Tuberculosis: How to screen for tuberculosis before and during biologic treatment?

This chapter is based on the previous chapter [1,2]. A systematic search was conducted, details of which can be found in the Methods & Evidence Report**.**

Results/Answer:

Current guidelines and recommendations for screening for tuberculosis (TB) vary between countries and specialties. There are variations in the recommended diagnostic tests, cut off values, follow up and preventive therapy regimens. A uniform approach for the diagnostic procedures and the interpretation of the test results for (latent) tuberculosis infection (LTBI) screening may reduce the cases of (re)activation/worsening, but binding pan-European recommendations are partly hampered by different regional regulations. For recommendation for which treatment TB screening is recommended, please see respective drug chapters.

We **recommend** screening for tuberculosis according to local regulations.	↑↑	
For pre-screening, we **recommend** taking a thorough patient history including tuberculosis history; a chest X-ray; TST and/or IGRA.	↑↑	STRONG CONSENSUS[1] 
We **recommend** remaining alert to the possibility of tuberculosis infection during therapy. This includes taking medical history and might include tuberculosis testing.	↑↑	EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

Tuberculosis screening

Diagnostic for TB, regardless Bacillus Calmette-Guérin (BCG) vaccination, prior to and during follow up with biologic. One must be alert for TB infections before, during biologic treatment and up to six months after discontinuation. During treatment, rescreening for LTBI is recommended and frequency should be based on: patient history, risk of exposure, as well as tuberculin skin test (TST) and interferon gamma release assay (IGRA) results.

1. Patient history:
    - Symptoms suspicious for TB
    - History of TB, adequate treatment
    - Exposure to TB
    - Origin from or recently stayed for a long time in an endemic area
    - High risk patient
    - BCG vaccination

2. Physical examination, to consider:
    - Auscultation of the lungs if symptomatic (not-specific for TB diagnosis)
    - Scar (left) upper arm (may indicate a BCG vaccination)
    - Enlarged lymph nodes, abscess scars

3. Chest X-ray: (If the chest X-ray has been performed more than 3 months ago, a new chest X-ray is required.)
    - Suspicious for active, LTBI or history of TB?
        → Consult pulmonologist if abnormalities

4. TST* and/or IGRA
    - If IGRA and TST are performed, the IGRA can best be drawn right after the TST is assessed. If drawing is done more than three days after the TST, the TST can booster the IGRA and result in a false-positive response.
    - The recommendation to perform IGRA testing rather than TST testing is strong for those who have received the BCG vaccination.

* It is necessary to follow the local recommendations, as the threshold for the TST is different among countries and even among regions within the same country. In most of the countries ≥ 5 mm is considered positive.

TST*	IGRA	Diagnosis	Policy
< 5 mm	negative	Depends on patient history	- If no TB suspicious patient history or symptoms, no history of TB, no TB exposure, no living in or travel to endemic area, and no high-risk patient, a biologic can be given. - If yes: Consult pulmonologist for any further diagnosis and treatment - TB infection can still be present in HIV-infected patients with a low CD-4 count
≥ 5 mm < 10 mm	negative	LTBI or active TB with false negative IGRA, or false positive TST	Consult pulmonologist for any further diagnosis and treatment
> 10 mm	negative	Strongly consider LTBI or active TB with false negative IGRA, or false positive TST	Consult pulmonologist for treatment
Every result	QFT-G 0.2-0.35 U/ml	Consider LTBI or active TB, or IGRA false positive	Consult pulmonologist for any further diagnosis and treatment
Every result	Positive (QFT-G > 0.35 U/ml)	Strongly consider LTBI or active TB	Consult pulmonologist for treatment

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Tuberculin skin test (TST)

False negative TST include those related to the protein purified derivative (PPD) (PPD expiration, experience or loss of antigen [e.g. subcutaneous administration]), and those related to the situation of the patient (HIV infection, recent infections and vaccinations, malignancy, metabolic diseases, immuno-suppressant therapy, or extreme ages [newborn, elderly]). False positive TST include those related to the administration and PPD lecture (inexperience, high amount of antigen), and cross-reactions (BCG vaccination, and most environmental nontuberculous mycobacteria). Although a BCG-vaccination or an atypical mycobacterial infection may cross-react with the TST, causing a false positive result, the tuberculin reaction would usually be much higher if active TB is truly present. The BCG vaccination may fade over time and no cross-reaction would occur. Regardless the BCG vaccination, in general, an assessment of ≥ 5 mm induration will be considered as positive. A patient may then be

referred directly to a pulmonologist. In patients with a history of BCG vaccination, IGRA testing is preferred over TST.

IGRA

IGRA is a specific blood test. After a *Mycobacterium Tuberculosis* infection, T cells will release interferon-gamma (IFN-γ) in response to contact with the TB antigens. Two measurements for interferon-gamma are known; the QuantiFERON®-TB Gold-test (QFT-G), based on the amount of IFN-γ that is released in response to the antigens, and the T-SPOT® TB test (T-SPOT), counting the number of T cells that produce IFN-γ in a sample of blood. The IGRA is not affected by prior BCG vaccination, however the interpretation of results (borderline results) might be limited due to issues in the cut-off values, shifting conversions and reversion rates over time, and varying test reproducibility. Neither TST or IGRA allow to distinguish between active or latent TB [3]. A suppressed immune system reduces the sensitivity of tests based on T cell responses. Only positive results will be convincing in that case, while negative results cannot rule out a TB infection. A negative IGRA, following a positive TST, can still suggest a LTBI. Besides, the IGRA can be unreliable (false negative) if other immunosuppressive medications were applied in advance. An IGRA is also recommended if the TST was less than 5 mm in induration. Negative results of TST or IGRA of HIV-infected patients with a low CD-4 count cannot rule out a TB infection.

Screening during biologic treatment

Physicians have to be aware that there is still a risk of active tuberculosis under biologic therapy, even if LTBI was correctly treated. Therefore, LTBI rescreening is preferable during biologic treatment. The frequency should take risk exposure into consideration. Besides medical history, both TST and IGRA are recommended, because of the influence that the biologic may have (false-negative) on these tests. A high index of suspicion should also be maintained for six months following discontinuation.

References

1. Nast A, Gisondi P, Ormerod AD *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 2277-94.
2. Nast A, Spuls PI, van der Kraaij G *et al.* European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology: JEADV* 2017; **31**: 1951-63.
3. Lewinsohn DM, Leonard MK, LoBue PA *et al.* Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis* 2017; **64**: 111-5.