Evidence-Based Commentary: Ascitic Adenosine Deaminase in the Diagnosis of Peritoneal Tuberculosis

Amol Sonyabapu Dahale[1] Ashok Dalal[2]

[1] Department of Medical Gastroenterology, Dr. D. Y. Patil Medical College, Dr. D. Y. Patil University, Pune, Maharashtra, India
[2] Department of Medical Gastroenterology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi, India

Address for correspondence Ashok Dalal, MD, DM, Department of Medical Gastroenterology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, New Delhi 110002, India (e-mail: drashokdalal83@gmail.com).

J Gastrointest Infect 2022;12:57–60.

How is Peritoneal Tuberculosis Suspected and Diagnosed?

Peritoneal tuberculosis (TBP) forms a significant proportion of abdominal tuberculosis (TB). Incidence of TBP in literature varies from 39 to 77% of total abdominal TB cases.[1] The myriad clinical presentations, paucibacillary nature of abdominal TB, and fastidious nature of tubercular bacteria make it very difficult to suspect TBP and near impossible to prove by routine microbial analysis. Peritoneoscopy with peritoneal biopsies for histopathology and bacteriological studies may be required if noninvasive methods are unable to clinch the diagnosis.[2,3] Peritoneoscopy is invasive with a 3% adverse events rate associated with it.[3] Additionally, most of these patients are surgically unfit and de facto high risk like having underlying cirrhosis. Given the higher incidence and limited resources in highly prevalent TB areas, highly sophisticated and invasive investigations may not be within reach of the majority of the population. Adenosine deaminase (ADA) in peritoneal fluid offers a feasible, sensitive, and highly specific test for TBP. Given the varied incidence of TB in developed and developing nations, the utility of ascitic ADA is likely to be more in high TB endemic regions. To add to the confusion, multiple testing methods and different cutoffs have been reported. Evaluation of the ascitic fluid including culture and measurement of ADA are the first line strategy for diagnosis of tuberculous peritonitis.

What is Adenosine Deaminase and Its Physiological Role?

ADA is an important enzyme in the purine metabolism pathway.[4,5] It degrades adenosine to inosine and ammonia which is further converted to uric acid. ADA helps in proliferation of T lymphocytes and monocytes. ADA has two isoenzymes: ADA1 and ADA2. ADA1 is ubiquitous in all cell forms including lymphocytes and monocytes. ADA2 specifically belongs to monocytes. Activity in TB is mainly attributed to ADA2.[6,7] But as separate analysis of ADA1 and ADA2 is not more useful than total ADA, generally total ADA is measured in view of low cost and wider availability. ADA activity can be measured by direct or indirect methods. Direct method devised by Giusti and Galanti measures rate of formation of either inosine or ammonia.[8] Another method devised by Slaats et al is an indirect method and measures decrease in NADH by spectrophotometry which reacts with ammonia generated.[9] There are few other methods with modifications but those are commercially not available. Given the fact that the basis remains the same, one expects high concordance among all methods, but no head-to-head comparison studies have been done. Still, looking at cutoffs in different studies the results among different methods appear to be concordant though not exact replicable. Most of the commercial kits of ADA available have a linearity of detection limit from 5 to 150 IU/mL.

received
April 16, 2022
first decision
May 1, 2022
accepted after revision
May 25, 2022

DOI https://doi.org/10.1055/s-0042-1757402.
ISSN 2277-5862.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

What is the Role of Ascitic Fluid Adenosine Deaminase in Diagnosis of Peritoneal Tuberculosis?

ADA plays a vital role in proliferation and differentiation of lymphocytes, especially T lymphocytes. It is essential for maturation of monocytes and their transformation to macrophage. Hence, ADA is a significant indicator of activity of cellular immunity. ADA deficient humans exhibit lymphopenia. In TB, mycobacterial antigen stimulates T cells which parallel the increase in ADA levels, especially in body fluids where active inflammation is going on. Hence, ADA has been proposed to be a useful surrogate marker for TB because it can be detected in body fluids such as pleural, pericardial, and peritoneal fluid. The only concern regarding it is its specificity, as it is a nonspecific marker of T cell activation.[6,7] So far, multiple studies in pleural and peritoneal effusions have demonstrated excellent sensitivity and specificity in highly endemic countries and suitable clinical scenarios. Very few nontubercular causes have been identified as differential diagnosis of increased ADA which can be sorted out with proper clinical evaluation and further investigations.

What are the Methods for Diagnosis of Peritoneal TB and What are Their Fallacies?

The most definitive test in diagnosis of PTB is peritoneoscopy with peritoneal biopsy demonstrating either caseating granuloma or bacteriological proof positive acid-fast bacteria (AFB) staining or culture.[2] Surprisingly, bacteriological yield even in peritoneal biopsy is poor and variable, for AFB positivity it ranges from 3 to 25% while for culture yields result in 38 to 92% samples. Even touted as a game changer for pulmonary TB the Gene-Xpert has sensitivity of 60% in large size peritoneal biopsies.[10] Furthermore, peritoneal biopsy is difficult to obtain, invasive in nature with a small but definite adverse event risk. Ascitic fluid tapping and analysis is easy to do as day care and yields immediate results. But as with all abdominal TB, TBP is a paucibacillary disease with very low yield of mycobacteria in all samples and by all methods. Given the low yield of mycobacterial TB in ascitic fluid (AFB positivity 3%, culture 35%, Gene-Xpert 30%), hunting for bacteriological yield in ascitic fluid is often futile.[2,11] ADA in ascitic fluid in such a scenario carries importance given its high sensitivity and specificity.

What is the Role of Ascitic Fluid Adenosine Deaminase in Diagnosis of Peritoneal TB?

First reports of ADA in tubercular diagnosis were published way back in 1983. Two years later studies in TBP were published. The first study published in English literature by Martinez-Vazquez et al showed 100% sensitivity and 100% specificity.[12] Another study by Voigt et al in 1986 showed sensitivity of 95% and specificity of 98% at a cutoff value of 32.3 IU/L.[13] Multiple studies were published after that albeit using different methods. At the same time two studies from India showed similar sensitivity (100%) and specificity (96.6%) at a cutoff of 33 IU/L.[14] A different cutoff has been there for different studies due to different methods used. Till date three meta-analyses have been published on the role of ADA in TBP. Each meta-analysis has employed different study inclusion and exclusion criteria. Given that not many high-quality studies have been done in this regard the strength of analysis remains low. Despite this, all meta-analyses have concluded that ADA is a highly accurate marker with high specificity and sensitivity (►**Table 1**).

What is the Role of Adenosine Deaminase in Special Population in Diagnosis of Peritoneal TB?

Human Immunodeficiency Virus Patients

Initial studies in human immunodeficiency virus (HIV) patients had shown low ADA values in TBP. Lymphopenia and immunosuppression with specific defects in T cells in HIV patients could be the explanation. Later study by Sathar et al has shown no difference in ADA value in HIV and non-HIV patients.[18] As of now ADA is being commonly employed for TBP diagnosis in all immunocompromised patients though systematic studies are lacking in this area.

Liver Cirrhosis

Value of ascitic fluid protein generally correlates with ADA values. As cirrhotic patients with TB often have low total protein value, the use of ADA in cirrhosis has always been debated. Initial studies suggested that the sensitivity of

Table 1 Meta-analysis published till date

Study	Journal	Year	Study screened	Study included	Sensitivity	Specificity	Cutoff	Suggested cutoff	Methods used in studies
Riquelme et al[15]	J Clin Gastro	2006	12	4	100%	97%	36–40 IU/L	39 IU/L	Giusti
Shen et al[16]	Arch Med Sci	2013	NA	16	93%	96%	30–40 IU/L	NA	Guisti-11 Non-Guisti-5
Tao et al[17]	Diagn Microbiol Infect Dis	2014	23	17	93%	94%	35 IU/L	NA	Guisti-12 Non-Guisti-5

Table 2 Fallacies in adenosine deaminase testing

False positive results	False negative results
Lymphoma	Early stage of peritoneal TB (where neutrophil dominate)
Malignant ascites	Partially treated peritoneal TB
Secondary bacterial peritonitis	Liver cirrhosis
Pyoperitoneum	Severe combined immunodeficiency
Connective tissue disorders	**Role unclear**
Pancreatic ascites	End-stage renal disease patients
Ascites secondary to lymphatic obstruction or lymphangiectasia	Patients on immunosuppression

Abbreviation: TB, tuberculosis.

ascitic ADA in the setting of cirrhosis is low.[19] But recently few good studies published have shown that ADA has been equally effective and accurate in cirrhotic in presence of TBP.[20] A recent study published sensitivity and specificity of 93 and 94%, respectively, at a cutoff of 39.9 IU/L.

In other special population groups like end-stage renal disease, pregnancy, and patients on immunosuppression, data are meager and hence conclusion cannot be drawn.

What are the Fallacies in Adenosine Deaminase Testing?

Though ADA is highly sensitive, false positive results are seen in pancreatic ascites, malignant ascites, and other infective ascites (►**Table 2**). But overall, such cases are uncommon and given the correct clinical scenario posttest probability of ADA positivity is very high in TBP.

What are the Alternative to ADA Testing?

Multiple markers alternative to ADA are being proposed to be used in diagnosis of TBP. Ascitic fluid glucose was found to be low, lactate dehydrogenase was found to be high, and CA-125 was found to be high, but none of this is specific and sensitive enough to be used. Only closest candidates to ADA for TBP diagnosis are immunological test like ascitic fluid interferon γ and ascitic fluid interferon γ release assay, which are equally sensitive and specific to ADA.[21] Despite that, the high cost, limited availability, and no additional advantage over ADA, these are never being incorporated into clinical practice.

What are the Current Gaps in Knowledge and Challenges in Use of Adenosine Deaminase in Peritoneal Tuberculosis?

Despite effort put and formation of guidelines like INDEX TB guidelines for extrapulmonary TB, a recent study found that 96.4% clinicians orders ADA for TBP diagnosis and cutoffs used by them are different.[22,23] Uniform methods of detection with a large number of study populations and multicenter studies are lacking in this field and this may be the reason of different practices employed. Given the problem with gold standard diagnosis, such studies in future seems to be unlikely and active efforts for such studies as well as education of clinicians appears to be necessary to improve practices in TBP diagnosis.

Conclusion

ADA is an important tool for diagnosis of TBP in countries like India with high prevalence of TB. It has very high sensitivity and specificity at a cutoff value of 39 IU/L and remains a cost-effective tool for the diagnosis of TBP.

Ethical Statement
Not applicable.

Author Contributions
Amol Dahale: Initial draft and approval. Ashok Dalal:- Initial draft, revision and approval.

Data Availability Statement
There is no data associated with this work.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
None.

References

1 Mimidis K, Ritis K, Kartalis G. Peritoneal tuberculosis. Ann Gastroenterol 2005;18(03):325–329
2 Sanai FM, Bzeizi KI. Systematic review: tuberculous peritonitis–presenting features, diagnostic strategies and treatment. Aliment Pharmacol Ther 2005;22(08):685–700
3 Bhargava DK, Shriniwas , Chopra P, Nijhawan S, Dasarathy S, Kushwaha AK. Peritoneal tuberculosis: laparoscopic patterns and its diagnostic accuracy. Am J Gastroenterol 1992;87(01): 109–112
4 Barua R, Hossain MA. Adenosine deaminase in diagnosis of tuberculosis: a review. Anwer Khan Modern Med Coll J 2014;5 (02):43–48
5 Boonyagars L, Kiertiburanakul S. Use of adenosine deaminase for the diagnosis of tuberculosis: a review. J Infect Dis Antimicrob Agents 2010;27(02):111–118
6 Alrajhi AA, Halim MA, al-Hokail A, Alrabiah F, al-Omran K. Corticosteroid treatment of peritoneal tuberculosis. Clin Infect Dis 1998;27(01):52–56
7 Pacheco R, Martinez-Navio JM, Lejeune M, et al. CD26, adenosine deaminase, and adenosine receptors mediate costimulatory signals in the immunological synapse. Proc Natl Acad Sci U S A 2005; 102(27):9583–9588

8 Giusti G, Galanti B. Colorimetric method. adenosine deaminase. In: Bergmeyer HU, ed. Methods of Enzymatic Analysis. 3rd ed. Weinheim: Verlag chemie; 1984
9 Slaats EH, Asberg EGMT, van Keimpema ARJ, Kruijswijk H. A continuous method for the estimation of adenosine deaminase catalytic concentration in pleural effusions with a Hitachi 705 discrete analyser. J Clin Chem Clin Biochem 1985;23(10):677–682
10 Dahale AS, Puri AS, Kumar A, Dalal A, Agarwal A, Sachdeva S. Tissue Xpert® MTB/RIF assay in peritoneal tuberculosis: to be (done) or not to be (done). Cureus 2019;11(06):e5009. Doi: 10.7759/cureus.5009
11 Sharma V, Soni H, Kumar-M P, et al. Diagnostic accuracy of the Xpert MTB/RIF assay for abdominal tuberculosis: a systematic review and meta-analysis. Expert Rev Anti Infect Ther 2021;19 (02):253–265
12 Martinez-Vazquez JM, Ocaña I, Ribera E, Segura RM, Pascual C. Adenosine deaminase activity in the diagnosis of tuberculous peritonitis. Gut 1986;27(09):1049–1053
13 Voigt MD, Kalvaria I, Trey C, Berman P, Lombard C, Kirsch RE. Diagnostic value of ascites adenosine deaminase in tuberculous peritonitis. Lancet 1989;1(8641):751–754
14 Dwivedi M, Misra SP, Misra V, Kumar R. Value of adenosine deaminase estimation in the diagnosis of tuberculous ascites. Am J Gastroenterol 1990;85(09):1123–1125
15 Riquelme A, Calvo M, Salech F, et al. Value of adenosine deaminase (ADA) in ascitic fluid for the diagnosis of tuberculous peritonitis: a meta-analysis. J Clin Gastroenterol 2006;40(08):705–710
16 Shen YC, Wang T, Chen L, et al. Diagnostic accuracy of adenosine deaminase for tuberculous peritonitis: a meta-analysis. Arch Med Sci 2013;9(04):601–607
17 Tao L, Ning HJ, Nie HM, Guo XY, Qin SY, Jiang HX. Diagnostic value of adenosine deaminase in ascites for tuberculosis ascites: a meta-analysis. Diagn Microbiol Infect Dis 2014;79(01):102–107
18 Sathar MA, Simjee AE, Coovadia YM, et al. Ascitic fluid gamma interferon concentrations and adenosine deaminase activity in tuberculous peritonitis. Gut 1995;36(03):419–421
19 Hillebrand DJ, Runyon BA, Yasmineh WG, Rynders GP. Ascitic fluid adenosine deaminase insensitivity in detecting tuberculous peritonitis in the United States. Hepatology 1996;24(06): 1408–1412
20 Dahale AS, Puri AS, Sachdeva S, et al. Reappraisal of the role of ascitic fluid adenosine deaminase for the diagnosis of peritoneal tuberculosis in cirrhosis. Korean J Gastroenterol 2021;78(03): 168–176
21 Sharma SK, Tahir M, Mohan A, Smith-Rohrberg D, Mishra HK, Pandey RM. Diagnostic accuracy of ascitic fluid IFN-gamma and adenosine deaminase assays in the diagnosis of tuberculous ascites. J Interferon Cytokine Res 2006;26(07):484–488
22 Sharma SK, Ryan H, Khaparde S, et al. Index-TB guidelines: guidelines on extrapulmonary tuberculosis for India. Indian J Med Res 2017;145(04):448–463
23 Dawra S, Sharma V, Sharma A, Dutta U, Chawla MPS, Kochhar R. Survey of practices in managing abdominal TB. Int J Tuberc Lung Dis 2020;24(10):1109–1111

