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Review

Recommendations for treating children with drug-resistant tuberculosis

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ABSTRACT

Tuberculosis (TB) is still one of the most difficult infectious diseases to treat, and the second most frequent cause of death due to infectious disease throughout the world. The number of cases of multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), which are characterised by high mortality rates, is increasing. The therapeutic management of children with MDR- and XDR-TB is complicated by a lack of knowledge, and the fact that many potentially useful drugs are not registered for pediatric use and there are no formulations suitable for children in the first years of life. Furthermore, most of the available drugs are burdened by major adverse events that need to be taken into account, particularly in the case of prolonged therapy. This document describes the recommendations of a group of scientific societies on the therapeutic approach to pediatric MDR- and XDR-TB. On the basis of a systematic literature review and their personal clinical experience, the experts recommend that children with active TB caused by a drug-resistant strain of *Mycobacterium tuberculosis* should always be referred to a specialised centre because of the complexity of patient management, the paucity of pediatric data, and the high incidence of adverse events due to second-line anti-TB treatment.

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1. Introduction

Tuberculosis (TB) is still one of the most difficult infectious diseases to treat and, after HIV infection, the second most frequent cause of death due to infectious disease throughout the world [1]. Of the estimated 9.6 million worldwide incident TB cases in 2014, approximately 1 million were children less than 15 years of age [1]. The number of cases of multidrug-resistant TB (MDR-TB) is increasing, and it is estimated that approximately 190,000 of the estimated 480,000 new cases in 2014 were fatal [1]: a very high rate of mortality in comparison with the incidence itself due to no possibility of access to appropriately drug-resistant TB treatment. MDR-TB is defined by both resistance to isoniazid and rifampin [1]. Jenkins et al. identified that MDR-TB reflects the local risk of transmitted MDR-TB in any age group and estimated that around 999,792 children developed TB disease in 2010, of whom 31,948 had MDR disease [2]. Dodd et al. showed that the incidence of pediatric TB is higher than the number of notifications, particularly in young children [3].

In the Figure, the woman shows the actual heavy burden of MDR- and XDR-TB, whereas the man represents the possibility of a reduced MDR- and XDR-TB burden in the future.

As a matter of fact, rifampin resistance is considered to be associated in about 90% of cases also with isoniazid resistance. TB associated with resistance to isoniazid and rifampin plus resistance to fluoroquinolone and a second-line injectable drug is defined extensively drug-resistant TB (XDR-TB) [1].

The therapeutic management of children with TB is complicated by the fact that many anti-TB drugs are not registered for pediatric use and there are no formulations suitable for children in the first years of life [4]. The situation is even more difficult in the case of MDR-TB and XDR-TB [5], since very little is known on pharmacokinetic and pharmacodynamic profiles and safety of the available drugs, which are burdened by major adverse effects that need to be taken into account, particularly in case of prolonged therapy. There is a limited evidence base to guide optimal treatment and follow-up in the pediatric population with MDR-TB and XDR-TB because in guidelines the care of children is often relegated to small "special populations" sections [6]. In addition, after 2012 no guidance including studies and opinion papers on pediatric MDR-TB has been published.

This document describes the recommendations of a group of scientific societies concerning the therapeutic approach to pediatric MDR- and XDR-TB. Recent different documents described recommendations of the same scientific societies on how to manage children exposed to TB (including those exposed to MDR-TB) [7], how to deal with neonatal TB [8], how to diagnose TB in pediatrics [9], hospitalization and re-admission in community in children with suspected or confirmed TB [10], first-line therapy (including treatment adherence and monitoring) in children with TB [11], management of TB in immunocompromised children (including those with TB-HIV co-infection) [12], and BCG vaccination [13].

2. Methodology

Using the Consensus Conference method on the basis of the National Institutes of Health and the Italian National Programme Guidelines (Table 1) [14,15], relevant publications in English were identified by means of a systematic review of MEDLINE and the Cochrane Database of Systematic Reviews from their inception until 31 December 2014. The search strategy was

> "children[Title/Abstract] OR pediatric[Title/Abstract] OR paediatric[Title/Abstract] AND tuberculosis[Title/Abstract] AND multi-drug resistant tuberculosis[Title/Abstract] OR MDR tuberculosis[Title/Abstract] or extensively-drug resistant tuberculosis[Title/Abstract] or XDR tuberculosis[Title/Abstract] or resistant tuberculosis[Title/Abstract] AND English[lang])".

The Working Group agreed on a list of clinical problems related to the management of MDR- and XDR-TB, and the evidence review procedures concentrated on patients aged 0–18 years, and included section-specific targeted searches as well as formal systematic reviews of selected aspects. All of the data were entered in tables of evidence for each subject. The literature was critically appraised by trained personnel using the Scottish Intercollegiate Guidelines Network methodological checklists [16], and the bibliographical material and a preliminary draft document were given to the panel members. The published evidence was presented and discussed at various meetings, and the Delphi method was used to reach a consensus when the evidence did not provide consistent and unambiguous recommendations [16]. The final text was revised on the basis of these discussions and submitted by e-mail to participants at the Consensus Conference for final approval.

The multidisciplinary panel of clinicians and experts in evidence-based medicine were identified with the help of the participating scientific societies, and included experts in the fields of general pediatrics, pediatric infectious diseases, neonatology, infectious diseases, pneumology, microbiology, radiology, pharmacology, public health and methodology. The panel was coordinated by the Italian Society of Pediatric Infectious Diseases (SITIP). No panel member declared any conflict of interest concerning the contents of the guideline topics. The panel met on three occasions, but many of the consultations involved in developing the document took place interactively by e-mail or telephone.

3. When should MDR- or XDR-TB be suspected in children?

Childhood TB is frequently paucibacillary in nature, which leads to specimens obtained for microbiological confirmation often having low rates of acid fast bacilli detection as well as polymerase chain reaction (PCR) and culture negative [17]. Therefore, the availability of genotypical and phenotypical drug susceptibility test (DST) results is rare and usually late. Consequently, one of the additional difficulties in treating pediatric TB is the absence of data concerning resistance to first- and second-line drugs. However, in most series the culture-positive TB cases among children are more