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## ABSTRACT

Early, accurate diagnosis of tuberculosis is one of the major pillars of the control of the disease. The purpose of this consensus statement is to provide health professionals with the most current, useful evidence for the diagnosis of tuberculosis in Brazil. To that end, the Tuberculosis Committee of the Brazilian Thoracic Association brought together 14 members of the Association with recognized expertise in tuberculosis in Brazil to compose the statement. A nonsystematic review of the following topics was carried out: clinical diagnosis, bacteriological diagnosis, radiological diagnosis, histopathological diagnosis, diagnosis of tuberculosis in children, and diagnosis of latent tuberculosis infection.

**Keywords:** Tuberculosis/diagnosis; Mycobacterium tuberculosis; Tuberculosis, multidrug-resistant/diagnosis; Latent tuberculosis/diagnosis.

## INTRODUCTION

The End TB Strategy, approved by the World Health Assembly of the WHO in 2014,<sup>(1)</sup> set targets for tuberculosis prevention, care, and control from 2015 onward. These targets, to be met by 2035, are to reduce the tuberculosis incidence rate to less than 10 cases/100,000 population and to reduce the number of deaths from tuberculosis by 95%. In Brazil, despite a downward trend in the incidence rate between 2010 and 2016, there was an increase in incidence in the 2017-2018 period, and the rate was 35.0 cases/100,000 population in 2019.<sup>(2)</sup> The mortality rate has remained stable since 2010, ranging from 2.2 to 2.3 deaths/100,000 population, and was 2.2 deaths/100,000 population in 2019.<sup>(2)</sup>

Early, accurate diagnosis of tuberculosis is one of the major pillars of the control of the disease.<sup>(3)</sup> The purpose of this consensus statement is to provide health professionals with the most current, useful evidence for the diagnosis of tuberculosis in Brazil.

## METHODOLOGY

The Tuberculosis Committee of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) brought together 14 members of the Association with recognized expertise in tuberculosis in Brazil to compose this consensus statement on the diagnosis of tuberculosis in Brazil. A nonsystematic review of the following topics was carried out: clinical diagnosis, bacteriological diagnosis, radiological diagnosis, histopathological diagnosis, diagnosis of tuberculosis in children, and diagnosis of latent tuberculosis infection.

## CLINICAL DIAGNOSIS

Tuberculosis manifests as an infectious syndrome, usually with a chronic course, and most patients present with fever, adynamia, anorexia, weight loss, and night

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sweats, as well as with symptoms that are specific to the affected site.<sup>(4-6)</sup> Approximately 85% and 15% of patients have pulmonary and extrapulmonary tuberculosis, respectively.<sup>(7)</sup>

### **Pulmonary tuberculosis**

Cough is one of the major symptoms of patients with pulmonary tuberculosis, and the time since the onset of cough should be considered, depending on the population. Therefore, tuberculosis screening should be performed, regardless of cough duration, in contacts of patients with tuberculosis, people living with HIV (PLHIV), prison inmates, homeless people, individuals living in shelters or long-term care institutions, indigenous people, health professionals, immigrants, and refugees (when there is increased vulnerability). In the general population seeking care at any health care facility and in patients with diabetes mellitus, tuberculosis screening should be performed for individuals in whom a cough has lasted two weeks or more. In cases in which a cough has lasted three weeks or more, health professionals should conduct active case finding in the general population.<sup>(4)</sup> The cough can initially be dry; as the disease progresses, it can be accompanied by expectoration, blood-streaked sputum, or even hemoptysis, and the patient can develop chest pain and dyspnea.<sup>(4,6)</sup>

### **Extrapulmonary tuberculosis**

The diagnosis of extrapulmonary tuberculosis is often presumptive because it is a paucibacillary form of the disease. Clinical sample collection depends on the suspected site of disease and requires invasive procedures. Therefore, a clinical diagnosis is not sufficient, and ancillary tests are required for confirmation and refinement of the diagnosis. All clinical samples should undergo bacteriological testing, molecular testing, and histopathological examination, and the patient should undergo imaging examinations.<sup>(6)</sup>

Pleural tuberculosis is the most common form of extrapulmonary tuberculosis, except in PLHIV. Patients can experience dry cough, pleuritic chest pain, and dyspnea, depending on the volume of pleural fluid.<sup>(4,6,8)</sup>

Lymph node tuberculosis, which is most common in children and women, is the most common form of extrapulmonary tuberculosis in PLHIV. The most commonly affected lymph node chains are the cervical lymph node chain, either unilaterally or bilaterally (and usually asymmetrically), the supraclavicular lymph node chain, and the mediastinal lymph node chain. Affected lymph nodes have a hard consistency, increase in volume, can coalesce, can adhere to deep planes, and can develop fistulas with secretion (scrofuloderma).<sup>(5,6)</sup>

Tuberculous meningoencephalitis is a severe form of tuberculosis and is difficult to diagnose. In its subacute form, it can present with diffuse headache, irritability, behavioral changes, sleepiness, photophobia, vomiting, paresthesia, and neck stiffness. It can also

present with paralysis of the (second, third, fourth, sixth, or seventh) cranial nerves. In the chronic form of the disease, the headache can last for weeks. In its localized form, tuberculoma, it can present with symptoms of intracranial hypertension, a reduced level of consciousness, or coma.<sup>(4,9)</sup>

In osteoarticular tuberculosis, the most commonly affected site is the spinal column, followed by the hip/thigh region, the knees, and the ankles. The most common manifestations are spondylitis, arthritis, and osteomyelitis. Tuberculous spondylitis affects the intervertebral disk; anterior involvement is mainly due to infection spreading under the ligaments and periosteum and can lead to involvement of multiple vertebral bodies, in a continuous or discontinuous way. As the spinal disease progresses, there can be destruction and collapse of the vertebral bodies leading to kyphoscoliosis, often causing deformity (Pott's disease). Pain, tumor formation, neurological changes, and gait changes can occur, and, if discovered late, the disease can lead to irreversible neurological deficits.<sup>(10)</sup>

## **BACTERIOLOGICAL DIAGNOSIS**

### **Smear microscopy**

Sputum smear microscopy is important for the diagnosis of tuberculosis because it identifies patients with active tuberculosis, who feed the chain of disease transmission. Smear testing for AFB is a rapid, inexpensive method.<sup>(11)</sup> However, although the sensitivity of direct smear microscopy examination of spontaneous sputum is as high as 80% in the presence of extensive cavitory lesions, it ranges, on average, from 40-60% in patients with minimal lesions, and smears are positive in only 20% of those patients.<sup>(11)</sup> In addition, smear microscopy has lower sensitivity (ranging from 20-60%) in patients coinfecting with HIV.<sup>(12)</sup>

Two to three sputum samples, at least one being collected in the early morning to optimize results, should be sent for smear microscopy.<sup>(13)</sup> The sputum volume should be greater than 3 mL, the optimal volume being 5-10 mL.<sup>(14)</sup>

Fluorescence microscopy can increase the capacity to detect mycobacteria by 10%, compared with conventional light microscopy. A 10-20% increase in the sensitivity of smear microscopy can also be achieved by using sputum centrifugation or sedimentation.<sup>(13)</sup>

Sputum induction with hypertonic saline solution is a useful technique in individuals who have negative sputum smears or who are unable to produce sputum, because it increases the yield of smear microscopy and culture.<sup>(13)</sup> Sputum induction with hypertonic saline solution has a diagnostic yield similar to that of bronchoscopy with BAL and is more cost-effective. If a diagnosis is not possible on the basis of spontaneous or induced sputum collection and suspicion of pulmonary tuberculosis persists, bronchoscopy and BAL fluid collection can be performed for smear microscopy and culture. Bronchoscopy also plays a role in the

diagnosis of smear-negative pulmonary tuberculosis, in cases of hemoptysis caused by tuberculosis, and in the exclusion of alternative diagnoses.<sup>(15-17)</sup>

In cases of suspected extrapulmonary tuberculosis, smear microscopy examination of the material collected is also indicated, although its sensitivity is lower. In cases of lymph node tuberculosis, the diagnosis is made by needle puncture-aspiration or lymph node resection. In pleural tuberculosis, the pleural fluid presents as an exudate with a predominance of lymphocytes but with a low yield for the detection of AFB (< 5%). Conversely, the yield of smear microscopy is high in tuberculous empyema. Increased adenosine deaminase levels (> 40 U/L) in the pleural fluid are considered highly suggestive of the diagnosis of pleural tuberculosis.<sup>(4)</sup>

### Culture

Mycobacterial culture of respiratory material has a sensitivity of approximately 80% and a specificity of 98%. In cases of smear-negative pulmonary tuberculosis, culture increases disease detection by 20-40%.<sup>(11)</sup> Culture methods that use seeding on solid media, such as Löwenstein-Jensen and Ogawa-Kudoh media, are the most commonly used because they have the advantage of being inexpensive and having a low rate of contamination.<sup>(4)</sup> However, the time to visible growth of mycobacteria on solid media is two to eight weeks. Therefore, if available, liquid media should be used in automated nonradiometric systems, such as the Mycobacteria Growth Indicator Tube (MGIT; Becton Dickinson, Sparks, MD, USA), for faster results (10-42 days).<sup>(4)</sup> If mycobacterial growth is detected, species identification and antimicrobial susceptibility testing is required.<sup>(18)</sup>

Species identification is performed using biochemical and phenotypic methods or using molecular techniques and consists in distinguishing mycobacteria of the *Mycobacterium tuberculosis* complex from nontuberculous mycobacteria (NTM).<sup>(4)</sup> Currently available methods of antimicrobial susceptibility testing include the proportion method, which is performed on solid media and yields results within the first 42 days of incubation, and the automated method, which is performed in liquid media and yields results within 5 to 13 days. The drugs tested include streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide. For cases of multidrug-resistant tuberculosis (MDR-TB), second-line drugs are tested.<sup>(4)</sup>

The WHO considers culture using solid or liquid media the gold standard for the diagnosis of tuberculosis.<sup>(13)</sup> Culture is also indicated in suspected cases of extrapulmonary tuberculosis.<sup>(14)</sup> In pleural tuberculosis, mycobacterial culture has a low yield (< 15%). In contrast, in tuberculous empyema, the yield of culture is high.<sup>(4)</sup> Induced sputum culture is positive in up to 50% of cases, even if the only abnormality visible on chest X-ray is pleural effusion.<sup>(19)</sup>

### Molecular testing

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is based on nucleic acid amplification for

detection of DNA of *M. tuberculosis* complex and screening for rifampin-resistant strains by real-time polymerase chain reaction (PCR), the results being available in approximately 2 h and only one sample being required. In 2011, the WHO endorsed the use of the Xpert MTB/RIF assay for the rapid diagnosis of tuberculosis and identification of rifampin resistance in individuals with suspected tuberculosis, even those infected with HIV. The sensitivity of the test in sputum samples from adults is approximately 90%. For rifampin resistance, its sensitivity is 95%.<sup>(4)</sup>

In Brazil, the Xpert MTB/RIF assay is known as the rapid molecular test for tuberculosis (RMT-TB) and is indicated for the diagnosis of new cases of pulmonary and laryngeal tuberculosis in adults and adolescents, being used with spontaneous sputum, induced sputum, BAL fluid, and gastric lavage samples; for the diagnosis of extrapulmonary tuberculosis in validated biological materials (i.e., cerebrospinal fluid, lymph nodes, and tissue macerate); for screening for rifampin resistance in cases of retreatment; and for screening for rifampin resistance in cases of suspected treatment failure.<sup>(4)</sup>

To improve the molecular diagnosis of tuberculosis, the Xpert MTB/RIF Ultra assay (Cepheid) has been developed. It is a new version of the Xpert MTB/RIF assay that has higher sensitivity for detecting tuberculosis, especially in paucibacillary samples. The sensitivity of the Xpert MTB/RIF Ultra assay is comparable to that of liquid culture,<sup>(20)</sup> and the test is already available in Brazil. The Xpert MTB/RIF Ultra results are reported as *M. tuberculosis* not detected (negative), *M. tuberculosis* detected (positive), and trace *M. tuberculosis* detected. This last result can be interpreted as positive, within the clinical context, in specimens from individuals with HIV/AIDS and children under 10 years of age, as well as in those obtained from the extrapulmonary materials mentioned above, because such materials are more commonly associated with the paucibacillary forms of tuberculosis. In other clinical situations, the result "trace *M. tuberculosis* detected" should be considered inconclusive and the investigation of tuberculosis should continue.<sup>(21)</sup>

Another type of molecular test approved and recommended by the WHO for use in respiratory material is the line probe assay, which, in addition to identifying the *M. tuberculosis* complex, identifies resistance to rifampin and isoniazid and which, in a separate test, can also detect resistance to fluoroquinolones and injection drugs.<sup>(22)</sup> In one meta-analysis, the sensitivity and specificity of the line probe assay was 96.7% and 98.8%, respectively, for detecting rifampin resistance, whereas they were 90.2% and 99.2%, respectively, for detecting isoniazid resistance.<sup>(23)</sup>

### RADIOLOGICAL DIAGNOSIS

The initial approach to patients with respiratory diseases should include imaging with chest X-ray and, if necessary, chest CT. These methods are considered

essential because they provide relevant information on the presentation of the disease, its extent, and its course during treatment. Because it is easy to perform, accessible, and inexpensive, as well as because it uses a low dose of radiation, chest X-ray is the method of choice for the initial assessment of patients who present with suspected tuberculosis. Despite having low diagnostic specificity, chest X-ray is extremely useful in defining the presentation, evaluating possible comorbidities, and monitoring the evolution during treatment. In addition, chest X-ray can be used as a screening method for tuberculosis, especially in prison inmates, among whom the incidence of tuberculosis is extremely high.<sup>(24)</sup> The basic routine X-ray protocol in patients with suspected tuberculosis includes the use of posteroanterior and left lateral views. An apical lordotic (Fleischner) view may complement the routine protocol in cases in which there is uncertainty in interpretation of the lung apices. In suspected intrapulmonary pleural effusion, the horizontal beam lateral decubitus (Hjelm-Laurell) view is being replaced by chest ultrasound.<sup>(24-26)</sup>

The pulmonary tuberculosis-related changes seen on chest X-rays can be addressed in relation to the following conditions: primary tuberculosis; and secondary tuberculosis (reactivation or exogenous reinfection). Although primary tuberculosis is more common in children, it can also occur in adults. In children, given the difficulty in establishing smear microscopy-based diagnoses, imaging methods play an even more relevant role. Among the multiple presentations of the disease, the most common X-ray findings consist of concurrent changes, including single or multiple parenchymal, segmental, or lobar opacities and enlarged hilar or mediastinal lymph nodes, which cause reduced lung volume (epituberculosis), the most well-known presentation being middle lobe syndrome (Chart 1). Occasionally, there are cavitory lesions with bronchial dissemination and a diffuse/miliary pattern, as well as involvement of other sites, such as the pleura.<sup>(26-28)</sup>

Secondary tuberculosis, caused by reactivation or exogenous reinfection, is the most common form of the disease among adolescents and adults, and, in such individuals, pulmonary involvement occurs in 85-90% of cases. There are many possible manifestations on X-rays, chief among which are incipient, nodular, pneumonic, cavitory, pseudotumoral, and extrapulmonary forms. Lesions more commonly affect the apical and posterior segments of the upper lobes, as well as the apical segments of the lower lobes. They usually involve more than one lobe and

are bilateral. Their manifestations are multiple, including small clustered nodules, heterogeneous segmental or lobar opacities, nodules measuring 1-3 cm in diameter, thick-walled cavities with bronchial dissemination, and areas of fibrosis (Chart 2).<sup>(26,27)</sup>

Although chest X-ray is the most important imaging method in the diagnosis and follow-up of patients with tuberculosis, chest CT has been increasingly used. Chest CT is more sensitive and more specific than is chest X-ray, being able to show early changes that are undetectable by chest X-ray, and it should be performed in patients with respiratory symptoms and poorly defined or unclear changes in whom the clinical and epidemiological context raises the possibility of tuberculosis. Chest CT should be performed in patients with respiratory symptoms but with negative sputum smear results, in individuals with suspected tuberculosis in whom chest X-ray was inconclusive, in cases in which further evaluation of the mediastinum is required, in cases of diffuse disease, and in patients with endobronchial abnormalities, as well as in those with respiratory symptoms and extensive sequelae that may require surgical intervention. Chest CT, unlike chest X-ray, can show changes suggestive of activity that occur at the level of the secondary pulmonary lobule, such as small airspace nodules exhibiting a tree-in-bud pattern or neatly arranged in a clover pattern ("clover sign"). Chest CT always provides additional information. There is a CT pattern that is consistent with active tuberculosis, characterized by consolidation (with or without air bronchogram), nodules, cavities, airspace nodules (tree-in-bud pattern), and bronchial abnormalities, such as wall thickening and dilatation.<sup>(26,27,29-34)</sup> Figures 1 and 2 show the X-ray and CT aspects of tuberculosis, respectively.

## HISTOPATHOLOGICAL DIAGNOSIS

Histopathology is an important method for diagnosing pulmonary and extrapulmonary tuberculosis on the basis of specimens of tissue infected with *M. tuberculosis*. The typical histopathological lesion in pulmonary tuberculosis is a granuloma with caseous necrosis, composed of epithelioid histiocytes around a necrotic center, usually accompanied by a variable number of multinucleated giant cells and lymphocytes, which are found in up to 80% of cases. Non-necrotic granulomas may also be present, especially in immunocompromised patients when there is an incomplete inflammatory reaction. Granulomas without caseous necrosis should be interpreted with caution and in conjunction with clinical and epidemiological

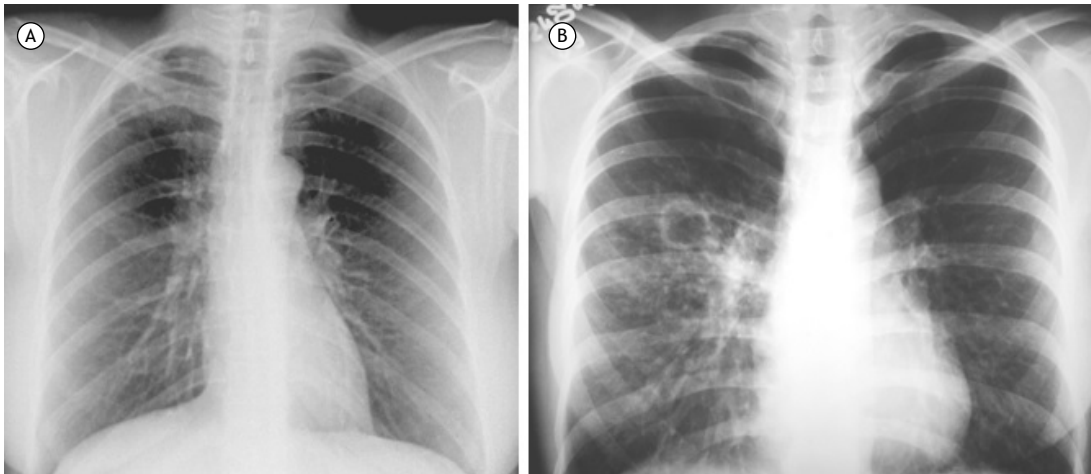
**Chart 1.** Most common changes in primary tuberculosis.

- Enlarged hilar or mediastinal lymph nodes
- Reduced lung volume (partial atelectasis)
- Segmental, lobar, or whole lung parenchymal opacities
- Cavities accompanied by airspace nodules (bronchial dissemination)
- Diffuse micronodules (miliary pattern) in children not vaccinated with BCG



**Chart 2.** Most common changes in secondary tuberculosis.

- Common bilateral involvement, affecting more than one lobe, with multiple lesions
- Faint, clustered, difficult-to-visualize nodular opacities, typically located in the apical, interclavicular-hilar, and axillary regions
- Heterogeneous parenchymal opacities affecting more than one segment or lobe
- Lobar opacity accompanied by lines that converge toward the hilum (hilum overlay sign)
- Well-defined nodule(s) measuring 1-3 cm in diameter
- One or more cavities, of varying size, with a wall thickness of 3 mm or more, with or without parenchymal opacities and satellite nodules
- Architectural distortion resulting from areas of fibrosis or fibrosis/atelectasis, predominantly in the upper lobes
- Diffusely distributed micronodules measuring 2-3 mm in diameter (miliary pattern)



**Figure 1.** Chest X-ray findings of tuberculosis. In A, small clustered opacities in the right infraclavicular area. In B, a thick-walled cavity located in the middle third of the right lung, accompanied by small airspace nodules, also known as satellite lesions, which are classically representative of bronchial dissemination of the disease.

findings, given that they can be found in other pulmonary and systemic granulomatous diseases, such as silicosis, mycoses, and sarcoidosis.<sup>(4,35)</sup>

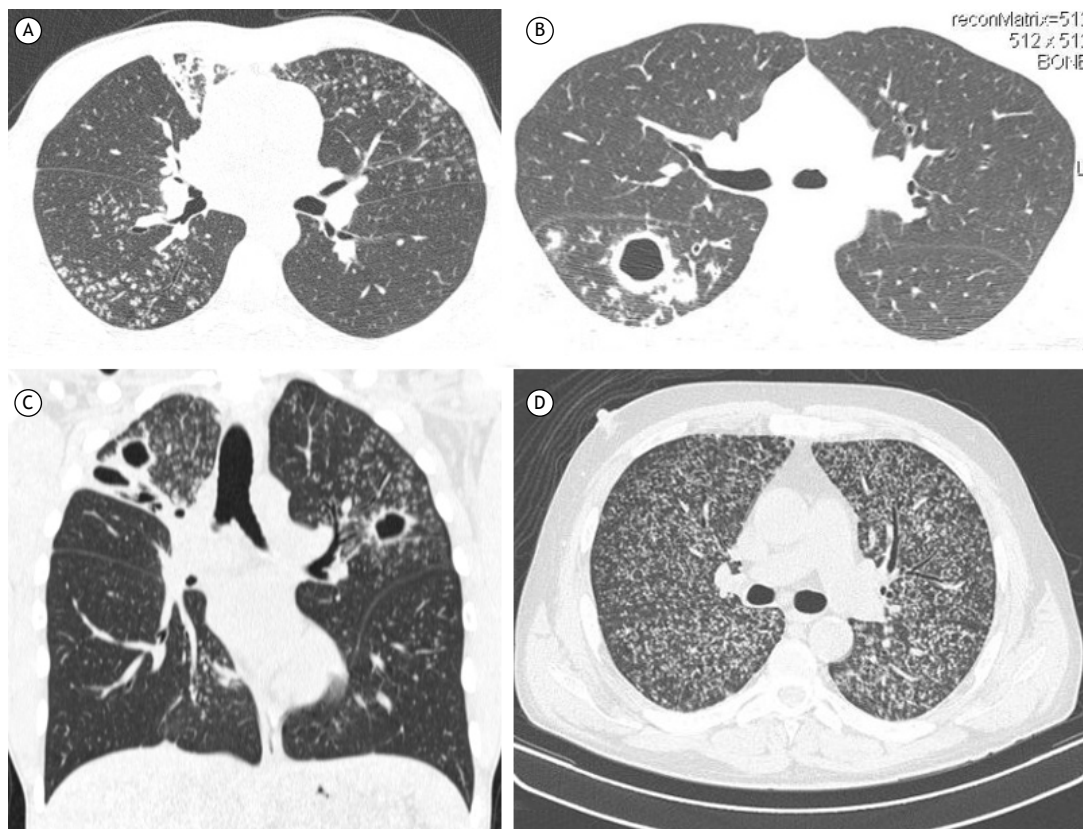
In immunocompetent patients with tuberculosis, smear microscopy of lung tissue is usually negative, whereas it is typically positive in immunocompromised patients. However, the only definitive diagnostic method is culture followed by biochemical or molecular confirmation of *M. tuberculosis*.<sup>(4)</sup>

The diagnosis of extrapulmonary forms of tuberculosis is more difficult because of the paucibacillary nature of samples, the lack of sufficient sample quantities or volumes, and the fact that samples are fractionated in order to perform several diagnostic tests, such as histology/cytology, biochemical analysis, microbiology, and molecular biology methods.<sup>(36)</sup>

In pleural tuberculosis, it is recommended that specimens be collected for histopathological examination, AFB testing, mycobacterial culture, and PCR. A definitive etiological diagnosis requires culture or PCR detection of *M. tuberculosis* in pleural fluid or pleural tissue. However, the presence of caseating granulomas, even in the absence of AFB or in the presence of negative culture, is considered highly

suggestive of tuberculosis. Pleural biopsy shows granulomas in 50-97% of cases, and culture is positive in 40-80% of cases. Noncaseating granulomas can also be seen, at which point it is necessary to make a differential diagnosis from sarcoidosis, fungal diseases, and rheumatoid disease. It is also necessary to test pleural fluid and pleural tissue for neoplastic cells, especially in older patients.<sup>(4,37)</sup>

Histopathology yields findings that are nonspecific for the diagnosis of lymph node tuberculosis in the absence of AFB, because they mimic those of other diseases, such as sarcoidosis and fungal infections. Fine-needle aspiration biopsy plays an important role in the diagnosis of lymph node tuberculosis. However, the amount of material obtained is usually insufficient for AFB testing and culture. Fine-needle aspiration biopsy cytology also has difficulty in differentiating tuberculosis from other granulomatous or NTM diseases. PCR methods in combination with cytology reduce the need for an open biopsy. Lymph node aspirate smears are positive in 10-25% of cases, lymph node aspirate culture is positive in 50-90% of cases, and granulomas can be seen in up to 90% of cases. Molecular biology methods, such as Xpert MTB/RIF Ultra (Cepheid), allow detection of *M.*



**Figure 2.** CT findings of tuberculosis. In A, diffuse airspace nodules, some of which are dichotomous, resulting in a tree-in-bud pattern. In B (same case as Figure 1B), a thick-walled cavity, accompanied by satellite nodules and marked bronchial wall thickening, in the apical segment of the right lower lobe. In C, coronal reconstruction showing thick-walled cavities and satellite nodules, bilaterally. In D, a miliary pattern of diffuse micronodules.

*tuberculosis* DNA and rifampin resistance in biopsy macerates. In a study involving 140 patients with lymph node tuberculosis, the rates of detection of *M. tuberculosis* by Xpert MTB/RIF, conventional PCR, and MGIT 960 culture were 25.71%, 20.71%, and 17.85%, respectively.<sup>(36)</sup>

In cutaneous tuberculosis of exogenous origin, there is at first a neutrophilic reaction with areas of necrosis accompanied by AFB. A granuloma with caseous necrosis is evident after three to six weeks, and AFB may or may not be present. In cutaneous tuberculosis of endogenous origin, there are granulomas with caseous necrosis, and AFB may be present. As the lesion progresses, granulomas may be replaced by a nonspecific chronic inflammatory infiltrate, and AFB may be scarce. In cutaneous tuberculosis resulting from hematogenous spread, there is a nonspecific inflammatory infiltrate with areas of necrotizing vasculitis, signs of thrombosis, and numerous AFB. Tuberculids (cutaneous manifestations of a distant paucibacillary focus) present as nodular vasculitis (erythema induratum of Bazin) and erythema nodosum.<sup>(38)</sup>

Intestinal tuberculosis primarily affects the ileocecal region, probably because there is a high density of lymphoid tissue in this region, as well as

neutral pH, and transport mechanisms that favor the absorption and persistence of *M. tuberculosis*. The most common histopathological finding is the presence of characteristically large (> 200 µm) granulomas with caseous necrosis in the intestinal mucosa and submucosa. Positive PCR results can be seen in 72-87% of cases, with greater sensitivity and specificity than those of smear microscopy and mycobacterial culture.<sup>(39,40)</sup>

Bone puncture biopsy is the most common invasive procedure for the diagnosis of bone tuberculosis. Because of the density of bone structures, the limited sample volumes, the paucibacillary nature of samples, and the atypical puncture sites, it is difficult to make the histopathological and bacteriological diagnosis of bone tuberculosis. The most common finding is granuloma, with or without caseous necrosis, and smear microscopy, culture, and molecular biology methods have varying yields. Because of the difficulties inherent in such procedures, the diagnosis is often based on epidemiological, clinical, and radiological findings.<sup>(41)</sup>

Figures 3 and 4 show diagnostic algorithms for pulmonary and laryngeal tuberculosis in adults, for new cases and cases of retreatment, respectively. Where the RMT-TB is unavailable, the diagnosis of

tuberculosis should be based on smear microscopy and culture.

### DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

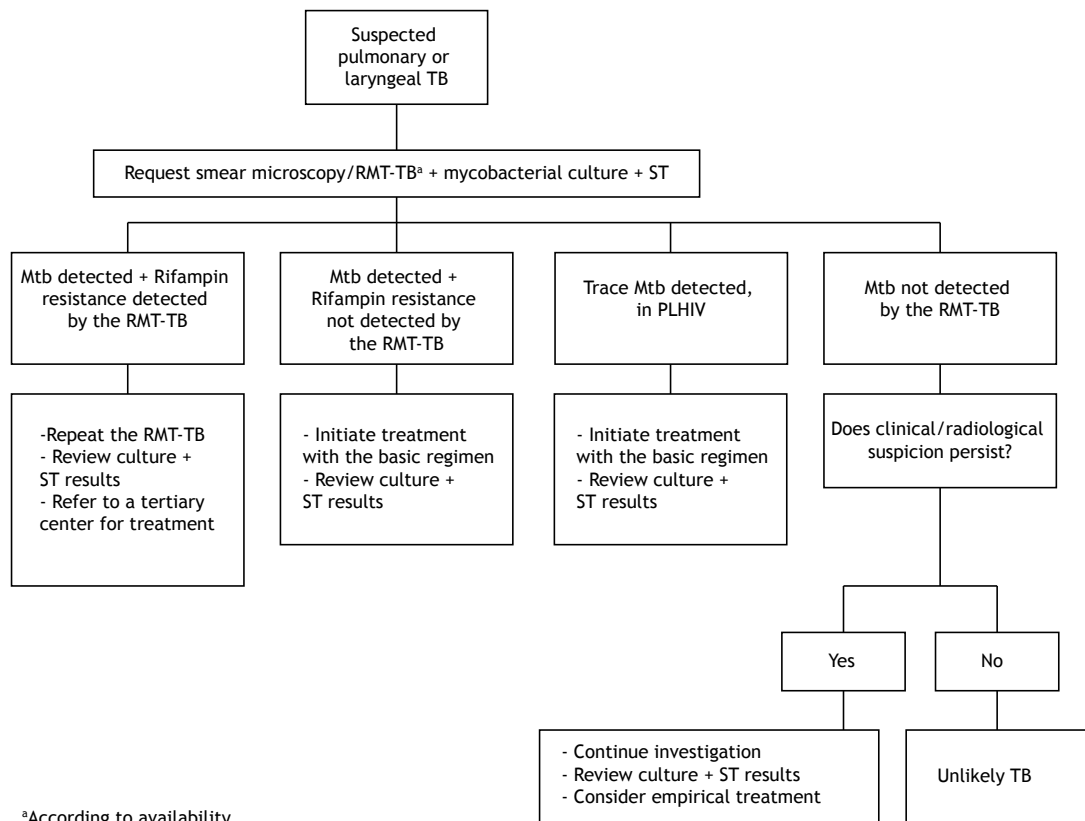
The WHO estimates that each year more than one million children become ill with tuberculosis worldwide—approximately 10% of the total number of cases—and that the incidence of childhood tuberculosis is underestimated because of the difficulty in diagnosing the disease in children. There are approximately 200,000 tuberculosis deaths per year among children and adolescents aged 0-14 years. Approximately 80% of those deaths occur among children under 5 years of age, and 17% occur in HIV-infected patients. Twenty-five thousand children under 14 years of age develop MDR-TB each year, although only approximately 5% receive treatment. The difficulties in diagnosis, contact tracing, and access to health care facilities would explain this challenge from a public health standpoint.<sup>(7,42)</sup>

In Brazil, the tuberculosis incidence rate in 2018 was higher among children 0-4 years of age than among those 5-14 years of age. In that same year, 75,709 new cases of tuberculosis were reported, 3.3% of which were in children under 14 years of age. It is

estimated that 6-7% of tuberculosis patients have HIV coinfection.<sup>(43)</sup>

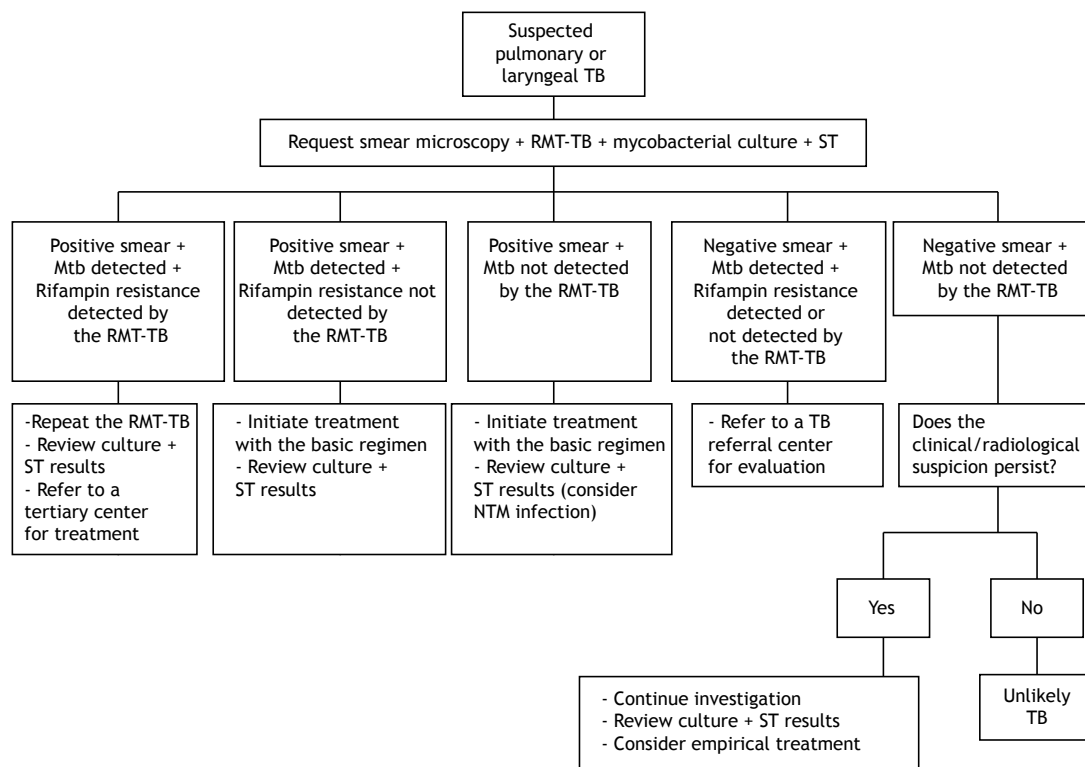
Children under 10 years of age typically have paucibacillary disease, which makes it difficult to detect *M. tuberculosis* in clinical specimens. Antituberculosis treatment is almost always started on the basis of clinical history, symptoms, and signs, as well as, when possible, on the basis of radiological findings and tuberculin skin test (TST) results.<sup>(4,44)</sup> Figures 5 and 6 show radiological features of tuberculosis in children.

The diagnosis of pulmonary tuberculosis in children is mainly based on clinical and radiological findings, epidemiological history of contact with adults with tuberculosis (typically active tuberculosis), and the interpretation of individual TST results. In a small number of cases, the diagnosis is based on bacteriological findings, because they are mostly cases of latent tuberculosis. The recent introduction of nucleic acid amplification methods has resulted in an increase in the rate of case confirmation. Slowly progressive infection, often showing no signs of being localized, with weight loss, anorexia, and occasionally sweating, is more common in children under 10 years of age than in children and adolescents 10-18 years age. Typically, those are cases of primary tuberculosis. Persistent cough and a history of contact with an adult with tuberculosis are clinical findings that are

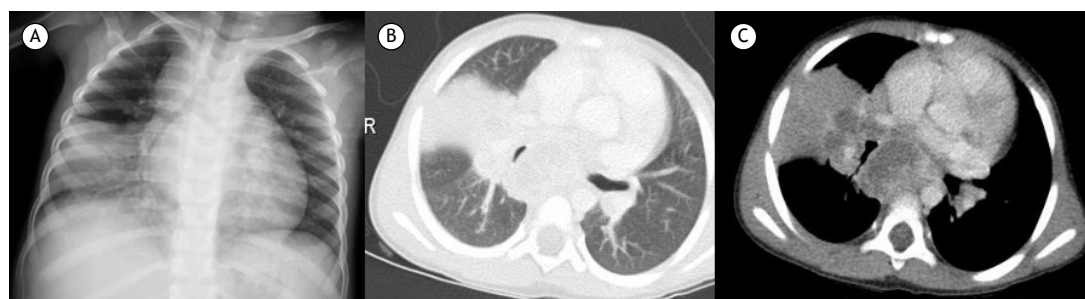


<sup>a</sup>According to availability.

**Figure 3.** Diagnostic algorithm for new cases of pulmonary and laryngeal tuberculosis in adults. TB: tuberculosis; RMT-TB: rapid molecular test for tuberculosis; ST: susceptibility test; Mtb: *Mycobacterium tuberculosis*; and PLHIV: people living with HIV.



**Figure 4.** Diagnostic algorithm for cases of pulmonary and laryngeal tuberculosis requiring retreatment in adults. TB: tuberculosis; RMT-TB: rapid molecular test for tuberculosis; ST: susceptibility test; Mtb: *Mycobacterium tuberculosis*; and NTM: nontuberculous mycobacteria.



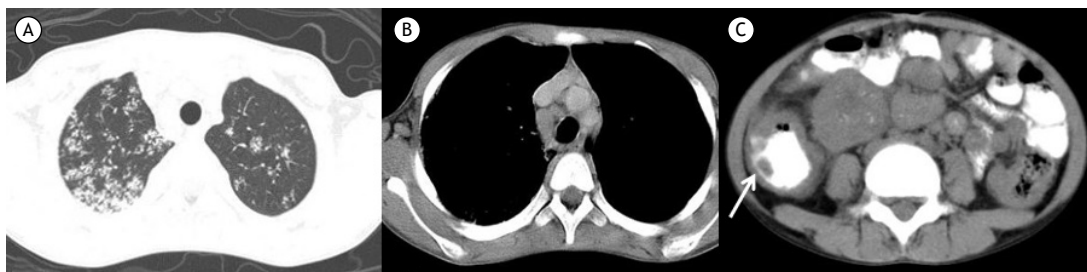
**Figure 5.** Primary tuberculosis in a child aged four years and nine months. In A, chest X-ray showing opacity in the right middle lower third accompanied by widening of the right paratracheal stripe, consistent with enlarged lymph nodes. In B, chest CT (lung window) showing opacity and extrinsic obstruction of the intermediate bronchus by enlarged lymph nodes, which are indicative of middle lobe syndrome. In C, chest CT (mediastinal window settings) showing enlarged lymph nodes of varying density in the right hilum and posterior mediastinum.

of great practical value in relation to tuberculosis in children.<sup>(4,44,45)</sup> However, some findings have been the subject of discussion. For example, prolonged cough (> 15 days) is thought to be a finding suggestive of pulmonary tuberculosis in children. However, children who have had a cough for a few days may also have pulmonary tuberculosis and go undetected. A history of contact with a person with tuberculosis and some chest X-ray features, such as unilateral enlarged hilar lymph nodes and a miliary pattern, are more common in children than in adolescents. In their daily lives, children are in closer contact with index cases of tuberculosis (usually adults) than are adolescents. Although the latter have greater autonomy in society,

they may engage in rebellious or challenging behavior and show poor adherence to tuberculosis treatment. The classical concept of tuberculosis transmission has been challenged in studies showing that, among children who are household contacts of patients with tuberculosis, less than 30% become infected. Another feature that is of value in the clinical diagnosis of tuberculosis in children is malnutrition or lack of weight gain. Studies have addressed malnutrition as either a cause or a consequence of tuberculosis, depending on the epidemiological scenario in question.<sup>(42)</sup>

Adolescents commonly develop adult-type tuberculosis. Extensive forms of tuberculosis are





**Figure 6.** Chest CT scans showing disseminated tuberculosis in a nine-year-old child. In A, airspace nodules exhibiting a tree-in-bud pattern. In B, enlarged right paratracheal lymph nodes. In C, marked thickening of the cecum (arrow).

common in this age group, and more than half of such patients have active tuberculosis.<sup>(4,44,46)</sup> The differences in findings between children and adolescents are summarized in Chart 3.

In view of the relative complexity of diagnosing pulmonary tuberculosis in children, the Brazilian National Tuberculosis Control Program of the Brazilian National Ministry of Health adopted, in 2002, a scoring system for the diagnosis of pulmonary tuberculosis in children and adolescents (when bacteriological findings or molecular test results are negative). The scoring system does not rely on procedures for the collection of material for bacteriological examination (e.g., sputum induction and gastric lavage) to establish the diagnosis. The Brazilian scoring system is one of the few that have been validated in HIV-infected and HIV-uninfected children, and it has performed well in real-life studies.<sup>(47,48)</sup> Over the years, changes have been made to the scoring system with regard to the interpretation of TST results. A TST induration  $\geq 5$  mm indicates infection with *M. tuberculosis*, even in patients vaccinated with BCG at birth. The latest version of the scoring system is summarized in Chart 4.<sup>(4)</sup>

Pulmonary tuberculosis may be suspected in children and adolescents with slowly progressive pneumonia; that is, pneumonia that is presumably caused by common germs and does not improve as expected with antimicrobial treatment. Often, what is of note is the clinical and radiological dissociation, that is, there may be improvement in symptoms and persistence or worsening of radiological findings. In adolescents, the diagnosis can be attempted by sputum examination either using conventional bacteriological methods or molecular methods. In Brazil, the standard method is the RMT-TB.<sup>(4,44)</sup>

One study of pediatric patients with pulmonary tuberculosis at a tertiary care hospital showed that RMT-TB positivity was 33% and 64% among the children and adolescents, respectively, whereas culture positivity was approximately 42% in both groups. The rate of rifampin resistance among the patients was 10%. However, the rate of rifampin resistance among only the patients with an RMT-TB result of “*M. tuberculosis* detected” was 17%, which is similar to that reported in the literature.<sup>(42)</sup> In 2017, the WHO started to recommend the use of Xpert Ultra, which is more sensitive than its predecessor, with good

prospects for use in paucibacillary cases, such as in children and individuals living with HIV/AIDS.<sup>(49)</sup>

In HIV-infected patients, the clinical presentation of tuberculosis may vary according to their degree of immunosuppression. The extrapulmonary and disseminated forms are more common in HIV-infected children. In general, the diagnostic workup requires the use of invasive methods, such as thoracentesis and lumbar puncture, as well as biopsy of solid organs, such as lymph nodes and the pleura.<sup>(4)</sup> In HIV-infected children, raising a diagnostic suspicion of pulmonary tuberculosis can be more complex because it is necessary to make a differential diagnosis from some HIV-related lung diseases, such as pneumocystosis, other mycoses, and lymphocytic interstitial pneumonia. In addition, TST sensitivity can be affected by HIV-induced anergy.<sup>(4,48)</sup>

### DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

The state of an individual in the “window period” between becoming infected with *M. tuberculosis* and developing active tuberculosis is known as latent tuberculosis infection (LTBI), that is, the individual is infected with the tuberculosis bacillus but shows no signs or symptoms of active disease.<sup>(4,50)</sup>

There are currently no methods capable of measuring the global prevalence of LTBI; however, one quarter of the global population is estimated to be infected with *M. tuberculosis*.<sup>(51)</sup> Being infected does not necessarily mean that the individual will develop active tuberculosis at some point in the future. However, we can infer that infected individuals are reservoirs of tuberculosis bacilli, which can be reactivated under conditions that alter the competence of the immune system, such as HIV infection.<sup>(4)</sup> In addition, the greatest risk of developing active disease occurs within the first 2 years after primary infection, which is why contacts of active tuberculosis cases should also be included in LTBI case finding.<sup>(52)</sup> The presence of other immunosuppressive conditions or conditions considered to be risk factors should be evaluated within the context of each epidemiological scenario.<sup>(53)</sup>

With the advent of biologic agents, greater attention has come to be focused on the LTBI status of patients on biologic therapy. Not all biologic agents currently

**Chart 3.** Clinical findings, radiological findings, and history of contact in children and adolescents with pulmonary tuberculosis.

		Children <sup>a</sup>	Adolescents <sup>a</sup>
Clinical findings	Persistent fever		
	Weight loss (or lack of weight gain)		
	Irritability		
	Persistent cough		
	Expectoration (sometimes streaked with blood)		
Contact	History of contact with tuberculosis		
Radiological findings	Pulmonary lymph node involvement		
	Opacity		
	Nodules		
	Cavitations		
	Pleural effusion		
	Miliary pattern		

<sup>a</sup>In gray: less common; and in blue: more common.

**Chart 4.** Diagnosis of pulmonary tuberculosis in children and adolescents with negative smear and/or rapid test results.

Clinical profile	Radiological profile	Contact with an adult with tuberculosis	TST	Nutritional status
Fever or symptoms such as cough, adynamia, expectoration, weight loss, and sweating for > 2 weeks (15 points)	Enlarged hilar lymph nodes or miliary pattern Condensation or infiltrate (with or without cavitation) that remains unchanged for > 2 weeks Condensation or infiltrate (with or without cavitation) for > 2 weeks, with worsening of symptoms or lack of improvement with the use of antibiotics for common germs (15 points)	Close contact within the past two years (10 points)	Induration between 5-9 mm (5 points)  Induration ≥ 10 mm (10 points)	Severe malnutrition (5 points)
Asymptomatic or symptomatic for < 2 weeks (0 points)	Condensation or infiltrate of any type for < 2 weeks (5 points)	Occasional or no contact (0 points)	Induration < 5 mm (0 points)	Weight ≥ 10th percentile (0 points)
Improvement in respiratory infection with the use of antibiotics for common germs or without the use of antibiotics (10 points)	Normal chest X-ray (5 points)			

TST: tuberculin skin test. Interpretation: ≥ 40 points (very likely diagnosis) → it is recommended that tuberculosis treatment be initiated; 30-35 points (possible diagnosis) → treatment should be initiated at the discretion of the physician; < 25 points (unlikely diagnosis) → further investigation of the child/adolescent should be undertaken.

used in clinical practice exponentially increase the risk of reactivation of tuberculosis in patients with LTBI. Anti-TNF-α biologic agents (anti-TNF-α antibodies and recombinant TNF-α-blocking proteins), which are mainly used in the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, are the most significant contributors to increasing the risk of LTBI progressing to active tuberculosis.<sup>(54,55)</sup> Nevertheless, the risks posed by other immunosuppressive agents, such as corticosteroids, methotrexate, and leflunomide, should not be overlooked.<sup>(56)</sup>

The WHO and the Brazilian National Ministry of Health differ in their lists of indications for investigation of LTBI (Chart 5).<sup>(4,53)</sup> There is currently no gold standard test for the diagnosis of LTBI, which is based not only on the

result of a diagnostic test but also on the exclusion of active tuberculosis. At present, the two methods that have been validated and are recommended in clinical practice are the TST and interferon gamma release assays (IGRAs). Both are imperfect and indirect methods, that is, they assess the response of an individual to exposure to mycobacterial antigens rather than detecting latent mycobacterial antigens in the body.<sup>(57)</sup> In addition, neither can predict disease progression nor differentiate latent from active tuberculosis.<sup>(58)</sup>

The TST is the oldest and most classically used method.<sup>(59)</sup> TST results reflect a delayed-type hypersensitivity reaction to the mycobacterial antigen, the standard positivity cutoff in Brazil being a 5-mm induration.<sup>(4)</sup>

Like the TST, IGRAs assess the cell-mediated immune response. However, unlike the TST, IGRAs assess this *in vitro* by measuring the IFN- $\gamma$  released by T lymphocytes in response to *M. tuberculosis*-specific antigens, overcoming the main limitations of the TST (BCG vaccination cross-reactivity and NTM infection).<sup>(53)</sup>

At present, the TST is the only method available via the Brazilian Unified Health Care System for the management of LTBI at public health care facilities. The only IGRA that is cleared by the Brazilian National Health Oversight Agency is QuantiFERON-TB (QFT; QIAGEN, Hilden, Germany). Although QuantiFERON-TB is approved by the Brazilian National Commission for the Incorporation of Technologies into the Brazilian Unified Health Care System, it is, at this writing, available only at private health care facilities and not at public ones, despite the fact that it has been cleared and is recommended by the Brazilian National Ministry of Health for use in the country.<sup>(4)</sup>

The advantages and disadvantages of the TST and IGRAs are well known and are summarized in Chart 6. The choice of which method to use should take into account the availability and accessibility of the methods.<sup>(53,60)</sup>

From a review of the literature and international recommendations, the following can be concluded:

- The TST and IGRAs can both be used as methods to diagnose LTBI, and the presence of active tuberculosis should be ruled out before recommending treatment for LTBI.
- There are insufficient data to recommend the use of either the TST or IGRAs as a first-line method to diagnose LTBI.
- Neither the TST nor IGRAs can predict LTBI progression to active tuberculosis.
- Neither the TST nor IGRAs can differentiate LTBI from active tuberculosis.
- BCG vaccination in childhood should not be a determining factor in deciding whether to use the TST, because it has a limited effect on the interpretation of TST results later in life.

Regardless of which method is used, individuals with documented TST or IGRA positivity should not be retested, even after a new exposure to *M. tuberculosis*.<sup>(4)</sup> That is because TST and IGRA results both reflect the response of an individual to previous exposure to mycobacterial antigens, rather than detecting mycobacterial antigens. Conversion of a TST or IGRA (from positive to negative) can occur as a result of intrinsic or drug-induced immunosuppression, errors in test administration, or

**Chart 5.** Indications for investigation of latent tuberculosis infection according to the Brazilian National Ministry of Health (NMH) and the WHO.

Indication	Brazilian NMH	WHO
Being a contact of an adult or child with pulmonary or laryngeal TB (in the past two years)	/	/
Being HIV-infected and having a CD4+ T-lymphocyte count $\geq 350$ cells/mm <sup>3</sup>	/	/
Being on a TNF- $\alpha$ inhibitor or a CCS (> 15 mg/day of prednisone or equivalent for more than one month)	/	/
Having fibrotic radiological changes suggestive of sequelae of TB	/	Not mentioned
Being a pre-transplant patient who is likely on immunosuppressive therapy	/	/
Having silicosis	/	/
Having head or neck cancer, lymphoma, or any other hematologic malignancy	/	Not mentioned
Being a cancer patient on immunosuppressive therapy	/	Not mentioned
Being a kidney failure patient on dialysis	/	/
Having diabetes mellitus	/	Not an indication
Having a low body weight (< 85% of ideal body weight)	/	Not an indication
Having an isolated calcification (without fibrosis) on chest X-ray	/	Not mentioned
Being a smoker ( $\geq 1$ pack per day)	/	Not an indication
Being a health professional or living or working in the prison system or long-term care institutions	/	/

TB: tuberculosis; and CCS: corticosteroid.

**Chart 6.** Advantages and disadvantages of the tuberculin skin test and IFN- $\gamma$  release assays.

TST	IGRAs
Requires complex training	Require simple training
Requires patients to return for the reading	Require just one patient visit for blood draw
Does not require special laboratory infrastructure	Require special laboratory infrastructure
Is inexpensive	Are expensive
Does not yield indeterminate results	Can yield indeterminate results
Is affected by BCG vaccination and NTM infection	Use <i>Mtb</i> -specific antigens

TST: tuberculin skin test; IGRAs: interferon gamma release assays; *Mtb*: *Mycobacterium tuberculosis*; and NTM: nontuberculous mycobacteria.

problems with the test. In the case of IGRAs, spontaneous conversion can reflect dynamic immunological processes, difficulties in the reproducibility of the test, or simply variations from person to person.<sup>(61)</sup>

## AUTHOR CONTRIBUTIONS

All authors participated in all stages of the development of this consensus statement, from conception to final approval.

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