Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Harnessing Novel Quantitative Pharmacology Approaches to Optimize the Treatment of Children With Tuberculosis

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The World Health Organization (WHO) estimates that a million children each year develop tuberculosis [1], with models suggesting that only a third of these children are diagnosed and started on treatment [2]. Although the WHO-recommended treatment regimen for children with drug-susceptible tuberculosis is generally well tolerated and leads to good treatment outcomes, 6 months of daily treatment can be challenging for children and families. For multidrug-resistant tuberculosis (disease caused by *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin), treatment regimens are long (often for >18 months) and are associated with significant toxicity. There is, therefore, a pressing case for new shorter, well-tolerated regimens that can treat both drug-susceptible and multidrug-resistant organisms.

Traditionally, when designing drug regimens for children with tuberculosis, the dosages advised and the duration of therapy are extrapolated from adult studies. However, the spectrum of disease seen in younger children (approximately ≤10 years) is very different from that in adolescents and adults. Although the majority of tuberculosis in young children consists of intra- and extrathoracic lymph node disease, these children, compared with older children and adults, more commonly develop severe forms of disease, such as miliary tuberculosis, tuberculous meningitis, and other extrapulmonary manifestations [3]. Both lymph node disease and disseminated disease are typically intracellular and paucibacillary, different from the disease processes seen in older children and adults where cavities occur and multibacillary and extracellular pathology predominates. This suggests that young children may require different drug serum concentrations (systemic exposures) and different durations of therapy than adults. Another difference between adults and children is the correlation between ingested dose and the resulting serum exposure—that is, the concentration of drug achieved in the serum. This field of pharmacokinetics is slowly being better understood for the first-line antituberculosis drugs, and it is now acknowledged that children metabolize antituberculosis drugs more rapidly than adults and require a higher milligram per kilogram oral dosage to achieve the same serum concentration [4]. Children also commonly tolerate drugs better than adults. However, the implications of adverse events, such as hearing loss, might be more consequential in a developing child than in an adult. For these reasons, it may not always be appropriate to extrapolate regimens, dosages, and durations of therapy from adults to children. Therefore, studies should be carried out in young children to determine the optimal dosing. However, there are significant technical and ethical challenges to carrying out such studies in children. Pharmacokinetic studies require intensive investigation with multiple blood draws. This can be technically difficult and distressing for children, and limited amounts of blood can be safely taken from a child within a specified time period. Efficacy studies are also difficult. Respiratory samples are difficult to obtain from young children, and are frequently smear negative and culture negative. These difficulties in confirming the diagnosis of tuberculosis in children raise questions regarding the definitions used to enter children into tuberculosis treatment trials and the definitions used to describe failure or relapse. The surrogate markers of efficacy that are commonly used in adult studies, such as early bactericidal activity or sputum smear (or culture) conversion, rely on demonstrating a change in the number of bacilli in the sputum. Given the highly successful WHO-recommended regimen, any clinical trial comparing the current standard of care against a novel regimen would require large numbers of children to be recruited and followed up in order to identify the small number who may fail therapy or relapse.

What is the answer? The series of articles in this supplement to *Clinical Infectious Diseases* provides one approach. This sequence of studies very persuasively provides a proof-of-concept

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framework for how we might identify optimal regimens for children, better predict desired drug exposures, and determine the required dosing needed to optimize mycobacterial killing in children, while limiting toxicity. In the first article, Swaminathan et al [5] describe a cohort of children in India treated for tuberculosis and use machine learning models to explore risk factors for treatment failure. After adjusting for multiple epidemiological and clinical characteristics, low serum exposures of the first-line drugs were associated with treatment failure, suggesting that inadequate exposures may well be contributing to failure of therapy. This study, in effect, justifies why the subsequent studies are necessary. The second article by Srivastava et al [6] outlines a roadmap, describing a 4-step laboratory program to develop an optimal treatment regimen in children and the required dosing to achieve the desired drug exposures. In the third article, Deshpande et al [7] investigate the effect of linezolid on *M. tuberculosis* and describe how a hollow fiber model can be used to mimic the intracellular nature of disseminated pediatric disease and the drug half-life of linezolid seen in children. This was then used to determine the exposure needed for optimal killing of the mycobacteria. In this article the authors also use transcriptomics to identify a gene signature associated with linezolid toxicity and then determine the maximal exposure threshold associated with toxicity. In the fourth [8] and fifth [9] articles, moxifloxacin and then faropenem are added to linezolid in a systematic way within the hollow fiber model to determine the optimal exposure for each drug and to assess synergy, antagonism, or additivity of the combinations. In the sixth article, Srivastava et al [10] used Monte Carlo modeling to determine the required dosage of the 3 drugs necessary to attain the desired exposures. Although this approach has been used in adults with tuberculosis, this is the first attempt to use this strategy to model the design of a pediatric antituberculosis drug regimen. Finally, Gumbo et al [11] have outlined how this proof-of-concept approach could be expanded to provide a comprehensive program to discover optimal drug combinations and dosing for children with tuberculosis.

Although much work remains to be done, these studies highlight an exciting and novel strategy. As suggested, a systematic approach to evaluate multiple drug combinations needs further exploration, and once optimal drug combinations and dosages are determined, they would need to be evaluated clinically in children. This rational, systematic scheme, starting in the laboratory and then progressing to clinical studies, should provide valuable new insight into drug regimen development. Determining whether duration of therapy can be shortened will be challenging, and it will be important to evaluate whether certain pharmacodynamic parameters are able to predict the required duration of therapy. However, we can be optimistic that this approach should be able to identify novel drug combinations and drug dosages that are safe and effective and that could lead to shorter duration of treatment for both drug-susceptible and drug-resistant tuberculosis in children.

Notes

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