



AN OBSERVATIONAL STUDY OF THE CLINICAL PROFILE AND OUTCOMES OF PATIENTS WITH MILIARY TUBERCULOSIS (TB).

Respiratory Medicine

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ABSTRACT

Objectives: This study aimed to evaluate the clinical profile and outcome of the patients with miliary tuberculosis (TB).

Methods: This was a retrospective observational study which involved evaluation of medical records of 44 patients with miliary TB in the department of respiratory medicine and internal medicine from 2016-2019. Miliary TB in these patients had been diagnosed on the basis of clinical symptoms, radiology and microbiology. The clinical profile of the patients in terms of age, gender, clinical presentations were recorded. Time duration for resolution of symptoms was noted. Radiological outcome was also studied. Final outcome was treatment success and mortality.

Results: The mean age of the patients were 37.07 years with 27 males. Most common complaints were fever (86.36%), cough (72.73%), expectoration (65.91%) and anorexia (45.45%). Laboratory findings showed hypertransaminasemia, anemia, and hyponatremia in 75.00%, 70.45%, and 43.18% patients, respectively. Standardized treatment (RHEZ) was given in 70.45% patients, and non-standardized treatment in 29.55% patients. Median duration of fever was relieved in 15 days. Mortality rate was 11.36% and drug induced liver injury (DILI) was seen in 4(9.09%) patients. Radiological resolution was seen in almost all of the patients except in 3 and in majority of patients clearing was seen within the first two months of initiation of treatment. Among all variables, hyperbilirubinemia showed significant association with mortality (OR=14.6, 95% CI 1.86 to 114.615, P=0.013).

Conclusion: In our series miliary TB presents most commonly in the third decade of life and is predominant among males. The clinical features were similar to pulmonary tuberculosis. There was frequent association with derangements in liver function, electrolyte, and hemoglobin. Hyperbilirubinemia was associated with significantly increased the odds of mortality. Non-standardized treatment regimens were associated with poorer outcome. Mortality rate in miliary TB was as high as 11.3% in our series.

KEYWORDS

miliary tuberculosis, prognosis, risk factors, tuberculosis

INTRODUCTION

As per the WHO 2020 report, Tuberculosis is one of the commonest causes of mortality worldwide. An incidence of ten million cases were reported in 2019, with a death rate of 1.2 million cases. Miliary tuberculosis (TB) is a severe form of Tuberculosis which carries a higher mortality. It refers to clinical disease resulting from hematogenous dissemination of Mycobacterium tuberculosis. Classic miliary TB is defined as millet like (mean size 2 mm, range 1-5 mm) seeding of TB bacilli in the lungs as evident on chest radiographs. Though miliary TB accounts for less than 1-3 % of all cases of Tuberculosis, it is fatal in almost all if left untreated. Risk factors for miliary TB includes extremes of age and medical conditions like alcohol abuse, malignancies, HIV infection, Diabetes mellitus, renal failure, corticosteroids and other forms of immunosuppressive therapies.

We report a retrospective series of 44 adult non-HIV patients with miliary tuberculosis treated at our center where we evaluated the clinical, radiological and biochemical profile along with their outcomes.

MATERIALS AND METHODS

A retrospective observational study was done of the medical records of 44 cases of miliary tuberculosis during the period of 2016-2019 in a tertiary care center of India.

Miliary TB had been diagnosed on the basis of: -

- (1) Clinical symptoms,
 - a) Fever
 - b) Anorexia
 - c) Weight loss
 - d) Cough
 - e) Breathlessness
 - f) Gastrointestinal symptoms like pain, nausea, vomiting
 - g) Headache or other CNS symptoms
 - h) Musculoskeletal symptoms
- (2) Radiographic imaging: chest X-ray or CT thorax
- (3) Sputum/bronchial wash microbiology
 - a) fluorescent staining for AFB
 - b) CBNAAT for MTB

Mycobacterium tuberculosis recovery from sputum specimen was the miliary TB microbiological criteria.

The chest X-ray characteristics of miliary infiltrates included Typical ("multiple 1-3-mm well-defined nodules throughout all lung fields") and atypical ("predominant nodules that measured >3mm or reticulonodular pattern").³ Other radiological lesions were also noted.

Evaluation of the data obtained from medical records of such patients was done. Standardized as well as Non-standardized antitubercular therapy as prescribed was also noted along with hematological, renal and hepatic parameters. Radiological findings were recorded from reports and films of chest X ray, CT of chest, abdomen and head, and ultrasound imaging of abdomen.

Statistical Analysis

The data entry was done in the Microsoft Excel spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 44 patients with miliary tuberculosis were included. The mean age of the patients was 37.07±19.4 years; majority of the subjects (61.36) were males. Majority of the patients 40(90.91%) belonged to rural area. Smokers constituted 15.91% of the patients, and alcohol intake was present in 15.91% patients. (table 1)

Table 1:-Distribution Of Demographic And Clinical Characteristics Of Study Subjects.

Demographic and clinical characteristics	Frequency	Percentage
Age(years)		
Mean ± SD	37.07 ± 19.4	
Median(25th-75th percentile)	34.5(20-55)	
Range	12-75	
Gender		
Female	17	38.64%
Male	27	61.36%
Area of residence		
Rural	40	90.91%

Urban	4	9.09%
Smoking	7	15.91%
Alcohol	7	15.91%

The common symptoms were fever in 86.36% patients, cough in 72.73%, expectoration in 65.91%, anorexia in 45.45%, and dyspnea in 40.91% patients. Other sign and symptoms were weight loss, nausea and vomiting, headache, altered sensorium, diarrhea, backache, abdominal distention, pain abdomen, hemiparesis, hemoptysis, seizure (Table 2).

Table 2:-Distribution Of Signs And Symptoms Of Study Subjects.

Signs and symptoms	Frequency	Percentage
Fever	38	86.36%
Cough	32	72.73%
Expectoration	29	65.91%
Dyspnea	18	40.91%
Weight loss	1	2.27%
Anorexia	20	45.45%
Nausea and vomiting	9	20.45%
Headache	6	13.64%
Altered sensorium	2	4.55%
Diarrhea	1	2.27%
Backache	2	4.55%
Hemiparesis	1	2.27%
Seizure	2	4.55%

Hematological and biochemical findings showed hypertransaminasemia in 75.00% patients, Anemia in 70.45% patients, Hyponatremia in 43.18% patients, Hypokalemia in 22.73% patients, Hyperbilirubinemia in 13.64% patients, and Hypoalbuminemia in two patients (Table 3).

Table 3:-Distribution Of Hematological And Biochemical Findings Of Study Subjects.

Hematological And Biochemical Findings	Frequency	Percentage
Anemia	31	70.45%
Hyponatremia	19	43.18%
Hypokalemia	10	22.73%
Hypertransaminasemia	33	75.00%
Hyperbilirubinemia	6	13.64%
Hypoalbuminemia	1	2.27%

Sputum was tested for AFB in 29 patients, which was negative in 26(59.09%) patients, scanty in 2(4.55%) patients, and 1+ in 1(2.27%) patient.

Chest X-ray showed miliary shadows, and other associated findings such as pneumothorax, pneumomediastinum with surgical emphysema, consolidation and cavitation in 1 case each.

Additional imaging was done in selected cases. USG showed hepatomegaly, splenomegaly with splenic abscess, hepatomegaly with splenomegaly, and periportal nodes in 1 patient each. CT head showed granuloma, frontal infarct with hydrocephalus, right MCA/ACA infarct, and tuberculoma in 1 patient each. MRI showed Pott's spine D11, D12, L1 and Pott's spine L3-L4 in 1 patient each. CSF examination findings were found to be suggestive of TBM in 1 patient.

Standardized treatment was given in 31 (70.45%) patients, where they received RHEZ, and Non standardized treatment was given in 13 (29.55%) patients. Non standardized treatment carried a significantly higher odds of mortality (OR 40.764, 95% CI 2.045 to 812.73, p=0.001). (Figure 1)

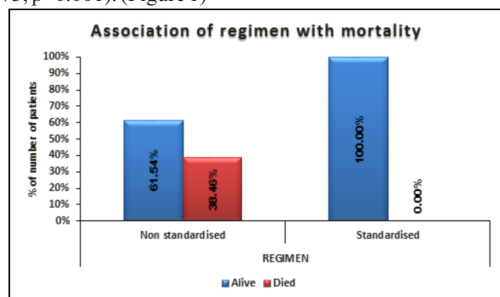


Figure 1:- Association Of Regimen With Mortality.

35 (79.5 %) patients were discharged and completed treatment, 4 (9.09%) patients developed Drug induced liver injury (DILI). Mortality occurred in 5(11.36%) patients all of which occurred within the first month of diagnosis and the most common cause of death was respiratory failure with multi organ dysfunction. At the completion of treatment all patients except 3 showed complete resolution of radiological abnormalities, 2 cases showed pleural thickening and one showed localized fibrosis. Radiological resolution was seen within the first month of initiation of treatment in majority of patients (51%), in 84.5 % by the end of second month and in 99.5% by the end of 4th month. No follow up sputum examination was done at end of treatment.

Median (IQR) duration of fever to be relieved was 15(15-20) days, and that of cough was 30(30-60) days, in dyspnea was 60(30-90) days.

Demographic and clinical characteristics showed no significant association with mortality as shown in Table 4.

Table 4:- Association Of Demographic And Clinical Characteristics With Mortality.

Demographic and clinical characteristics	Alive (n=39)	Died (n=5)	Total	P value	Odds ratio (95% CI)
Gender					
Female	14 (35.90%)	3 (60%)	17 (38.64%)	0.359 [†]	1
Male	25 (64.10%)	2 (40%)	27 (61.36%)		0.406 (0.068 to 2.425)
Area of residence					
Rural	35 (89.74%)	5 (100%)	40 (90.91%)	1 [†]	1
Urban	4 (10.26%)	0 (0%)	4 (9.09%)		0.717
Smoking	6 (15.38%)	1 (20%)	7 (15.91%)	1 [†]	1.718 (0.201 to 14.66)
Alcohol	5 (12.82%)	2 (40%)	7 (15.91%)	0.173 [†]	4.48 (0.639 to 31.438)
Age(years)	30 (20-50)	55 (35-56)	34.5 (20-55)	0.282 [†]	1.027 (0.983 to 1.073)

[†]Mann Whitney test, [†]Fisher's exact test

Higher mortality was associated with male gender (OR=0.406, 95 CI 0.068 to 2.425, P=0.359), higher age (OR=1.027, 95 CI 0.983 to 1.073, P=0.282), urban residence (OR=0.717, P=1), smoking (OR=1.718, 95 CI 0.201 to 14.66, P=1) and alcohol intake (OR=4.48, 95 CI 0.639 to 31.438, P=0.173).

Presenting signs and symptoms showed no significant association with mortality as shown in Table 5.

Table 5:-Association Of Signs And Symptoms With Mortality.

Signs and symptoms	Alive (n=39)	Died (n=5)	Total	P value	Odds ratio (95% CI)
Fever	34 (87.18%)	4 (80%)	38 (86.36%)	0.538 [†]	0.478 (0.054 to 4.271)
Cough	28 (71.79%)	4 (80%)	32 (72.73%)	1 [†]	1.211 (0.158 to 9.296)
Expectoration	25 (64.10%)	4 (80%)	29 (65.91%)	0.647 [†]	2.24 (0.227 to 22.052)
Dyspnea	14 (35.90%)	4 (80%)	18 (40.91%)	0.142 [†]	5.276 (0.715 to 38.951)
Weight loss	0 (0%)	1 (20%)	1 (2.27%)	0.114 [†]	26.341 (0.256 to 2708.266)
Anorexia	16 (41.03%)	4 (80%)	20 (45.45%)	0.16 [†]	4.273 (0.581 to 31.404)
Nausea and vomiting	8 (20.51%)	1 (20%)	9 (20.45%)	1 [†]	1.235 (0.153 to 9.947)
Headache	6 (15.38%)	0 (0%)	6 (13.64%)	1 [†]	0.469 (0.018 to 11.945)
Altered sensorium	1 (2.56%)	1 (20%)	2 (4.55%)	0.217 [†]	8.55 (0.451 to 162.152)
Diarrhea	1 (2.56%)	0 (0%)	1 (2.27%)	1 [†]	2.333 (0.023 to 235.808)

Backache	2 (5.13%)	0 (0%)	2 (4.55%)	1 [†]	1.365 (0.03 to 62.638)
Hemiparesis	1 (2.56%)	0 (0%)	1 (2.27%)	1 [†]	2.333 (0.023 to 235.808)
Seizure	2 (5.13%)	0 (0%)	2 (4.55%)	1 [†]	1.365 (0.03 to 62.638)

† Fisher's Exact Test

Among hematological and biochemical parameters, only hyperbilirubinemia showed significant association with mortality (OR=14.6, 95% CI 1.86 to 114.615, P=0.013), while anemia (OR=1.364, 95% CI 0.179 to 10.366, P=1), hyponatremia (OR=1.994, 95% CI 0.336 to 11.824, P=0.638), hypokalemia (OR=1.07, 95% CI 0.136 to 8.451, P=1), hypertransaminasemia (OR=4.439, 95% CI 0.2 to 98.436, P=0.309), and hypoalbuminemia (OR=2.333, 95% CI 0.023 to 235.808, P=1) showed no significant association with mortality (Table 6).

Table 6:- Association Of Hematological And Biochemical Findings With Mortality.

Hematologic al and biochemical findings	Alive (n=39)	Died (n=5)	Total	P value	Odds ratio (95% CI)
Anemia	27 (69.23%)	4 (80%)	31 (70.45%)	1 [†]	1.364 (0.179 to 10.366)
Hyponatremia	16 (41.03%)	3 (60%)	19 (43.18%)	0.638 [†]	1.994 (0.336 to 11.824)
Hypokalemia	9 (23.08%)	1 (20%)	10 (22.73%)	1 [†]	1.07 (0.136 to 8.451)
Hypertransaminasemia	28 (71.79%)	5 (100%)	33 (75%)	0.309 [†]	4.439 (0.2 to 98.436)
Hyperbilirubinemia	3 (7.69%)	3 (60%)	6 (13.64%)	0.013 [†]	14.6 (1.86 to 114.615)
Hypoalbuminemia	1 (2.56%)	0 (0%)	1 (2.27%)	1 [†]	2.333 (0.023 to 235.808)

† Fisher's Exact Test

DISCUSSION

Though miliary TB accounts for less than 1-3 % of all cases of Tuberculosis, it is fatal in almost all if left untreated.² In spite of stringent tuberculosis control programs worldwide, the incidence of miliary tuberculosis is expected to rise due to widespread use of immunosuppressive medications and the HIV/AIDS pandemic. Miliary TB has a tendency to affect organs with rich blood supply, such as the eyes, liver, lungs, adrenals, kidneys, and well as bone marrow as the spread of bacilli occurs via hematogenous route.

In the present study, mean age of the patients were 37.07 ± 19.4 years, with majority being males (61.36%). In similar study by Jemma et al, median age was 41 years; 50% of the patients were males. In the study by Mert et al,⁵ mean age was 44 years, and 54% of the patients were males. The predominance of male population in our study and other studies alike may be attributed to greater prevalence of smoking and hazardous occupational exposures among males.

Patients with miliary TB may have clinical findings and laboratory results that suggest this diagnosis, but they are not considered as diagnostic. From ARDS to fever of unknown origin (FUO), tuberculosis encompasses a wide spectrum of clinical manifestations. Fever, malaise, night sweats, cough, dyspnea, low appetite, and weight loss that lasts for usually >3 weeks were noted to be some of the common symptoms.

The most common signs and symptoms reported in the present study were fever, cough, sputum, anorexia, and dyspnea in 86.36%, 72.73%, 45.45%, 45.45%, and 40.91% patients, respectively. Similar findings were reported in the study by Mert et al.,⁵ with the most common clinical presentations being those of fever, fatigue, anorexia, and weight loss in 91%, 85%, and 66% patients, respectively. The findings included fever, lymphadenopathies, hepatomegaly, and splenomegaly in 100%, 21.3%, 20%, and 19% patients, respectively. The clinical profile of the patients in the present study is consistent with the findings in earlier studies.^{2,7,10}

The clinical importance and role of hematological parameters in miliary TB has been controversial through several studies

(agranulocytosis, monocytosis, pancytopenia, leukopenia, anemia, leukemoid reaction, leukocytosis, and thrombocytopenia).^{7,9,10}

The most common is anemia of chronic illness. Pancytopenia is uncommon, although leukopenia as well as thrombocytopenia is more common.⁵

In present study, hypertransaminasemia was present in majority (75.00%) of the patients; anemia, hyponatremia, hypokalemia, and hyperbilirubinemia were present in 70.45%, 43.18%, 22.73%, and 13.64% patients, respectively. This is likely due to tendency of miliary tuberculosis to affect liver function. Only hyperbilirubinemia significantly affected the mortality, while rest of the variables showed no significant association. Similarly, the correlation between hematological findings of the patients and their prognosis was not found in case series by Wang JY et al⁷ and Maartens G et al. Compared to our study, in the study by Mert et al.,⁵ majority of the patients were anemic (86%); hypoalbuminemia was present in 75% patients, lymphopenia (48%), hypertransaminasemia (37.6%), hyponatremia (12%), and pancytopenia was seen in 12% patients. Literature reports about 50% of the patients with increased levels of alkaline phosphatase and transaminase.⁷ Mert et al.,⁵ reported that in about one-third of the patients, levels of transaminase and alkaline phosphatase were increased.

In miliary TB, the levels of albumin, which is a negative acute phase reactant, are reported to be decreased. In the present study also, hypoalbuminemia was present in majority (75%) of the patients. Similarly, Mert et al.,⁵ found that hypoalbuminemia was seen in the majority of the patients (75%).

Radiologically, miliary nodules are classified into micronodules (1 to 3 mm) or macronodules (3 to 10 mm). Micronodules are considered as the classical miliary nodules; these are visualized on chest X-ray as "typical miliary pattern", and macronodules are visualized in the form of "atypical miliary nodules". In the present study, radiological findings included presence of miliary nodules in all the cases, and additional findings included pneumothorax, consolidation, cavitation and pneumomediastinum with surgical emphysema which were seen in 1 patient each.

Chest X-ray findings from our study were consistent with those of studies of Hussain SF et al¹¹ and Kim JH et al.⁹ with presence of miliary nodules in the range of 40–100%. The absence of miliary infiltrations at the time of hospital admission, however, does not rule out the diagnosis. Duration of minimum 2.5 weeks following the onset of fever is needed for radiographic detection of the lesions. As a result, if miliary tuberculosis is suspected, successive chest X-ray investigations should be performed.

In the study by Mert A et al.,⁵ the diagnosis was confirmed by detecting a miliary pattern on chest X-ray and/or HRCT in 90% of patients.⁵ It is advisable to perform a high-resolution computed tomography (HRCT) because HRCT demonstrates better sensitivity compared to chest X-ray for micronodules.

Survival of patients with miliary tuberculosis requires anti-TB medication. In the published miliary TB series, there is lack of consistency on the optimal duration of therapy. The duration of treatment was mentioned as 24 months by Sharma SK et al,¹⁰ 6 months by Wang JY et al.,⁷ and 9 months by Hussain SF et al.¹¹ As recommended in the guidelines by the "American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America" and British Thoracic Society, in miliary TB without meningitis, 6 months' therapy should be continued. In the present study, standardized treatment in form of RHEZ was given in 31 (70.45%) patients, and non-standardized treatment was given in 13 (29.55%) patients.

Among the various sociodemographic, clinical and laboratory parameters, in the present study, only hyperbilirubinemia showed significant association with mortality (P=0.013). Compared to our study, as reported by Kim JH et al⁹ and Hussain SF et al,¹¹ increasing age, dyspnea, changes in mental health, meningitis, and inability to start therapy timely are the main risk factors that predict mortality. Among these, the important ones include failure to confirming diagnosis and treat timely.⁵

In the study by Mert et al.,⁵ there was significant association between factors such as age, level of albumin and hemoglobin, miliary pattern, and mental changes with mortality with negative correlation.

Among the various symptoms, fever being the commonest, it has been observed that prolonged fever carries an adverse prognosis.⁵ Our study reports a good recovery from the fever over a median duration of 15 days. In concordance with our study where mean duration of fever was found to be 21 days (80.65% cases), Mert et al.⁵ reported fever resolution in 75% within 21 days (mean duration 24 days). A better fever recovery rate in our study might be because we initiated standardized treatment in most of the patients which may have led to better outcome. It was significantly determined in our study that all deaths were among the patients who took non-standardized treatment. However, this fact needs further validation.

Cases of miliary tuberculosis if left untreated, have a mean life expectancy of 1 year.^{2,10} The mortality rate as reported by previous studies was approximately 25% (in the range of 14% to 30%), and appears to have been constant in the past 25 years.^{2,7,9,10} The mortality rate in present study was 11.3% as compared to the study by Mert et al.⁵ which reported a higher mortality rate (17%) and Jemma MB et al⁶ which reported lower mortality rate (4.5%).

Our study results suggest a lower mortality with a standardized treatment and managing hyperbilirubinemia, which carried a significantly higher risk of mortality.

Limitations Of The Study

There were certain limitations of this study. First limitation is the retrospective design. But as miliary TB is rarely found, conducting a prospective cohort study will take more time. Also, because this was a retrospective study, information on factors may be missing.

CONCLUSION

Our study concludes that miliary tuberculosis occurs more commonly in the third decade of life and is more prevalent in males. Clinical presentations may be variable and oftentimes include extra-pulmonary signs, symptoms as well as radiological features. The most frequently deranged hematological parameters include dyselektrolytemia and deranged liver function wherein hyperbilirubinemia has a greater association with mortality than others. Miliary tuberculosis, though rare, requires prompt identification and timely initiation of treatment with standardized regimes as delay thereof carries significant risk of mortality.

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REFERENCES

- Chakaya J, Khan M, Ntoumi F, Aklilu E, Fatima R, Mwaba P, et al. Global Tuberculosis Report 2020 – Reflections on the Global TB burden, treatment and prevention efforts. *International Journal of Infectious Diseases* 2021;S1201971221001934. <https://doi.org/10.1016/j.ijid.2021.02.107>.
- Ray S, Talukdar A, Kundu S, Khanra D, Sonthalia N. Diagnosis and management of miliary tuberculosis: current state and future perspectives. *Ther Clin Risk Manag* 2013;9:9-26.
- Mert A, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, et al. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology* 2001;6(3):217-24.
- Mert A, Ozaras R. Clinical importance of miliary pattern in the chest X-ray of a patient with fever of unknown origin. *Intern Med Tokyo Jpn* 2005;44:161.
- Jemaa MB, Koubaa M, Ayed HB, Marrakchi C, Trigui M, Hammami F, et al. 768. Epidemiological and clinical profile of miliary tuberculosis in Southern of Tunisia Maissa Ben Jemaa. *Open Forum Infectious Disease* 2018;5(suppl_1):S275-S276.
- Wang JY, Hsueh PR, Wang SK, Jan IS, Lee LN, Liaw YS, et al. Disseminated tuberculosis: a 10-year experience in a medical center. *Medicine (Baltimore)* 2007;86(1):39-46.
- Maartens G, Willcox PA, Benatar SR. Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. *Am J Med* 1990;89:291-6.
- Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. *Rev Infect Dis* 1990;12:583-90.
- Sharma SK, Mohan A, Pande JN, Prasad KL, Gupta AK, Khilnani GC. Clinical profile, laboratory characteristics and outcome in miliary tuberculosis. *QJM* 1995;88(1):29-37.
- Hussain SF, Irfan M, Abbasi M, Anwer SS, Davidson S, Haqqee R, et al. Clinical characteristics of 110 miliary tuberculosis patients from a low HIV prevalence country. *Int J Tuberc Lung Dis* 2004;8(4):493-9.
- Andreu J, Mauleón S, Pallisa E, Majó J, Martínez-Rodríguez M, Cáceres J. Miliary lung disease revisited. *Curr Probl Diagn Radiol* 2002;31(5):189-97.
- Collazos J, Guerra E, Mayo J, Martínez E. Tuberculosis as a cause of recurrent fever of unknown origin. *J Infect* 2000;41(3):269-72.
- Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society of America. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167(4):603-62.
- Joint T. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1998;53(7):536-48.