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# Common Alternative Diagnoses among a Pediatric Hospital-Based Cohort Evaluated for Tuberculosis in Karachi, Pakistan: The Need for Facilitated Referral in Tuberculosis Clinics

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## Abstract

**Background:** Children evaluated for tuberculosis (TB) are often diagnosed with miscellaneous conditions that mimic TB. Knowledge of differentials informs policy on service provision through liaison with referral centers offering definitive diagnosis and treatment for common alternative disorders. **Methods:** We reviewed medical records of children who were offered diagnostic testing for TB (culture or Xpert MTB/RIF) at a tertiary care hospital in Karachi, Pakistan to identify common alternative diagnoses among children who are evaluated for TB. **Results:** From January 2014 to December 2015, of 126 culture or Xpert MTB/RIF negative children presenting with chronic symptoms, 31 were diagnosed and treated for TB based on clinical criteria (5 of 48 children with pulmonary and 26 of 78 with extrapulmonary presentations; 10.4% and 33.3%, respectively). Among remaining 95 patients, common alternative diagnoses to pulmonary TB ( $n = 43$ ) were bacterial pneumonia or empyema (60.5%,  $n = 25$ ) and underlying bronchiectasis (20.9%,  $n = 9$ ). Among 52 extrapulmonary presentations, the most common alternative diagnoses were lymphoproliferative disorders ( $n = 11$ , 21.1%), bacterial infections ( $n = 11$ , 21.1%), and autoimmune disorders ( $n = 9$ , 17.3%). Of note, five children were diagnosed with underlying primary immunodeficiencies (9.6%). Children with alternative disorders were treated for TB in 25 of 95 cases (26.3%). Although 77.8% ( $n = 98$ ) children were followed up at the facility, 15.9% ( $n = 20$ ) were lost to follow-up. **Conclusions:** Pediatric TB mimics many disorders that primary level centers are not equipped to diagnose or manage, leading to suboptimal outcomes. Knowledge of common alternative diagnoses is essential to inform facilitated referral for common mimicking disorders in children.

**Keywords:** Alternative diagnoses, bronchiectasis, cystic fibrosis, facilitated referral, lymphoma, pediatric tuberculosis

## INTRODUCTION

Children assessed for tuberculosis (TB) are often diagnosed with miscellaneous pediatric disorders after extensive radiological, immunological, and microbiological investigations.<sup>[1]</sup> With the current emphasis on TB case finding, patients with alternative disorders are at a greater risk of being misdiagnosed with TB, especially in situations where diagnostic sampling is problematic such as in primary care, or diagnostic yield is suboptimal, as is often the case among children.<sup>[2,3]</sup> Incorrect clinical diagnosis of TB can lead to unnecessary antituberculous therapy (ATT) resulting in added healthcare costs,<sup>[4]</sup> patient morbidity from adverse effects, and suboptimal patient outcomes due to missed alternative diagnoses.<sup>[5]</sup> Where

vertical programs exist, and services are not integrated, pediatric TB programs are not equipped to facilitate either the diagnosis or management of alternative disorders.<sup>[6]</sup> It is, therefore, necessary for pediatricians as well as national programs to provide referral or management for pediatric

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disorders, especially those that commonly mimic TB.<sup>[7]</sup> Knowledge of such diseases is lacking among pediatricians and programs alike but it is important to inform policy on service provision and liaison with referral centers treating common alternative disorders.

As no previous data are available from Pakistan on childhood disorders mimicking TB, we evaluated a cohort of childhood TB suspects to establish common differentials of TB among children in this setting.

## METHODS

### Data source, extraction, and synthesis

All children 0–17 years of age admitted to the Aga Khan University Hospital (AKUH) in Karachi, Pakistan and evaluated for TB through culture or Xpert MTB/RIF<sup>®</sup> (Cepheid, Sunnyvale, USA) results from January 2014 to December 2015 were included in the study. AKUH is a tertiary care center located in the most populous city of Pakistan and provides advanced diagnostic and treatment services to a large catchment population, many of whom are referred from other public and private centers. The hospital, therefore, serves as a reference center for some communicable and noncommunicable illnesses; however, referrals are not coordinated through vertical disease control programs. The hospital and its affiliated laboratory are accredited by the Joint Commission International (JCI), USA and follow JCI patient safety and healthcare quality goals and guidelines.

To determine the most common alternative disorders among children evaluated for TB, a relational laboratory database was created to identify children for whom mycobacterial cultures or Xpert MTB/RIF<sup>®</sup> results were negative for all evaluated samples. The project commenced in June 2016. Medical records were examined for ICD-9 coded hospital diagnoses (diagnoses alternative to TB or clinical diagnosis of TB despite negative cultures), comorbidities, and age, for both pulmonary and extrapulmonary presentations. The database was then refined to include children with pulmonary and extrapulmonary syndromic presentations, to increase specificity by excluding children who were investigated as TB contacts. For pulmonary presentations, children with chronic cough, hemoptysis, recurrent pneumonia, pneumonia in HIV infected children, and loculated pleural effusions were included. For extrapulmonary presentations, children with lymphadenopathy, chronic abdominal symptoms, pericarditis, central nervous system (CNS) disorders indicated by fever, headache and/or seizures, pyrexia of unknown origin (PUO), and chronic skin and soft tissue and bone and joint infections were included. Data collected included patients' age, sex, diagnoses, and the use of ATT in primary care before facility presentation where available, hospital diagnosis at the study facility, and surgical and medical care administered at the facility. The follow-up to date, and where possible, disease outcomes were documented (long-term follow-up care, death, loss to follow up, transfers, and palliative care).

### Data analysis

Data entry and analysis were carried out with IBM SPSS Statistics version 19.0 (IBM Corp, New York, USA). Frequencies, medians, and interquartile ranges were calculated using the same software.

### Ethics

The study protocol was reviewed and approved by the Ethical Review Committee for the Aga Khan University (approval number 4168-Pat-ERC-16) and was exempted from individual informed consent.

## RESULTS

### Description of the cohort

The initial laboratory database identified 270 pediatric patients from January 2014 to December 2015 evaluated for TB but with negative microbiology results. Database refinement by presentation resulted in the exclusion of 137 patients. Of 126 patients with negative culture or Xpert results, 38.1% ( $n = 48$ ) were evaluated for pulmonary TB (pulmonary presentations), whereas 61.9% ( $n = 78$ ) were investigated for disseminated or extrapulmonary disease (extrapulmonary presentations). The median age of the cohort was 8 years (IQR 8.25). The male-to-female ratio was 1.6 overall and for both pulmonary and extrapulmonary presentations.

Table 1 shows the distribution of the final cohort across pulmonary and extrapulmonary presentations and diagnoses.

### Alternative diagnoses for pulmonary presentations

Although multiple alternative pulmonary disorders were observed in the cohort [Table 1], a high proportion of underlying bronchiectasis was detected. Of the 9 patients with bronchiectasis, none had a past history of being treated for asthma, TB, pertussis, and/or measles, and were presumptively diagnosed with "cystic fibrosis" (CF) on the basis of clinical symptom complex representing chronic and recurrent pneumonia, excessive sputum production, weight loss, and incremental loss of pulmonary function, despite normal sweat chloride levels and unavailable CF transmembrane regulator gene mutation testing.<sup>[8]</sup> Bacterial pneumonia with loculated empyema ( $n = 25$ ) was the most frequently identified alternative infection, with most children with prior histories of inadequate treatment of community-acquired pneumonia. Of note, these children improved on antibiotics, chest intubation, and video-assisted thoracoscopic surgery (VATS) for debridement of the pleural space. Five patients were diagnosed with TB on the basis of clinical criteria (Kenneth Jones) and treated for TB, one of whom was empirically treated for multidrug-resistant TB but was lost to follow-up after 2 months.

### Alternative diagnoses for extrapulmonary presentations

Among extrapulmonary presentations, TB remained the most common diagnosis despite negative microbiological investigations ( $n = 26$ , 33.3%). Lymphoproliferative disorders (lymphomas, leukemias, and hemophagocytic lymphohistiocytosis-[HLH]) ( $n = 11$ , 21.1%), and bacterial

**Table 1: Alternative final diagnoses and patient outcomes among children with negative tests tuberculosis, January 2014-December 2015**

Presenting syndrome/ indication for TB testing	Patients (n)	Median age years (IQR)	Samples tested	Final diagnoses (n)	Patient outcomes (n)	Empiric ATT use during course of illness, n/N (%)*
Pulmonary presentations	48	7 (7)			Followed up (38), LTFU (7), expired (3)	9/43 (20.9)
Chronic cough	20		Gastric aspirate (12) Sputum/tracheal aspirate (7), pus from abscess (1)	Bronchiectasis (4), TB (3), necrotizing pneumonia (2), lung abscess (2), <i>H. influenzae</i> pneumonia (1), pneumococcal pneumonia (1), <i>M. kansasii</i> pneumonia (1), aspiration pneumonia (1), reactive airway disease (1), CGD (1), fungal pneumonia (1), CCAM (1), neuroendocrine tumor (1)		
Loculated pleural effusion/ empyema	15		Pleural tissue (15) obtained after VATS	Empyema requiring thoracotomy and VATS: TB (1), presumed bacterial empyema (10), pneumococcal empyema (2), <i>S. typhimurium</i> infection with SCID (1), <i>P. aeruginosa</i> empyema (1)		
Recurrent pneumonia	7		Sputum (3), bronchial (1), gastric aspirate (2), lung tissue (1)	Underlying bronchiectasis (5), ventricular septal defect with bacterial pneumonia (1), foreign body aspiration (1)		
Pneumonia in HIV	4		Gastric aspirate (3), pleural fluid (1)	Bacterial pneumonia (3)		
Hemoptysis	2		Sputum (2)	Bacterial pneumonia (1); pulmonary TB, suspected MDR (1)		
Extrapulmonary presentations	78	9 (8)			Followed up (60), LTFU (13), expired (3), sent home on palliative care (1), transferred to MDR TB facility (1)	16/52 (30.8)
Abdominal symptoms	13					
Ascites	2			Primary Budd-Chiari (1), TB (1)		
Diarrhea	1			Crohn's disease (1)		
Perforation/ obstruction	3			Abdominal tuberculosis (3)		
Chronic pain/ distension	7			Abdominal tuberculosis (5), Burkitt's lymphoma (1), appendiceal abscess (1)		
Acute respiratory distress and pericarditis	4			MICE (1), idiopathic (1), Pompe's disease (1), <i>Campylobacter</i> pericarditis in HIV (1)		
CNS	23					
Space occupying lesion	8			Bacterial abscess (3), fungal abscess (1), tuberculoma (1), tumor (3)		
Meningitis-encephalitis	10			TBM (7), subdural haemorrhage (1), multisystem cerebral leukoclastic angiitis (1), acute cerebellitis (1)		
Lower limb paresis	5			Transverse myelitis (2), Ewing's sarcoma (2), ADEM (1)		
PUO	30			TB (8), lymphoma (7), leukemia (2), enteric fever (2), <i>M. kansasii</i> disseminated infection (1), JRA (2), HLH (1), AIHA (1), CVID (2), CGD (1), neuroendocrine tumor (1), Neimann-Pick disease (1), intestinal amebiasis (1)		

Contd...

Table 1: Contd...

Presenting syndrome/ indication for TB testing	Patients (n)	Median age years (IQR)	Samples tested	Final diagnoses (n)	Patient outcomes (n)	Empiric ATT use during course of illness, n/N (%)*
Other (lymphadenitis, septic arthritis, chronic weight loss)	8			Paradoxical response to ATT (2), <i>S. aureus</i> infections (3), TB (1), malabsorption syndrome (1), unresolved (1)		
Total	126	8 (8.25)				25/95 (26.3)

\*Those clinically diagnosed with TB excluded. CGD: Chronic granulomatous disease, CCAM: Congenital cystic adenomatoid malformation, CNS: Central nervous system, PUO: Pyrexia of unknown origin, TBM: Tuberculous meningitis, SCID: Severe combined immune deficiency, MICE: Mesothelial/monocytic incidental cardiac excrescence, JRA: Juvenile rheumatoid arthritis, HLH: Hemophagocytic lymphohistiocytosis, AIHA: Autoimmune hemolytic anemia, CVID: Common variable immune deficiency, TB: Tuberculosis, IQR: Interquartile range, ATT: Antituberculous therapy, LTFU: Lost to follow-up, VATS: Video assisted thoracoscopic surgery, MDR: Multidrug resistant, ADEM: Acute disseminated encephalomyelitis, *H. influenza*: *Haemophilus influenza*, *M. kansasii*: *Mycobacterium kansasii*, *S. typhimurium*: *Salmonella typhimurium*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *S. aureus*: *Staphylococcus aureus*

infections (enteric fever, bacterial brain abscess, appendiceal abscess, *Staphylococcus aureus* infections, *Mycobacterium kansasii* disseminated disease, and *Campylobacter* pericarditis in an HIV-infected patient) ( $n = 11$ ; 21.1%) were the most frequent mimickers of TB among extrapulmonary presentations, followed by autoimmune disorders (Crohn's disease, transverse myelitis, juvenile rheumatoid arthritis-JRA, autoimmune hemolytic anemia, leukoclastic angitis, acute cerebellitis, and acute disseminated encephalomyelitis) ( $n = 9$ , 17.3%). Primary immunodeficiencies were identified in 9.6% of patients ( $n = 5$ ; chronic granulomatous disease-[CGD], common variable immunodeficiency [CVID], and severe combined immunodeficiency).

### Primary and secondary care tuberculosis diagnosis among children with alternative disorders

Of 95 children in whom TB was ruled out and alternative diagnoses were established, 25.8% ( $n = 25$ ) were diagnosed with and treated for TB for the same presenting complaints (similar episode of illness) before being evaluated at the study facility (9 of 43, 20.9% in the pulmonary group, and 16 of 52, 30.8% in the extrapulmonary group). Bronchiectasis was the most frequent pulmonary condition among children misdiagnosed as having TB in the primary healthcare setting ( $n = 5$ ), others being CGD, *Pseudomonas aeruginosa* empyema, *M. kansasii* pneumonia, and pulmonary neuroendocrine tumor. Lymphoproliferative disorders were most frequently misdiagnosed as TB among extrapulmonary presentations ( $n = 8$ ), where 4, patients with Hodgkin's lymphoma, and 1 patient each with T-cell acute lymphoblastic leukemia, diffuse large b cell lymphoma, Burkitt's lymphoma, and HLH, respectively, received ATT but failed to improve. Other disorders where patients were prescribed ATT without subsequent improvement included Ewing's sarcoma ( $n = 2$ ), transverse myelitis ( $n = 1$ ), *S. milleri* brain abscess ( $n = 1$ ), CVID ( $n = 1$ ), intestinal amebiasis ( $n = 1$ ), JRA ( $n = 1$ ), and malabsorption syndrome ( $n = 1$ ).

### Patient outcomes

Six patients died during the hospital course ( $n = 6$ , 4.8%, one each with pneumococcal pneumonia, necrotizing *P. aeruginosa*

pneumonia, bronchiectasis, HLH, Hodgkin's lymphoma, and disseminated TB). A large proportion of patients were lost to follow-up ( $n = 20$ , 15.9%).

## DISCUSSION

Although differentials for TB are legion,<sup>[9]</sup> they help in drawing attention to common diagnostic pitfalls. Our analysis shows that pediatric disorders mimicking TB and treated with ATT include nonTB bronchiectasis and CF, unresolved bacterial pneumonia ± empyema without underlying bronchiectasis, lymphoproliferative disorders, autoimmune disorders, and primary immunodeficiencies.

Cystic fibrosis is a previously under-recognized differential of pediatric pulmonary TB, and an underdiagnosed entity in Pakistan due to limitations of diagnostic tests available.<sup>[10]</sup> This presents a serious challenge given the lack of reference centers for diagnosis or for multidisciplinary management for CF in Pakistan.<sup>[11]</sup> Survival of CF patients is negatively impacted by the limited availability of pediatric pulmonology services, thoracic imaging, bronchoscopy, pulmonary function testing, and lung transplantation facilities to support diagnosis and care.<sup>[12]</sup> Such services need to be established to facilitate management of CF in Pakistan.

Another major differential of TB was unresolved bacterial pneumonia and loculated empyema. This is likely due to inadequate treatment of childhood bacterial pneumonia in primary care, leading to either residual or recurrent infection, sepsis, and loculated effusions requiring surgical management. As with the care of CF, availability of centers with facilities for advanced pulmonary care and VATS is necessary for optimal management of such patients.<sup>[13]</sup>

Pediatric lymphoproliferative disorders emerged as a principal differential for extrapulmonary presentations such as PUO, where such patients received empiric ATT. This reflects the inadequate identification of these disorders in primary care, a concern which has been highlighted before by Mushtaq *et al.*<sup>[14]</sup> A high index of suspicion is required to diagnose and



manage hematological malignancies early to reduce resulting morbidity and mortality.

Tuberculosis remained a frequent diagnosis in children with negative microbiological tests for *Mycobacterium tuberculosis*, especially for extrapulmonary (PUO, CNS and abdominal) presentations. Based on the inherent difficulty of diagnosing extrapulmonary TB among children, this result was expected.<sup>[15]</sup> Microbiological tests available for TB at the time were subpar<sup>[16,17]</sup> owing to low analytical sensitivities; however, detection rates are expected to improve with wider implementation and use of Xpert Ultra for extrapulmonary TB.

Our results highlight the need to implement changes in the health system at three levels. First, equipping HCPs at the primary and secondary level to build a practical differential and investigate as per resource locally, when children present with pulmonary and extrapulmonary illnesses which may mimic TB. Second, for cases that remain unresolved at the primary and secondary level referral to tertiary care/advanced pediatric care facility through a recognized facilitated referral loop established by the Local Health Ministry to confirm diagnoses and manage common childhood disorders such as bacterial pneumonia and childhood malignancies. Third, we have highlighted the need to develop, validate, and implement algorithms for the diagnosis and management of difficult clinical entities such as autoimmune disorders and CF at all levels of health care. As a first step, at the primary and secondary care level, physicians have to be educated and case files regularly audited to assess patient outcomes. There is also an imminent need to establish reference centers specializing in the management of children who are excluded from the TB register. To prevent loss to follow-up and to ensure continuity of clinical care, referrals to these centers need to be organized actively or facilitated.

In modestly organized health systems with vertical programs, the facilitated referral has been shown to work effectively in optimal management of medical conditions.<sup>[18]</sup> Facilitated referral in childhood infectious disorders is expected to reduce morbidity and mortality while monitoring referral practices.<sup>[19]</sup> Since adequate diagnosis and management of several alternative disorders identified here require modalities, expertise, and equipment that may only be available in tertiary care settings<sup>[20,21]</sup> facilitated referral is superior to passive referral which usually results in high levels of loss to follow up. In resource limited settings, facilitated referral is likely the best option to manage disorders mimicking TB. It is therefore important to identify common differentials and relative occurrence of TB in each setting to advise referral service linkages.<sup>[22]</sup> An example is the child lung health program in Malawi which was modeled on the prevalence and epidemiology of childhood diseases.<sup>[23]</sup> Rasmussen *et al.*<sup>[24]</sup> advocated strengthening measures in developing countries to facilitate optimal management in healthcare settings. For optimal management of pediatric patients, TB program clinics in Pakistan serving pediatric populations should be linked with

centers for diagnosis and facilitated management of chronic childhood pneumonia, bronchiectasis, CF, and pediatric malignancies.

Our results, while instrumental in understanding the need for facilitated referral, have limitations. First, we derived a laboratory-centric database and not a syndromic database as the primary data source due to its ready availability. However, purposive refinement of this database allowed us to determine alternative diagnoses by clinical features at presentation. Second, data from one hospital may not be generalizable to the entire country's population. Diagnostic skills of pediatricians (index of suspicion, clinical judgment, knowledge, and experience with alternative presentations such as CF) involved may also have impacted our results due to inherent difficulties in diagnosing childhood TB. Heterogeneity due to variations in clinical practice means that incidence figures cannot be derived as proportions are not a true depiction of the population.

## CONCLUSIONS

This study highlights the importance of continuing care and surveillance for children who are ineligible for enrollment in TB registers but continue to need high-level medical care. Children who test negative for TB should be referred to tertiary care centers to improve their health outcomes by identification and management of some alternative disorders which have high morbidity and mortality. Facilitated referral strategies are a time-honored solution to optimize resources while addressing such challenges.

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## Conflicts of interest

There are no conflicts of interest.

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