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GeneXpert MTB/Rif to Diagnose Tuberculous Meningitis: Perhaps the First Test but not the Last

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Tuberculous meningitis (TBM) is the most severe form of tuberculous with substantial mortality. In May 2015, 54 researchers from 10 countries met in Da Lat, Vietnam, to discuss advances in TBM. Among the attendees were researchers involved in pivotal studies on the use of Xpert MTB/Rif for TBM diagnosis. Attendees discussed the 2014 World Health Organization strong recommendation favoring the use of Xpert "in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid (CSF) if the sample volume is low or if additional specimens cannot be obtained to make a quick diagnosis." Attendees were concerned that the limitations of Xpert testing for TBM are not emphasized. Clear guidance is needed for the investigational pathway for TBM, including recommendations on the diagnostic package of investigations, which does not stop with Xpert testing. Second, emphasis on the large CSF volumes (ideally 8–10 mL) needed for Xpert testing is required. Guidelines should also emphasize that TBM is a medical emergency and early treatment reduces mortality.

Keywords. tuberculous; meningitis; diagnosis; guideline; perspective.

Tuberculous meningitis (TBM) is the most severe form of tuberculous with substantial mortality. In May 2015, 54 TBM researchers from 10 countries met in Da Lat, Vietnam, to discuss advances in TBM. Among the attendees were researchers involved in pivotal studies on the use of Xpert MTB/Rif (Xpert, Cepheid, Sunnyvale, California) for TBM diagnosis [1, 2]. During the meeting, the World Health Organization (WHO) strong recommendation favoring the use of Xpert "in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid" (CSF) if the sample volume is low or if additional specimens cannot be obtained to make a quick diagnosis" was discussed [3, 4]. In agreement with previous concerns [5], attendees concurred that caution is required in interpreting the recommendations of the 2014 WHO Xpert MTB/Rif implementation manual [4], as the limitations of Xpert testing for TBM are not emphasized.

Rapid TBM diagnosis and treatment is a strong prognostic indicator for reduced death and neurologic deficit. Available TBM diagnostic tests are inadequate, for the most part due to low bacillary loads in CSF [6]. In locations where TBM is less common, missed diagnosis and delayed treatment are common

[7]. CSF Ziehl-Neelsen staining is rapid, but sensitivity is poor (approximately 10%–20%) [2, 8]. Although mycobacterial culture is more sensitive (approximately 60%–70%), culture often takes ≥2 weeks [1, 8]. Clinical diagnostic algorithms have been developed, but their use outside of populations in which algorithms were derived is largely untested. A consensus clinical TBM case definition was developed to standardize research but was not intended to aid diagnosis in clinical practice [9]. Clinicians are therefore often left with a diagnostic dilemma [10], and TBM diagnosis can only be made at autopsy.

Given the lack of adequate TBM diagnostics, Xpert appeals as a new diagnostic tool. However, PCR testing of CSF for TBM diagnosis has important limitations. Three cohort studies have evaluated the use of Xpert on CSF in TBM suspects [1, 2, 8]. The first study, from South Africa, found 67% sensitivity for Xpert detecting microbiologically proven TBM but only 36% sensitivity against a clinical case definition in a predominantly human immunodeficiency virus (HIV)-infected population [2]. In a subset of 27 TBM cases using higher volumes (3 mL vs 1 mL), Xpert exhibited 82% sensitivity [2].

In Vietnam, Nhu and colleagues found 59% sensitivity for Xpert used on CSF vs a clinical TBM case definition [1]. This study routinely centrifuged CSF and then divided the pellet apportioning 40% for Xpert testing and 20% for each of microscopy, culture, and storage [1]. The volumes used for Xpert testing were modest with 78% of persons having an effective volume used for Xpert testing of ≤2 mL.

The WHO 2013 meta-analysis to assess the diagnostic performance of Xpert for TBM included the cohorts by Patel

and by Nhu and numerous studies with small numbers of meningitis cases among extrapulmonary tuberculous cohorts (total 117 cases in 16 studies) [1–3]. The pooled Xpert sensitivity in this meta-analysis was 79.5% (95% confidence interval [CI], 62.0%–90.2%) with culture as a reference gold standard. When a clinical gold standard was used, sensitivity was only 55% with 84% negative predictive value (NPV). In high prevalence TBM settings, this NPV equates to 1 in 6 persons with TBM tested by Xpert being missed.

A 2015 Ugandan study (not included in the WHO meta-analysis) showed with small numbers (n = 18) that centrifugation of larger CSF volumes (median: 6 mL, interquartile range: 4–10 mL) resulted in 72% (13/18) sensitivity, which was equivalent to culture (71%, 12/17) [8]. Using 2 mL of un-centrifuged CSF had only 28% sensitivity (5/18) [8]. The reference standard was any positive polymerase chain reaction or culture. Importantly, neither Xpert nor culture of centrifuged CSF would have detected each case of microbiologically-proven TBM, with only

39% of TBM cases being positive both by culture and Xpert testing [8]. These findings emphasize "missed cases" will occur should clinicians rely solely on Xpert to diagnose TBM. Even when using large volumes of centrifuged CSF, the NPV was 94% (77/82) in a moderate tuberculous setting [8]. As Boyles and Thwaites noted [5], for a test to adequately rule out a life-threatening disease, a high NPV is needed. Such a TBM test does not exist. Even next generation molecular tests (eg, Xpert Ultra) are unlikely to exceed the sensitivity of culture.

Considering the current evidence [1, 2, 8], we wish to caution against the use of Xpert as the sole diagnostic test for TBM, as this practice may lead to missed TBM cases and deaths. We encourage clinicians to use large CSF volumes with Xpert, but to remember that a negative Xpert test does not exclude TBM. Xpert should be used in combination with other diagnostic tests (eg, cryptococcal antigen of blood and CSF), clinical findings, and when possible, radiologic data to inform their overall suspicion for TBM.
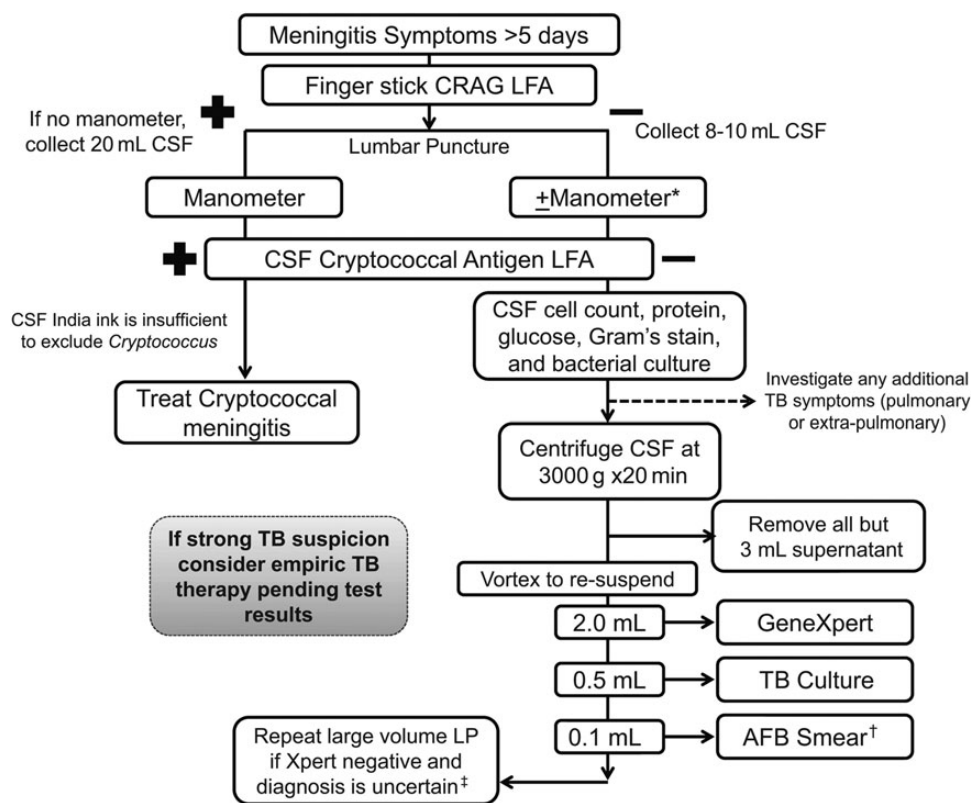

.Figure 1. Suggested algorithm for diagnosis of Subacute Meningitis in population with high human immunodeficiency virus (HIV) and tuberculous (TB) prevalence. The algorithm is the suggested method of the authors and is meant as guidance. The circumstances of any individual clinical situation may render deviation from this algorithm preferable, and expert physician opinion remains vital. The figure describes our preferred method for investigating meningitis suspects with symptoms for >5 days in settings with moderate to high endemic levels of TB and HIV. *If possible use a manometer in these cases as well; however, if cost is a limitation a manometer is of most use in those suspected to have cryptococcal meningitis and so could be omitted in cases not suspected to have cryptococcal meningitis. †In areas of high utility (eg, southeast Asia), acid-fast bacillus (AFB) microscopy should be included if laboratory technicians have adequate time to perform a thorough investigation. However, the AFB microscopy should be omitted in other settings where sensitivity is much lower. ‡Tests to exclude other causes for neurologic syndromes should be performed as clinically indicated and available (eg, cerebrospinal fluid [CSF] syphilis serology, viral polymerase chain reaction testing, cytology, anti-N-methyl D-aspartate [NMDA] receptor antibodies). Consider brain imaging (computerized tomography/magnetic resonance imaging) as available for focal neurologic deficit(s) and/or to aid in tuberculous meningitis diagnosis. Abbreviations: CRAG, cryptococcal antigen; LFA, lateral flow assay; LP, lumbar puncture.

In Figure 1, we describe our preferred methodology for investigating meningitis suspects with symptoms for >5 days in settings with moderate to high endemic levels of tuberculous and HIV. As stated above, we encourage the early use of the cryptococcal antigen lateral flow assay on blood and CSF given the high sensitivity, ease of use, and low cost. If symptoms of tuberculous exist they should be investigated as able (eg, chest radiograph and sputum isolation for pulmonary tuberculous, lymph node biopsy for suspected tuberculous lymphadenitis, etc.). Basic CSF testing such as total protein, cell count, and glucose should be performed with the idea of risk stratification—not definite diagnosis. Finally, we recommend obtaining 8–10 mL of CSF if possible (recognizing this may be difficult) and using centrifugation to concentrate the specimen. All but approximately 2.5 mL supernatant should be drawn off and the remaining volume reconstituted with 2 mL being used for Xpert and 0.5 mL for culture (and 0.1 mL for acid-fast bacillus [AFB] stain if included). We strongly advocate empiric therapy in the case of high suspicion at the time of testing and retesting if strong suspicion in the face of negative testing..

We would encourage WHO to revise the current recommendations to first emphasize the limitations of Xpert for TBM; second, provide clear guidance on the investigational pathway for TBM, including recommendations on the diagnostic package of investigations; and third, emphasize the need for large CSF volumes (>5 mL). Guidelines should also emphasize that TBM must be considered a medical emergency and treatment initiated immediately (and often empirically) to reduce mortality.

Notes

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