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The Diagnostic Utility and Sensitivity of the Xpert® MTB/RIF Assay in Diagnosing Mycobacterium tuberculosis in Bone Marrow Aspirate Specimens

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Abstract : In South Africa, the World Health Organisation estimated 454000 new cases of Mycobacterium tuberculosis (M.tb) infection (MTB) in 2015. Disseminated tuberculosis arises from the haematogenous spread and seeding of the bacilli in extrapulmonary sites. The gold standard for the detection of MTB in bone marrow is TB culture which has an average turnaround time of 6 weeks. Histological examinations of trephine biopsies to diagnose MTB also have a time delay owing mainly to the 5-7 day processing period prior to microscopic examination. Adding to the diagnostic delay is the non-specific nature of granulomatous inflammation which is the hallmark of MTB involvement of the bone marrow. A Ziehl-Neelson stain (which highlights acid-fast bacilli) is therefore mandatory to confirm the diagnosis but can take up to 3 days for processing and evaluation. Owing to this delay in diagnosis, many patients are lost to follow up or remain untreated whilst results are awaited, thus encouraging the spread of undiagnosed TB. The Xpert® MTB/RIF (Cepheid, Sunnyvale, CA) is the molecular test used in the South African national TB program as the initial diagnostic test for pulmonary TB. This study investigates the optimisation and performance of the Xpert® MTB/RIF on bone marrow aspirate specimens (BMA), a first since the introduction of the assay in the diagnosis of extrapulmonary TB. BMA received for immunophenotypic analysis as part of the investigation into disseminated MTB or in the evaluation of cytopenias in immunocompromised patients were used. Processing BMA on the Xpert® MTB/RIF was optimised to ensure bone marrow in EDTA and heparin did not inhibit the PCR reaction. Inactivated M.tb was spiked into the clinical bone marrow specimen and distilled water (as a control). A volume of 500mcl and an incubation time of 15 minutes with sample reagent were investigated as the processing protocol. A total of 135 BMA specimens had sufficient residual volume for Xpert® MTB/RIF testing however 22 specimens (16.3%) were not included in the final statistical analysis as an adequate trephine biopsy and/or TB culture was not available. Xpert® MTB/RIF testing was not affected by BMA material in the presence of heparin or EDTA, but the overall detection of MTB in BMA was low compared to histology and culture. Sensitivity of the Xpert® MTB/RIF compared to both histology and culture was 8.7% (95% confidence interval (CI): 1.07-28.04%) and sensitivity compared to histology only was 11.1% (95% CI: 1.38-34.7%). Specificity of the Xpert® MTB/RIF was 98.9% (95% CI: 93.9-99.7%). Although the Xpert® MTB/RIF generates a faster result than histology and TB culture and is less expensive than culture and drug susceptibility testing, the low sensitivity of the Xpert® MTB/RIF precludes its use for the diagnosis of MTB in bone marrow aspirate specimens and warrants alternative/additional testing to optimise the assay.

Keywords : bone marrow aspirate , extrapulmonary TB, low sensitivity, Xpert® MTB/RIF
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