Challenges in Diagnosing Childhood Tuberculosis

Mycobacterium tuberculosis (Mtb) is the leading global killer from a curable infectious agent yet the true scope of disease in children is not known. In 2014, estimates approximated 1 million cases of childhood TB and 136,000 deaths. However, the actual number of cases disclosed to national TB programs were vastly different: only 36% of estimated pediatric TB cases were reported.[1] Reasons behind the under-recognition and under-reporting are multifactorial, but all speak to the urgent need for improved TB diagnostics for children.

Compared to adults, there are important differences in how children manifest with TB. The severity of disease at presentation often follows a bi-modal age distribution: young children, especially those who are less than two years of age, are at higher risk of developing severe disseminated forms of disease and adolescents are at higher risk of developing adult-type or cavitary disease; the remainder are more likely to present with intrathoracic disease with a predilection for isolated mediastinal lymph node involvement.[2] These varied and often non-specific symptoms contribute to misdiagnosis.

Once TB is considered on the differential diagnosis, our diagnostic "tool-kit" is limited to non-specific tests. Immunologic biomarkers, including the century-old tuberculin skin test and newer interferon-gamma release assays, rely upon cell-mediated immunity which is conditionally impaired in those at highest risk of disease—children who are very young, malnourished, and/or HIV-infected. Furthermore, these tests fail to distinguish Mtb infection from disease, making them less useful as a confirmatory test. Chest radiographs can aid in the determination of the presence and severity of active disease. However, the findings consistent with intrathoracic TB disease in a child can be heterogeneous and often times subtle at the earlier stages of progression, again lending a supportive but not confirmatory role.[3]

"Gold standard" TB tests, including the acid-fast bacilli (AFB) smear, Mtb culture, and Mtb molecular assays, detect microorganisms from respiratory specimens. The difficulties in obtaining adequate respiratory specimens impart notable logistic challenges because children lack the tussive force and oromotor coordination to expectorate on command thereby calling for skilled procedures such as gastric lavage, sputum induction and/or nasopharyngeal aspiration. Once a specimen is obtained, the yield is hindered by the paucibacillary nature of childhood disease-- AFB smear, the most widely available TB diagnostic test worldwide, has a sensitivity of 10-15% among children with "probable TB". The newer GeneXpert MTB/RIF assay has a yield of 65-76% among hospitalized children when testing two specimens, however this is in comparison to TB culture which also carries an unacceptably low yield of 30-40%.[4]

The successful detection of a child with TB represents the proverbial "tip of the iceberg." Reliance on traditional microbiologic confirmation from respiratory specimens is insensitive, however reliance on clinical grounds alone is non-specific, resulting in increased morbidity and mortality. Further work is urgently needed to identify accurate biomarkers of disease, ideally from feasibly-obtained pediatric specimens. As we work towards a public health goal of "zero childhood deaths from TB," [5] we owe it to each child to think about TB early in the clinical presentation and use our current tools with knowledge of their limitations, while advocating for simple, accurate and pediatric-friendly diagnostics for TB.

References

1. World Health Organization. *Global tuberculosis report 2015*. 20th ed ed. Geneva: World Health Organization; 2015.
2. Marais BJ, Gie RP, Schaaf HS, *et al*. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis.* Mar 2004;8(3):278 285.
3. Swaminathan S, Datta M, Radhamani MP, *et al*. A profile of bacteriologically confirmed pulmonary tuberculosis in children. *Indian Pediatr* 2008; 45(9):743-747.
4. Chiang, SS, Swanson DS, Starke, JR. New Diagnostics for Childhood Tuberculosis. *Inf Dis Clin N Am.* 2015 (29): 477-502
5. World Health Organization. Roadmap for childhood tuberculosis: towards zero deaths. Geneva, Switzerland 2013

Thomas, Tania A
Division of Infectious Diseases and International Health,
University of Virginia, Charlottesville, Virginia, USA.
Email: tat3x@virginia.edu