Factors that effect sputum culture convertion rate in hospitalized patients with pulmonary tuberculosis who were applied directly observation therapy and non-directly observation therapy

Ayşe UZUNDAĞ İŞERİ[1], Güngör DULKAR[2], Özlem SELÇUK SÖNMEZ[2], Leyla YILMAZ AYDIN[2], Birsen YILMAZ[3]

[1] Server Gazi Hastanesi, Göğüs Hastalıkları, Denizli,
[2] Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Ankara,
[3] İl Sağlık Müdürlüğü, Halk Sağlığı Bölümü, Isparta.

ÖZET

Doğrudan gözetimli tedavi uygulanan ve uygulanmayan akciğer tüberkülozlu yatan hastalarda balgam kültür konversiyonunu etkileyen faktörler

Doğrudan gözetimli tedavi (DGT) tüberküloz kontrolünün esasıdır. Bu çalışmada, DGT uygulanan ve uygulanmayan, yatarak tedavi alan tüberküloz hastalarında balgam kültür konversiyonuna etki eden faktörleri tespit etmek amaçlanmıştır. Çalışmaya Nisan 2001-Nisan 2002 tarihleri arasında DGT uygulanmayan 50 kültür pozitif akciğer tüberkülozu ve Mayıs 2002-Mayıs 2003 tarihleri arasında DGT uygulanan 60 kültür pozitif akciğer tüberkülozu olgusu alındı. Kültür konversiyon oranı ile yaş, cinsiyet, sigara ve alkol kullanımı, öksürük, hemoptizi, basil yükü, diabetes mellitus (DM) varlığı ve radyolojik yayılım arasındaki ilişki araştırıldı. Kültür konversiyon oranı DGT uygulanan hastalarda %68.3, DGT uygulanmayan hastalarda %62 idi. İki grup arasında öksürük, balgam, gece terlemesi, basil yükü, hemoptizi, DM, primer ilaç direnci ile kültür konversiyonu arasında istatistiksel olarak anlamlı fark yoktu. DGT uygulananlarda sigara ve alkol kullanımı istatistiksel anlamlı fark yaratıyordu. Kültür konversiyon hızı ile ilişkili saptanan faktörler aynı konuda yapılan diğer çalışmalarda elde edilen sonuçlarla benzerdir. Çalışmamızda istatistiksel olarak anlamlı olmasa da DGT uygulanan hastalarda kültür konversiyon hızı DGT uygulanmayanlara göre yüksek bulunmuştur.

Anahtar Kelimeler: *DGT, ilaca dirençli tüberküloz, balgam kültür konversiyonu, tüberküloz tedavisi, tedavi sonuçları.*

Yazışma Adresi (Address for Correspondence):
Dr. Özlem SELÇUK SÖNMEZ, Mareşal Fevzi Çakmak Caddesi No: 10/6 06500 Bahçelievler,
ANKARA - TURKEY
e-mail: drosonmez@yahoo.com

SUMMARY

Factors that effect sputum culture convertion rate in hospitalized patients with pulmonary tuberculosis who were applied directly observation therapy and non-directly observation therapy

Ayşe UZUNDAĞ İŞERİ[1], Güngör DULKAR[2], Özlem SELÇUK SÖNMEZ[2], Leyla YILMAZ AYDIN[2], Birsen YILMAZ[3]

[1] Department of Chest Diseases, Server Gazi Hospital, Denizli, Turkey,
[2] Department of Chest Diseases, Ataturk Chest Diseases and Chest Surgery Training and Research Hospital, Ankara, Turkey,
[3] Department of Public Health, Isparta City Department of Turkish Ministry of Health, Isparta, Turkey.

Directly observation therapy (DOT) has been accepted as the basic method for controlling tuberculosis. The present study aimed to determine the risk factors that affect sputum culture conversion rate in the DOT managed and non-DOT managed hospitalized patients. The study was included 50 cases with positive sputum cultures between the dates April 2001-April 2002 when DOT was not applied and 60 cases between the dates May 2002-May 2003 when DOT was applied. The relation between sputum culture conversion rate and the risk factors of age, gender, cough, hemopthysis, primary drug sensitivity, high initial bacillary load, smoking and alcohol consumption, presence of diabetes mellitus (DM), and radiological dissemination were determined. In the present study, sputum culture conversion rate was found 68.3% in DOT managed patients, 62% in non-DOT managed patients. In DOT managed and non-DOT managed patients; there was no statistically significant difference between complaints of cough, sputum, night sweating, hemopthysis, DM, bacillary load, primary drug resistance and culture conversion rate. In DOT managed patients; a significant difference was determined between smoking and alcohol consumption and culture conversion rate. The factors determined above as being related with the sputum culture conversion rate were similar with the results of the other studies investigating the same topic. Despite no statistical significance, an increase in the sputum culture conversion rate in DOT managed patients, when compared with non-DOT managed patients was determined.

Key Words: *DOTS, drug resistance tuberculosis, sputum culture convertion, tuberculosis treatment, treatment results.*

Today, 32% of the world population is infected by tubercule bacilli. Every year nearly 8 million people contract the disease and nearly 2 million of them die (1). Every year 1% of the world population gets infected by tubercule bacilli. Under the leadership of the World Health Organization (WHO), directly observed therapy (DOT) strategy has spread rapidly since 1991 and has today been accepted as the basic method for controlling tuberculosis (2).

In our country, among all causes of death, tuberculosis ranks 27th. According to the 2002 report of the WHO: Turkey's population is 66.668.000 and the number of newly diagnosed patients is 18.038, with the incidence being 27 per 100.000 (2).

At the end of the year 2000, DOT strategy was applied in 148 countries in the world. In 1999 success rate of treatment in smear positive patients was 82.2% in DOT applied areas and 27.6% in non-DOT applied areas (2).

In our country, DOT applications were first started at hospitals in 1997. While application in dispensaries of tuberculosis control was first started in Nazilli in 2000, it became common in all dispensaries as of 2006 (2). The purpose of the present study was to determine the factors that affect sputum culture conversion rate in hospitalized patients during DOT applied and non-DOT applied periods in the present hospital.

MATERIALS and METHODS

The study was performed at Ataturk Chest Diseases and Chest Surgery Training and Research Hospital, Ankara, Turkey and included 50 cases

with positive sputum smears and cultures between dates April 2001-April 2002 when DOT was not applied, retrospectively and 60 cases between the dates May 2002-May 2003 when DOT was applied, prospectively.

Inclusion Criteria

1. Being older than 18 years of age,
2. Not having tuberculosis treatment history,
3. Being human immunodeficiency virus negative,
4. Having a positive initial sputum culture,
5. Not having extrapulmonary tuberculosis.

Approval of a localy ethic comitee was obtained. A signed informed consent form was received from DOT applied patients. Patient history, family history, habits, accompanying diseases, primary drug resistance, and radiological diagnoses of all patients included in the study were recorded. Radiological evaluation was performed according to postero-anterior (PA) chest roentgenogram. In all patients, results of sputum smears and culture examinations, all of which were carried out three times at the beginning and every month thereafter, were recorded. After all sputum samples were homogenized and decontaminated with N-acetylcysteine and 4% sodium hydroxide, a smear was prepared from this suspension and cultures were performed in Löwenstein-Jensen medium at the bacteriology laboratory of the present hospital. All preparations were stained with Ziehl-Neelsen method and then examined microscopically. At least 300 fields were controlled in order to evaluate each preparation. Sputum culture evaluation was performed at the sixth-eighth week following the culture of the material in Löwenstein-Jensen medium (3).

Resistance tests were evaluated with indirect proportion method in the present laboratory. It was accepted resistant if greater than 1% of number of colonies in the control tube for isoniacid, rifampicin, and ethambutol and greater than 10% for streptomycin. All the patients treated according to the recommend of WHO about newly diagnosed smear positive pulmonary tuberculosis patients' treatment. During the periods when DOT was not applied, antituberculosis medication of every patient was delivered by department nurses to their rooms and the patients were asked to take them by themselves. However, whether they have taken them or not was not controlled. After May 2002, when DOT was started to be applied, all patients came to the therapy room at 9.30 AM and took their medication under the surveillance of the department nurse in charge.

All patients were hospitalized until results of their sputum smear became negative three times. When this was achieved, the patients were discharged and called for monthly controls. DOT was applied only during the hospitalization. Patients having three negative sputum culture results, following an initial positive result, were defined as sputum culture negative (4,5). All results regarding the periods in which DOT was and was not applied were evaluated about sputum culture conversion as defined previously. Demographic characteristics (age, gender), initial symptoms, accompanying diseases, habits (smoking, alcohol, and drug use), primary drug resistance, bacillary load in initial sputum smear, and the relevance of the radiological dissemination and appearance and sputum culture conversion rate were studied (4,6,7). Analyses were performed by SSPS 10.0 software program. Upon evaluation; definitive statistics (average, standard deviation), importance test for the difference between two means (Student's t-test), and chi-square tests were carried out. A p value less than 0.05 ($p < 0.05$) wasconsidered as statistically significant.

RESULTS

Of the 110 patients included in the study, DOT was applied on 60 (54.5%) cases.

Mean age of patients was 40.55 ± 16.02 (18-83) years and 44.10 ± 16.57 (18-81) years for DOT managed and non-DOT managed patients, respectively.

Of the 87 male patients included in the study, 49 (56%) were DOT managed and 38 (43.7%) were non-DOT managed. For the remaining 23 female patients, 11 (47.8%) were DOT managed while 12 (52.2%) were non-DOT managed.

Demographic characteristics (age, gender), initial symptoms, accompanying diseases, habits (smoking, alcohol, and drug use), primary drug resistance, bacillary load in initial sputum smear, and the relevance of the radiological dissemination of the disease and sputum culture conversion rate for all newly diagnosed pulmonary tuberculosis cases are demonstrated in Table 1-3. On PA chest roentgenogram, parenchyma involvement of both lungs was defined as widespread disease while involvement of one lung was defined as localized disease.

Table 1. Age, gender, symptoms, habits, accompanying diseases, tuberculosis contact stories, and sputum bacillary load frequencies of patients.

	DOT managed		Non-DOT managed		Total	
	Number	%	Number	%	Number	%
Age groups						
Under 25 years	12	70.6	5	29.5	17	100
Between 25-50	33	54.1	28	45.9	61	100
Over 50 years	15	46.9	17	53.1	32	100
Gender						
Female	11	47.8	12	52.2	23	100
Male	49	56.3	38	43.7	87	100
Cough	54	54.5	45	45.5	99	100
Sputum	40	49.5	41	50.6	81	100
Night sweating	33	55.0	27	45.0	60	100
Hemopthysis	23	57.5	17	42.5	40	100
Smoking	47	55.9	37	44.1	84	100
Alcohol	16	53.3	14	46.7	30	100
Diabetes mellitus	7	41.2	10	58.8	17	100
Initial bacillary load						
(+)	14	48.3	15	51.7	29	100
(++)	7	46.7	8	53.3	15	100
(+++)	15	53.6	13	46.4	28	100
(++++)	24	63.2	14	36.8	38	100

DOT: Directly observed therapy.

Table 2. Distribution of the results of primary drug sensitivity of patients.

	DOT managed		Non-DOT managed		Total	
Drug sensitivity	Number	%	Number	%	Number	%
Sensitive to all drugs:	28	43.0	37	57.0	65	100
Sensitive to 1 ≥ drugs	32	71.1	13	28.9	45	100
H sensitivity	12	85.7	2	14.3	14	100
R sensitivity	6	50.0	6	50.0	12	100
S sensitivity	7	63.6	4	36.4	11	100
E sensitivity	1	100	–	–	1	100
MDS	6	85.7	1	14.3	7	100

H: Isoniacid, R: Rifampicin, S: Streptomycin, E: Ethambutol, MDS: Multidrug sensitive, DOT: Directly observed therapy.

Table 3. Distribution of the radiological appearance seen in patients.

Radiological dissemination	DOT managed		Non-DOT managed		Total	
	Number	%	Number	%	Number	%
With disseminated cavitary disease	17	51.5	16	48.5	33	100
Without disseminated cavitary disease	14	58.3	10	41.7	24	100
With local cavitary disease	13	44.8	16	55.2	29	100
Without local cavitary disease	16	66.7	8	0.3	24	100

DOT: Directly observed therapy.

Table 4. Sputum culture conversion rate at the end of the initial phase according to DOT management.

	Culture conversion during the initial phase		Culture conversion during the maintenance phase	
	Number	%	Number	%
DOT managed (n= 60)	41	68.3	19	31.7
Non-DOT managed (n= 50)	31	62.0	19	38.0
p	> 0.05		> 0.05	

DOT: Directly observed therapy.

In DOT managed patients, mean time for sputum smear and culture conversion was 3.2 ± 1.9 (1-7) and 2.2 ± 1.08 (1-7), respectively. In non-DOT managed patients mean time for sputum smear and culture conversion were 3.3 ± 1.6 (1-7) and 2.2 ± 1.1 (1-6) months, respectively. No statistically significant difference was determined regarding sputum culture conversion average rates between two groups (p> 0.05) (Table 4). Factors that affect sputum culture conversion rate in DOT managed and non-DOT managed patients are shown in Table 5.

In DOT managed and non-DOT managed patients; there was no statistically significant difference between complaints of cough, sputum, night sweating, and hemopthysis and culture conversion rate (p> 0.05). In DOT managed patients; a significant difference was determined between smoking and culture conversion rate (p< 0.05). At the end of the initial phase, sputum culture conversion was observed in 59.6% of smokers and 100% of non-smokers. There was a statistically significant difference between alcohol use and culture conversion rate (p< 0.05). Culture conversion was observed in 43.7% of alcohol users and in 77.5% of non-users. In non-DOT managed patients; no statistically significant difference was found between culture conversion rate and neither smoking nor alcohol use (p> 0.05).

In DOT managed and non-DOT managed patients; no statistically significant difference was found between culture conversion rate and patients with or without diabetes mellitus (p> 0.05).

In DOT managed and non-DOT managed patients; no significant difference was demonstrated between initial bacillary load and culture conversion rate (p> 0.05) (Table 5).

In DOT managed and non-DOT managed patients; the effect of primary drug resistance results on culture conversion rate at the end of the initial phase was shown in Table 6. In DOT managed and non-DOT managed patients; no significant difference between primary drug resistance results at the beginning of the treatment and culture conversion rate was established (p> 0.05). Smear culture conversion was observed in 71.4% of patients who were resistance to all drugs and in 37.5% of patients who were sensitive to one or more drugs.

Table 5. Factors that affect culture conversion rate at the end of the initial phase in DOT managed and non-DOT managed patients.

	DOT managed			Non-DOT managed		
	Number	%	p	Number	%	p
Age groups						
25 years ↓ (n= 14)	11	91.7		4	80.0	
25-50 years (n= 33)	21	63.6	**0.070**	14	50.0	> 0.05
50 years ↑ (n= 15)	9	60.0		13	76.5	
Gender						
Female (n= 11)	10	90.9	> 0.05	11	91.7	**0.037**
Male (n= 49)	31	63.3		20	52.6	
Smoking						
Yes (n= 47)	28	59.6	**0.015**	20	54.1	> 0.05
No (n= 13)	13	100.0		11	84.6	
Alcohol						
Yes (n= 16)	7	43.8	**0.031**	6	24.9	> 0.05
No (n= 44)	34	77.3		25	69.4	
Bacillary load						
(+) (n= 14)	11	78.6		10	66.7	
(++) (n= 7)	6	85.7	> 0.05	5	62.5	> 0.05
(+++) (n= 15)	9	60.0		7	53.8	
(++++) (n= 24)	15	62.5		9	64.3	
Radiological response						
Stable (n= 16)	9	56.3	> 0.05	10	58.8	> 0.05
Regression (n= 44)	32	72.7		21	63.6	

DOT: Directly observed therapy.

Table 6. Effect of primary drug sensitivity results on culture conversion rate at the end of the initial phase in DOT managed and non-DOT managed patients.

	DOT managed			Non-DOT managed		
	Number	%	p	Number	%	p
Sensitive	20	71.4	> 0.05	25	67.5	> 0.05
Resistant	12	37.5		6	46.1	
H resistance						
Yes	6	50.0	> 0.05	1	50.0	> 0.05
No	35	72.9		30	62.5	
R resistance						
Yes	4	66.7	> 0.05	2	33.3	> 0.05
No	37	68.5		29	65.9	
S resistance						
Yes	5	71.4	> 0.05	2	50.0	> 0.05
No	36	67.9		29	63.0	
MDR						
Yes	4	66.7	> 0.05	-	-	
No	37	68.5		31	63.3	> 0.05

DOT: Directly observed therapy, H: Isoniacid, R: Rifampicin, S: Streptomycin, MDR: Multidrug resistant.

DISCUSSION

Early diagnosis and effective treatment of newly diagnosed smear positive pulmonary tuberculosis patients, play crucial roles in decreasing new infections significantly and in preventing of multidrug resistant (MDR) tuberculosis. Non-compliance of tuberculosis patients with the treatment is an important problem. Symptoms rapidly get better especially in short time periods like one or two months after the initiation of treatment and patients think they are recovered and thus stop the treatment (8). In many dispensaries in our country, nearly 10% of the new cases and 20% of the previously treated cases stop the treatment (9).

The most effective way to solve this problem is to perform surveillance on patients by a trained and supervised attendant. DOT has been accepted as the basic strategy by the WHO in 1991 (8).

In publications investigating the relation between DOT and sputum smear and culture conversion rate, it generally has been demonstrated that DOT application accelerates the conversion rate of sputum smear and culture. However, there also are studies claiming the opposite.

With DOT application, treatment success and cure rates increase while the incidence of disease decreases. In addition, recurrence and drug resistance rates have also shown to decrease (7,10-12).

According to the WHO 2006 data, in smear positive cases newly diagnosed in the year 2003, the global treatment success was 82% for DOT managed group, while it was 45% for non-DOT managed group (13).

The aim of the present study was to determine the factors that affect sputum culture conversion rate in patients with newly diagnosed smear positive pulmonary tuberculosis during the periods in which DOT was and was not applied in our hospital.

The results of an 11 years study by Chaulk et al., revealed that the conversion rate of sputum smear culture at the third month was 90.7% in DOT managed cases while it was 76.1% in non-DOT managed cases ($p< 0.05$) (14).

In a study conducted at Dispensary of Tuberculosis Control at Nazilli by Arpaz et al., with DOT application, the conversion rates of smear and culture at the second month was found as 90% and 96%, respectively (15).

However, another study in Thailand showed that, in contrast to the aforementioned studies, DOT had no effect on the conversion rates of sputum smear and culture (16). As a result of this, it has been underlined that it is not right to compare DOT managed and non-DOT managed patient groups without randomization and that, applying DOT only for two months could lead to insufficient results and additionally pointed out that DOT could not be a cure for every disease but could only be a part of good case control in order to obtain cure for tuberculosis patients (17).

In the present study, culture conversion rate at the end of the initial phase was determined as 68.3% and 62% in DOT managed and non-DOT managed patients, respectively. Effect of DOT application on culture conversion rate was not statistically significant. The small size of the study group and DOT being applied not throughout the treatment but only during hospitalization can contribute to this result.

In a study by Liu et al. involving DOT application on 780 patients with positive sputum culture results, conversion rate at the end of the initial phase in patients at the age groups of younger than 25 years old, 25-44 years, 45-65 years, and older than 65 years old were determined as 62.7%, 64.6%, 63.7%, and 36% respectively. In cases younger than 25 years old, sputum culture conversion was twice the rate observed at patients older than 65 years old ($p< 0.05$) (4).

Telzak et al. did not detect a significant difference between age and the conversion rates of sputum smear and culture in their study ($p> 0.05$) (6). In the present study, there was no statistically significant difference between sputum smear conversion rate and age groups, neither in DOT managed nor non-DOT managed patients ($p> 0.05$).

When the effect of gender on sputum culture conversion rate was taken into consideration; in the studies conducted there was no statistically significant difference between male and female

patients (4). On the other hand, in a study by Petchawan et al. it was shown that conversion rates of sputum smear and culture in women were twice higher than men (17).

In the study, during the period in which DOT was not applied, it was observed that sputum smear conversion rate was 7.1 times more in female patients than males (odds ratio: 7.1, 95% CI: 1.5-36.9). In the present study, in DOT managed patient group, it was observed that sputum cultures of no-smoking patients all became negative at the end of the initial phase while in smoking patients, 59.6% sputum cultures became negative ($p< 0.05$). Smoking cause tissue destruction and fibrosis in the lungs by increasing free oxygen radicals and the effectiveness of antituberculosis drugs decrease depending on the presence of fibrosis. This result may be related with these mechanisms (18,19).

On the other hand, in non-DOT managed patient group no statistically significant difference between smoking and sputum culture conversion rate was demonstrated ($p< 0.05$). Non-DOT managed patient group has fewer individuals than DOT managed patient group. This can also contribute to the insignificant result.

In a study by Liu et al. culture conversion rate was reported as 77.9% for alcohol users and 58.5% for non-alcohol users (4).

In the present study, sputum culture conversion rate in DOT managed patient group was 43.8% for alcohol users and 77.3% for non-alcohol users ($p< 0.05$). In non-DOT managed patient group, no statistically significant effect of alcohol consumption on sputum culture conversion rate was detected. Difference of individual numbers between the two groups may have an effect on the result. In studies by Telzak et al. and Liu et al., no statistically significant difference between culture conversion rate and drug sensitivity pattern (sensitive to all drugs, resistant to 1 ≥ drugs, MDR) was demonstrated (4,6).

In the present study, in accordance with the abovementioned studies, no statistically significant difference between sputum culture conversion rate and drug sensitivity was found in neither DOT managed nor non-DOT managed patients (Table 6).

No statistically significant difference between bacillary load and culture conversion rate was detected in the present study in both groups, too. In the study by Telzak et al., for cases with cavitary disease time of conversion was 51 ± 17.2 days and 48 ± 12.5 days for smears and cultures, respectively, while for cases without cavitary disease, these numbers were 28 ± 6.9 days and 28 ± 5.3 days, respectively. The difference between the conversion rates of these two groups showed statistical significance (6).

However, in two other studies it was reported that in cases with or without cavitary disease, there was no statistically significant difference between groups in terms of sputum smear and culture conversion rates (16,20).

In the present study, no statistically significant difference was detected in DOT managed patients among four groups of radiological dissemination in term of sputum conversion rates. The reason of this result was thought to be the compliance of patients being provided through DOT.

In non-DOT managed patients, culture conversion rate was detected as 37.5% in patients with widespread cavitary disease while it was 73.5% in patients without widespread cavitary disease. The difference between these two patients group was statistically significant by the chi-square test. In conclusion; under DOT, new prospective studies aimed at determining the risk factors that affect the sputum culture conversion rate at the end of the initial phase are needed. Albeit our study includes only hospitalized patients and the results can not be generalized to all newly diagnosed smear positive pulmonary tuberculosis patients; it is important to know sputum culture conversion rate affecting factors prior to treatment. Patients can be classified according to them and health professionals can be more cautious. In countries with limited resources like ours, all of the treatment may be given under direct surveillance for patients with one or more risk factors affecting sputum culture conversion rate, while for patients without risk factors treatment may be given under direct surveillance only until the end of the initial phase.

REFERENCES

1. *Dye C, Scheele S, Dolin P, et al. Consensus statement. Global burden of tuberculosis: Estimated incidence, prevalence and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999; 282: 677-86.*
2. *Özkara Ş, Aktaş Z, Özkan S, Ecevit H. Türkiye'de Tüberkülozun Kontrolü için Başvuru Kitabı. Ankara: Ofset Basımevi, 2003: 7-52.*
3. *Sonnenwirth AC, Jarrett L. Cradwohl's clinical laboratory methods and diagnosis. 1699-703.*
4. *Liu Z, Kennet LS, Herman ME. Predictors of sputum culture conversion among patients with tuberculosis in the era of tuberculosis resurgence. Arch Intern Med 1999; 159: 1110-6.*
5. *Schon T, Elias D, Moges F, et al. Arginine as an adjuvant to chemotherapy improves clinical outcome in active tuberculosis. Eur Respir J 2003; 21: 483-8.*
6. *Telzak EE, Fazal BA, Pollard CL, et al. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. Clin Infect Dis 1997; 25: 666-70.*
7. *Lienhardt C, Manneh K, Bauchier V, et al. Factors determining the outcome of treatment of adult smear-positive tuberculosis cases in the Gambia. Int J Tuberc Lung Dis 1998; 2: 712-8.*
8. *Özkara Ş, Arpaz S, Özkan S ve ark. Tüberküloz tedavisinde doğrudan gözetimli tedavi (DGT). Solunum Hastalıkları 2003; 14: 150-7.*
9. *Özkara Ş, Kılıçarslan Z, Öztürk F ve ark. Bölge verileriyle Türkiye'de tüberküloz. Toraks Dergisi 2002; 3: 178-87.*
10. *Feng-Zeng Z, Murray C, Spinaci S. Result of directly observed short-course chemotherapy in 112842 Chinese patients with smear-positive tuberculosis. Lancet 1996; 347: 358-62.*
11. *Wilkinson D, Davies GR, Connolly C. Directly observed therapy for tuberculosis Rural South Africa, 1991 through 1994. Am J Public Health 1996; 86: 1094-7.*
12. *Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relaps in tuberculosis. N Engl J Med 1994; 330: 1179-84.*
13. *Global Tuberculosis Control Surveillance, Planning, Financing. WHO 2006 Geneva, World Health Organization (WHO/HTM/TB/2006. 362).*
14. *Chaulk CP, Moore-Rice K, Rizzo R. Eleven years of community-based directly observed therapy for tuberculosis. JAMA 1995; 274: 945-51.*
15. *Arpaz S, Keskin S, Sezgin N ve ark. Nazilli Verem Savaş Dispanseri DOTS deneyimleri sonuçları. Toraks Dergisi 2001; 2 (Ek 1): 40 (özet, SS.151).*
16. *Kolsuz M, Ersoy M, Küçükkebabcı C ve ark. Akciğer tüberkülozu olgularında balgam tetkiklerinin sonuçları ve bunları etkileyen faktörler. Solunum Hastalıkları 2003; 14: 193-9.*
17. *Pungrassami P, Chongsuvivatwong V, Olsen J. Has directly observed treatment improved outcomes for patients with tuberculosis in southern Thailand? Trop Med Int Health 2002; 7: 271-9.*
18. *Kolappan C, Gopi PG. Tobacco smoking and pulmonary tuberculosis. Thorax 2002; 57: 964-6.*
19. *Emri S. Sigara ve sağlık. Barış YI (editör). Solunum Hastalıkları Temel Yaklaşım. Ankara: Kent Matbaası, 1995: 471-9.*
20. *Ataç G, Sevim T, Güngör G ve ark. Akciğer tüberkülozlu olgularda yayma ve kültür negatifleşme süresini etkileyen faktörler. Toraks Dergisi 2001; 2: 16-20.*