"TB in the resource poor area – What can we teach the developed world?"

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Tuberculosis continues to be a major public health challenge in most part of the developing world. The disease, time and again, also comes up amongst the native as well as immigrant populace of the rich countries in the west. The difference in the two situations does not merely arise out of the disparate magnitude abut also due to difference in the epidemiology in these communities. In the context of management of childhood tuberculosis the developing countries differ a lot from the developed countries due to lack of sometimes even the basic investigations, far away from the realm of more advanced diagnostic tools like nucleic acid probes, restriction fragment length polymorphism and interferon gamma release assays as used in the west. One wonders about the possible areas where the west can learn from the resource poor countries as the working paradigms of the two are far from comparable. The experience gained by high burden poor countries regarding the disease profile, response to treatment, paradoxical responses and the status of different investigations certainly can be a worth sharing with the pediatricians in the west who do not see much of this formidable enemy.

In the past decade or so, another major change in the management of tuberculosis has been an approach for supervised therapy. The governments of several countries with the support of the World Health Organization and other international technical agencies have implemented the DOTS (directly observed therapy, short-course) strategy for tuberculosis (TB) control. The current strategy focuses on passive detection of patients with sputum smears positive for acid-fast bacilli (AFB). Children with TB are far less likely to have sputum smears positive for AFB, and hence considered to be less infectious than adults, inherently get lower priority within DOTS strategy. This approach has been further justified because of the treatment of infectious adult patients shall lead to containment of infectious pool and hence less disease in children. The present paper shall allude to these issues in greater details further.

The confirmation of the diagnosis of TB in children is particularly difficult and enigmatic. Little efforts are usually made to bacteriologically confirm a diagnosis of TB in a child because of poor yield on direct smear, poor access to appropriate specimen, need for high resources and trained personnel for culture. Children aged under 5 years rarely expectorate sputum for evaluation, and even when specimens are obtained, children, especially young children, are rarely smear-positive for acid-fast bacilli (AFB) on routine sputum microscopy. Gastric aspirates, an alternative in young children, are positive on smear in less than 20% of children, and on culture in less than 50%. While there are studies showing comparable yield from more easily accessible specimens like nasopharyngeal aspirates or induced sputum, they are currently not used routinely. In addition to the technical difficulties and lack of culture facilities, it is the mind set of the pediatricians, that the pediatric TB is usually smear negative, which forms the major
hurdle. While it may is true that the primary tuberculosis – hilar or mediastinal lymph nodes with or without a parenchymal lesion are paucibacillary and therefore perhaps not worth attempting a bacteriological diagnosis, the same can not be said about the progressive primary form and the adult type fibro-cavitary disease as seen in many adolescents.

Due to the poor acceptability and limited utility of the bacteriological tests, often the reliance is placed on indirect epidemiological clues. The triad of positive tuberculin skin test, an abnormal chest radiograph and history of exposure to an adult with probable or definite tuberculosis remains the most commonly employed method for diagnosing tuberculosis in children. Often a non response of symptoms- particularly with persistence of the radiological shadows- to potent antibiotics is used as an additional ground for suspecting tuberculosis. It must be pointed out that over-diagnosis of hilar adenitis in children with slightly rotated or expiratory films is a common mistake in clinical practice. Thymus, body of manubrium, etc. can be mistaken for a paratracheal lymphadenopathy. Even in well taken radiographs, there are large inter- and intra-observer error for assessing TB.

CT is more sensitive than chest radiography for detecting intra thoracic adenopathy and is often considered a gold standard. On contrast enhancement, mediastinal lymphadenitis-especially when it exceeds 2 cm in diameter- have a characteristic appearance consisting of central areas of low attenuation associated with peripheral rim enhancement and obliteration of the perinodal fat. Although this pattern is suggestive of tubercular adenitis but similar findings may also be seen in atypical mycobacterial infection and lymphoma. Further, there is only moderate agreement between readers on the presence of the lymph node lesion on CT, particularly in the anterior mediastinum. In one study the readers not only had difficulty in distinguishing lymphadenopathy from normal thymus; they were unable to distinguish normal from pathological nodes without a predetermined size threshold for abnormality. The risk of radiation exposure with CT in children is significant and should always be kept in mind. CT accounts for the largest component of medical radiation, second only to background (or natural) sources of exposure to the population.

Due to problems in the diagnosis of childhood, symptom based diagnostic approaches are often promoted in high burden settings. However, this is fraught with danger as the poorly defined symptoms, traditionally associated with tuberculosis, are too common in children from these communities to be of real diagnostic value. In a cross sectional, community based survey in South Africa, comparison of individual symptoms (cough, dyspnoea, chest pain, haemoptysis, anorexia, weight loss, fatigue, fever, night sweats) in children with and without tuberculosis revealed that only weight loss differed significantly while the combination of cough and weight loss was most significant. Careful symptom characterization may be essential to improve their diagnostic value. These characteristics include persistent, non-remitting symptoms of recent onset. TB is however, one disease with many protean presentations. Usually, it is associated with persistent and prolonged symptoms but in a Zambian post mortem study, TB occurred in 18% of HIV-infected and 26% of HIV-uninfected children and was the second most commonly identified cause of death in children older than 1 year. History of household contact can be a very important pointer in the children in low burden communities.
Tuberculin or Mantoux’s test using Purified Protein Derivative (PPD) has been a mainstay supportive test for diagnosis of TB among children. The world had 2 standard tuberculins – PPD-S and PPD RT23 which were prepared as big standard lots in 1950s. Currently there seem to be shortage of these standard lots in many countries. Countries like India which have standardized the cutoff values for the PPD skin reaction based on 1TU of PPD RT23 in their communities are now facing a major challenge as the same is not easily available at an affordable cost. Interferon Gamma release assays (IGRAs) using CFP-10 and ESAT 6 antigen may be a future replacement of the PPD test as they have no cross reaction to BCG and do not require a repeat visit. The head to head comparison between PPD and IGRAs shows them to be similar in sensitivity and specificity in the field conditions. At the present juncture these tests are far more expensive and technically advanced to be used routinely in the developing resource constrained world and they either have to look up to the international community for sharing the relatively scarce PPD standard or develop a new standardised preparation. The world is looking for another Florence Seibert to make a fresh lot for the future half century or more. And that shall only be a beginning point before the reactivity of the new preparation is tested and quantified.

Monitoring of the treatment of Tuberculosis without the bacillary activity as a marker, as is often the case in children with paucibacillary and extra-pulmonary disease creates another problem. The treating pediatrician needs to be aware of the paradoxical reactions such as enlargement of lymph nodes or appearance of new lymphadenopathy, radiographic worsening of pulmonary infiltrates or appearance of miliary infiltrates or pleural effusions, peritonitis, tenosynovitis, worsening or development of new soft tissue lesions, and appearance of new contrast-enhancing intracranial tuberculomas despite adequate therapy. The occurrence of paradoxical reactions appears more often in patients coinfected with HIV. It is important for clinicians to recognise paradoxical tuberculous reactions as inflammatory responses to treatment, and to understand that they do not necessarily indicate drug resistance or an inadequate response to therapy.

Standard Treatment guidelines are now available. Thankfully the developing world has most of the essential anti tuberculous drugs now available due to the global efforts at controlling tuberculosis. The bigger danger is development of multi or extensive drug resistance strains due to uncontrolled and irrational use of these short course drugs particularly Rifampin. Direct observation of treatment (DOTS) is the current strategy to combat this problem where in all medications is given to the patient under the direct supervision of a health worker. National programs world over are adopting this strategy under the aegis of WHO. The DOTS strategy is focused primarily on treating and curing over 80% of the infectious patients in a community. Recent efforts to promote the DOTS strategy, which relies on sputum smear microscopy for diagnosis have had the unintentional effect of de-emphasizing TB in children as a priority for National Tuberculosis Programs (NTPs). Nevertheless, TB is an important cause of morbidity and mortality in children worldwide. There is longstanding concern worldwide about the burden of childhood TB. The general rule of thumb is that children represent approximately 15% of the TB burden in the developing world; however, current data on TB incidence from some countries such as Afghanistan and Pakistan show it to be higher than 20%. 

8
A case of TB in a child is a sentinel event in that it represents recent transmission of TB in a community. In addition, because young children are at high risk of progression from infection to disease, ‘a deterioration in the control of TB thus immediately hurts the youngest generation’. Children can transmit *Mycobacterium tuberculosis*, as has been well-documented in large school-based and community outbreaks; however, it is not clear how frequently this occurs. Finally, infected children, including those who recover from primary disease, represent the reservoir of future disease. Thus, any efforts to reduce the long-term trends of TB worldwide should consider the role played by infected and diseased children.

In India the pediatric bodies have taken up the issue of being more inclusive for the children with the NTP managers. This led to a consensus statement based on a combined workshop of the pediatricians, tuberculosis and public health experts. The management of pediatric cases has now been included as a special area under RNTP and patient wise boxes of pediatric formulations have been made available in the country. The linkages between the public health and the pediatric experts are being developed for a seamless care and hopefully that shall be another experience worth sharing with others.

References: