Value of Adenosine Deaminase (ADA) in Ascitic Fluid for the Diagnosis of Tuberculous Peritonitis

A Meta-analysis

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Background and Goals: Adenosine deaminase (ADA) levels are used for diagnosing tuberculosis in several locations and although many studies have evaluated ADA levels in ascitic fluid. These studies have defined arbitrary cut-off points creating difficulties in the clinical application of the results. The goals of this study are: to determine the usefulness of ADA levels in ascitic fluid as a diagnostic test for peritoneal tuberculosis (PTB) and define the best cut-off point.

Study: A systematic review was done on the basis of 2 independent searches. We selected prospective studies that included consecutive patients. Diagnosis of PTB had to be confirmed by bacteriologic or histologic methods and ADA levels determined by the Giusti method. Inclusion/exclusion criteria were applied by 2 independent reviewers. A receiver operating characteristic curve was constructed to establish the optimal cut-off point and the likelihood ratios (LRs) estimated using fixed-effect pooled method.

Results: Twelve prospective studies were found. Four of them met the inclusion criteria and were thus included in the meta-analysis. They included 264 patients, of which 50 (18.9%) had PTB. ADA levels showed high sensitivity (100%) and specificity (97%) using cut-off values from 36 to 40 IU/L. The included studies were homogeneous. Optimal cut-off point was determined at 39 IU/L, and LRs were 26.8 and 0.038 for values above and below this cut-off.

Conclusions: This study supports the proposition that ADA determination is a fast and discriminating test for diagnosing PTB with an optimal cut-off value of 39 IU/L.

Key Words: adenosine deaminase, ascites, tuberculous peritonitis, meta-analysis

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Tuberculosis (TB) is an endemic disease in several regions, particularly in developing countries.[1] Its incidence is also rising in developed countries. For example, in the United States this higher incidence is associated with people who are homeless, in jail, immigrants, and people with underlying conditions such as acquired immunodeficiency syndrome, malignancies, diabetes mellitus, and under peritoneal dialysis.[2–4] Though pulmonary presentation is the most frequent, extrapulmonary presentation is not unusual, affecting 10% to 15% of immunocompetent patients and 50% to 70% of acquired immunodeficiency syndrome patients. Peritoneal tuberculosis (PTB) is currently the sixth most frequent extrapulmonary location and it increases proportionally to the rising incidence of TB worldwide.[5]

It is well known that confirmation of PTB is difficult and slow due to the need for histologic confirmation of caseous granulomas or bacteriologic confirmation by ascitic fluid (AF) acid-fast smears or mycobacterial cultures. Because the results of mycobacterial cultures might take more than 4 weeks and acid-fast stained smears are disappointingly insensitive,[6] confirmation often requires invasive procedures such as laparoscopy. Therefore a quick, noninvasive test for the diagnosis of PTB would be most helpful.

Adenosine deaminase (ADA) is a purine-degrading enzyme, catalyzing adenosine deamination in an irreversible way, producing inosine in this biochemical process. ADA is an enzyme widely distributed in tissues and body fluids. However, the most important biologic activity is related to lymphoid tissue, because ADA is necessary for proliferation and differentiation of T lymphocytes. T lymphocytes have ADA levels 10 to 12 times higher than B lymphocytes. ADA activity varies depending on proliferative status and maturity of cells. During lymphocyte proliferation, the enzyme activity varies inversely to the maturity state of lymphocytes.[7]

Several studies demonstrate the use of ADA in the diagnosis of TB in other fluids including meningeal, pleural, and pericardial,[8] suggesting that an increasing

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ADA activity relates to the intensity of stimulation and the maturation state of the lymphocyte, due to the immune cellular response against *Mycobacterium tuberculosis*. ADA level measurement in body fluids has emerged as an attractive alternative for the diagnosis of TB because the description of fast determination methods, such as the technique described by Giusti in 1981[9] which is the most extensively described in the literature and is one of the most used in clinical practice among countries with high prevalence of TB. Even though its use has become popular in many countries, there is no consensus regarding its current usefulness in clinical practice, having limited use in the United States.[10]

Considering the controversy about the current role of ADA as a diagnostic tool for PTB,[10–12] we conducted a systematic review of the literature and a meta-analysis to determine the usefulness of ADA levels in diagnosing PTB and the optimal cut-off point of ADA levels to guide clinical practice.

METHODS

Study Identification and Selection

Two independent reviewers searched MEDLINE using the following strategy: [(''ADA'' or ''adenosine deaminase'') and (''tuberculosis'' or ''tuberculous'') and ''peritonitis''], from 1966 to October 2003. There were no limits regarding language of publication. After this first searching stage, the reference lists of all related articles were hand searched. The MEDLINE search was updated from October 2003 to February 2006, and we did not find any more eligible studies.

Our inclusion criteria were: prospective studies including consecutive patients; ADA levels determined by Giusti method; and a diagnosis of PTB on the basis of positive mycobacterial cultures or positive acid-fast stain or biopsy showing granulomatous or caseous lesions. Studies using other spectrophotometrical methods such as the one described by Slaats et al,[13] or alternative biochemical determinations[10]; studies using clinical response as diagnostic gold standard for PTB; review articles; case reports and articles with less than 25 patients were excluded from meta-analysis. Studies not reporting ADA levels in AF for individual patients and that failed to do so after the author was contacted were also excluded.

The inclusion/exclusion criteria were applied by 2 independent reviewers. Definite inclusion of articles depended upon concordance between reviewers.

Quantitative Analysis

The κ coefficient was calculated as a measure of agreement between reviewers using ''Measurement of Clinical Agreement for Categorical Data: The Kappa Coefficients'' software (created by Louis Cyr and Kennon Francis, 1992). A set of receiver operating characteristic (ROC) curves was constructed to establish the best cut-off point for each study separately and then to obtain an homogeneal optimal cut-off point for all the studies. For this, the software developed by Med-Calc (version 7.6.0.0) was used. Heterogeneity among studies assessed by χ^2 test and the discriminatory power of the meta-analysis determined by a sROC curve were calculated with the software Meta-Disc version 1.1.1.[14] Likelihood ratios (LRs) and 95% confidence intervals were computed using the method described by Simel et al. Fixed-effect pooled estimates of the LRs (with $\delta = 0.25$ added to each cell count) applying the general meta-analytic method advanced by Fleiss. Other operations were performed by Microsoft Excel 97 software.

RESULTS

Forty-three related articles in MEDLINE and 21 additional articles were identified by hand searching reference lists. From these 64 studies, 21 articles were clinical series, prospective and retrospective studies. After exclusion of nonprospective studies, 12 prospective articles were found.[8,12,15–24] The characteristics of these 12 studies, including the methods used to determine ADA activity, are described in Table 1. Four prospective articles were excluded from the meta-analysis because

TABLE 1. Characteristics of Prospective Trials

Study	N	GS	ADA Activity/Method	Sensitivity (%)	Specificity (%)	Cut-off Value
Sathar et al[19]	92	B+H	Spectrophotometric method	93	96	30 IU/L
Sapunar et al[24]	25	B+H	Giusti method	UP	UP	UP
Voigt et al[16]	64	B+H	Giusti method	100	96	32 IU/L
Brant et al[17]	44	B+H	Giusti method	100	92	31 IU/L
Martinez-Vazquez et al[23]	66	B+H	Giusti method	UP	UP	UP
Bhargava et al[12]	87	B+H	Giusti method	100	97	36 IU/L
Ribera et al[22]	86	B+CE	Giusti method	100	97	40 IU/L
Sathar et al[21]	52	H+CE	Kinetic determination	96	100	30 IU/L
Burgess et al[15]	178	H+CE	Giusti method	94	92	30 IU/L
Segura et al[8]*	136	B+H	Modified Giusti method	100	92	0.71 ukat/L
Martinez Vasquez et al[18]*	57	B+H+CE	Giusti method	100	95	43 IU/L
Soliman[20]	50	B	Ellis and Goldberg	94.4	100	28 IU/L

*Studies including measurement of ADA activity from different body fluids.

B indicates positive bateriology (culture or acid-fast stain); CE, clinical evolution and treatment response compatible with TB; GS, gold Standard used in the study; H, positive histology (biopsy showing granulomatous or caseous lesions); UP, unpublished data.

TABLE 2. Description of ADA Cut-off Value, Sensitivity, and Specificity Among the Selected Articles

Study	Cut-off ADA Value (IU/mL)	Sensitivity (%)	Specificity (%)	ROC Curve Best Cut-off*	Sensitivity (%)*	Specificity (%)*
Ribera et al[22]	>40	100	97	>37	100	97
Bhargava et al[12]	>36	100	97	>32	100	97
Martinez-Vazquez et al[23]	—	—	—	>43	100	100
Sapunar et al[24]	—	—	—	>38	100	100

(—) Not reported.
*Sensitivity, specificity, and cut-off value calculated using ROC curve analysis.

they used non-Giusti methods.[8,19–21] If we analyze the results of these studies, ADA activity using non-Giusti methods showed high sensitivity, ranging from 93% to 100%, and high specificity, ranging from 92% to 100% using cut-off values arbitrarily assigned by the authors.[8,19–21] Another 4 prospective studies were excluded because they used clinical response as the diagnostic gold standard for PTB[15–21] or did not report the ADA levels in AF for individual patients and that failed to do so after author was contacted.[16,17] Therefore, only 4 articles were finally selected for the meta-analysis, according to the inclusion criteria previously described, as shown in Table 2.[12,22–24] The selection process is explained in detail in Figure 1. The κ coefficient between the 2 reviewers for article selection was 0.43.

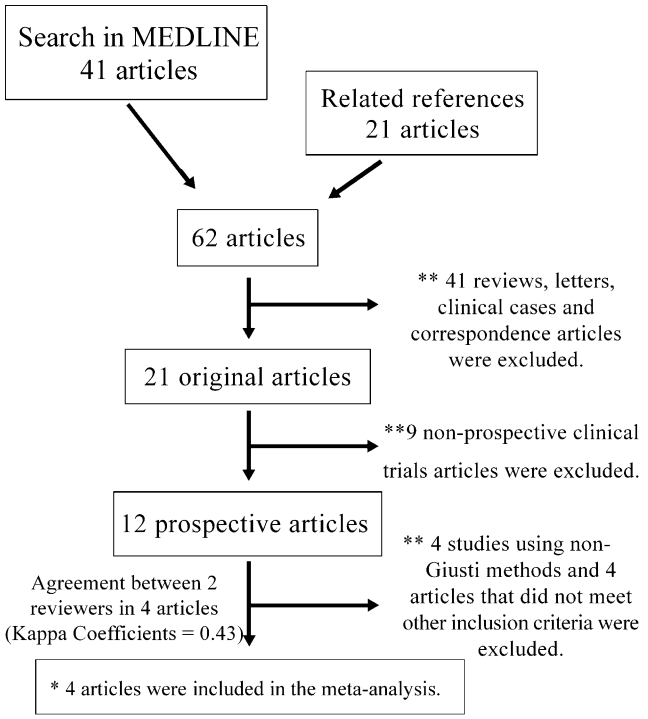

FIGURE 1. Selection process of articles from meta-analysis. *Inclusion criteria: prospective studies including consecutive patients; ADA levels determined by Giusti method; and a diagnosis of PTB on the basis of the positive mycobacterial cultures or positive acid-fast stain or biopsy showing granulomatous or caseous lesions. **Exclusion criteria: studies using non-Giusti methods; studies using clinical response as diagnostic gold standard for PTB; review articles; case reports and articles with less than 25 patients were excluded from meta-analysis. Studies not reporting ADA levels in AF for individual patients and that failed to do so after the author was contacted were also excluded.

The 4 selected articles measured ADA activity in AF of patients with ascites secondary to various illnesses, as shown in Table 3. From a total of 264 patients with ascites, 50 (18.92%) were caused by PTB.

Sensitivity and specificity of different cut-off values, arbitrarily assigned by the authors, were reported in 2 studies. Sensitivity was 100% (CI 95% 100-100) and specificity 97% (CI 95% 93-100) for both. The other 2 studies reported the ADA value of each individual patient. AF ADA levels proved to have high sensitivity and specificity for diagnosing PTB in all studies. Sensitivities and specificities for different cut-off points, determinated by individual ROC curves, ranging from 32 to 43 IU/L are shown in Table 2.

The sROC curve using the combined data of the included articles showed an area under curve of 0.99 (SE: 0.0003) with a Q* test of 0.97 (SE: 0.0009) (Fig. 2).

The meta-analysis of the 4 articles (264 patients) using fixed-effect model and a cut-off ADA value of 39 IU/L established a sensitivity of 100% (CI 95%: 92.9-100) heterogeneity test: $\chi^2 = 0.0$ $P = 1$, and a especificity of 97.2% (CI 95%: 94-99) heterogeneity test: $\chi^2 = 1.14$ $P = 0.768$. The LR for values equal or higher than 39 IU/L was 26.8 (CI 95%: 13.3-54.0) heterogeneity test: $\chi^2 = 0.16$ $P = 0.984$, and the LR for values below 39 IU/L was 0.038 (CI 95%: 0.01-0.150) heterogeneity test: $\chi^2 = 0.24$ $P = 0.9$.

DISCUSSION

PTB usually arises from reactivation of latent tuberculous foci in the peritoneum established from hematogenous spread from a primary lung focus.[4] It is manifested clinically as ascites of insidious onset, abdominal pain, and fever.[25]

Diagnosis of PTB currently depends on invasive techniques such as laparoscopic biopsy, or cultures that, in addition to having a low sensitivity (approximately 20%), require long incubation periods.[6] It has been

TABLE 3. Frequency of the Different Etiologies of Ascites Among Patients Described in the Selected Articles

	TBC		Cancer		SBP*		Cirrhosis		Others†		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ribera et al[22]	16	18.6	18	20.9	18	20.9	20	23.3	14	16.3	86	100
Bhargava et al[12]	17	19.5	22	25.3	7	8.0	31	35.6	10	11.4	87	100
Martinez-Vazquez et al[23]	10	15.1	17	25.7	8	12.1	23	34.8	8	12.1	66	100
Sapunar et al[24]	7	28.0	6	24.0	4	16.0	7	28.0	1	4.0	25	100
Total	50	18.9	63	23.9	37	14.0	81	30.7	33	12.5	264	100

*Spontaneous bacterial peritonitis.
†Less frequent conditions such as pancreatic ascites, Meigs syndrome and quilous ascites.

clearly established that a delayed diagnosis, such as waiting for cultures, is associated with an increased mortality.[25] PTB could have a poor prognosis even with appropriate treatment due to a delay in starting specific antituberculous therapy and mortality over 50% have been reported.[25] The diagnosis of PTB supported by the use of ADA in AF in small clinical series demonstrated a time reduction in the diagnosis from 35 to 6 days.[25]

Our systematic review on the usefulness of a noninvasive, fast method like ADA for the diagnosis of PTB might help clinicians to decide whether to treat or not for TB in patients with ascites.

An important strength of systematic reviews is to summarize the evidence regarding a focused clinical question, allowing to include a wide selection of articles. Our review includes studies in several languages (Spanish, Italian, Portuguese, and English) some of them from developing countries, with a higher prevalence of TB than developed countries. Therefore our results may be applied in different settings.

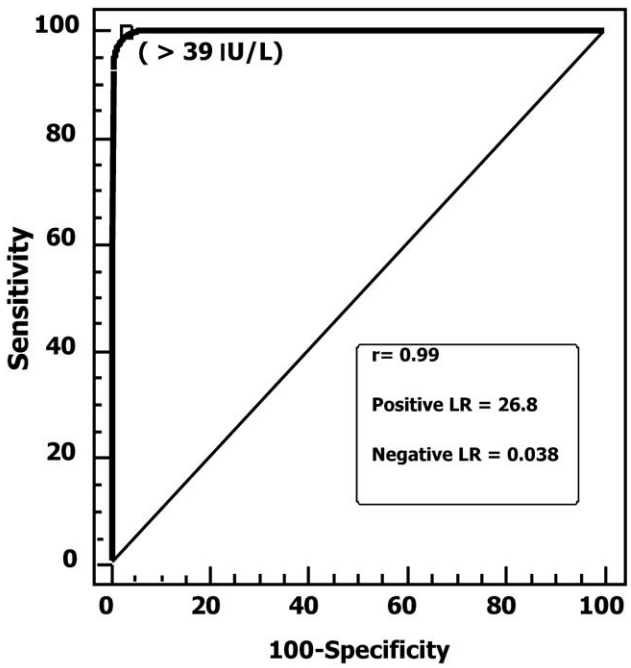

FIGURE 2. ROC curve for ADA value in the diagnosis of PTB. A cut-off ADA value ≥ 39 IU/L has a sensitivity of 100% and a specificity of 97.2% with a positive LR of 26.8. $r = 0.99$.

The agreement of the independent reviewers, represented by κ coefficient value, was only moderate probable due to the low number of selected articles. Therefore, a disagreement in 1 article produced an important decrease in the coefficient number.

To avoid heterogeneity among studies and maintain the possibility to calculate the optimal meta-analyzed cut-off point for this method, we chose to include only 1 ADA technique, the method described by Giusti, which has been the most extensively described in the literature and one of the most used in clinical practice among the countries with high prevalence of PTB. The meta-analysis was carried out considering the studies that successfully met the inclusion criteria, measuring ADA levels with the Giusti method.[9] However, we included in the systematic review those studies that fulfill the inclusion criteria measuring ADA activity with other, non-Giusti method.[8,10,13,19–21] All the studies found that ADA is a sensible and specific method in the diagnosis of PTB, independently of the method used to measure the ADA activity (Table 1).

Hillebrand et al,[10] made one of the most important contributions to the current knowledge of ADA activity and ascites in a retrospective study, including 356 frozen AF samples. However, we were not able to include it in the meta-analysis because the study did not fulfill the inclusion criteria and they used a non-Giusti method. It is important to consider that is not clear in the description of the methodology if some patients had more than 1 AF sample, which could affect the validity of the results. Despite these issues, Hillebrand et al[10] found that ADA activity showed a high specificity for the PTB diagnosis. They used a non-Giusti method to determine ADA activity, obtaining a lower cut-off value in comparison with Giusti method, showing it is not possible to have a unique cut-off value for all the different techniques.[10]

Several studies have stated the importance of establishing the use of ADA in the diagnosis of PTB in patients with cirrhosis due to specific differences in this particular condition. Firstly, 50% of patients with PTB in United States have cirrhosis as a primary cause of ascites and PTB.[5] The second reason is because patients with cirrhosis have an increased susceptibility to develop PTB

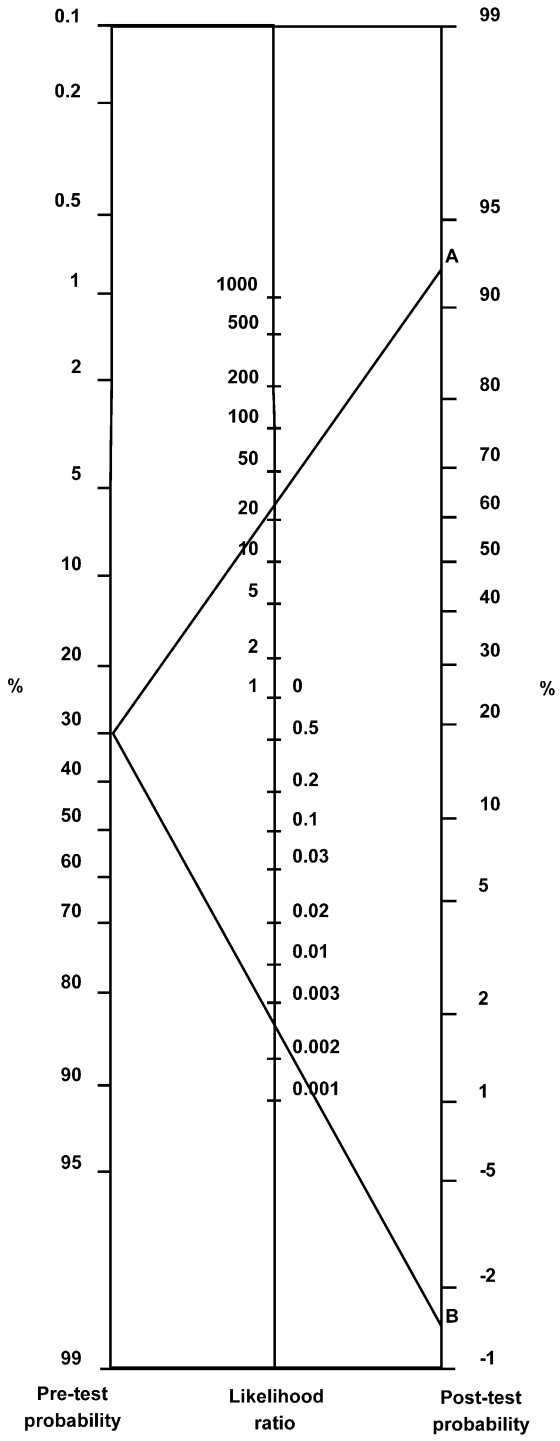

FIGURE 3. Nomogram for interpreting diagnostic test results, adapted from Fagan.[33] A, Posttest probability for a patient with ADA value >39 IU/L (92%). B, Posttest probability for a patient with ADA value <39 IU/L (1%).

and this complication could be related to the higher risk of spontaneous bacterial peritonitis observed in patients with cirrhosis.[26] Finally, we need to consider that laparoscopy and laparotomy are frequently contraindicated in those patients due to a high risk in the anesthesic and surgical procedures.[27]

Some authors found lower levels of ADA activity in patients with cirrhosis in comparison with patients without cirrhosis. In particular, Hillebrand et al showed a lower sensitivity of ADA for diagnosing PTB among patients with this condition, perhaps due to dilution of AF, thus reducing ADA activity. Our study cannot conclude if such is the case using the Giusti method, because none of the 4 articles included in our analysis established the presence or absence of cirrhosis in the group of patients with PTB. It is important to consider that a study comparing PTB in cirrhotic and noncirrhotic patients found an elevated ADA in all cirrhotic patients, suggesting that it may actually have good sensitivity in this clinical scenario.[28] We can reach no conclusions as to whether AF ADA levels will render the same results for patients with or without cirrhosis, because the included studies did not give this information.

A few publications shown that patients HIV(+) with PTB could have lower ADA levels in comparison with patients HIV(−) with PTB, explained by a low lymphocyte activity due to the CD4 lymphocyte compromise in HIV. In relation to the same issue, Sathar et al[29] shown no significant differences in the ADA activity levels of patients with PTB with or without HIV.

The 4 trials included a total of 264 patients, with a PTB frequency of 18.92%. This is higher than the reported rate of PTB as cause of ascites in the United States (approximately 2%).[30] It must be stressed that our study includes population from Chile and India, where a higher frequency of TB was observed at the time when studies were performed.

Of the 264 patients with ascites, 50 where caused by TB, and all of them had ADA values ≥ 39 IU/L. Only 6 patients with ADA value over this cut-off point had other diagnosis, but ADA values ≥ 56 were associated only with the PTB diagnosis. It is generally accepted that a diagnostic test with a LR < 0.1 has a high power of discrimination to rule out a disease and that a LR > 10 generally confirms a particular disease.[31] We found that ADA levels higher than or equal to 39 IU/L were associated to a LR of 26.8 and an ADA value lower than 39 IU/L had a LR of 0.038. According to this, a cut-off point of 39 IU/L will allow accurate confirmation or not of the diagnosis of PTB.

Hence a hypothetical 55-year-old Chilean patient without clinical cirrhosis, has a 28% pretest probability of having PTB,[24] if the AF study shows an ADA level of 43 IU/L. He has a 92% posttest probability of having PTB. The same patient with an ADA value of 36 would have a posttest probability of having PTB of 1%. This result was obtained applying the LR to the nomogram adapted from Fagan, shown in Figure 3.[32] The clinical relevance of this test is evident ever because it may avoid the need to confirm the diagnosis with invasive techniques such as laparoscopy.

Of the 4 false-positive patients, 3 were caused by peritoneal cancer and 1 by spontaneous bacterial peritonitis. This can be explained because ADA is an enzyme related to proliferation and differentiation of lymphocytes that are present frequently in both exudates.

One of the most important problems associated with the diagnosis and treatment of PTB supported by ADA activity is related with the appearance of *Mycobacterium tuberculosis* resistant to antibiotic therapy. The recommendation of Center for disease control is to start with an empiric treatment using a 4-drug combination. We must consider that Center for disease control insists in the need of a sensitivity in vitro test in every patient with PTB to determine the epidemiology of *Mycobacterium tuberculosis* in United States.[33,34] However, it is known that even using the most advanced techniques to isolate the *Mycobacterium*, the rate of positive test is still low and we consider ADA activity a practical and useful approach to take therapeutic decision in patients with suspected PTB.

In conclusion, measurement of ADA level in AF is a fast and accurate test for diagnosing PTB. It has enough discriminatory power to either confirm or rule out the diagnosis of PTB in most cases. The beginning of empirical treatment when a patient has a high ADA value in AF seems to be a good approach while waiting for the results of mycobacterial cultures or biopsies.

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