Xpert MTB/RIF for Diagnosis of Tuberculosis and Drug Resistance in Indian Children

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Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs. Extensively-resistant tuberculosis (XDR-TB) is defined as resistance to at least isoniazid and rifampicin, and to any fluoroquinolone, and to any of the three second-line injectables (amikacin, capreomycin, and kanamycin) [1]. Pre XDR-TB is defined as people with MDR-TB, but who also have some resistance to second line drugs, but not sufficient for them to be categorized as having XDR-TB [2]. World Health Organization's current policy recommends that Xpert MTB/RIF (Mycobacterium tuberculosis/Rifampicin) should be used as an initial diagnostic test in children suspected of having tuberculosis [3]. We conducted this study to determine efficacy of Xpert MTB/RIF for diagnosis of tuberculosis, and also to compare rifampicin resistance found on Xpert MTB/RIF with that of drug susceptibility tests (DST).

Thirty-four children (age 3 mo-15 yr) newly diagnosed clinically as tuberculosis [4], and referred to the Pediatric TB clinic at a tertiary children's hospital in Mumbai, and who had underwent Xpert MTB/RIF, cultures by Mycobacteria growth indicator tube (MGIT) and smear examination for acid-fast bacillus (AFB) as part of their diagnostic work-up were enrolled in the study. Both pulmonary and extrapulmonary cases were included. Specimens sent for testing included respiratory specimens [sputum, bronchial or tracheal aspirates, bronchoalveolar lavage (BAL) and gastric lavage (GL)] and extrapulmonary specimens [tissue biopsy, pus from abscess, cerebrospinal fluid (CSF), ascitic and pericardial fluid].

Xpert MTB/RIF was positive in 20 (58.8%) patients. TB MGIT culture revealed *M tuberculosis* in 19 (63.3%) out of 30 patients tested. Acid-fast bacillus (AFB) positivity of smear was seen in 10 (29.4%) patients. Association of Xpert MTB/RIF with culture is depicted in ***Table* I**.

Xpert MTB/RIF was positive in 58.8% of clinically diagnosed cases of tuberculosis, and had sensitivity of 78.9% and specificity of 81.8%. Sensitivity and specificity of Xpert MTB/RIF for bacteriologically (either AFB or culture positive) confirmed cases of tuberculosis was 80% and 71.4%, respectively (P=0.003)

On DST, Pre XDR-TB was present in 5 (29.4%) patients, MDR-TB was seen in 5 (29.4%) and 1 (9%) had polyresistant TB. In 6 (35.2%), there was no resistance seen. Rifampicin-resistance was seen in 11 (55%) on Xpert MTB/RIF of which 3 (27.3%) were subsequently found to be pre-XDR on DST, 3 (27.3%) were MDR with additional resistance to ethambutol, streptomycin and ethionamide and 2 (9%) were MDR-TB. Of the 11 patients with rifampicin-resistance on Xpert MTB/RIF, DST was not done in 2 patients and 1 was culture negative. One patient with no rifampicin-resistance on Xpert MTB/RIF was found to have pre-XDR TB on conventional DST. One patient each with pre-XDR TB, polyresistant TB (rifampicin and streptomycin resistance) and MDR-TB had a negative Xpert MTB/RIF result. Sensitivity of Xpert MTB/RIF to pick up drug resistant TB as compared to conventional DST was 72.7% and specificity was 83.3%.

The study area has a high background resistance rate [5]. Most cases of Xpert MTB/RIF with positive rifampicin resistance had additional resistance to other 1st and 2nd line anti-tuberculosis treatment (ATT). Moreover, patients who were not identified to have rifampicin-resistance on Xpert MTB/RIF or those with negative Xpert MTB/RIF results were subsequently diagnosed to have resistant TB on DST. Zetola, *et al*. [6] in their study of 37 patients had 7 (18.9%) patients with phenotypic DST discordant results. Thus, if only Xpert MTB /RIF is used for diagnosis of TB and to identify resistance, additional drug resistance may be missed. In our patients, the patients with pre-XDR TB also had additional resistance to

TABLE I RESULTS OF XPERT MTB/RIF WHEN COMPARED WITH AFB SMEAR AND TB CULTURES

	Xpert MTB/ RIF positive	*Xpert MTB/ RIF negative*	*Total*
MTB culture positive	15 (79%)	4 (21%)	19
MTB culture negative	2 (18.2%)	9 (81.8%)	11
AFB smear positive	8 (80%)	2 (20%)	10
AFB smear negative	12 (50%)	12 (50%)	24

ethambutol, pyrazinamide, streptomycin, ofloxacin and moxifloxacin, and most patients with MDR had additional resistance to ethambutol, streptomycin and ethionamide. If these patients were started on MDR treatment as per revised national tuberculosis control program (RNTCP) [7], most patients would be actually getting only 2 effective drugs – cycloserine and kanamycin. This may lead to more drug resistance. Thus the place of Xpert MTB/RIF in the diagnostic algorithm, should be according to the milieu the patient comes from, and all Xpert Rif resistance positive cases should have a DST as far as possible.

We conclude that although Xpert MTB/RIF test could be a useful tool for rapid identification of rifampicin resistant *M. tuberculosis* the test results must always be confirmed by culture and DST to increase the yield of bacteriological diagnosis, and also to detect additional drug resistance.

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Percutaneously Inserted Central Venous Catheter Tip Position in Preterm Neonates and Complications

Percutaneously inserted central venous catheter (PICC) tips are recommended to be placed in a central vein: the superior vena cava (SVC) or the inferior vena cava (IVC) [1]. There is disagreement about how central catheters fare against those with tips in non-central veins like the brachiocephalic, subclavian, axillary, iliac and femoral [2-4]. We determined the association between PICC tip location and complication rates in preterm neonates.

We collected data retrospectively from records at two tertiary-level neonatal intensive care units from July 2013 to February 2015, wherein 105 PICC were placed in preterm neonates born at ≤32 weeks of gestation or with birth weight ≤1500 g. Vygon 28G PICC (Premicath) were used in all the cases. All tip locations were confirmed by radiography. No patient had two PICC at the same time. Catheter tips were defined as 'Central' if in the SVC or IVC; 'Midline' if in the brachiocephalic, subclavian and iliac veins; and 'Noncentral' if located in the axillary, femoral or any other vein. Indications for insertion primarily included parenteral nutrition or dextrose concentration exceeding 12.5%. Catheter removal was carried out for all complications: leakage, extravasation, phlebitis, central line associated bloodstream infection (CLABSI), catheter occlusion, or mechanical malfunction. Analysis of variance, chi-square test and t-test were used for statistical analysis.

The mean (SD) gestational age and birth weight were 29.9 (2.5) weeks and 1198 (285) g, respectively. One hundred and five successful PICC insertions in 96 babies accounted for 890 catheter-days, with 9 re-insertions; 8