfu/mL suspension) was inoculated into three control LJ tubes and into one tube containing either 4 µg/L SM, 0.2 or 1 µg/L INH, 40 µg/L RIF, or 2 µg/L EMB. Colonies were counted after 21, 28 and 42 days of incubation at 37°C. The criterion for resistance was 1% or more colonies in the drug-containing medium when compared to the number of colonies developing in the drug-free medium [1, 3, 7-9, 11].

Mycobacterial Growth Indicator Tube-Antibiotic Susceptibility Test (MGIT-AST): MGIT-AST (Becton Dickinson, Sparks, MD, ABD) was performed as recommended by the manufacturer. MGIT tubes were prepared by adding 0.8 mL of oleic acid-albumin-dextrose-catalase in each of the five tubes that together constituted an MGIT-AST kit: growth control, INH, SM, EMB and RIF. Antibiotics were added at a volume of 100 µL to stock solutions. Final concentrations were 1.0 µg/L for SM, 0.1 µg/L for INH, 1 µg/L for RIF, and 5.0 µg/L for EMB. A 1:5 sterile saline concentration of McFarland 0.5 standard suspension was inoculated into each tube at a volume of 0.5 mL. Drug susceptibility testing sets were entered into the MGIT instrument and continuously monitored until a susceptible or resistant result was obtained. The drug susceptibility testing set results was reported by the instrument (determined by the software algorithms, once the GC becomes positive) [2, 4-6].

Table 1. Type of specimens

Type of specimens	Number of specimens
Sputum	28
Bronchoalveolar lavage	7
Cerebrospinal fluid	7
Gastric aspirate	3
Urine	5
Pleural fluid	4
Other	6
Total	60

Table 2. Comparison of susceptibilities of 60 *M. tuberculosis* strains to INH, RIF, EMB and SM

Number of strains		Susceptibility by the indicated test							
		MOP				MGIT			
no	%	INH	RIF	SM	EMB	INH	RIF	SM	EMB
45	75.0	S	S	S	S	S	S	S	S
2	3.3	S	S	R	S	S	S	S	S
2	3.3	R	R	R	S	S	S	S	S
1	1.6	R	S	S	S	S	S	R	S
1	1.6	R	R	R	S	R	R	S	R
2	3.3	R	R	R	R	R	R	R	R
1	1.6	S	R	S	S	R	S	S	R
1	1.6	R	R	S	S	R	S	S	S
1	1.6	S	S	R	R	R	S	R	R
1	1.6	R	S	R	S	R	S	R	S
1	1.6	R	R	R	S	R	R	R	S
1	1.6	R	R	R	R	R	R	R	S
1	1.6	R	S	S	S	R	R	S	S

S: susceptible; R: resistant; MOP: method of proportion; MGIT: mycobacterium growth indicator tube
INH: isoniazid; RIF: rifampin; SM: streptomycin; EMB: ethambutol

Statistical Analysis

The χ^2 test (Spearman's correlation test) was used for comparing susceptibility results of MGIT with MOP.

Results

Sixty strains of *M. tuberculosis* were isolated from various clinical specimens (Table 1).

Sixty strains of *M. tuberculosis* were studied for susceptibility to all four anti-tuberculosis agents. Using MOP on LJ medium, we found that eleven strains were resistant to at least INH, 8 strains were resistant to RIF, 10 strains were resistant to SM, 4 strains were resistant to EMB, and 6 strains were MDR-TB (resistant to INH and RIF). Using MGIT, we found that ten strains were resistant to at least INH, 6 strains were resistant to RIF, 7 strains were resistant to SM, 5 strains were resistant to EMB, and 5 strains were MDR-TB (Table 2).

When compared, the results of susceptibility testing in this study detected resistance in 18.3% and 16.7% of the isolates for INH, 13.3% and 10.0% for RIF, 16.7% and 11.7% for SM and 6.7% and 8.3% for EMB by MOP and MGIT, respectively (Table 3). The χ^2 test (Spearman's correlation test), which was used for comparing susceptibility results of the BACTEC MGIT 960 with MOP, found no statistically significant difference between the means ($\chi^2 = 0.568$, $p > 0.05$).

Discussion

The importance of rapid availability of *M. tuberculosis* drug resistance results is universally acknowledged. Detection of resistance at the genetic level by the presence of mutations in certain loci, although promising, is still far from finding its place among the techniques of diagnostic mycobacteriology. Furthermore, this approach is hindered by the presence of multiple resistance mechanisms for the majority of anti-mycobacterial drugs [3].

Phenotypic susceptibility testing, therefore, remains the method of choice. Standard methods for determining the drug susceptibility of *M. tuberculosis*, such as MOP on Middlebrook 7H10 agar and LJ, require 3 to 4 weeks to complete. Meanwhile, patients with resistant organisms receive treatment with an ineffective drug regimen. This delay may lead to additional drug resistance and failure to control the disease. Given the increasing rate of TB, there is a need to develop more rapid and efficient methods for mycobacterial testing (diagnosis, susceptibility testing). Of the commonly used methods, only the BACTEC 460 system can provide results within 30 days. Unfortunately, both the cost and the management of radioactive waste limit the use of the BACTEC system. MGIT, a broth-based non-radiometric system is an alternative to the radiometric system. By adding *M. tuberculosis* suspension to a drug-containing MGIT tubes, an anti-mycobacterial susceptibility test (AST) can be

Table 3. The Results of Susceptibility Testing by Method of proportion (MOP) and Mycobacterium Growth Indicator Tube (MGIT)

Drug	MOP				MGIT			
	Resistant		Susceptible		Resistant		Susceptible	
	no	%	no	%	no	%	no	%
Isoniazid (INH)	11	18.3	49	81.7	10	16.7	50	83.3
Rifampin (RIF)	8	13.3	52	86.7	6	10.0	54	90.0
Streptomycin (SM)	10	16.7	50	83.3	7	11.7	53	88.8
Ethambutol (EMB)	4	6.7	56	93.3	5	8.3	55	91.7
MOP: method of proportion; MGIT: mycobacterium growth indicator tube								

performed. MGIT-AST is a new test that is based on critical concentrations and developed in liquid media. MGIT-AST results can be obtained in less than 14 days. Furthermore, the handling of MGIT-AST is easy and secure [1-6, 8, 9, 11-14]. In this study, we evaluated the reliability of MGIT in comparison with the reference method (MOP on LJ medium) using 60 strains of *M. tuberculosis*.

When compared, the results of susceptibility testing in this study detected resistance in 18.3% and 16.7% of the isolates for INH, 13.3% and 10.0% for RIF, 16.7% and 11.7% for SM and 6.7% and 8.3% for EMB by MOP and MGIT, respectively. The χ^2 test (Spearman's correlation test), which was used for comparing susceptibility results of the BACTEC MGIT 960 with MOP, found no statistically significant difference between the means $\chi^2 = 0.568$, $p > 0.05$.

The performances (sensitivity, specificity, rapidity) of MGIT and MOP seemed comparable in several studies conducted recently. Birinci et al. [15] found a better correlation between MGIT and MOP on LJ medium. Said et al. [16] reported that the MGIT 960 system performed well for SM and EMB when compared to MOP (sensitivity in detecting resistance 95% and 92%, respectively). Safwat et al. [11] reported that the total efficiency of MGIT was 82% for susceptibility testing to SM, while it was 96% for INH, 90% for RIF and 80% for EMB. Safwat et al. [11] suggested that the MGIT system is not yet sufficiently accurate to warrant the elimination of LJ media for susceptibility testing to first line anti-tuberculosis drugs. Cambau et al. [1] found that the concordance between the two methods was 95.3-100% when considering the results for each drug/strain combination separately. Kontos et al. [9] reported that the overall agreement between MGIT and MOP was 99.1%. High sensitivity (the ability to detect true resistance) and specificity (the ability to detect true susceptibility) values of the MGIT system were demonstrated by this study for susceptibility testing of *M. tuberculosis*. Aktas et al. [17] reported the concordance between the MGIT and MOP susceptibility tests for first-line drugs as 100% and 90%; 98% and 90% for INH; 100% and 90% for RIF; and 98% and 94%

for EMB, respectively. Another study found INH and RIF with 97.1% and 100% concordance, and SM and EMB with 91.4% and 94.2% concordance between the two methods, respectively [14].

The emergence of MDR-TB and, more recently, of extensively drug-resistant (XDR-TB) is a real threat to TB control and elimination. Over 400,000 new cases of MDR-TB occur each year, and although the true incidence is currently unknown, XDR cases are recognized in every setting where there has been the capacity to detect them. The long-term vision for the full control of MDR-TB requires the scaling-up of culture and drug-susceptibility testing capacity, which is very limited in disease-endemic countries, and the expanded use of high-technology assays for rapid determination of resistance [18].

In our study, 60 strains of *M. tuberculosis* were evaluated for susceptibility to all four anti-tuberculosis agents. Using MOP on LJ medium, we found that eleven strains were resistant to at least INH, 8 strains were resistant to RIF, 10 strains were resistant to SM, 4 strains were resistant to EMB, and 6 strains were MDR-TB. Using MGIT, we found that ten strains were resistant to at least INH, 6 strains were resistant to RIF, 7 strains were resistant to SM, 5 strains were resistant to EMB, and 5 strains were MDR-TB.

Surveillance of drug-resistance has not been performed at the national level in Turkey, however, local studies have reported various ranges of MDR-TB. Gonlugur et al. [19] reported resistance rates of 17.7% for INH, 11.4% for SM, 4.4% for RIF, 5.1% for EMB and 3.8% for MDR-TB. Ucar et al. [20] reported resistance rates in seven different regions of Turkey between 2003 and 2006 as 12.3%, 10.1%, 6% and 15.8% for INH, RIF, EMB and SM, respectively. The MDR-TB rate was 10% for this 4-year period in the same study.

In another study, Saygan et al. [21] detected resistance rates in three provinces of Turkey as 13.3% for INH and RIF (67 strains of each), 9.1% for SM, 3.4% for EMB, and 7.9% for MDR-TB. The highest resistance rate was detected in isolates sent from Bursa province (located in northwestern Turkey). In the same study, MDR-TB rates (18.8% and 10.6%, respectively)

were detected in the strains sent from Elazig and Van provinces (both located in eastern Turkey). Tas et al. [22] detected resistance rates in young soldiers (data from 14 military hospitals in Turkey) as 12.5% (n=13), 7.7% (n=8), 5.8% (n=6) and 0.9% (n=1) for INH, RIF, EMB and SM, respectively. In the same study, the MDR-TB rate was 5.8% (n=6). Aydın et al. [23] reported resistance rates of 6.1% for INH, 0.5% for RIF, 5.2% for SM, and 2.4% for EMB, and 4.8% for MDR-TB. Yurtsever et al. [24] detected *M. tuberculosis* resistance rates of 19.7%, 42%, 40.8% and 18% for SM, INH, RIF and EMB, respectively.

In our study, resistance to INH was detected in 18.3% and 16.7% of the isolates for INH, 13.3% and 10.0% for RIF, 16.7% and 11.7% for SM and 6.7% and 8.3% for EMB by MOP and MGIT, respectively. The MDR-TB rates detected in our study were 10% (6 strains) using MOP and 8.3% (5 strains) using MGIT.

In conclusion, our results showed that there were no statistically significant differences in susceptibility testing results between MGIT and MOP. MGIT-AST is a reliable method that produced results congruent with those obtained by the proportion method on LJ medium for routine drug susceptibility testing of *M. tuberculosis*.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ethics Committee of Ataturk University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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References

1. Cambau E, Truffot-Pernot C, Boulahbal F, et al. Mycobacterial Growth Indicator Tube Versus The Proportion Method on Löweinstein-Jensen Medium for Antibiotic Susceptibility Testing of Mycobacterium tuberculosis. Eur J Clin Microbiol Infect Dis 2000; 19: 938-42. [\[CrossRef\]](#)
2. Siddiqi S, Ahmed A, Asif S, et al. Direct Drug Susceptibility Testing of Mycobacterium tuberculosis for Rapid Detection of Multidrug Resistance Using The Bactec MGIT 960 System: A Multicenter Study. J of Clin Microbiol 2012; 50: 435-40. [\[CrossRef\]](#)
3. Tortoli E, Benedetti M, Fontanelli A, et al. Evaluation of Automated BACTEC MGIT 960 System for Testing Susceptibility of Mycobacterium tuberculosis to Four Major Anti-tuberculous Drugs: Comparison With The Radiometric BACTEC 460 TB Method and The Agar Plate Method of Proportion. J of Clin Microbiol 2002; 40: 607-10. [\[CrossRef\]](#)
4. Bemer P, Palicova F, Rüscher-Gerdes S, et al. Multicenter Evaluation of Fully Automated BACTEC Mycobacteria Growth Indicator Tube 960 System for Susceptibility Testing Of Mycobacterium tuberculosis. J of Clin Microbiol 2002; 40: 150-4. [\[CrossRef\]](#)
5. Scarparo C, Ricordi P, Ruggiero G, et al. Evaluation of Fully Automated BACTEC MGIT 960 System for Testing Susceptibility of Mycobacterium tuberculosis to Pyrazinamide, Streptomycin, Isoniazid, Rifampin, and Ethambutol and Comparison With Radiometric BACTEC 460 TB Method. J of Clin Microbiol 2004; 42: 1109-14. [\[CrossRef\]](#)
6. Rüscher-Gerdes S, Pfyffer GE, Casal M, et al. Multicenter Laboratory Validation of The BACTEC MGIT 960 Technique for Testing Susceptibilities to Classical Second-Line Drugs And Newer Antimicrobials. J of Clin Microbiol 2006; 44: 688-92. [\[CrossRef\]](#)
7. National Committee for Clinical Laboratory Standards, 2000. Susceptibility Testing of Mycobacteria, Nocardia, and Other Aerobic Actinomycetes. Tentative Standard M24-T2, 2nd.ed. NCCLS Wayne, P.A.
8. Varma M, Kumar S, Kumar A, et al. Comparison of E-Test and Agar Proportion Method of Testing Drug Susceptibility of M. tuberculosis. Ind J Tub 2002; 217-20.
9. Kontos, Kontos F, Maniati M, Costopoulos C, et al. Evaluation of The Fully Automated Bactec MGIT 960 System for The Susceptibility Testing of Mycobacterium tuberculosis to First-Line Drugs: A Multicenter Study. J Microbiol Methods 2004; 56: 291-4. [\[CrossRef\]](#)
10. Sanic A, Gunaydin M, Coban AY, et al. A Comparison of The E-Test and Proportion Methods for Susceptibility Testing of Mycobacterium tuberculosis. J Chemother 2000; 12: 491-4. [\[CrossRef\]](#)
11. Safwat TM, Elmasry AA, Salem HM, et al. BACTEC MGIT 960 System in The Susceptibility Testing of Mycobacterium tuberculosis to The Four First-Line Anti-Tuberculous Drugs. Comparison With Löweinstein-Jensen. Egyptian Journal of Bronchology 2012; 6: 44-50.
12. Springer B, Lucke K, Calligaris-Maibach R, et al. Quantitative Drug Susceptibility Testing of Mycobacterium tuberculosis by Use of MGIT 960 and Epicenter Instrumentation. J of Clin Microbiol 2009; 47: 1773-80. [\[CrossRef\]](#)
13. Yew WW, Tong SCW, Lui KS, et al. Comparison of MB/Bact System and Agar Proportion Method in Drug Susceptibility Testing of Mycobacterium tuberculosis. Diagn Microbiol Infect Dis 2001; 39: 229-32. [\[CrossRef\]](#)
14. Macando EA, Ba F, Gaye-Diallo, et al. Rapid Susceptibility Testing of Mycobacterium tuberculosis by The Mycobacteria Growth Indicator Tube (MGIT AST SIRE). Clin Microbiol Infect 2006; 6: 361-5. [\[CrossRef\]](#)
15. Birinci A, Coban AY, Ekinci B, et al. Comparison of the Proportion Method With Mycobacteria Growth Indicator Tube and E-Test

- for Susceptibility Testing of Mycobacterium tuberculosis. Mem Ins Oswaldo Cruz 2002; 97: 351-2. [\[CrossRef\]](#)
16. Said HM, Kock MM, Ismail NA, et al. Comparison Between The BACTEC MGIT 960 System and The Agar Proportion Method for Susceptibility Testing of Multidrug Resistant Tuberculosis Strains In A High Burden Setting of South Africa. BMC Infect Dis 2012; 12: 369. [\[CrossRef\]](#)
 17. Aktas E, Ozkutuk N, Surucuoglu S, et al. Mycobacterium tuberculosis'in Birinci Seçenek Antitüberküloz İlaçlara Karşı Duyarlılığının Belirlenmesinde Dört Farklı Yöntemin Karşılaştırılması. Enfeksiyon Derg 2008; 22: 43-8.
 18. Matteelli A, Migliori GB, Cirillo D, et al. Multidrug-Resistant and Extensively Drug-Resistant Mycobacterium tuberculosis: Epidemiology and Control. Expert Rev of Anti-Infect Ther 2007; 5: 857-71. [\[CrossRef\]](#)
 19. Gönlgür U, Bakici MZ, Gönlgür TE, et al. Resistance Rates to Antituberculous Drugs In Sivas Province. Mikrobiyol Bult 2007; 41: 459-63.
 20. Uçar E, Kılıç A, Ceyhan I, et al. Resistance Rates to Major Anti-Tuberculosis Drugs in Mycobacterium tuberculosis Strains Isolated From Seven Different Regions Of Turkey In 2003-2006 Period. Mikrobiyol Bul 2010; 44: 11-9.
 21. Sayğan MB, Ocak F, Cesur S, et al. Susceptibilities of Mycobacterium tuberculosis Strains Collected From Regional Tuberculosis Laboratories to Major Antituberculous Drugs. Mikrobiyol Bult 2007; 41: 403-9.
 22. Taş D, Taşçı C, Demirel E, et al. Tuberculosis Incidence and Primary Drug Resistance Rates in Young Soldiers: Data From 14 Military Hospitals in Turkey. Mikrobiyol Bul 2012; 46: 26-32.
 23. Aydın F, Kaklıkkaya N, Bayramoğlu G, et al. Resistance Rates of Mycobacterium tuberculosis Complex Strains Isolated From Clinical Specimens. Mikrobiyol Bul 2011; 45: 36-42.
 24. Yurtsever SG, Biçmen C, Gündüz AT. Comparison of Proportion Method in Löwenstein-Jensen Medium with The BACTEC 460 TB System for Antimycobacterial Susceptibility Testing of Mycobacterium tuberculosis Isolates. Mikrobiyol Bul 2011; 45: 623-31.