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SPECIAL CONTRIBUTION

Management of Infants and Children who are Contacts of Contagious Tuberculous Patients

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معالجة الرضع و الأطفال المخالطين للمرضى المصابين بمرض السل المعدي

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الملخص: التحقيق وعلاج الأشخاص المخالطين لمرضى السل (الدرن) يشكل مفتاح مكافحة هذا المرض في البلدان التي تعد حالات الإصابة فيها منخفضة. سلطنة عمان كأحدى الدول المعروفة بانخفاض حالات وقوع السل، اعتمدت تطبيق التحقيق ومعالجة الأشخاص المتصلين بالمرضى المصابين بهذه العدوى كإحدى الاستراتيجيات المهمة لمكافحة السل. على الرغم من ذلك، لا توجد مبادئ توجيهية واضحة للتحقيق والمعالجة لا سيما فيما يتعلق بالأطفال المخالطين لمرضى السل. إن الفشل في معالجة مثل هذا الاتصال عند الأطفال يعد فرصة ضائعة للحد من انتشار المرض بين السكان الذي قد يعرضهم لخطر التقدم السريع للمرض ومضاعفاته. هذا المقال يحاول توفير نهج موجز عن عملية التحقيق وعلاج الرضع والأطفال المخالطين لمرضى السل ويناقش بإيجاز الخطوات الاساسية في مجموعة من السيناريوهات المحتملة.

مفتاح الكلمات: السل؛ الأطفال؛ عدوى سل خاف؛ اختبار التوبركولين؛ عُمان.

ABSTRACT: Contact investigation and management form the key for tuberculosis (TB) control in countries with a low tuberculosis incidence. Oman, with a low TB incidence, has implemented contact investigation and management as one important strategy to control TB. However there is a lack of clear guidelines for the investigation and treatment of contacts, especially with regard to children who are contacts of TB cases. The failure to manage children in contact with infectious TB cases indicates a missed opportunity to prevent TB disease in a population which is prone to progress rapidly to severe and complicated illness. This article attempts to provide a concise and practical approach for managing infants and children who are in contact with TB patients. Essential steps in a variety of possible scenarios are briefly discussed.

Keywords: Tuberculoses; Children; Latent Tuberculosis Infection; Tuberculin Tests; Oman.

Investigation of people exposed to cases of infectious tuberculosis (TB), also called contact investigation, is the key to TB control, especially in countries with a low incidence of TB. Recent literature suggests that contact investigation also merits serious consideration as a means to improve early case detection and decrease the transmission of *Mycobacterium tuberculosis* (MTB) even in high-incidence areas.[1] Oman, with a low TB incidence and high *Bacillus* Calmette-Guérin (BCG) vaccine coverage at birth, has implemented contact investigation and management as an important strategy for the control of TB.[2] The incidence of sputum smear-positive TB in Oman was 5.1 per 100,000 Omanis in 2011. Incidence rates of TB as well as sputum smear-positive TB has shown an almost static trend over the past decade [Figure 1].[3]

Contact investigation and the management of children who are exposed to an infectious adult source case are considered the most efficient ways to prevent paediatric TB disease. Missed opportunities to prevent cases of TB disease in children can be due to a delay in the diagnosis or management of the adult source case, a delay in the reporting of a source case to the local public health/TB control authority, a failure to identify a child during contact investigations, or lack of knowledge on how to manage and follow-up paediatric contact cases.[4]

Although contact management is an important strategy, there is a lack of clear guidelines for the investigation and treatment of contacts, especially

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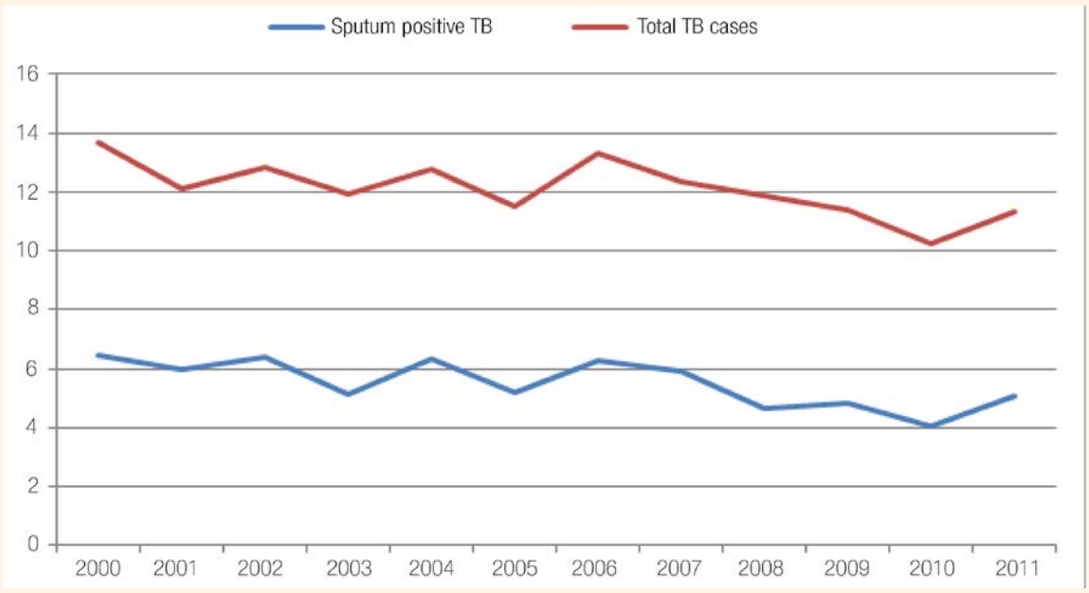

Figure 1: Annual tuberculosis incidence among the Omani population (per 100,000).
TB = tuberculosis.
Adapted from: Annual Statistical Reports, Ministry of Health, Muscat, Oman.

when it comes to children. This is primarily due to a lack of awareness regarding the various aspects of childhood TB. In addition, TB contact investigations typically require interdependent decisions which sometimes are based on incomplete data. Simple decision trees are often not applicable and the decision making is often a complex process.[5] In Oman, these challenges are more prominent in the primary care setting where most of the contact screening and management of TB cases are undertaken. Due to these factors, although an outline for managing paediatric contacts of contagious TB is provided in the TB manual published by the Omani Ministry of Health, the authors have noted that a significant proportion of formal and informal consultations are done in this regard.[2] Thus, there is an obvious need to provide the essential principles and approach to such cases in a clear and concise manner for the primary healthcare setting in Oman. This outline is derived from current practice in a tertiary care setting in Oman which is essentially based on the latest guidelines issued by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA. This is not an exhaustive review of all the relevant publications nor is it a national TB programme guideline. Our objective is to provide a practical approach for managing infants and children who are in contact with TB patients that would be helpful in the Omani context.

The manifestations of TB infection, after exposure to a person with active infectious TB, are very different in infants and children. Therefore, the management should vary from that of an adult who is exposed to the same. Children pose three unique challenges to TB control. First, the diagnosis of TB disease in children under 5 years of age can be difficult because they often have nonspecific signs and symptoms and a paucity of *Mycobacteria*. Second, TB in children is considered a sentinel event usually indicating recent transmission. Finally, children, especially infants, are at an increased risk of progressing from latent TB infection (LTBI) to active and sometimes severe TB disease.

Infection with MTB is usually the result of inhaling into the lungs infected droplets produced by someone who has laryngeal TB or pulmonary TB and is coughing. The source of infection for most children is thus an infectious adult in their close environment, usually the household. This exposure leads to the development of a primary parenchymal lesion (Ghon's focus) in the lung which spreads to the regional lymph node(s).[6] The immune response (delayed hypersensitivity and cellular immunity) develops about 4–6 weeks after the primary infection. In most cases, the immune

Table 1: Average age-specific risk for disease development after untreated primary infection

Age at primary infection	Manifestations of disease	Risk of disease (%)
	No disease	50
<12 months	Pulmonary disease	30–40
	TB meningitis or miliary disease	10–20
	No disease	70–80
12–23 months	Pulmonary disease	10–20
	TB meningitis or miliary disease	2–5
	No disease	95
2–4 years	Pulmonary disease	5
	TB meningitis or miliary disease	0.5
	No disease	98
5–10 years	Pulmonary disease	2
	TB meningitis or miliary disease	<0.5
	No disease	80–90
>10 years	Pulmonary disease	10–20
	TB meningitis or miliary disease	0.5

TB = tuberculosis.
Adapted from Marais et al.[7]

response stops the multiplication of TB *bacilli* at this stage. However, a few dormant *bacilli* may persist. The primary infection may be associated with complications, especially in children under 5 years of age.[7,8] The parenchymal lesion may enlarge and caseate, or nodes may enlarge and compress or erode through a bronchus, causing wheezing, segmental pneumonia or atelectasis. The occult subclinical bacteremia that usually accompanies primary infection may result in severe TB diseases such as disseminated TB or central nervous system TB. The risk of TB disease and severe forms of it after exposure is inversely related to age [Table 1].[7]

Children living in close contact with a source case of smear-positive pulmonary TB or laryngeal TB are at particular risk of TB infection and disease. No safe exposure time to airborne MTB has been established. If a single *bacterium* can initiate an infection leading to TB disease, then even the briefest exposure entails a theoretical risk. The risk of infection is greatest in the case of close and prolonged contact, such as the contact an infant or toddler has with the mother or other caregivers in the household. The risk of developing disease after infection is much greater for infants and young children under 5 years of age than it is for children aged 5 years or above. The risk of progression gradually decreases through childhood.[7] Also, infants and younger children are more likely to develop life-threatening forms of TB, especially meningeal and disseminated disease, compared to older children and adults.[9]

If disease does develop, it usually does so within two years of infection, but in infants the time-lag can be as short as a few weeks. Isoniazid (INH) preventive therapy for young children with infection who have not yet developed disease will greatly reduce the likelihood of TB during childhood with a risk reduction of 70–90%.[10] A tuberculin skin test (TST), interferon gamma release assay (IGRA), or chest X-ray (CXR) is the best method to screen for TB disease among contacts.[6,9]

Terminology

Some of the terminologies used in this article need explanation.[2,9]

- Close contact: A child living in the same household as a source case (e.g. the child's caregiver) or who is in frequent contact with a source case.
- Contagious or infectious TB: Pulmonary TB or laryngeal TB.
- Exposure: A situation in which a child has significant contact with an adult infected with a contagious form of TB. A child exposed to MTB does not necessarily become infected. The recommended minimum period between the most recent exposure and tuberculin skin testing should be 8–10 weeks.
- Exposure history and time frame: The start of infectious period for an index case cannot be determined with precision through the available methods. However, on the basis of expert opinion, a date three months prior to the date of diagnosis is to be assigned as the starting date for infection and this duration should be considered as the infectious period.[9] In those circumstances where there is a longer duration of symptoms or protracted illness, it is wiser to have an earlier start based on the duration of the illness.
- LTBI: A condition in which MTB has entered the body and typically has elicited immune responses. LTBI is an asymptomatic condition that follows the initial infection; the infection is still present but is dormant and believed not to be currently progressive or invasive. The only sign of TB infection is a positive reaction to the TST

or a positive result with the currently available blood test—the IGRA. For practical purposes, a child with LTBI is someone with a positive TST, no clinical evidence of disease, and a CXR that is either normal or demonstrates evidence of remote infection, such as a calcified parenchymal nodule and/or a calcified intrathoracic lymph node. Although these abnormal CXR findings do not strictly come under the definition of LTBI, it is also not considered an active disease and it is prudent to treat it as LTBI. People with a latent TB infection are not infectious; however, some of them develop TB disease depending on their immune status and the presence of other risk factors.[8]

• TB disease: The diagnosis is based on symptoms, radiological changes and microscopy. Positive culture results for MTB are typically interpreted as both the indication and the confirmation of TB disease. For persons whose immune systems are weak, especially those with human immunodeficiency virus (HIV) infection, the risk of developing TB disease is significantly higher than it is for persons with normal immune systems.

• Multidrug resistant TB (MDRTB): This is defined as TB caused by MTB resistant *in vitro* to the effects of isoniazid and rifampicin, with or without resistance to any other drugs.[11]

Diagnosis

The definition used here for a positive TST is based on the CDC guidelines.[9] Oman is a country with a low prevalence of TB and high BCG coverage at birth; thus, the interpretation of a positive test has to be done cautiously. There is neither a compelling need to adopt a lower cut-off for positivity, nor is it advisable to use a higher cut-off. Therefore, a special cut-off seems warranted in the context of TB control in Oman. When the induration following a TST (Mantoux test) is ≥5 mm, it should be considered as positive in the following situations: children in close contact with known/suspected contagious cases of TB; children suspected to have TB disease; findings in CXR consistent with active/previously active TB; clinical evidence of TB disease; children with HIV infection or immune deficiency states; children receiving immune suppressive therapy including immunosuppressive doses of corticosteroids (>15 mg prednisolone/day for one month or more) and anti-neoplastic agents.

When the induration following a TST (Mantoux test) is ≥10 mm, it should be considered as positive in the following situations: children with frequent exposure to adults at high risk; birth in or recent immigration (<5 years) from a high-prevalence country; children who had travelled or been exposed to visitors from high-prevalence countries, or children with malnutrition, chronic renal failure, diabetes mellitus or lymphoma.

In the case of children exposed to contagious TB, the management should be adapted according to the age of the child and his/her immune status.[5,9] The investigations and management of newborns and children who are contacts of TB cases would differ; thus, the discussion should focus on the following settings: (1) a newborn whose mother or other household contact has a contagious form of TB or LTBI; (2) children less than 5 years of age with exposure to a contagious case of TB or more than 5 years of age with exposure to a contagious case of TB; (3) children with exposure to a non-contagious case of TB, another child with TB disease, or an adult with MDRTB, or (4) a child who has a contact who is known to be HIV-infected.

Management of Newborns

In a newborn whose mother or other household contact has a contagious form of TB, the management should also vary according to the situation. If the mother is known or suspected of having TB disease, a maternal evaluation to rule out pulmonary or extra pulmonary disease including uterine TB needs to be done. An HIV serology should be undertaken if her prenatal screening is not done or is unavailable. A BCG vaccine should not be given to a newborn. However, an evaluation for congenital TB should be carried out if the newborn is symptomatic or in the cases where the mother is still acid fast *bacilli* (AFB)-positive or has disseminated disease that was not treated or was partially treated. An evaluation should also be carried out in cases of maternal endometrial TB regardless of treatment status with CXR, gastric aspirates for AFB and a TB culture of 3 early morning consecutive samples, an abdominal ultrasound or a lumbar puncture followed by submitting cerebrospinal fluid for AFB and TB cultures.[9] If the

newborn is found to have TB disease, then treatment should be initiated promptly with the appropriate regimen in consultation with a paediatric infectious diseases specialist. If congenital TB is excluded, treatment for LTBI with INH (10 mg/Kg/day) should be administered until the infant is at least 3 months of age and then a TST should be performed. If the repeated TST is positive, the child should be reassessed for active TB. If the disease is absent, a full course of treatment for LTBI should be given based on the sensitivities of the index strain. If the TST is negative and TB disease is ruled out, and the mother or the household contact has become non-contagious, then the INH should be stopped and a BCG vaccine administered to the baby who should then be followed-up on a monthly basis.[9]

For infection control, the newborn should be separated from any active TB case in the household including his/her mother during the evaluation period and any mother/adult contact should wear a facemask while handling the baby while following the isolation precautions. Once the baby is on INH and the mother or adult source is on full treatment, there is no need to separate the baby, and the mother can again breastfeed the baby.[9,12] Management is different if the mother has MDRTB, as is described later in this article.

In a newborn whose mother or other household contact has LTBI, the mother or household contact should be treated for LTBI. Since a positive TST result could be a marker for an unrecognised case of contagious TB within the household, other household members should be investigated for TB disease/LTBI. The newborn needs no special evaluation, and a BCG vaccine can be given if no infectious case of TB disease is identified in the household.[9]

Management of Children under 5 Years

In the management of children under 5 years of age with exposure to a contagious case of tuberculosis, the investigation for TB disease should include a TST (gastric juice for AFB is required only if the CXR is abnormal or the child is symptomatic). If a child has TB disease, the child should be started on a regimen of 3–4 anti-TB drugs in consultation with a paediatric infectious disease specialist and followed up. If TB disease is ruled out, all children in this category should be started on INH. Further follow-up depends on the child's TST status. If TB disease is ruled out, but the child has a positive TST, INH should be continued for 9 months. These children should be followed-up closely and reinvestigated for TB disease after 3 months. If the reinvestigation rules out TB disease, INH should be continued for 9 months and, if the child has impaired immunity, INH should be continued for 12 months. There is no need to repeat the TST at 3 months while reinvestigating for TB disease. If TB disease is ruled out and the TST is negative, INH should be continued and the child reinvestigated after three months. If the reinvestigation rules out TB disease, and if the repeat TST is negative, then INH should be stopped and the child followed-up [Figure 2].[5,9]

Management of Children over 5 Years

In children above 5 years of age with exposure to a contagious case of TB, the child needs to be investigated for TB disease; however, gastric juice for AFB or sputum examination is required only if the CXR is abnormal or if the child is symptomatic. If TB disease is ruled out and TST is found to be negative, there is no need for any treatment in the case of a child with a normal immune status. However, if the child has impaired immunity, then s/he should be started on INH prophylaxis. These children should be followed-up and reinvestigated for TB disease after three months.[5,9]

If TB disease is ruled out again but the repeat TST is positive, INH should be started and the case treated as LTBI. The duration of treatment should be decided on the basis of the child's immune status. If the TST is negative, there is no need for any treatment or follow-up.[5] If the child is HIV-positive, INH should be continued for one year [Figure 3].[2]

In children with exposure to a non-contagious case of TB, an investigation is required because there could be an unrecognised contagious case in the household.[5,9] If the TST is positive, they should be managed as a case of LTBI.[2]

In a child exposed to another child with TB disease, the TB disease in children need not be considered contagious unless the child has a cavitating adult form of pulmonary TB or has laryngeal TB. Both these conditions are very rare

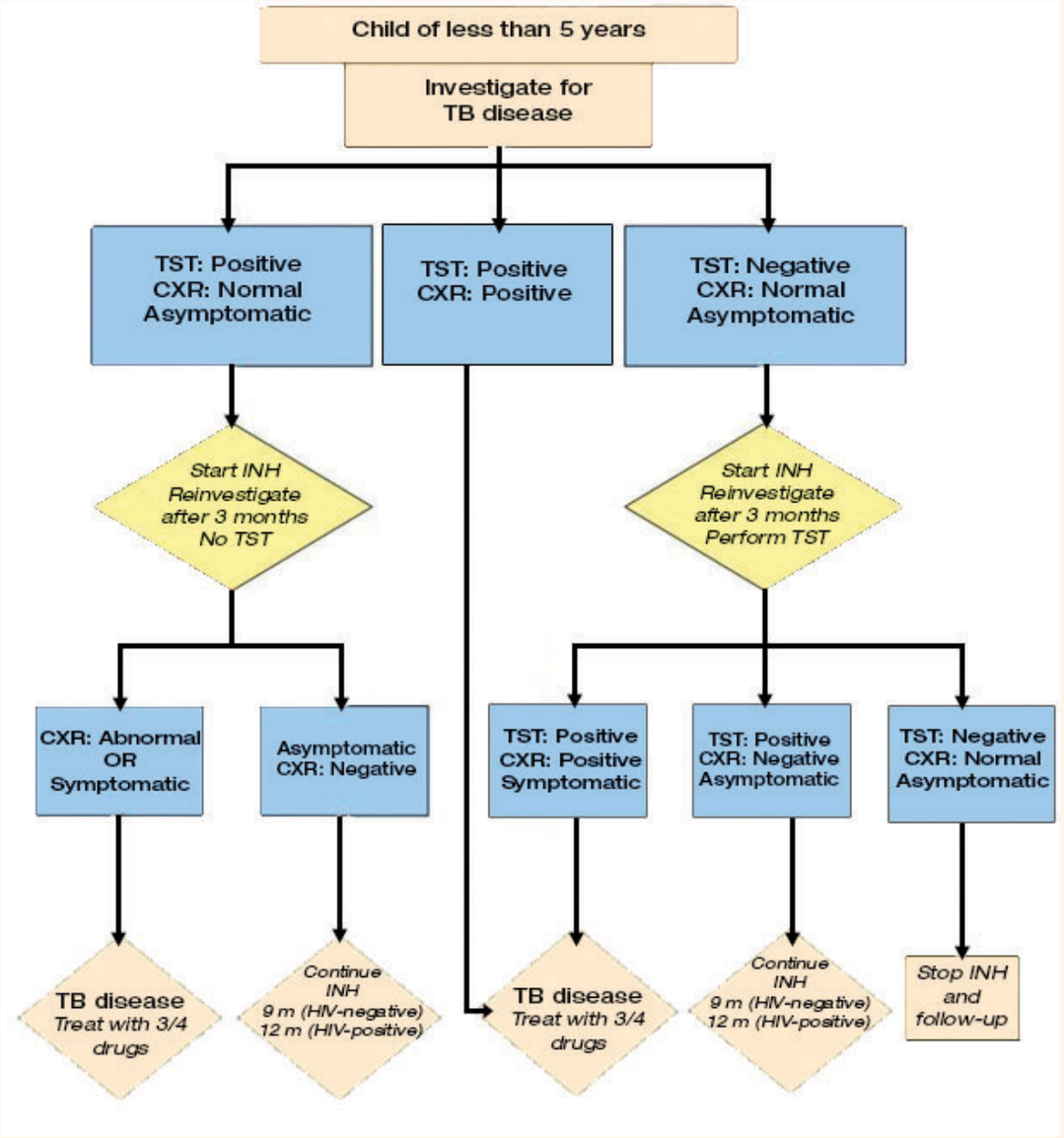

Figure 2: Flowchart showing the proposed management of children of less than 5 years of age with exposure to a contagious case of tuberculosis.
TB = tuberculosis; TST = tuberculin skin test; CXR = chest X-ray; INH = isoniazid; HIV = human immunodeficiency virus.

and so there is no contraindication for children with these types of TB disease to attend schools or play with normal children.[5,9]

For the same reason, when children are admitted for the investigation of TB, there is no need to keep them in isolation rooms unless there is some uncertainty regarding the status of attendants who are quite often the source of TB transmission in paediatrics wards. Children with TB are rarely contagious, but that is not necessarily the case with their caregivers.[12,13]

Children and Multidrug Resistant Tuberculosis

In a child with exposure to an adult with MDRTB, the optimal therapy for those with LTBI caused by an organism resistant to INH and rifampicin is not known. In these circumstances, multidrug regimens have been used. Drugs that are considered for these regimens include pyrazinamide, fluroquinolone, and ethambutol depending on the susceptibility of the isolated organisms. Consultation of infectious disease experts for the management of such children is recommended.[11,12]

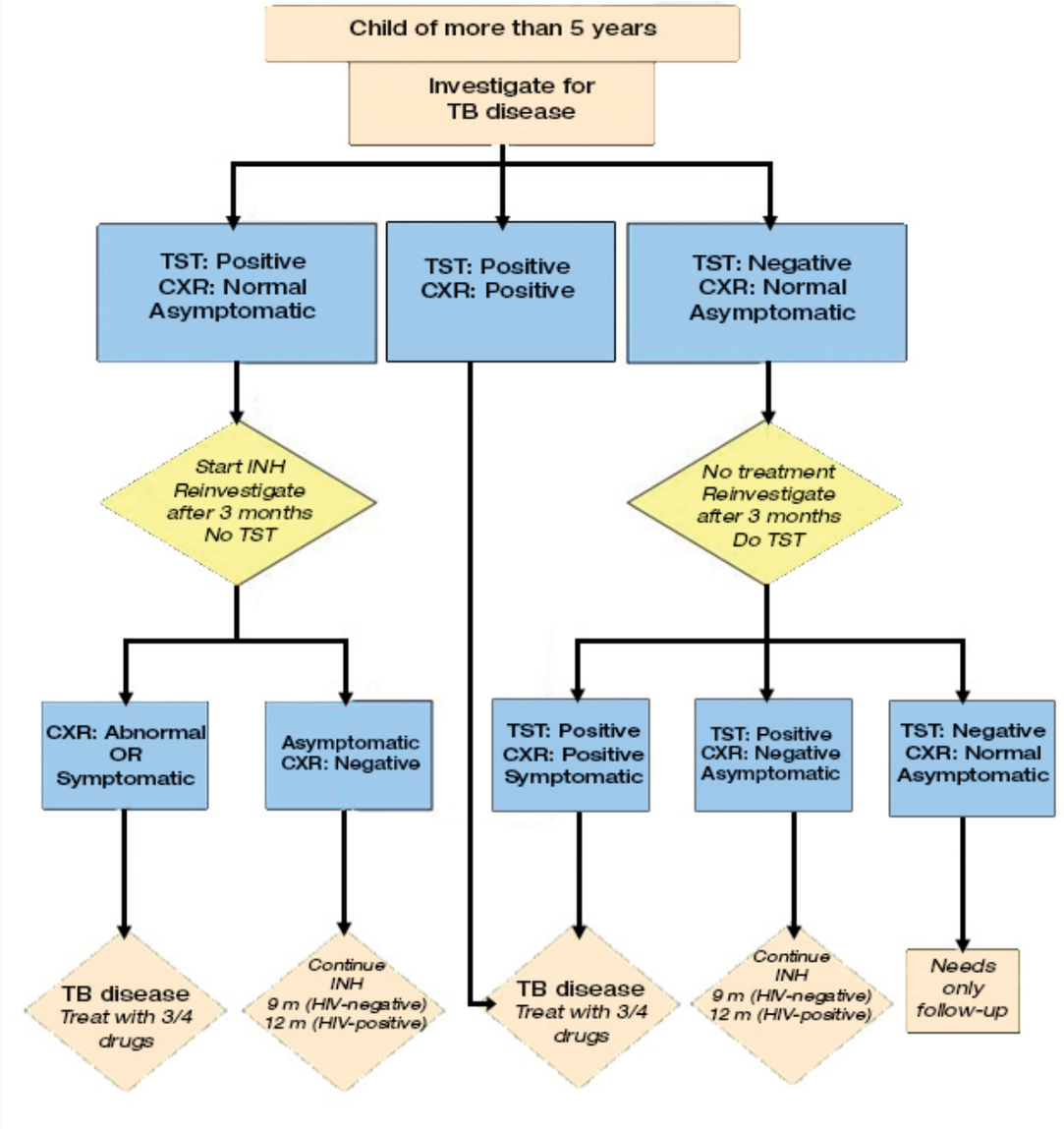

Figure 3: Flowchart showing the proposed management of children over 5 years of age with exposure to a contagious case of tuberculosis.

TB = tuberculosis; TST = tuberculin skin test; CXR = chest X-ray; INH = isoniazid; HIV = human immunodeficiency virus.

HIV-Infected Children

If the child contact is HIV-infected and asymptomatic, then INH therapy should be considered for all ages, including those who are 5 years and older. As with other contacts, active disease should be ruled out before providing HIV-infected children with INH treatment. HIV-infected children who have symptoms should be carefully evaluated for TB disease as they are at an increased risk of developing active disease after TB exposure/infection; therefore, the use of INH is justified once active TB has been excluded.[12]

Therapies

INH is widely used as the drug of choice for LTBI treatment with the standard recommended dose being 10–15 mg/Kg/day (maximum dose: 300 mg/day). Young children eliminate INH faster than older children and adults and, consequently, require a higher dosage to achieve similar levels. The drug is well absorbed orally and is best absorbed when consumed on an empty stomach. The primary possible adverse reactions include hepatitis (age-related), peripheral neuropathy and hypersensitivity reactions. Other reactions include optic neuritis,

arthralgia, nervous system changes, drug-induced lupus, diarrhoea and cramping with liquid product. Routine laboratory monitoring is not recommended for children receiving INH monotherapy.[9,14]

For patients receiving multiple TB drugs or other hepatotoxic drugs and for those with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity.[2,9,12] Laboratory testing should be obtained upon the first sign or symptom of a possible adverse event. In 10–20% of patients, aminotransferase levels will elevate 2–3 times during the first months of therapy; these levels will usually return to normal despite the continuance of the drug. In the absence of symptoms, INH should be discontinued if aminotransferase values are 5 times the upper limit of normal. In the presence of symptoms, INH should be discontinued if aminotransferase values are 3 times the upper limit of normal. INH therapy may be reinstituted when liver function tests return to baseline and symptoms of toxicity resolve. Vitamin B_6 should be used in situations where high-dose INH is employed, and in the case of children with diabetes, uraemia, HIV infection, malnutrition, or peripheral neuropathy. Additionally, exclusively breastfed infants should receive vitamin B_6 while taking INH. For persons who cannot tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen constitutes 4 months of rifampicin (10–20 mg/Kg/day).[9,14]

IGRA detects the release of interferon-gamma (IFN-γ) in fresh heparinised whole blood from sensitised persons when it is incubated with mixtures of synthetic peptides representing two proteins present in MTB: early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). In direct comparisons, the sensitivity of IGRA was statistically similar to that of the TST for detecting infection in persons with untreated culture-confirmed TB, and the CDC recommends that IGRA may be used in all circumstances in which the TST is currently used, including contact investigations. The specificity of IGRA is higher than that of TSTs because the antigen used is not found in BCG or most pathogenic non-tuberculous *Mycobacteria*. Experience with testing in children with IGRAs is less extensive than adults, but a number of studies have shown that IGRAs perform well in immunocompetent children of 4 years of age and older.[15] Implementation of IGRA testing in children can be done with less caution for those who are ≥5 years old. This is because they are less likely to develop active TB or severe forms of it compared to children who are under 5 years old and in them it is logistically easier (e.g. in the ability to draw sufficient quantities of blood).[16] Evaluation of this test has been hampered by the lack of a gold standard for LTBI, and limited paediatric data on their use. It appears that it is more specific than the TST and may be useful for evaluating TST-positive patients at low risk of true LTBI. Moreover, it may provide valuable information on sensitivity if used in addition to the TST in immunocompromised patients, very young children, and those in close contact with infectious adults.[17] Additional larger studies are needed to evaluate the performance of IGRAs in children.[16]

Conclusion

In countries with low TB incidence, such as Oman, that are working towards TB elimination, there is an emphasis on contact investigation and management. The process of investigation and management for children who are contacts of contagious TB have been described and simple algorithms provided for easy application in the primary care setting. The importance of Mantoux testing and its timing have been highlighted, along with a brief summary of interferon testing and latent TB infection treatment. We have provided a concise and practical approach aimed at enhancing contact investigation effectiveness and management of infants and children who are in contact with a contagious case of TB.

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