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Susceptibility Testing with the Manual Mycobacteria Growth Indicator Tube (MGIT) and the MGIT 960 System Provides Rapid and Reliable Verification of Multidrug-Resistant Tuberculosis

Kati Ådjers-Koskela† and Marja-Leena Katila*

Department of Clinical Microbiology, Kuopio University Hospital, 70211 Kuopio, Finland

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The objective of the study was to compare the manual Mycobacteria Growth Indicator Tube (MGIT) method and the BACTEC MGIT 960 system to the BACTEC 460 method for susceptibility testing of *Mycobacterium tuberculosis*. The evaluation was based on testing of 36 *M. tuberculosis* strains with various susceptibilities to isoniazid (INH), rifampin (RMP), ethambutol (EMB), and streptomycin (SM). In addition, five of the strains generating discrepant results in testing for EMB were analyzed for heteroresistance. For INH, the susceptibility test results obtained by the MGIT 960 and the manual MGIT systems agreed with the BACTEC 460 results in 94 and 97% of the cases, respectively. The results of susceptibility to RMP were all in agreement. For SM, 78 and 72% of the results obtained by the MGIT 960 and the manual MGIT systems, respectively, agreed with the BACTEC 460 results. In contrast, less than 80% of the results for susceptibility to EMB obtained by the two MGIT methods agreed with the BACTEC 460 results. All five strains analyzed for EMB heteroresistance were found to consist of resistant and susceptible subpopulations. The average turnaround times were 6.4 days for the MGIT 960 system, 6.5 for the manual MGIT system, and 8.7 days for the BACTEC 460 method. Both MGIT methods can be regarded as accurate and rapid alternatives to the BACTEC 460 method for detection of strains resistant to INH and RMP. However, more studies are needed for solving the problems associated with susceptibility testing to EMB and SM.

Emergence of multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis caused by a strain resistant to isoniazid (INH) and rifampin (RMP), is complicating tuberculosis control efforts (11). Consequently, laboratories are challenged to provide rapid antimicrobial susceptibility testing (AST) to ensure effective treatment of tuberculosis, and to prevent further development of drug resistance in the causative strain due to inadequate drug combinations for extended periods of time (15). In the current clinical routine, AST of *Mycobacterium tuberculosis* is performed by either methods using solid media or the radiometric BACTEC 460 method (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.) (5) (see also the Becton Dickinson product and procedure manual MA-0029). The BACTEC 460 provides the best validated rapid approach for AST, but it has some disadvantages, e.g., use of radioactive medium, requirement of needles and syringes in transfer of inocula, and expensive instrumentation (8, 16).

The Mycobacteria Growth Indicator Tube (MGIT), introduced by the same company as a nonradiometric approach for the detection of mycobacteria, has proven both rapid and sensitive (2, 7, 12). The MGIT contains modified Middlebrook 7H9 broth in a tube with a fluorescence-quenching-based oxygen sensor embedded in the bottom of the tube. The level of fluorescence that the tube emits corresponds to the amount of oxygen consumed by organisms in the tube, and it is proportional to the number of bacteria present. The fluorescence can be detected by manual transillumination with a 365-nm UV light, e.g., a Wood's lamp. Preliminary studies have reported that the MGIT method can also be used for AST (4, 12, 13, 14, 18).

An application of the MGIT, the BACTEC MGIT 960 (BD Biosciences, Sparks, Md.) is a fully automated, continuous-monitoring instrument-based system with a capacity to test 960 MGITs simultaneously. The instrument collects fluorescence data from each tube every 60 min, and when a certain increase is detected the instrument indicates the tube as positive. The MGIT 960 has been reported as a sensitive and rapid method for the detection of mycobacteria (6, 9, 10, 17, 19). So far it has been evaluated for AST only in a few studies (1, 3, 16).

In the present study, we evaluated the reliability of the manual MGIT and the MGIT 960 system for susceptibility testing of *M. tuberculosis* to first line drugs. The evaluation was based on testing of a selection of 36 *M. tuberculosis* strains with various susceptibility to first line drugs, distributed for external quality control by the World Health Organization (WHO). The MGIT results were compared to those obtained by the BACTEC 460 method and also to expected results as given by the WHO. Due to a discrepancy in test results for ethambutol (EMB), we additionally tested selected strains for heteroresistance.

MATERIALS AND METHODS

Strains. A selection of 36 *M. tuberculosis* strains with a variety of resistance patterns (Table 1), obtained from the supranational susceptibility reference center (Swedish Institute for Infectious Disease Control, Stockholm, Sweden), belonged to a collection distributed by the WHO as external quality control strains for susceptibility testing. The strains had been stored in Middlebrook 7H9

* Corresponding author. Mailing address: Department of Clinical Microbiology, Kuopio University Hospital, P.O. Box 1777, 70211 Kuopio, Finland. Phone: 358-17-17 3210. Fax: 358-17-17 3202. E-mail: marja-leena.katila@kuh.fi.

† Present address: Finnish Lung Health Association, 00250 Helsinki, Finland.

TABLE 1. Expected susceptibility results and those obtained using BACTEC 460, MGIT 960 and manual MGIT methods

Strain	Expected result[a]				Result[d] obtained by method													
					BACTEC 460				MGIT 960					MGIT man.				
	INH	RMP	EMB	SM	INH	RMP	EMB	SM	INH	RMP	EMB low[b]	EMB high[c]	SM	INH	RMP	EMB low[b]	EMB high[c]	SM
LT 10	R	R	R	R	R	S	R	S	R	S	R	R	R	R	S	R	R	R
LT 19	R	S	R	R	R	S	S	S	R	S	R	S	R	R	S	R	S	R
LT 32	R	S	S	R	R	S	B	R	R	S	R	S	R	R	S	R	S	R
LT 77	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 104	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 128	S	R	S	S	S	R	S	S	S	R	S	S	S	S	R	R	S	S
LT 145	R	R	S	R	R	R	S	R	R	R	S	S	R	R	R	S	S	R
LT 165	R	S	R	S	R	S	S	S	R	S	R	R	S	R	S	R	R	S
LT 179	R	R	S	R	R	R	S	B	R	R	S	S	R	R	R	S	S	R
LT 185	R	S	R	R	R	S	S	S	R	S	R	S	R	R	S	R	S	R
LT 203	R	S	S	R	R	S	S	R	R	S	R	S	R	R	S	R	S	R
LT 227	R	R	S	R	R	R	S	B	R	R	S	S	R	R	R	S	S	R
LT 242	S	R	S	S	S	R	S	S	S	R	S	S	S	S	R	S	S	S
LT 257	S	S	S	S	S	S	S	S	R	S	S	S	S	R	S	S	S	S
LT 278	S	S	S	S	S	S	S	S	S	S	S	S	R	S	S	S	S	R
LT 299	S	S	S	S	S	S	B	S	R	S	S	S	S	S	S	S	S	S
LT 511	R	R	R	R	R	R	R	R	R	R	R	S	R	R	R	R	S	R
LT 516	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 545	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
LT 555	R	R	R	R	R	R	B	R	R	R	R	S	R	R	R	R	S	R
LT 574	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 582	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 595	R	R	R	R	R	R	S	R	R	R	R	S	R	R	R	R	S	R
LT 607	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	R
LT 622	R	R	R	R	R	S	B	R	R	S	R	R	R	R	S	R	R	R
LT 648	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R
LT 654	R	R	R	R	R	S	S	S	R	S	R	R	R	R	S	R	R	R
LT 669	R	R	R	R	R	S	S	R	R	S	R	R	R	R	S	R	S	R
LT 691	S	S	S	S	S	S	S	R	S	S	S	S	S	S	S	S	S	S
LT 703	R	S	S	R	R	S	S	R	R	S	S	S	R	R	S	S	S	R
LT 725	S	S	S	R	S	S	S	R	S	S	S	S	R	S	S	S	S	R
LT 740	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 752	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	R
LT 759	R	S	S	R	R	S	S	R	R	S	S	S	R	R	S	S	S	R
LT 779	S	S	S	R	S	S	S	S	S	S	S	S	S	S	S	S	S	S
LT 795	S	S	S	S	S	S	S	R	S	S	S	S	R	S	S	S	S	R

[a] Results expected according to the WHO.
[b] EMB concentration of 3.5 μg/ml.
[c] EMB concentration of 7.5 μg/ml.
[d] Abbreviations: S, susceptible, R, resistant; B, borderline.

broth (7H9) with oleic acid-albumin-dextrose (OADC) enrichment (Difco Laboratories, Detroit, Mich.) at −70°C until the present study.

Five of the strains (LT 19, LT 165, LT 185, LT 595, and LT 648) with discordant susceptibility test results for susceptibility to EMB in the initial susceptibility testing round were analyzed for subpopulations with deviating EMB resistance. Each strain was streaked on Middlebrook 7H11 agar (7H11) (Difco Laboratories), and after 14 days' incubation at 35°C in 6% CO_2 atmosphere, 10 subcultures were made from solitary colonies. These subcultures were used in testing for EMB susceptibility to evaluate existence of heteroresistant subpopulations among the initial strain obtained.

Preparation of inocula. The isolates were grown on Middlebrook 7H11 agar plates at 35°C in a 6% CO_2 atmosphere. Colonies no older than 4 weeks were used to prepare the inocula. For the BACTEC 460 method, the standard protocol was used (according to the Becton Dickinson product and procedure manual). For the MGIT methods, the colonies were transferred into a sterile tube containing 3.0 ml of 7H9 with 8 to 10 sterile glass beads. The suspension was vortexed for 1 to 2 min and left standing undisturbed for 30 min. The supernatant was transferred into a sterile tube and the turbidity was adjusted to 0.5 McFarland standard with 7H9. A 1:5 dilution of this suspension in sterile saline was used.

Drug solutions. Lyophilized drugs (BACTEC S.I.R.E. drug kit; BD Biosciences) were dissolved according to the manufacturer's instructions. From the dissolved drug solutions, 0.225 ml was pipetted into a 7-ml MGIT, and 0.1 ml was pipetted into a BACTEC 12B vial containing 4.5 ml of medium. In both MGIT methods, the final drug concentrations used were 0.1 μg/ml for INH, 1.0 μg/ml for RMP, 3.5 and/or 7.5 μg/ml for EMB, and 0.8 μg/ml for streptomycin (SM) (14). In the BACTEC 460 method, the final concentrations were 0.1 μg/ml for INH, 2.0 μg/ml for RMP, 7.5 μg/ml for EMB, and 2.0 μg/ml for SM.

In addition to the primary testing, 12 of the strains were tested for susceptibility to SM in concentrations of 0.4, 2.0, and 4.0 μg/ml by both MGIT methods, and to concentrations of 4.0, 6.0, and 8.0 μg/ml by the BACTEC 460 method.

Controls in the MGIT methods. Each growth control tube without drugs was enriched with the MGIT OADC supplement. For a positive control, the broth in an uninoculated MGIT was replaced by 7.0 ml of a 0.4% sodium sulfite solution. For a negative control, an uninoculated MGIT was used.

AST by MGIT. A volume of 0.225 ml of each final drug solution and 0.875 ml of OADC supplement were aseptically added into each MGIT containing 7.0 ml of broth followed by 0.875 ml of the final inoculum suspension. The manual MGITs were incubated at 37°C and examined for fluorescence under a Wood's lamp daily from day 3 to day 13. The tubes deposited in the MGIT 960 instrument were incubated at 37°C and automatically monitored for the increase rate of fluorescence. A print of the fluorescence of each tube location was taken daily at the same hour. A strain was considered resistant if the drug-containing tube indicated significant growth within 2 days of positivity of the growth control tube, and it was regarded as susceptible if no fluorescence was detected within 2 days.

TABLE 2. Susceptibility test results of 36 *M. tuberculosis* isolates obtained using the MGIT 960 and the manual MGIT methods compared with BACTEC 460 results

Antibiotic (concn [μg/ml])	Method	Result[d]	Expected result[a]			BACTEC 460				Sensitivity (%)[b]	Specificity (%)[c]
			S[e]	R[e]	Agreement (%)	S[e]	B[e]	R[e]	Agreement (%)		
INH	MGIT 960	S	15		94	15			94	100	88
		R	2	19		2		19			
	Manual MGIT	S	16		97	16			97	100	94
		R	1	19		1		19			
RMP	MGIT 960	S	22	4	89	26			100	100	100
		R		10				10			
	Manual MGIT	S	22	4	89	26			100	100	100
		R		10				10			
EMB (7.5)	MGIT 960	S	24	5	86	25	3	1	75	67	86
		R		7		4	1	2			
	Manual MGIT	S	24	6	83	26	3	1	78	67	90
		R		6		3	1	2			
EMB (3.5)	MGIT 960	S	22		94	21	1		67	100	72
		R	2	12		8	3	3			
	Manual MGIT	S	21		92	20	1		64	100	69
		R	3	12		9	3	3			
SM	MGIT 960	S	14	1	92	14		1	78	93	74
		R	2	19		5	2	14			
	Manual MGIT	S	12	1	86	12		1	72	93	63
		R	4	19		7	2	14			

[a] The "true" results as supplied by the WHO.
[b] The sensitivity, i.e., the ability of MGIT methods to detect the true resistance, when compared with the BACTEC 460 results.
[c] Specificity, i.e., the ability of MGIT methods to detect the true susceptibility, when compared with the BACTEC 460 results.
[d] Abbreviations: S, susceptible; R, resistant.
[e] Values are numbers of isolates.

If the growth control tube showed fluorescence on day 3, or if it did not turn fluorescent before day 13, the AST was repeated.

AST by BACTEC 460. For the BACTEC 460 method, the AST was performed according to the standard protocol.

RESULTS

The expected susceptibility results of the 36 *M. tuberculosis* strains are presented in Table 1 together with the respective results generated by the two MGIT methods and the BACTEC 460 method. For susceptibility to INH, the results obtained by the MGIT 960 system and the manual MGIT agreed with the BACTEC 460 results in 34 (94%) and 35 (97%) cases, respectively (Table 2). For the two MGIT methods, the sensitivity, i.e., the ability to detect the true resistance, was 100%, and the specificity, i.e., the ability to detect the true susceptibility, was 88 and 94% for the MGIT 960 and the manual MGIT methods, respectively. The INH results obtained by the BACTEC 460 method were in full agreement with the expected results.

When testing for susceptibility to RMP, the results obtained by the MGIT 960, the manual MGIT, and the BACTEC 460 systems were in full agreement. However, these results disagreed with the WHO expected results in four cases (Table 2).

Two concentrations of EMB were applied in testing for EMB susceptibility. With an EMB concentration of 3.5 μg/ml in the MGIT methods, the test results of the MGIT 960 and the manual MGIT methods agreed with the BACTEC 460 results in 24 (67%) and 23 (64%) cases. Most of the discordant results were tested resistant by the MGIT methods and susceptible with the BACTEC 460. Using this concentration, the sensitivity of both MGIT methods was 100%, but the specificities were 72 and 69% for the MGIT 960 and the manual MGIT, respectively. These results obtained with the MGIT 960 and the manual MGIT agreed with the expected results in 34 (94%) and 33 (92%) cases, respectively. The discordant results were resistant with the MGIT methods and susceptible according to WHO.

When an EMB concentration of 7.5 μg/ml was used in all methods, the results obtained by the MGIT 960 and the manual MGIT methods agreed with the BACTEC 460 results in 27 (75%) and 28 (78%) cases, respectively. Among the discordant results, five and four were tested as resistant with the MGIT 960 and the manual MGIT, respectively, but susceptible or borderline with the BACTEC 460. In contrast, four tested as susceptible in both MGIT methods but resistant or borderline by the BACTEC 460 system. Thus, compared with the BACTEC 460 results, the sensitivity of both MGIT methods was 67%, and the specificities were 86 and 90% for the MGIT 960 and the manual MGIT methods, respectively. However, the results generated by the BACTEC 460 method agreed with the expected results in only 25 cases (69%). In contrast, the results obtained by the MGIT 960 and the manual MGIT were in agreement with the expected results in 31 (86%) and 32 cases (83%), respectively. All conflicting results applied EMB susceptibility. They included five susceptible results generated by the MGIT 960 method and six susceptible results generated by the manual MGIT method. All these isolates were classified as resistant by WHO.

For testing of heteroresistance we selected the five isolates

found problematic in several laboratories in the same quality assurance round that we participated in. These strains which showed discrepant results when tested for EMB concentrations of 3.5 μg/ml in comparison with expected susceptibility data were analyzed for possible deviating subpopulations. According to the WHO, all of the strains analyzed were expected to be susceptible to EMB. In all five strains, a varying number of the subpopulations analyzed was found to be resistant to EMB by both the MGIT methods and the BACTEC 460 method. The proportion of resistant subpopulations varied from 2 to 9 among the 10 subcultures analyzed of each strain.

In testing of the 36 isolates for susceptibility to SM, the results obtained by the MGIT 960 and the manual MGIT methods were in agreement with the BACTEC 460 results in 28 (78%) and 26 cases (72%), respectively (Table 2). Among the discordant results, five and seven strains were tested as resistant by the MGIT 960 and the manual MGIT methods, respectively, but as susceptible by the BACTEC 460 method. One strain was tested as susceptible by the MGIT methods and resistant by the BACTEC 460 method. The sensitivities of the both MGIT methods were 93%, and the specificities were 74 and 63% for the MGIT 960 and the manual MGIT, respectively. When compared with the expected results given by WHO, results obtained by MGIT 960 were in agreement in 33 cases (92%), and those of the manual MGIT were in agreement in 31 cases (86%). The discordant results were found resistant with the two MGIT methods but reported susceptible by WHO with one exception. One strain was found susceptible by the MGIT methods though reported as resistant by the WHO.

Twelve of the strains found difficult to qualify in SM testing in primary external quality control rounds were examined for an optimal SM concentration. The results obtained by the two MGIT methods agreed best with the BACTEC 460 results when the SM concentration used in the MGIT methods was 0.8 μg/ml, but a concentration of 2.0 μg/ml was used in the BACTEC 460 method. Using these concentrations, however, five discordant results were obtained. All discordant strains were tested resistant by the MGIT methods and susceptible or borderline by the BACTEC 460 method. All of them were reported as resistant by the WHO.

The average turnaround times for AST were 6.4 days for the MGIT 960, 6.5 days for the manual MGIT, and 8.7 days for the BACTEC 460. When the MGIT methods were used, the ASTs had to be repeated in two cases because of the fluorescence appearing on day 3 and in one case because the fluorescence did not appear at all. When the BACTEC 460 method was used, the number of repeated ASTs was 12.

DISCUSSION

The aim of the study was to evaluate the accuracy of the manual MGIT and the MGIT 960 methods for susceptibility testing of *M. tuberculosis* strains against first-line drugs. The manual MGIT system was included as a potential tool for rapid detection of MDR-TB in situations where high technology instruments are out of reach. The results obtained by the BACTEC 460 method, the most widely used and best validated rapid method available at the moment, were used as the reference. The results were also compared to information provided for these strains by the WHO. According to the results, both the manual MGIT and the MGIT 960 methods were found equally reliable as the BACTEC 460 method in rapid detection of MDR-TB strains. For the 36 strains tested, the RMP susceptibility results obtained by the three methods were in full agreement. Yet, among them, four strains were discordant with the expected results. The INH susceptibility results generated by the MGIT methods were in full agreement with the expected results but disagreed in 3 to 6% of the cases with the BACTEC 460 results. In preliminary studies which compared the manual MGIT and BACTEC 460 methods, highly similar results were obtained (13, 14). The INH and RMP susceptibility results obtained in the studies which compared the MGIT 960 and BACTEC 460 methods were also similar to our results (1, 3, 16).

In contrast, both EMB and SM testing pointed out some problems in use of the two MGIT methods as well as the BACTEC 460 system. In case of EMB, less than 80% of the results obtained by the MGIT methods agreed with those obtained by the BACTEC 460 system. The MGIT results agreed best with the BACTEC 460 results when an EMB concentration of 7.5 μg/ml was used in all methods. However, the MGIT results agreed better with the expected results given by the WHO when an EMB concentration of 3.5 μg/ml was used. Our results indicated that the EMB concentrations commonly applied are suboptimal for both the MGIT methods and the BACTEC 460 method. In addition, our results indicated that the five isolates tested for heteroresistance to EMB truly consisted of resistant and susceptible subpopulations. This probably explains at least partly the discordant results obtained. The heteroresistance also indicates that these isolates are not optimal for use as quality control strains.

In the case of SM, fewer than 80% of the results obtained by the MGIT methods were in agreement with the BACTEC 460 results when the SM concentration of 0.8 μg/ml was used in the MGIT methods and the concentration of 2.0 μg/ml was used in the BACTEC 460 method. This is difficult to understand, because both methods use 7H9 broth as the culture medium. However, the results suggested that the optimal SM concentration for all methods could be in the range of 1 to <2 μg/ml.

The mean times required to obtain susceptibility results were very similar in the three methods tested: 6.4 and 6.5 days for the MGIT 960 method and the manual MGIT method, respectively, and 8.7 days for the BACTEC 460 method. Thus, both MGIT methods can provide susceptibility test results for *M. tuberculosis* isolates even more rapidly than the BACTEC 460 system.

In all, both MGIT methods performed well in detection of resistance to INH and RMP, and therefore they can reliably be used for rapid detection of *M. tuberculosis* classified as MDR-TB. Particularly in areas with limited resources where purchase of expensive instruments such as the MGIT 960 system is out of scope, the use of manual MGITs for rapid susceptibility testing for MDR-TB could be a possibility. No special instrumentation other than a UV lamp is needed, and test results for susceptibility to INH and RMP can be made available in less than a week from detection of visible colonies on solid media. This would allow rapid release from isolation of patients with tuberculosis susceptible to INH and RMP, and rapid adjustment of the initial drug combination if indicated. If necessary,

conventional solid media could be used in further testing of the strain. With EMB and SM we experienced problems somewhat similar to those reported earlier (3), which points out the need for more extended studies. It needs to be evaluated whether these problems could be solved by adjusting the concentrations of EMB and SM. It also needs to be evaluated whether the heteroresistance to EMB is a reason for problems observed earlier in testing for EMB resistance (3).

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