

Is Shorter Treatment Regimen for Multidrug-resistant Tuberculosis feasible in Indian Children?

Traditionally, patients with rifampicin-resistant (RR) or multi-drug resistant tuberculosis (MDR-TB) are treated with a combination of second-line drugs, usually for 18 months or more [1]. Recently, World Health Organization (WHO) recommended a shorter and cheaper treatment regimen for MDR-TB [2]. Standardized shorter MDR-TB regimen consists of seven drugs and a treatment duration of 9-12 months [1]. The regimen consists of 4-6 months of kanamycin, high-dose moxifloxacin (12 mg/kg/day, not to exceed 800 mg daily), prothionamide or ethionamide, clofazimine, pyrazinamide, high dose isoniazid (15 mg/kg, not to exceed 900 mg daily) and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol [1]. These recommendations were based on studies carried out in several countries – mostly in Africa [1,3].

Ideally, shorter MDR-TB regimen should be given to persons (adults or children) with MDR-TB if they have not been previously treated with second-line drugs, and if additional resistance to pyrazinamide, ethambutol or the second-line drugs used in the regimen is unlikely. Therefore in children knowing the drug susceptibility (DST) result of the source case (if identified) or the entire DST results of all the first and second line drugs in the patient's sample is important when considering the use of the shorter regimen.

In a study from Mumbai, pre-XDR TB [(MDR-TB along with resistance to either a fluoroquinolone or an aminoglycoside (apart from streptomycin)] was the most common form of drug-resistant tuberculosis with observed prevalence at 56.8% compared to 29.4% for MDR-TB in adults [4]. The proportions of patients with ofloxacin, moxifloxacin and ethionamide resistance were 75.3%, 69.5% and 52.5%, respectively in adults [4]. In

children with drug-resistant tuberculosis, moxifloxacin resistance was 46%, ofloxacin was 47.6%, ethionamide resistance was 49.2%, pyrazinamide resistance was 55.6% and ethambutol resistance was 60.3% [5]. There is also an increase in prevalence of pre-XDR TB in children as compared to MDR-TB [5]. Most of these children would have resistance to isoniazid, rifampicin, ethambutol, pyrazinamide, quinolones and ethionamide. Thus the shortened MDR-TB regimen may provide inadequate treatment to these patients. Starting this regimen in children based only on the geneXpert results of rifampicin-resistance without testing for DST to all the first and second line drugs would be a logistical mistake, and may lead to more drug-resistant forms of tuberculosis, and treatment failures. Treatment of drug-resistant tuberculosis should be individualized based on the DST results.

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Is Vitamin D Deficiency Linked to Critical Illness?

In recent years, dozen of studies have demonstrated that the prevalence of vitamin D deficiency (VDD) among

critically-ill children at admission to pediatric intensive care unit (PICU) was in range of 25%-84% [1-5]. Few of these demonstrated that VDD was associated with greater severity of illness and longer PICU stay [1-3].

We read with interest the research article on the topic by Shah, *et al.* [5]. Authors demonstrated a high

prevalence of VDD (83.1%) among 154 critically-ill children. They noted no differences in severity of illness at admission, mortality, and duration of PICU stay among vitamin D-deficient and non-deficient children. The high prevalence of VDD in this study cohort could be due to high prevalence of malnutrition (65.6%) and presence of chronic illness (55.4%), which directly or indirectly could have influenced vitamin D status. It could have been better if authors had included matched controls to account for the baseline prevalence of VDD in the given population.

Recently, we demonstrated that the prevalence of VDD (level <20 ng/mL) among 124 critically-ill children with sepsis and 338 healthy controls was 50.8% and 40.2%, respectively ($P=0.04$) [4]. We also noted that the severity of illness assessed by PRISM III and SOFA scores was not significantly different between cases with VDD and those with non-deficient levels of vitamin D, though the PRISM III score was slightly higher in cases with VDD. Also, there was a trend toward increased occurrence of septic shock and MODS, requirement for catecholamines and mechanical ventilation, development of healthcare associated infections, and occurrence of hypocalcemia in cases with VDD; though the difference was not statistically significant. Whereas Shah, *et al.* [5] noted lower mortality, shorter PICU stay, lesser requirement and duration of mechanical ventilation, and lesser incidence of ARDS in vitamin D-deficient cases. This was in contrast to previous studies [1-4]. Shah, *et al.* [5] mistakenly mentioned non-vitamin D deficient children as 19.8% in abstract section, which should be 16.9%.

Larger multicentric studies are needed to determine the prevalence of VDD, association of VDD with clinically important outcomes, and effect of supplementation of vitamin D in critically-ill children. Till then, it is important for critical care physicians to carefully examine the results of available studies before clinical applicability.

Acknowledgement: Dr Renu Suthar for providing intellectual inputs and critically reviewing manuscript.

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AUTHORS' REPLY

We thank the authors for the interest in our article [1]. High prevalence of malnutrition and presence of chronic illness in our study population could have influenced vitamin D level, and we therefore agree with their suggestion to include matched control to assess the baseline prevalence of vitamin D deficiency. We considered this thought during the process of study design, but from ethical standpoint, it was difficult to draw blood samples for vitamin D level alone in apparently healthy children.

We observed a trend towards lower mortality, shorter duration of PICU stay, and lesser requirement and duration of mechanical ventilation in vitamin D-deficient children compared to that of non-vitamin D deficient. However, none of these associations reached statistical significance. Therefore, we were unable to draw a firm conclusion on the association. We regret the printing error in the abstract.

Due to limited studies in children, and differences in the result on association of vitamin D level with clinical outcomes from various studies, we agree with the authors' concluding remark on being cautious on interpretation of the result of studies. We certainly need trials to determine if vitamin D supplementation is beneficial in critically ill children.

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