RESEARCH PAPER

Profile of Children With Tuberculosis in a Pediatric Intensive Care Unit in Mumbai

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Objective: This study was done to analyze the profile of confirmed pediatric TB patients seen in an intensive care setting.

Methods: Data of all children admitted in our PICU with bacteriologically proven tuberculosis (smear, culture, poly-merase chain reaction, genotypic testing or Pyrosequencing) between January, 2007 and December, 2019 were retrieved. Drug resistance was classified as per World Health Organization definitions.

Results: 59 children (28 boys) met the inclusion criteria (median (IQR) age 8 (4,13) years). About a third (22/59) had past history of treatment with antituberculosis drugs. The indications for admission to PICU were monitoring and management of neurological status in 31 children, post procedure monitoring in 20 children and respiratory failure in 8 children. Severe ARDS was seen in 2 children. Out of 37 children with neuro-tuberculosis, 19 children had TB in additional sites, and 9 children died. Sample positivity rate for CSF culture was 66%. Drug sensitivity testing (DST) of positive culture was done in 35 cases and showed multidrug resistance in 4 children, pre-XDR (extreme drug resistance) in 10 and XDR in 5 children.

Conclusion: Neurotuberculosis was the commonest reason for admission to PICU. Concerted efforts should be made to obtain samples for culture and drug sensitivity testing in critically ill children with tuberculosis.

Keywords: *Drug-resistance, Management, Mortality, Neurotuberculosis, Outcome.*

Tuberculosis continues to be an important cause of morbidity and mortality [1]. The commonest reasons for intensive care unit admission in adults with tuberculosis are acute respiratory failure, multi-organ dysfunction and shock [2]. There is limited data on critically ill children with tuberculosis [3,4].

METHODS

All children admitted to the pediatric intensive care unit (PICU) with suspected tuberculosis between January, 2007 and December, 2019 were identified from the PICU database and hospital medical charts. Those with bacteriologically proven tuberculosis (smear, culture, or molecular testing) were then studied. A chart review was carried out to extract clinical details including age, sex, weight, history of anti-tubercular treatment (ATT), history of contact, time from symptom onset to diagnosis, tuberculosis location, investigations and outcome. Ethics committee approval was obtained prior to start of the study.

Bacterial TB culture was obtained by Mycobacterial Growth Indicator Tube (MGIT) 960 system (Becton Dickinson). The following molecular tests were used: polymerase chain reaction (PCR), CBNAAT using Xpert MTB/RIF assay (Cepheid), Line probe assay (Genotype MTBDR plus, Hain life science) and pyrosequencing reactions were conducted using a repurposed Qiagen PyroMark Q96 ID system (Qiagen, Valencia). Genotyping testing and drug sensitivity testing were performed at the discretion of the treating physician. Clinical and laboratory standards were used for drug sensitivity testing (DST) by phenotypic testing. Drug resistance was classified as per WHO definitions [5].

Statistical analysis: Data recording was done in MS Excel format. Descriptive statistics are used to present the data.

RESULTS

The total number of PICU admissions during the study period was 4628. There were 75 patients suspected to have tuberculosis and 108 samples were sent from these children. Fifty nine children were bacteriologically proven tuberculosis; mycobacterial culture or smear was positive in 48 patients, molecular testing or pyrosequencing were

positive in an additional 11. The cultutre positivity from 108 samples were as follows: 28/42 for cerebrospinal fluid, 13/22 for bronchoalevolar lavage, 16/23 for tissue, 4/7 for ascitic/ pleural/pericardial fluid and 1/8 for gastric lavage.

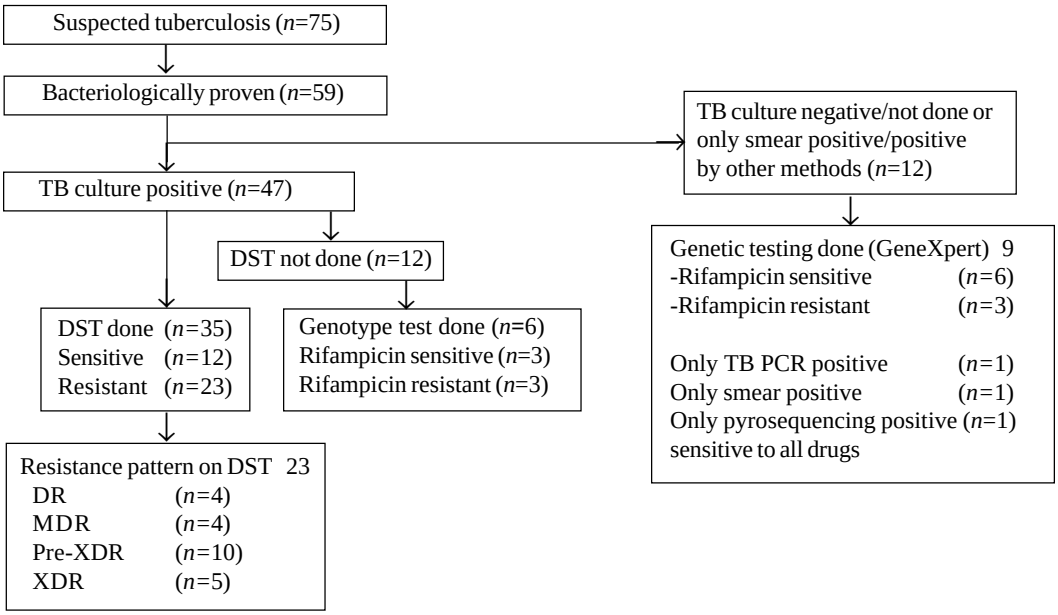
Data of only these 59 children (28 boys) were further analyzed. The median (IQR) age was 8 (4,13) years. Indication for the initial admission to PICU were as follows: 31 children were admitted for monitoring of neurological status (10 for management of raised intracranial pressure, 17 for altered sensorium, and 4 for status epilepticus), 20 for procedure or post- operative monitoring (post-operative 12, BAL 7), and eight with respiratory failure of whom two children had severe acute respiratory distress syndrome (ARDS) and three had underlying neuromuscular disease with pneumonia, and 3 had inability to maintain airway. Operative procedures included spinal cord decompression, pneumonectomy, pericardiectomy, hemicolectomy, and temporal lobe granuloma biopsy.

The commonest symptom was fever seen in 45 (76%) patients. Neurotuberculosis was present in 37 children (62%) of whom 19 also had tuberculosis in additional sites (lung, spine, peritoneum, abdomen, eyes). Tuberculosis of the spine was seen in 8 children. There were five children on immune-suppressive therapy (chemotherapy for malignancy or long term steroids), 26 children (44%) were malnourished, one child was HIV-positive, and one was on home ventilator therapy for a congenital myopathy.

History of treatment with ATT for more than 1 month was found in 22 children (37%) with a median (IQR) duration of 5 (1,9) months. History of contact with a case of tuberculosis in the previous two years was seen in 9 (15%) children ; 2 children had family contacts with poor compliance for ATT, 1 child had lost both parents due to tuberculosis and HIV, and for 1 child DST of the contact (Extremely drug resistant TB, XDR TB) was available. The median (IQR) time to appropriate ATT was 2 (2,6) months. Chest *X*-Ray was abnormal in 30 children; miliary TB was seen in 9, cavitation in 4 (2 were younger than 6 months), parenchymal lesions in 9, nodal involvement in 3 and mixed lesions in 5 children.

Mycobacterial culture was positive in 62 samples from 47 patients (47/75, 62%). Tuberculosis was confirmed by smear or molecular testing in an additional 12 patients (**Fig. 1**). Drug sensitivity testing (DST) was done in 35 (74%) cases out of 47 with positive MTB cultures; multi-drug resistance (MDR) was seen in isolates from 4, pre-extensively drug resistant (pre-XDR) in 10 and XDRTB in 5 children. An additional 4 children had isolates showing sensitivity to rifampicin but drug resistance to INH and/or streptomycin and/or ethambutol and/or ethionamide. All isolates were sensitive to clofazimine (**Web Fig. 1**).

GeneXpert testing was positive in an additional 15 patients who were culture negative or culture positive but DST was not done, and showed rifampicin resistance in 6.



DST: drug sensitivity testing; Drug resistance: resistance to streptomycin and/or INH and/or ethambutol and/or ethionamide; multidrug resistance: resistance to INH, rifampicin; pre-XDR: resistance to INH, rifampicin, any fluoroquinolone; XDR: resistance to INH, rifampicin, any fluoroquinolone (oofloxacin, moxifloxacin) and any injectable second line aminoglycoside (amikacin, capreomycin, kamamycin).

Fig. 1 Mycobacterial testing in patients with suspected tuberculosis.

These children were treated as MDR-TB. Pyrosequen-cing was done in 1 child who was GeneXpert and culture negative and was positive for sensitive mycobacteria. Drug sensitivity or GeneXpert testing was not available in 8 children who were treated with first lineATT.

Mechanical ventilation was needed in 12 children, of whom 2 had acute respiratory distress syndrome (ARDS), 3 had pneumonia with underlying neuromuscular disorder and 7 had raised intracranial pressure or inability to maintain airway. Inotropic support was needed in 3 children; 2 for peritonitis with septic shock and 1 for severe ARDS with shock and multi organ dysfunction,

On discharge after their first ICU admission, 36 children had improved, 19 had sequelae and 4 children died. A further 4 children died during subsequent admissions to PICU; 3 children within 6 months of presentation and 1 child after 2 years of treatment failure. An additional child with severe sequelae post-TB meningitis died at home 8 months after presentation. All 9 children who died had TB meningitis, and apart from 1 child, the rest had involvement at other sites as well (lung =7, spine=5, abdomen=3, eye=1). The causes of death included extensive infarcts from vasculitis, ARDS, peritonitis with septic shock, aspiration pneumonia and ventriculitis. The sequelae included hydrocephalus, stroke, paraparesis, cognitive deficit, seizures, optic atrophy, visual deficit and hearing loss. Six children had multiple ICU admissions for ventriculo-peritoneal shunt related complications.

DISCUSSION

Children with tuberculosis may need intensive care for tuberculous meningitis, ARDS or septic shock [6]. Majority of children with tuberculosis requiring ICU admission in our study had neuro-tuberculosis, similar to a study from Pune [3]. However, a study from South Africa reported that 72% of 57 children were admitted with respiratory failure and only 8 children had tuberculous meningitis [7]. Although chest *X*-ray findings were abnormal in 30 children in our study, severe ARDS was seen in only two children. A case series from Europe of children with miliary tuberculosis involving lung and brain showed that vasculitis due to TB meningitis leads to poor outcome rather than the lung involvement; in fact the extent of lung involvement on chest *X*-ray did not correlate with respiratory insufficiency [6]. Children with TB meningitis had a high mortality (24%), similar to previous reports [3,7].

An important finding in the study is the high rates of culture positivity in our patients (66%) – many of them having neurotuberculosis, a particularly pauci-bacillary disease thought to have low rates of culture positivity. Earlier rates of positive cultures in clinically diagnosed tuberculous meningitis were often as low as 10-20%, especially from developing countries [8]. However, studies from Vietnam have shown a high rate of bacteriologic confirmation similar to ours (positive smear in 58% and culture in 71%), especially with use of large CSF volume and increased time spent while doing microscopy [9]. It is also possible that the high rates of MDR-TB may have contributed to a higher bacteriological load with lower rates of culture-conversion in treated patients, as has been demonstrated in sputum samples of pulmonary TB [10]. In addition, diagnostic yield was increased by sampling from multiple sites such as broncho-alveolar lavage, and pleural and ascitic fluid [11].

Similar to our findings, increasing drug resistance is being reported in children [12]. Out of 21 TB patients who were resistant to rifampicin on DST, 13 were resistant to quinolones, which would be missed by Gene Xpert testing. It is therefore important to make all efforts to perform drug sensitivity and avoid treating only on the basis of GeneXpert [13]. A meta-analysis of 8955 patients with MDR-TB and XDR-TB found that drug sensitivity testing provides useful information to guide treatment, and that in vitro susceptibility to a drug was significantly associated with treatment success. In our study, one patient was detected only by pyrosequencing with all her other tests being negative [14]. It should be used as an adjunct to culture-based DST methods due to its rapid turnaround time, especially if drug-resistant tuberculosis is suspected [14].

The limitation of our study is that besides the retrospective nature, it suffers from significant referral bias as our cohort consists mostly of severely ill patients admitted in an intensive care setting of a tertiary care center. More than a third of patients had a poor response to first line ATT. DST was also available in only 35/47 of all culture positive patients.

In a South African study by Schaaf, et al. [15], the correlation between the drug susceptibility results of the child's and adult source case's isolates was 68%. Whenever available, the source's DST should be sought and followed, and if necessary, second line drugs started early in the treatment if MDR-TB has been found in the source. It is important to do screening and follow up of all children who are household contacts of adult cases with MDR-TB; this would need collaboration between adult physicians and pediatricians.

In conclusion, neurotuberculosis was the commonest presentation of children with tuberculosis needing PICU admission in our cohort. In children with suspected tuberculosis, all efforts should be made to get samples for culture and drug sensitivity testing.

WHAT THIS STUDY ADDS?

- Critically ill children with tuberculosis most commonly present with neurotuberculosis.
- Drug sensitivity testing /other available tests should be done early to determine appropriate treatment at the first presentation.

Ethics clearance: Institutional ethics committee: PD Hinduja Hospital and Medical Research Center; No.1426- 20 - SR dated Dec 17, 2020.
Contributors: SR, RS and DW did the data collection and initial preparation of work. SU and VU contributed to the conception and design of the work, finalization of the draft and critical revision of the work. All authors approved the final version of manuscript and are accountable for all aspects related to the study.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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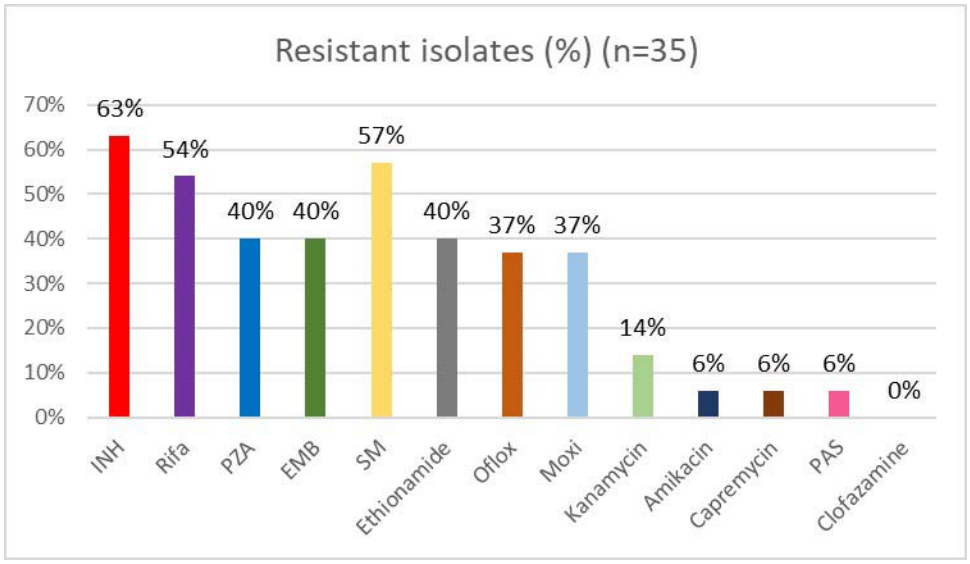

Web Fig. I. *Resistance to anti-tuberculosis drugs on drug sensitivity testing of mycobacterium tuberculosis isolates from 35 patients.*