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Indications to Hospital Admission and Isolation of Children With Possible or Defined Tuberculosis

Systematic Review and Proposed Recommendations for Pediatric Patients Living in Developed Countries

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Abstract: Tuberculosis (TB) is a re-emerging health problem in developed countries. This paper is part of large guidelines on the global management of TB in children, by a group of scientific societies. It describes the indications to hospitalization of children with suspected or diagnosed TB, the isolation measures, hospital discharge, and re-admission into the community.

Using the Consensus Conference method, 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.

Available data on indications to hospitalization were mainly indirect and largely derived from observational studies. They include: (1) host-related risk factors, the main being age <12 months, immune deficiencies, and malnutrition; (2) TB-related clinical conditions that resemble those of pneumonia but also include drug-resistance; and (3)

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social and logistic conditions. The latter are based on opinion and depend on local conditions. Analysis of the literature showed that patients hospitalized with suspected pulmonary TB should be put in precautionary respiratory isolation regardless of their age while they await diagnosis. The general conditions for re-admission into the community are at least 14 days of effective treatment and negative microscopic tests of 3 consecutive samples in previously microscopically positive patients.

This is the first paper that provides indications to hospitalization of children with TB. Most recommendations are generally applicable in all developed countries. Some might need an adaptation to local setting, epidemiological, parameters, and availability of specific health-care facilities.

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Abbreviations: EPTB = extrapulmonary TB, MDR = multi-drug resistant, MTB = meningeal tuberculosis, OR = odds ratio, RR = relative risk, SITIP = Italian Society of Pediatric Infectious Diseases, TB = tuberculosis, WHO = World Health Organization, XDR = extensively drug-resistant.

INTRODUCTION

Tuberculosis (TB) is the second most frequent infectious cause of death after HIV infection worldwide.[1] The latest World Health Organization (WHO) report estimates that, in 2012, there were 8.6 million incident cases of TB worldwide (the equivalent of 122 cases per 100,000 inhabitants) and 1.3 million TB-related deaths (including 940,000 HIV-negative and 320,000 HIV-positive subjects).[1] The massive immigration rates from endemic areas toward developed countries contributes to TB spreading and triggered a major interest in the management of patients who have developed any of the stages of the infection. Children with peculiar clinical manifestations often require a specific expertise. However, any global strategy for TB control must also take into account measures to address the social and environmental issues that are inextricably linked with TB.[2]

The management of TB is based on a probabilistic approach in which the clinical history, the exposure to contacts, selected host-related underlying conditions, and the clinical features are evaluated in order to define the infection state and to search for signs and symptoms of active TB disese. These are then used for medical decision and management, including treatment, hospitalization, re-admission in community, and follow-up. However, in recent years a progressively increasing number of cases come from at risk countries with refugees and immigrants. It is estimated that in the year 2014 ~170,000 to 200,000 refugees arrived in Italy, and then reached other European countries, after crossing the Mediterranean sea. Often, in this population, previous clinical history or information on exposure is not available. In addition, the incidence of risk factors such as malnutrition or coinfection with HIV is relatively common. The social conditions, the language and other cultural barriers add to the problem of management of this fragile population and hamper the probabilistic approach to TB. Another issue is the lack of information on previous TB immunization that raises problems in the interpretation of skin test. Specific interferon gamma tests may be used to diagnose infection and discriminate this from immunization, although they are not fully validated in infants and young children.

TB has multiple implications and should be managed based on clinical consideration but also taking into account public health as well as social and logistical aspects and obviously human rights and ethical issues. In line with this vision, very recently the Global TB Programme of the WHO recommended to address the vulnerable and hard-to-reach groups and to specifically address special needs of migrants and cross-border issues as a priority to limit the infection spreading and move toward TB elimination in low-incidence countries.[3]

This paper was prepared in the light of the challenges linked to this evolving scenario of TB in children. There is no reference paper or guidelines to indicate hospitalization and pediatricians need to move with no specific protocols. To cover this gap, the Italian Society of Pediatric Infectious Diseases (SITIP) coordinated a panel of expert from several scientific societies with the aim of producing a paper with the indications to hospital admission of children with possible or defined TB. Isolation measures, hospital discharge, and readmission into the community were also revised based on available data and indications from health institutions and organisms. This document describes the recommendations derived from the consensus made by the group of experts.

METHODS

Using the Consensus Conference method described in the National Institutes of Health Guidelines and the Italian National Guidelines Programme,[4,5] relevant publications in English were identified by systematically reviewing MEDLINE and the Cochrane Database of Systematic Reviews from their inception until 31 December 2014. The key search words were: children[Title/Abstract] OR pediatric[Title/Abstract] OR paediatric[Title/Abstract] AND tuberculosis[Title/Abstract] AND Hospital[Title/Abstract] OR Hospitalization[Title/Abstract] OR Admission[Title/Abstract] OR Re-admission[Title/Abstract] OR Isolation [Title/Abstract] OR Length of stay[Title/Abstract] OR Complications[Title/Abstract] OR Referral[Title/Abstract] OR Consultation[Title/Abstract] OR Medical visit [Title/Abstract] AND English[lang], and the Working Group agreed on a list of clinical problems related to pediatric hospitalization due to TB and TB management. The evidence review focused on patients in the age group 0 to 18 years and included section-specific targeted searches and formal systematic reviews of selected items. In addition, the clinical recommendations made in the updated, relevant international guidelines were reviewed and critically compared. All data were entered in tables of evidence for each item and extensively discussed.

Trained investigators critically appraised the available data using the Scottish Intercollegiate Guidelines Network methodological checklists (Table 1)[6] and, subsequently, the bibliographical material and a preliminary draft of the document were provided to the panel members. During meetings, the published evidence was presented and discussed, and the Delphi method was used to reach a consensus when the evidence did not provide consistent and unambiguous recommendations.[6] The final text was revised on the basis of these discussions and submitted by e-mail to the participants at the Consensus Conference for final approval. According to the Italian National Guidelines Programme,[4] only publications approved by the Ethics Committee of the authors can be included in a systematic review, but it is not requested that the authors of a systematic review have to request the approval from their Ethics Committee for the analysis of the literature and the preparation of a guideline or a Consensus document. The members of the multidisciplinary panel of clinicians and experts in evidence-

TABLE 1. Quality of Evidence and Strength of Recommendation

Quality of evidence	
I	Evidence from >1 properly designed, randomized, controlled study, and/or systematic review of randomized studies
II	Evidence from 1 properly designed, randomized, controlled study
III	Evidence from cohort studies or their meta-analysis
IV	Evidence from retrospective case-controlled studies or their meta-analysis
V	Evidence from case series without control group
VI	Evidence from opinions of respected authorities, based on clinical experience
Strength of recommendation	
A	The panel strongly supports a recommendation for use
B	The panel moderately supports a recommendation for use
C	The panel marginally supports a recommendation for use

based medicine were indicated by the national scientific societies, and included experts in the fields of general pediatrics, pediatric infectious diseases, neonatology, infectious diseases, pneumology, microbiology, radiology, public health, pharmacology, and methodologists; the panel was coordinated by the SITIP. No panel member declared conflict of interest. The panel met on 3 occasions, but many of the consultations involved in developing the document took place interactively by e-mail or telephone.

RESULTS

Indications to Hospital Admission of a Child With Suspected or Diagnosed TB

The indications to hospitalization of children with suspected or confirmed TB are largely indirect and based on observational studies. Even the latest international guidelines do not provide recommendations based on data.[7,8]

The suspicion and/or diagnosis of TB and treatment are not *per se* indications to hospitalization.[9] The hospitalization of patients with suspected TB should be based on 3 sets of criteria: (1) host-related conditions, (2) clinical criteria (eg, severity, suspected, or proved drug resistance), and (3) social and logistic criteria (eg, homeless, people living with immunocompromised subjects, and community residents).[7,8]

As specific indications to hospital admission are not available and comparative studies are unethical, the panel extrapolated potential indications to hospital management identifying those conditions at higher risk of severe disease course or death.

Child age and the presence of underlying conditions may require hospital management (Table 2). According to available evidence, children aged < 1 year have a significantly higher risk of severe outcomes and a greater frequency of extrapulmonary, miliary, and disseminated TB and demonstrated a higher risk of death compared to older children.[10–12]

TABLE 2. Risk Factors for Severe Course, Complication or Death in Children With Tuberculosis (TB)

Host-Related Factors	Risk	Estimated Risk (95% CI)	References
Child age			
< 1 year	Risk of death	OR 2.06 (1.18–3.57)	8
	Risk of severe outcome, EPTB, military, and meningitis	–	8, 9, 10
	Risk of developing neurological sequelae during meningeal TB	RR 2.9	23
< 3 years	Risk of miliary TB		19
	Risk of developing neurological sequelae during meningeal TB	RR 3.0	23
< 5 years	Risk of developing neurological sequelae during meningeal TB	RR 1.9	23
Underlying conditions			
HIV infection	Risk of death	OR 24.7 (1.79–341.1)	11
	Risk of death for class C according to CDC classification	RR 2.4	22
	Risk of death for those with no improvement after 6 months of therapy	RR 3.7	22
	Risk of miliary TB	OR 10.9 (XX)	20
	Risk of developing neurological sequelae during meningeal TB	RR 2.3	23
Malnutrition	Risk of persistent positive sputum	OR 3.71 (1.22–11.3)	11
	Risk of treatment failure	OR 3.21 (1.15–8.96)	11
	Risk of death	OR 9.56 (1.79–51.2)	11
	Risk of clinical or radiologic worsening after 10 days after therapy onset	OR 3.45 (1.1–10.0)	12
	Risk of death in children with HIV infection and malnutrition	RR 2.6	22
Solid organ or bone marrow transplantation	Risk of TB and possible dissemination with EPTB	OR 40–50	24
Clinical feature			
EPTB	Risk of severe outcomes, death, and treatment failure	–	8, 11
Meningeal TB	Risk of death	OR 3.22 (1.09–9.52)	10
Glasgow Coma Scale < 11	Risk of death	OR 11.7 (3.10–53.2)	11
	Risk of neurological sequelae	OR 3.8 (1.45–9.94)	11
Multidrug resistant TB	Risk of death	OR 63.9 (4.84–843.2)	11

CDC = Centers for Disease Control and Prevention, CI = confidence interval, EPTB = extrapulmonary TB, TB = tuberculosis.

Irrespective of age, patients with HIV are at high risk of a poor outcome.[10,13] Excluding the studies characterized by multiple confounding factors, HIV has been found to be an independent risk factor that increases the risk of death in children with TB by up to 24 times[13] (Table 2). Although this is probably associated only with severe immune deficiency, hospitalization is indicated for any child with HIV/TB coinfection at least at the initial diagnosis.

Other chronic conditions may be associated with a risk of complications and severe course of TB. Malnutrition (defined as a weight below the third percentile) is associated with a greater risk of persistently positive expectorate, failure to respond to antitubercular therapy and death.[13] A Canadian study found that low-weight children (<25th percentile) were at greater risk of clinical and/or radiographic worsening of existing lesions or the development of new lesions associated with clinical/radiographic changes occurring 10 or more days after the onset of antitubercular treatment and after documented initial clinical response (Table 2).

In addition to host-related factors, the decision to hospitalize a child with suspected or diagnosed TB should be guided by clinical factors[14] (Table 2).

As pulmonary TB is still the most frequent clinical feature in children, the clinical indications to hospitalization of patients with nonspecific community-acquired pneumonia can be applied for children with pulmonary TB.[15–17] Accordingly, children with respiratory distress and/or blood oxygen saturation levels of < 92% should be hospitalized because of the greater risk of severe complications.[15–17]

Extrapulmonary TB (EPTB) accounts for ~20% of the cases of pediatric TB and is characterized by increased severity and a worse clinical course including death or a failure to respond to treatment.[10,13] Meningeal TB (MTB) is a cause of death or neurologic permanent sequelae: children with MTB are 3 times more likely to die than those with other forms of TB.[12] Furthermore, patients with Glasgow Coma Scale scores of < 11 and those requiring ventriculo-peritoneal shunt are at high risk of death.[13] Considering the risk of complications, children presenting with EPTB and MTB should be referred to hospital (Table 2).

Finally, both pulmonary and extrapulmonary forms of TB that are resistant to first-line drugs lead to management difficulties, and may therefore require hospitalization at least during the early phases of diagnosis and treatment. One study carried out in South Africa found a markedly increased risk of death in children with TB caused by multidrug resistant (MDR) strains.[13]

In addition, there are specific diagnostic (ie gastric aspiration) and therapeutic (ie intravenous treatment) procedures that cannot be instituted at home or in an outpatient setting and therefore require hospitalization.[18]

Referral to a Tertiary Care Center of Children at Risk of Developing Complicated TB

The management of children with suspected or diagnosed TB should generally be entrusted to healthcare personnel with specific training and experience in pediatric TB.

In addition, there are particular conditions associated with a high risk of complicated TB that strongly require the highly specialized management such as that provided by a pediatric TB reference centre.

Observational data showed that some condtions are related with a high risk of miliary TB, complication, handicap, or neurological sequelae during MTB and hence should be managed in referral centers.

Neonate and preschool children have a higher risk of complications and should be managed in an age-specific appropriate setting. A meta-analysis of 170 newborns with congenital TB derived from a large number of case series showed that 46.8% had a miliary form and 11.1% multiple pulmonary nodules.[19] The highest mortality rates were observed in patients with intracranial lesions (65% vs 20.8%, $P < 0.001$) and in those whose symptoms appeared before the third of week of life (76.5% vs 52.2%, $P = 0.004$).

Age < 5 years has been identified as a risk factor for miliary TB and MTB in 3 studies carried out in South Africa. In the population studied by Marais et al the majority (84.2%) of the children with these forms were < 3 years of age.[20] Van den Bos et al found that their patients with concomitant miliary TB and MTB were significantly younger than those with MTB alone ($P = 0.04$).[21]

Two South African prospective studies found that HIV-infected children more frequently presented with complicated and miliary forms of TB (odds ratio [OR] 10.9) and had a consequently higher rate of mortality ($P = 0.003$).[20,22] In those children, the presence of CD4 + lymphocytes ≤15% at the time of the diagnosis was significantly associated with miliary TB ($P = 0.05$).[23] The advanced stage of HIV infection (clinical category C: relative risk [RR] 2.4), considerable degree of malnutrition (RR 2.6), and failure to respond after 6 months of antitubercular therapy (RR 3.7) were all significantly associated with a high risk of mortality.[24]

Young age (0–1 year: RR 2.9, $P < 0.001$; 1–2 years: RR 3, $P < 0.001$; 2–5 years RR 1.9, $P = 0.03$) and HIV infection (RR 2.3, $P = 0.05$) are also significantly associated with handicaps or sequelae in children with proven or probable MTB, as demonstrated in a retrospective study of 554 children.[25]

A similar risk of complication was found in children with African ethnicity ($P = 0.008$), disease stage ($P < 0.001$), the presence of brainstem dysfunction ($P < 0.001$), and the presence of an infarction revealed by a brain computed tomography scan ($P = 0.001$) in multivariate analysis.[25]

It is likely that patients with congenital immunodeficiencies and those treated with immunosuppressants or immunomodulating biological drugs also have a greater tendency to develop EPTB, but the data are largely limited to single cases or small series. However, 1 large-scale Spanish study of children who underwent solid organ or bone marrow transplantation showed 40- to 50-fold increased incidence of TB compared to general pediatric population, with a prevalence of disseminated forms during the first post-transplant year.[26]

Indications to Isolation of Children With Suspected or Diagnosed TB

Hospitalized patients with suspected pulmonary TB should be admitted into preventive respiratory isolation regardless of their age while they await diagnosis.[27,28] Pediatric patients are often considered to be relatively noncontagious at least until they reach adolescence. At this age the clinico-radiological characteristics of pulmonary TB become similar to those observed in adults consisting in a high incidence of cavitary lesions that are associated with respiratory spreading of infection.[29–31] Three studies performed in United States demonstrated a complete lack of transmission from children with typical pulmonary TB (ie, without the characteristics of adult-type TB) to healthcare workers despite the occurrence

of uncontrolled exposure.[32–34] However, anecdotal reports of transmission (including in-hospital transmission) involving young patients are available.[35–39] Table 3 reports the hallmarks of potential contagiousness in children with suspected or confirmed TB.

Respiratory isolation should be carried out by confining the patient to a single-bedded hospital room identified by clearcut signals including the date isolation onset.[40] Isolation in a negative-pressure chamber (that fulfills specific, legally required technological specifications) should be considered for suspected or proved MDR or extensively drug-resistant (XDR) TB, and in suspected drug-sensitive TB if there are immunocompromised patients in the same ward.[40]

Patients in respiratory isolation must wear a specific protective devices every time they leave their room, which should only be allowed when it is medically necessary (eg, in order to undergo diagnostic procedures).[40] Healthcare staff and visitors should adopt measures of individual protection.[40] However, various studies (mainly carried out in the USA) reported a suboptimal compliance with these indications, without any substantial increase in nosocomial transmission.[41–44]

If patients do not require hospitalization for other reasons and are at risk of spreading the infection, respiratory isolation can be implemented at home provided that there is sufficient family/social support and there are no risks for household members or the community at large.[40] However, this decision needs to be carefully considered in each case.

Indications to Hospital Discharge and Re-Admission to the Community

Discharge from hospital and readmission in the community are not only based on clinical criteria but also they should take into account the risk of spreading the infection to other subjects.

Data on discharge are very limited. Patients with gastric aspiration/sputum-negative TB can be considered at no risk of spreading the infectiion after 2 weeks of treatment (supported by a negative result of cultured specimens). In contrast, sputum-positive patients may be contagious for longer time[45] and the initial bacterial positivity and the presence of cavitary pulmonary lesions predict a slower microbiological conversion.[46,47] Observational data suggest that, in patients with bacilliferous TB, culture tests of cough-produced aerosol became negative within the third week of treatment.[48,49] Ritchie et al suggest the use of bacterial load as an indicator of the time necessary for the negativization of culture: ie 7 days for patients with sputum scores of + 1 and + 2 (respectively 1–9 alcohol/acid-fast bacilli/100 fields and 1–9 alcohol/acid-fast bacilli/10 fields), 14 days for those with a score of + 3 (1–9 alcohol/acid-fast bacilli/field), and 25 days for those with a score of + 4 (10 alcohol/acid-fast bacilli/field).[50] However, molecular biology studies have demonstrated that a decrease in selected RNAs sequences (antigen-alpha, antigen 85, isocitrate lyase) early during therapy is a reliable measure of mycobacterial replication and viability that reflects the efficacy of treatment and indicates noncontagiousness.[51–54]

Respiratory isolation (in hospital or at home) can be discontinued as soon as at least 3 samples of sputum have been found to be microscopically negative. Data collected in adults but not in children suggest that 2 negative samples may be sufficient because it is very unlikely that the third would be positive.[55–57]

The management of MDR cases deserves a specific consideration, although it is not clearly addressed in available guidelines. A study of a large patient cohort carried out in South Africa reported repositivization of culture tests in 11.6% and 5.4% of 336 adults with MDR TB 1 and 2 months after conversion respectively, thus supporting the WHO's indication that treatment should monitored by at least 2 consecutive negative tests after conversion with an interval of at least 30 days in subjects with MDR TB.[1,58]

The identification of unequivocal criteria for allowing children with TB to return to the community is based on common sense and a careful clinical assessment in order to guarantee safe and reasonably rapid return to normal life without risks. Although they do not always address the question specifically or exhaustively, the guidelines produced by leading international societies suggest that the necessary conditions are 3 consecutive microscopically negative sputum/gastric aspirate samples, clinical remission, and treatment compliance.[27] Furthermore, WHO recommends confirmation of culture test conversion after 3 weeks,[1] based on specific data.[59] The American Academy of Pediatrics indicates that pediatric patients can be readmitted in the community and resume their normal activities provided that treatment has been started, is regularly taken, and has led to a clinical improvement.[60]

DISCUSSION

Summary of Evidence

The multidisciplinary panel, after reviewing and evaluating the data available for each clinical question, developed clinical recommendations based on evidence and, when insufficient, on consensus of expert. Grading of evidence is reported for each recommendation.

Hospitalization Criteria

As shown in Table 4, indications to hospital admission are essentially based on 3 groups of criteria: (1) host-related

TABLE 3. Hallmarks of Potential Contagiousness

	Indicators	Supporting References
Clinical	Persistent productive cough Adolescence Suspected laryngeal/ bronchial TB Suspected drug-resistant TB Congenital TB Need for invasive investigations of the respiratory tree	30,31,39
Radiological	Excavated pulmonary lesions involvement of the apical segments of the inferior lobes	27
Microbiological	Microscopic positivity for acid/alcohol-fast bacilli in a sputum sample or broncho-alveolar lavage fluid	26

TB = tuberculosis.

TABLE 4. Indications to Hospitalization in Children With Suspected or Diagnosed Tuberculosis (TB)

	Criteria for Hospital Admission			
	Strongly Recommended	**Grading***	**To be Considered (but not Necessarily Required)**	**Grading***
	Age < 1 year	V-B	Severe malnutrition (<3rd percentile)	III-A
Host-related conditions	Chronic underlying disease and/or exposed to a greater risk of severe manifestations or disseminated TB infection (eg chemotherapy)	III-A		
	Underlying T lymphocyte immunodeficiency and/or defects in phagocytic oxidase-reductase metabolism (eg HIV, primary immunodeficiency)	III-A		
	Severe pulmonary symptoms (eg respiratory insufficiency, respiratory distress, oxygen saturation <92%, hemoptysis)	III-A	Drug-induced adverse events	VI-B
Clinical features	Neurological signs and symptoms suggesting meningeal TB	III-A		
	EPTB (excluding isolated lymphnode TB)	III-A		
	TB due to drug-resistant mycobacteria	III-A	Proved or suspected tubercular disease due to resistant mycobacteria	III-A
Social and logistic criteria	Need for in-hospital medical interventions (invasive diagnostic procedures)	V-A	Poor compliance with anti-tubercular therapy	VI-B
	Need for respiratory isolation in a negative-pressure chamber	VI-B	Presence of socio-economic risk factors	VI-B

EPTB = extrapulmonary TB, TB = tuberculosis.
* Quality of evidence and strength of recommendation according to criteria reported in Table 1.

conditions, (2) clinical features, and (3) social and logistic criteria. According to these parameters, hospitalization should either be ''strongly recommended'' or it can be ''considered although not necessarily urgently required'' by the physician (Table 4).

Children with TB may be managed in primary and secondary-care pediatric hospital units providing the structures fulfill isolation criteria. These indications may change according to each country and the organization of health-care facilities. Children who are considered at risk of developing complicated forms of TB should always be referred to a tertiary care center specialized in the diagnosis and treatment of pediatric TB. Those include children with the following characteristics: congenital TB, newborn children of women with TB, age < 3 years, malnutrition, HIV infection with low CD4 + cell count, underlying T lymphocyte immunodeficiency and/or defects in phagocytic oxidase-reductase metabolism, subjects in the first year after a solid organ transplant or bone marrow transplantation with graft vs host disease [V-B], MTB, and EPTB excluding isolated lymph node TB [III-A] and subjects with proved or suspected tubercular disease due to resistant mycobacteria [III-A].

Isolation Measures

All children hospitalized for suspected contagious TB under preliminary observation should be put in preventive respiratory isolation (Table 5) (VI-A). Respiratory isolation is also indicated in all children hospitalized with suspected or proved drug-resistant TB (VI-A).

This should be carried out by confining the patient to a single-bedded hospital room identified by clear signals that must also indicate the date on which the isolation is started (VI-A).

Isolation in a negative-pressure chamber (that respects specific, legally required technological equipment) should be considered in the case of suspected or proved MDR or extensively drug-resistant (XDR) TB, or in the case of suspected drug-sensitive TB if there are immunocompromised patients in the same ward (VI-A).

Patients in negative-pressure isolation should only be allowed to leave the room wearing a protective device and exclusively when it is medically necessary (eg, diagnostic procedures) (VI-A). Healthcare staff and visitors should weare individual protective devices (VI-A).

Respiratory isolation at home is recommended in cases of suspected contagious TB whose diagnostic/therapeutic management does not require ordinary hospitalization (eg, in the presence of family/social conditions compatible with outpatient/domiciliary management) (VI-A).

Discharge and Re-Admission to the Community

The decision to discharge a patient should be based on careful clinical evaluation and on conditions of social/family support, including full treatment compliance and the consideration that there is no risk for household members or the community at large (Table 6 A) (VI-A).

TABLE 5. Isolation Measures for Children With Tuberculosis (TB)

Isolation Measures	Indication*
Home respiratory isolation	Suspected contagious TB whose diagnostic/therapeutic management does not require ordinary hospitalization (ie family/social conditions favouring outpatient/domiciliary management)
Hospital respiratory isolation	All hospitalized patients with suspected contagious TB under preliminary observation suspected or ascertained drug-resistant TB
Negative pressure chamber	Suspected or ascertained MDR or extensively drug-resistant (XDR) TB Suspected drug-sensitive TB if there are immunocompromised patients in the same ward

MDR = multi-drug resistant, TB = tuberculosis, XDR = extensively drug-resistant.
* According to the available evidence in support, all recommendations were graded VI-A (see Table 1).

Potentially contagious patients who are treatment-compliant and have appropriate family/social support can be discharged after at least 2 weeks of treatment has led to clinical improvement even if microscopic examination of sputum/gastric aspirate samples are not yet negative provided that conditions allow the continuation of respiratory isolation at home (VI-A).

If respiratory isolation at home is not feasible, 3 consecutive samples of gastric aspirate (2 in the case of induced expectorate) negative for alcohol/acid-fast bacilli should be obtained to decide discharge (VI-A).

If sputum/gastric aspirate samples are negative from the onset, discharge can be considered after 7 to 14 days of regularly taken treatment have led to a clinical improvement (VI-A). Discharge can be decided in the case of treatment compliant, asymptomatic/paucisymptomatic patients (VI-A).

In the case of proved drug-resistant TB, discharge can be planned only after obtaining negative culture test results, eg after a clinical improvement and 3 consecutive microscopically negative expectorate/gastric aspirate samples (VI-A). Furthermore, it is necessary to assess the adequacy of domiciliary treatment including adherence (VI-A).

The general indications for readmission to the community (Table 6B) are:

(1) no less than 14 days of regularly taken treatment have led to a clinical improvement in the case of initially sputum-negative patients (VI-A);
(2) three consecutive microscopically negative sputum/gastric aspirate samples in the case of patients who were previously microscopically positive (if possible using the same type of biological sample as that used for the first microbiological test), together with a clear clinical improvement (regression of the symptoms present at onset) and compliance to treatment (VI-A);
(3) in the case of MDR or XDR forms, community readmission is only indicated after culture negativization

TABLE 6. Summary of the Main Criteria for Hospital Discharge (A) and Readmission to the Community (B) in the Pediatric TB Population

A)

Clinical Scenario	Discharge Criteria	Level of Evidence*
Smear-positive patients	Two weeks of effective treatment along with clinical improvement and family/social support smear conversion is requested in patients for whom domiciliary isolation in not applicable or not therapy adherent	VI-A
Smear-negative patients	7–14 days of effective therapy along with clinical improvement	VI-A
Suspected or ascertained drug-resistant TB	Conversion to negative of culture results, or smear conversion along with clinical improvement and domiciliary respiratory isolation in therapy compliant patients	VI-A

B)

Clinical Scenario	Community Re-admission Criteria	Level of Evidence*
Smear-positive patients	Smear conversion along with clinical improvement and therapy compliance	VI-A
Smear-negative patients	No <2 weeks of effective treatment	VI-A
Ascertained drug-resistant TB (MDR or XDR TB)	Culture conversion and clinical improvement in treatment compliant patients under regular monitoring	VI-A

MDR = multi-drug resistant, TB = tuberculosis, XDR = extensively drug-resistant.
* Quality of evidence and strength of recommendation according to criteria reported in Table 1.

(preferably confirmed by 2 consecutive samples with an interval of 15–30 days between them) and on therapeutic continuity/monitoring (VI-A).

LIMITATIONS

This paper has some limitations. First of all, supporting evidence is limited and its quality varies for each recommendation. Criteria for hospitalization and isolation are based on strong evidence demonstrating that selected conditions are associated with a higher risk of severe outcomes and death. On the other hand, indications to discharge and re-admission into community, whose principes include consideration of the risk of contagiousness, mainly comes from data on adult population and opinion of experts. However, all the indications have been formulated on the best available data derived from a rigorous systematic review of the literature and the recommendations were discussed by a multidisciplinary panel of experts including clinicians, radiologists, microbiologists, and public health experts from different scientific societies.

CONCLUSIONS

This paper was produced with the aim of providing clinicians with indications to admission, isolation and discharge of children with suspected or confirmed TB, as part of a global guidelines document on management of TB in children.

Recommendations must take into account social and logistical conditions as well as costs related to disease's management together with the classical clinical parameters. According to the algorithm of TB, child contagiuosness, exposition to contacts, presence of underlying risk factors and prevalence of MDR are key elements for the management of children with TB. Those elements are essential also to set up appropriate isolation measures, hospitalize or readmit into the community subjects who can potentially spread the infection.

However, the scenario of TB in developed countries is rapidly changing due to the increasing migration fluxes from countries where the infection is endemic. This paper was discussed in the light of the challenges linked to the evolving situation associated with problems in applying the available algorithms for diagnosis and treatment of TB. In terms of diagnosis, the interpretation of the skin tuberculin test should take into account the risk of exposure, previous clinical history, and immunization status. Those conditions are often poorly known in at risk children coming from at risk areas.

The indications to hospital management and isolation measures are particularly relevant in order to prevent spreading of infection where information on the TB exposition and contacts is not available, knowledge of host-related risk factors is often limited and hampered by linguistic barriers, domiciliary isolation, and follow-up are not feasible, and widespreding of MDR TB is a true risk.

Starting from the need of guidelines addressing this topic, our document is intended as a temptative reference paper and the indications to hospital admission, isolation, and discharge of children with TB need to be validated after implementation at local level. Most recommendations developed by the multidisciplinary team are applicable in all developed areas, altough some may need tailoring to local setting, epidemiological parameters, and availability of health-care facilities. In order to adopt the probabilistic model of management of TB to the present scenario, a close collaboration between clinicians, public health authorities, and field-workers is all the more essential.

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