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Management and outcomes of severe childhood tuberculosis in the pediatric intensive care setting: can we identify best practices?

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Tuberculosis continues to be a clinical and public health priority. In 2017, there were an estimated 10.0 million new cases of tuberculosis and 1.3 million deaths from the disease, approximately 1.0 million of the cases and 195,000 of the deaths occurring in children under 15 years of age.[1,2] Tuberculosis is now recognized as one of the top 10 leading causes of death in children under 5 years of age living in areas with a high tuberculosis incidence. Historically, attention has been focused on pulmonary tuberculosis in adults, because it is the most infectious form. Adults with pulmonary tuberculosis transmit the disease through infectious aerosol particles, which are typically produced when a patient with cavitary lung disease coughs. Young children are less likely to have cavitary lung disease and are therefore not considered to pose a major transmission risk.[3-6] It is also more difficult to diagnose tuberculosis in children, and the burden of disease is therefore generally underestimated.

Recently, there has been increased awareness of the global burden of tuberculosis in children, resulting in more attention being given to pediatric tuberculosis from a clinical, public health, and research perspective.[1,2,7-11] Improving the accuracy of the diagnosis of tuberculosis in children is made more difficult by the paucibacillary nature of their disease; the fact that the symptoms and signs they present, as well as the radiological findings, are often nonspecific; and the inability of immunodiagnostic tests (interferon-gamma release assays and tuberculin skin tests) to differentiate between infection with *Mycobacterium tuberculosis* and active disease. Expanding the evidence available in the scientific literature to support quality diagnostic and treatment guidelines specific to pediatrics is a core issue,[1,2,7-11] as is the need to increase the availability of the child-friendly drug formulations that are now available through the Global Drug Facility of the international Stop TB Partnership.[12]

Despite the extensive morbidity and mortality caused by the severe forms of tuberculosis in children (tuberculous meningitis and miliary tuberculosis), scarce attention has been paid to the optimal management of tuberculosis in children admitted to the ICU. Ongoing research and reviews are attempting to explore and define best practices in adult tuberculosis cases treated in the ICU.[13] The admission of adults with tuberculosis to the ICU is most often due to extensive pulmonary involvement, leading to ARDS, life-threatening hemoptysis, or lung surgery.[14] In immunocompromised adults, neurological deterioration due to tuberculous meningitis might be another reason for ICU admission. Approaches to recognizing and managing such presentations have been discussed in the literature.[15] Overall, the mortality in ICU patients with tuberculous is quite high, usually exceeding 50%.[16]

We drew upon our experience at the National Pediatric Reference Department for Respiratory Infections, in Sofia, Bulgaria, to identify research feasibility and gaps in the treatment of severe pediatric tuberculosis. Between 2015 and 2018, five children with tuberculous meningitis were admitted to the hospital, with a mean age of 1.2 years (range, 0-3 years) and a mean body weight of 9.6 kg (range, 6-13 kg). Two had non-HIV immunosuppression and no other major comorbidities. On the basis of cultures (of cerebrospinal fluid, in 3 cases, and gastric aspirate, in 2), all five children had a confirmed diagnosis of infection with drug-susceptible strains of *M. tuberculosis*; one patient was also smear positive on Ziehl-Neelsen staining. All of the children had non-cavitary pulmonary involvement on chest X-ray, bilateral disease suggestive of miliary tuberculosis being seen in two. None of the children had respiratory distress severe enough to require ventilatory support, and none developed any signs of sepsis. Routine treatment with isoniazid, rifampin, ethambutol, and pyrazinamide was initiated an average of 4.4 days after presentation (range, 1-16 days). The mean time to culture conversion, based on monthly cultures, was 43.2 days (range, 40-46 days). In all five children, a clinical cure was achieved after 10-12 months of treatment with an all-oral

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regimen. Although the evidence from those five clinical cases is limited, it provides an encouraging picture in terms of the potential outcomes of severe childhood tuberculosis treated in the ICU. Nevertheless, the cases described represent a small number of children with a limited range of tuberculosis disease manifestations. In addition, none of those children received a treatment regimen that was optimized to penetrate the central nervous system. Therefore, there is a need for a more comprehensive review of all pediatric patients with tuberculosis who are admitted to the ICU. Although children with miliary tuberculosis have disseminated disease, they often do not appear critically ill, no cases of children presenting with classic sepsis or septic shock having been documented. However, more information is needed in order to accurately describe the full range of manifestations of severe tuberculosis in children. Similarly, there have been only a few reports of ARDS in children with acute pneumonia-like symptoms secondary to tuberculosis, which can be easily confused with acute bacterial coinfection.[17] More insight is necessary in order to describe the epidemiology, presentation, and management of such cases in pediatric ICUs.[18]

Experience from adult cases demonstrates the complexity of the pharmacokinetics and pharmacodynamics of antituberculosis drugs in critically ill patients. Absorption of oral antituberculosis drugs may be reduced by 70% due to gastroparesis, intestinal paralysis, pharmacological prophylaxis against gastric ulcers, and altered gut microbiota. Suboptimal drug levels, in blood and affected tissues, can be attributed to several factors, including impaired circulation efficiency, with fluid accumulation, and glomerular hyperfiltration, with increased renal clearance.[19,20] Although this experience seems to be transferable to pediatric cases, no specific documented evidence is available for such cases. There are other concerns unique to children, including variable drug distribution and metabolism among different age groups.[21] The need to ensure adequate blood and tissue levels of the available oral and intravenous tuberculosis drug formulations, as well as to provide optimal supportive care, are key factors in managing such complex cases of tuberculosis. There are still few pharmacokinetic data for very young or critically ill children treated with first- or second-line tuberculosis drugs, and much more remains to be done.

The paucity of evidence on childhood tuberculosis in the context of ICU care of critically ill patients calls for a collective effort to determine the magnitude of this unmet medical need, as well as for the development of best practice guidelines. Although we have described a few cases of tuberculous meningitis requiring ICU care, there is a need for a more comprehensive overview of the full spectrum of the disease and its clinical presentations, as well as the best management approaches, in children who require ICU admission for severe tuberculosis. That can be achieved only in collaborative multicenter observational studies using standard data collection tools and a shared data platform.

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