Review

RESP

Recent advances in the diagnosis and management of tuberculosis infection and its application in prison inmates

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ABSTRACT

This review examines the current evidence on screening recommendations for *M. tuberculosis* infection (MTB), contemporary diagnostic approaches, and the indications and components of treatment-namely, who should be treated, when treatment is warranted, and which pharmacotherapeutic options are appropriate. To this end, World Health Organization (WHO) recommendations have been compiled, analyzing the changes introduced in recent years, particularly those following the development and implementation of a new class of MTB antigen-based skin tests.
In the therapeutic domain, the classical long-course isoniazid regimen (6-9 months) is subjected to a critical comparative appraisal against shorter rifamycin-based regimens. For this purpose, documents issued by the WHO and by major national and international guidelines and consensus statements have been reviewed. The review focuses particularly on screening, diagnosis, and treatment in the incarcerated population.

Key words: *Mycobacterium tuberculosis*; latent tuberculosis; diagnostic screening programs; prisons; antitubercular agents.

RESUMEN

Revisión que aborda la información disponible sobre recomendaciones de cribado de la infección por *Mycobacterium tuberculosis* (MTB), los actuales métodos diagnósticos y la indicación y el contenido del tratamiento: a quién tratar, cuándo y con qué fármacos. Para ello, se han recogido las recomendaciones de la Organización Mundial de la Salud (OMS), analizando los cambios introducidos en los últimos años, especialmente tras la aparición y el uso de una nueva clase de pruebas cutáneas basadas en antígenos de MTB.
En cuanto al tratamiento, se compara críticamente la pauta clásica (uso de isoniazida, en pautas de 6-9 meses) frente a las pautas más cortas basadas en rifamicinas. Con este objeto, se han revisado los documentos elaborados por la OMS y los de las principales guías y documentos de consenso, nacionales e internacionales. La revisión se ha centrado especialmente en el cribado, diagnóstico y tratamiento en la población reclusa.

Palabras clave: *Mycobacterium tuberculosis;* tuberculosis latente; programas de detección diagnóstica; prisiones; antituberculosos.

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INTRODUCTION

Tuberculosis (TB) is currently the main infectious cause of mortality worldwide[1]. 10.8 million persons contracted TB in 2023: 6 million men, 3.6 million women and 1.3 million children[2]. Spain, considered to be a country with low endemicity, reported levels of TB notification of 8.8 cases per 100,000 inhabitants in 2024, with an increasing incidence in recent years[3]. This rate is even greater in certain population groups such as prison inmates, where the incidence is estimated to be between 6 and 30 times higher[4,5].

It is also calculated that one fourth of the world's population is infected with *M. tuberculosis* (MTB)[6]. Tuberculosis infection (TBI) is a persistent state of a reaction by the immune system to previously acquired MTB antigens, with no evidence of active TB, hence the traditional term of "latent tuberculosis infection" for this condition. As is the case with TB, TBI is not uniformly distributed and groups such as inmates have a significantly higher prevalence than non-inmates, irrespective of the economic level[7], financial situation and national TB load of the country concerned[8]. A recent study of male and female inmates in Cataluña that used the conventional tuberculin test and interferon gamma release assays (IGRA) estimated that the prevalence of TBI in the Catalonian prison population was 25.2%[9]. In other words, this figure was about double the level for the Spanish general population 20 years ago[10] and, after applying current diagnostic criteria, which make comparisons more difficult, about half of what Catalonian inmates[11] and those of Spain in general[12] were found to have 10-15 years ago. Determining the magnitude of TBI is very important if one bears in mind that infected persons run a 5%-10% risk of reactivating TB throughout their lives[13-15], the majority in the first 5 years after being infected.

Guidelines for managing and responding to TBI, and possible treatment in medium/high income countries with incidence levels of TB <100 cases per 100,000 inhabitants, were published by the WHO in 2015[16]. The chapter on diagnosis was subsequently modified in September 2022 to include the use of a new class of skin tests based on MTB antigens for the first time[17,18], which we shall discuss below. In 2015, the WHO was already equating the utility of the classic regimen (isoniazid 6 or 9 months) to other shorter-acting approaches based on rifamycin (1 or 2 drugs) for TBI treatment, and highlighted the fact that most experts favoured the use of the latter regimen16. New evidence and studies have appeared since then. Are also scientific agencies and societies such as the CDC and the American Thoracic Society[19,20] have also expressed support, as did the Spanish Society of Respiratory Pathologies (SEPAR), the Society of Infectious Diseases and Clinical Microbiology and the Ministry of Health[21], which in a recent document recommended short courses as a first line of treatment. It therefore seems advisable to review this section as well if the guides that are commonly used do not match with this recommendation.

SCREENING FOR INFECTION

Screening recommendations

The WHO recommends systematic screening of TBI in some groups: persons infected with HIV, adults and children who have come into contact with someone who has pulmonary TB, patients commencing biologic therapy, patients undergoing renal replacement therapy, patients with silicosis and persons preparing for a transplant. It also recommends considering screening for healthcare workers, migrants from countries where TB is highly endemic, homeless persons, consumers of illegal drugs and prison inmates, depending on the local epidemiology and the resources available. In Spain, the 2019 Plan for the Prevention and Control of Tuberculosis in Spain[22], and the joint document drawn up by the scientific societies of the SESP, SEPAR and SEIMC[23] also recommends evaluating exposure to TB and TBI diagnosis for the inmates of Spanish prisons.

Diagnostic tests

Until recently, the tests available for diagnosing TBI were the convention tuberculin test (TT) and the IGRA, although a new diagnostic method was recently included: the C-Tb or Cy-Tb skin test, also known as Siiltibcy®, based on specific MTB antigens[17,18]. Other promising diagnostic options include immune biomarkers such as chemokine IP-10 induced by INF-γ[24,25] or cellular markers from flow cytometry[26].

The TT has long been the most widely used standard test, while the IGRA has been highly recommended by experts for its specificity[21,27], although its use has generally been limited to certain groups of patients (immunosuppressed patients, children under 5 years and persons vaccinated with BCG) and to some screenings in specific population[28]. The lower levels of use of IGRA are due to its high financial costs and because using it in community screenings can be complex, since not only does blood need to be extracted, but transport and conservation also require

careful management. IGRA tests are protocolised in Catalan prisons and are commonly used. However, its use in centres managed by the Ministry of the Interior appears to be more restricted[29,30]. The reason for this may be that the current "Program for the Prevention and Control of Tuberculosis in Prisons"[23] was prepared over 15 years ago and at that time the TT test was almost the only one to be recommended, although interpretation of its results can be unsafe in some situations. An example is using TT for screening migrant inmates, who are often vaccinated with BCG. This process is not very sustainable in countries with medium-high economic resources like Spain, since it implies the risk of: a) obtaining "false positive" results that can inflate infection[31,32]; b) recommending treatment for people who are not actually infected[32]; and c) a paradoxical increase in the economic impact, given that although IGRA tests are more expensive, some studies have found that there are medium-long term financial savings when IGRAs are used on populations such as migrants vaccinated with BCG[33,34] or on vaccinated persons in contact studies[34]. For this reason and for others[28], to improve recommendations in force and adapt them to current evidence, our group[30] and other professionals[29] have called for updates of the current Program of Prevention and Control of TB in prisons, which has been very useful for many years and has helped to control TB in prisons. However, we now feel that the program urgently requires revision.

Inclusion of C-Tb (Siiltibcy®) to diagnosis of infection

Studies with C-Tb, also known as Cy-Tb, commenced more than 25 years ago, while the first data published in the literature appeared about 10 years later[35,36]. However, the approval and definitive marketing of this test, which is now known as Siiltibcy®, took place quite recently in 2022 in India and in 2024 in the European Union[37]. It is a skin test based on the antigens rdESAT-6 and rCFP-10, used to diagnose MTB infection, including detection in persons with TB. The use of specific MTB recombinant antigens eliminates crossed reactivity with the BCG vaccine and other mycobacteria that are different from MTB. This test, however, cannot be used as an independent tool for TB diagnosis. Radiological studies and other diagnostics methods should also be considered alongside the risk evaluation for subjects who are suspected of having the disease[38].

Siiltibcy® was recently marketed in Spain as an injectable solution (Figure 1) and should be administered by a health professional via an injection into the skin of the forearm, using the Mantoux technique. When it is administered to a person infected with MTB, the type 1 T helper cells (T_H1) of the skin are stimulated by rdESAT-6 and rCFP-10, releasing cytokines that cause a delayed hypersensitivity reaction in the form of a measurable induration after 48-72 hours. If the size of the induration is ≥5 millimetres between 48 and 72 hours after the injection, then there is an infection. The positive threshold is universal, i.e., it is similar in all types of patients and scenarios. It is important to point out that carrying out a test in the 6-8 weeks after being exposed to MTB may give a false negative. False positives may also appear if the test is repeated less than 6 weeks after the first one, so there should an interval of over 6 weeks before repeating any tests. This point is particularly important for screening programs or conventional contact studies[38].

Knowledge about the efficacy and safety of Siiltibcy® is based on data from three phase III trials[39-41], which included 2,625 adults and children. The data were compared with TT tests and QuantiFERON-TB Gold in-Tube® (QTF). Two of the studies included persons who had never been exposed to MTB or who were strongly suspected of having TB[39,40], while the third study included patients with confirmed TB[41]. The findings showed that as exposure to MTB increased, so did the likelihood of the test providing a positive diagnosis. The sensitivity of Siiltibcy® was similar to the IGRA tests and slightly lower than the TT test, while its specificity was slightly better than the TT and the QTF. Table 1 shows the data on the sensitivity and specificity of the three diagnostic tests obtained in the trials, in the entire population that was analysed and in groups of patients considered to be important.

As regards safety, the technical sheet[38] shows the adverse effects, which were slight and generally

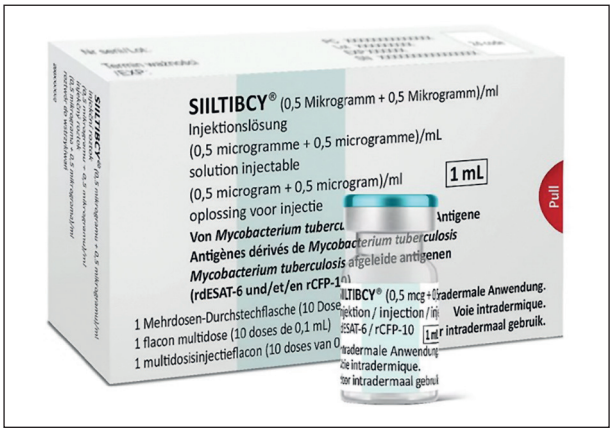

Figure 1. Graphic image of Siiltibcy® recently marketed in Spain.

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Table 1. Sensitivity and specificity of Siiltibcy®, the conventional tuberculin test and the QuantiFERON-TB Gold in-Tube®, overall and in some groups of patients as observed in three pivotal trials of Siiltibcy®[30-32].

	Siiltibcy® n (%)	TT* n (%)	QTF† n (%)
Sensitivity (population with confirmed TB‡)			
In general	808 (74.1)	780 (85.8)	905 (71.1)
Infected by HIV§	213 (67.6)	210 (78.1)	242 (64.9)
Not infected by HIV	566 (76.5)	541 (88.5)	648 (73.2)
BCG‖ positive	353 (75.1)	330 (81.8)	402 (69.2)
BCG negative	73 (75.3)	65 (92.3)	77 (77.9)
Minors (0-17 years)	36 (75.0)	36 (77.8)	18 (72.2)
Specificity (negative control population)			
In general	513 (94.7)	463 (91.1)	512 (92.6)
Infected by HIV	NA	NA	NA
Not infected by HIV	305 (93.1)	289 (90.3)	304 (89.8)
BCG positive	354 (94.6)	354 (90.7)	353 (91.5)
BCG negative	154 (97.4)	104 (96.2)	154 (96.8)
Minors (0-17 years)	104 (83.7)	101 (85.1)	102 (76.2)

Note. *TT: conventional tuberculin test; †QTF: QuantiFERON-TB Gold in-Tube®; ‡TB: Tuberculosis; §HIV: Human Immunodeficiency Virus; ‖BCG: Bacillus Calmette-Guèrin; ¶NA: not available.

local (itching, pain and/or hematoma, mainly at the injection site) and easily managed. Other practical comparative aspects of interest (active ingredient, storage, shelf life of vial, excipients, etc.) are shown in Table 2.

TREATMENT OF INFECTION

To achieve the objectives in the "End TB Strategy"[42] proposed by the WHO, it is essential to eliminate the TBI reservoir, given that if this does not happen, ending TB will not be a feasible option. It is estimated that TBI progresses to a disease in 5-10% of infected subjects[13-15] and in countries with a low incidence the endogenous reactivation of a past infection is the main cause of the appearance of new cases. The risk of progression depends on a range of factors, such as the immune status, the age of the infected person and the time from when infection took place. The risk is greater in the first two years after infection and high in the first five years, after which it drops. Diagnostic tests do little to identify the risk, since neither the intradermal or IGRA tests differentiate between recently infected persons and those infected some time ago, not even amongst infected individuals or active TB cases. Therefore, the first measure to be taken in a case of TBI is to rule out TB and if there is, prevent the risk of transmission, treat disease and check for transmission with a conventional contact study. If no TB is present, treatment of TBI should be assessed.

Recommendations for treatment and possible regimens

Treating all infected persons means treating 90-95% of patients who will not progress. Therefore, as some experts have suggested[28], we are faced with a dilemma: treating the largest number of infected subjects to have a greater impact on controlling TB, or focusing efforts on recently infected persons and high-risk groups, which are cases in which treatment has been shown to be clearly cost-effective. These groups are children under 2 years of age, recent converters, persons in close contact with a person who is shedding TB bacilli, immune-suppressed persons, patients with fibrotic pulmonary lesions, and persons who are going to receive biologic treatment or preparing for a transplant.

The regimens currently used to treat TBI have levels of efficacy that vary between 60% and 90%[43]. One or two antibiotics are normally prescribed, given that resistance to medication is unlikely due to the small number of viable bacteria in such cases. The most widely used treatment is isoniazid in regimens of 6-9 months. This particular drug is recommended

Table 2. Features distinguishing conventional TT, Siiltibcy® and IGRA.

Variables	Diagnostic tests		
	TT*	Siiltibcy®	IGRA†
Active principle	RT-23 Purified protein derivative 0.6 ug	0.5 ug rdESAT-6 Recombinant dimer of *Mycobacterium tuberculosis* early secretory antigenic target plus 0.5 ug rCFP-10 Recombinant culture filtrate protein of *Mycobacterium tuberculosis*	0.5 ug rdESAT-6 Recombinant dimer of *Mycobacterium tuberculosis* early secretory antigenic target
Excipients (with known effect)	Polysorbate 80 Hydrogen phosphate of disodium dihydrate = 0.76 mg potassium dihydrogen phosphate = 0.145 mg Potassium sulphate of hydroxyquinoline = 10 ug Sodium chloride = 0.48 mg	Polysorbate 20 = 0.011 mg Hydrogenated disodium phosphate dihydrate (E339) Dihydrogen potassium orthophosphate (E340) Potassium chloride (E508) Sodium chloride Phenol	
Administration	Intradermal skin test	Intradermal skin test	Blood analysis
1 dose	0.1 ml = 2 TU§ = 0.04 ug RT23	0.1 ml = 0.05 ug rdESAT-6 and 0.05 ug rCFP-10	
Vial	2 TU/0.1 ml. injectable solution (10 doses)	(0.5 ug rdESAT-6 + 0.5 ug rCFP-10)/ml injectable solution (10 doses)	
Shelf life unopened vial	3 years	2 years	
Shelf life opened vial	Maximum 24 hours between 2ºC and 8ºC	28 days between 2ºC and 8ºC	
Storage	Between 2ºC and 8ºC	Between 2ºC and 8ºC	Before collection, keep at 4-25ºC
Contents of container	1 vial contains 10 doses of 0.1 ml	1 vial contains 10 doses of 0.1 ml	Several sizes of container in the market
Target population	Adults Paediatric Suitable for pregnant women	Adults Paediatric (> 28 days) Suitable for pregnant women	
BCG vaccine	Can give false positives	Not affected by BCG‖ vaccine	Not affected by BCG vaccine
Price	1.7 euros/dose	4-5 euros/dose	30 euros/dose¶

Note. *TT: conventional tuberculin test; †IGRA: interferon gamma release assay; §TU: Tuberculin unit; ‖BCG: Bacillus Calmette-Guèrin.
¶Average agreed price, although it may be slightly higher or lower due to specific purchasing agreements.

in the 2019 Plan for the Prevention and Control of Tuberculosis in Spain[22]. However, the duration of treatment, hepatotoxicity and frequent non-compliance have traditionally been obstacles in applying this treatment. Furthermore, most guides and recommendations (WHO[16,44], CDC, American Thoracic Society[19,20], SEPAR, SEIMC and the Spanish Ministry of Health[22]) strongly encourage[16,44] or recommend[19,20,22] the use of shorter regimens based on rifamycin, which are just as effective as treatment with isoniazid, but involve a lower risk of toxicity and better rates of treatment completion, thus increasing their effectiveness[20]. According to the WHO, these regimens are preferred by clinicians and patients[44]. This is especially important if one bears in mind that the rate of completion for TBI treatment is initially suboptimal in some groups such as prison inmates and the use of regimens that are more attractive to inmates

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and increase compliance levels has been suggested to improve the situation[45].

The potential disadvantages of regiments based on rifamycin include interactions with other drugs such as warfarin, oral contraceptives, azole antifungals, many antiretroviral drugs and opiate agonists (methadone and buprenorphine)[46]. The number of drug users and HIV+ inmates is higher, and therefore there is an increased use of antiretroviral drugs and maintenance therapy with opiate agonists. When this happens, the most recommendable option is to use the conventional regimen with isoniazid, which presents a better profile for drug interactions.

Table 3 shows a summary with the main recommendations for treating TBI, including the agency or society that recommends it and if the regimen is defined as the first choice or as an alternative approach.

CONCLUSION

The European Medicines Agency recently approved C-TB (Siiltibcy®)[47], as it is regarded as an alternative to the tests available to date. When compared to C-TB, IGRA tests have their advantages and disadvantages. They are faster (results in less than 24 hours), with extremely valid results (there are no errors in administration or interpretation), very consistent (repeating the test does not alter the outcome) and involves less work (visits/patient). But it is also true that Siiltibcy® is comparable in terms of sensitivity and specificity, is much more economical, does not need a laboratory and is easier to use in large screenings. When compared to TT tests, which have been the most widely used approach, Siiltibcy® has the advantage of a universal positivity threshold (5 mm for all patients) and, above all, it avoids false secondary positives from appearing from BCG vac-

Table 3. First choice regimens or alternatives in treating tuberculosis infection according to the WHO[44], the CDC[20] and the National Tuberculosis Control Plan in Spain[21].

Drug(s) used in regimen	Duration	Dosage/weight	Frequency	Total doses	Type of regimen
INH* +Rp†	3 months	a) Rp: 10.0-14 Kg: 300 mg 14.1-25 kg: 450 mg 25.1-32 kg: 600 mg 32.1-50 kg: 750 mg b) INH: >12 years: 15 mg/kg; 900 mg max. 2-11 years: 25 mg/kg; 900 mg max.	Weekly	12	First choice for CDC‡ [20] and WHO§ [44]. Recommended in DOT‖.
INH+R¶	3 months	a) R: Children: 15-20 mg/kg; 600 mg max. Adults: 10 mg/Kg 600 mg max. b) INH: Children: 10-20 mg/kg 300 mg max. Adults: 5 mg/Kg 300 mg max.	Daily	90	First choice for CDC[20], WHO[44] and y SEPAR** / SEIMC†† /Spanish Ministry of Health[21] due to better adherence, identical efficacy and no higher toxicity[20]. Alternative for NTP‡‡ [21]
R	4 months	Adults: 10 mg/Kg Children: 15 mg Habitual: 600 mg	Daily	120	First choice for CDC[20] and alternative for WHO[44] and NTP[21].
INH	6 o 9 months	Adults: 5 mg/Kg Children: 10 mg Habitual 300 mg/day	Daily	180 o 270	First choice for NTP[21] and WHO[44]. Less preferred by the WHO. Alternative for the CDC[20].

Note. *INH: isoniazid; †Rp: Rifapentine (not marketed in Spain); ‡CDC: Centers for Disease Control and Prevention; §WHO: World Health Organization; ‖DOT: directly observed therapy; ¶R: rifampicin; **SEPAR: Spanish Society of Pulmonology and Thoracic Surgery; ††SEIMC: Spanish Society of Infectious Diseases and Clinical Microbiology; ‡‡NTP: National Tuberculosis Plan.

cination, which is an important drawback with the classical TT test.

The most widely used treatment for TBI has traditionally been isoniazid for 6-9 months, although international scientific evidence has recently recommended[20,44] using treatments based on rifamycin (one or two drugs) in short regimens. As commented above, this approach is equally effective but less toxic and the shorter duration of treatment makes it more attractive, with a positive impact on treatment compliance and effectiveness. There are guides that recommend their use[48] and they are now recommended by experts in Spain[21].

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