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

This chapter is based on the corresponding chapter in the previous versions of the guideline. [1-3]. A search was conducted, details of which can be found below**.**

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 recommendations for which treatment TB screening is recommended, please see respective drug chapters.

We **recommend** screening for tuberculosis according to local regulations.	↑↑	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS
For pre-screening, we **recommend** taking a thorough patient history including tuberculosis history; a chest X-ray; TST and/or IGRA.	↑↑	
We **recommend** remaining alert to the possibility of tuberculosis infection during therapy. This includes taking medical history and might include tuberculosis testing.	↑↑	

[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 and risk of exposure.

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 a chest X-ray has been conducted **in the past**, the decision to repeat the X-ray should be based on the psoriasis treatment selected, time since the last x-ray, the patient's risk profile, potential exposure or local guidelines.
    - Suspicious for active, LTBI or history of TB?

    → consult pulmonologist if abnormalities

4. TST* and/or IGRA
    - If IGRA and TST are both 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

* 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.

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 [4]. 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.

Review of the evidence on psoriasis and tuberculosis

What was the aim of this review?

The aim of this review was to inform the guideline development group about new evidence on the risk of tuberculosis (TB) in patients with psoriasis vulgaris who are about to be treated with a therapy other than TNFis. The goal was to potentially update the chapters on tuberculosis screening and tuberculosis management.

Research questions

1. Which antipsoriatic drugs (other than TNFi) are associated with a risk of activating latent tuberculosis?
2. How to screen for tuberculosis during biologic treatment?

The second research question will be addressed in the next update of the guideline.

Screening criteria

	Inclusion criteria	Exclusion criteria
Patients	Adult patients (psoriasis, psoriasis arthritis, inflammatory bowel disease, ankylosing spondylitis, rheumatic disease, rheumatoid arthritis or autoimmune disease) with primarily positive Quantiferon test (or equivalent) or Tuberkulin skin test in screening prior to initiation of immunsuppressive therapy and consecutive exclusion of active TB Secondary: Studies reporting TB activation as an adverse event in a population that did not have a positive quantiferone test, Studies reporting on efficacy and safety of TBC prophylaxis	Children Animal studies
Intervention	**conventional systemic treatment:** acitretin, apremilast, ciclosporin, fumarates, methotrexate **biologicals:** anti-IL12/23: ustekinumab anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab anti-IL23: guselkumab, risankizumab, tildrakizumab tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new))	

	Inclusion criteria	Exclusion criteria
Comparator	For RCTs: another included drug and/or placebo If TNFi is comparator, include as single-arm study or case series	
Outcomes	Cases of activation of tuberculosis (symptoms, tests) with or without TB prophylaxis	
Study Design	Primary: Systematic reviews	non-systematic reviews in-vitro studies expert opinions without primary data letters (if of narrative character or expert opinion only) randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies, letters (if primary data is presented)

Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for all entries up until February 27, 2023. The full search strategy is shown below. Two methodologists conducted a topic specific screening of all identified systematic reviews (for filter see chapter “Search strategy”) independently. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria by one methodologist and cross-checked by another one.

Methodological quality assessment

The AMSTAR-2-Tool was used for all systematic reviews, that were included following title and abstract screening and had a “prioritized study design”and an “adequate research question”.

Search strategy (28.02.2023)

Filter for identification of systematic reviews and meta-analysis: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. (https://pubmed.ncbi.nlm.nih.gov/17082841/) (high specificity strategy)

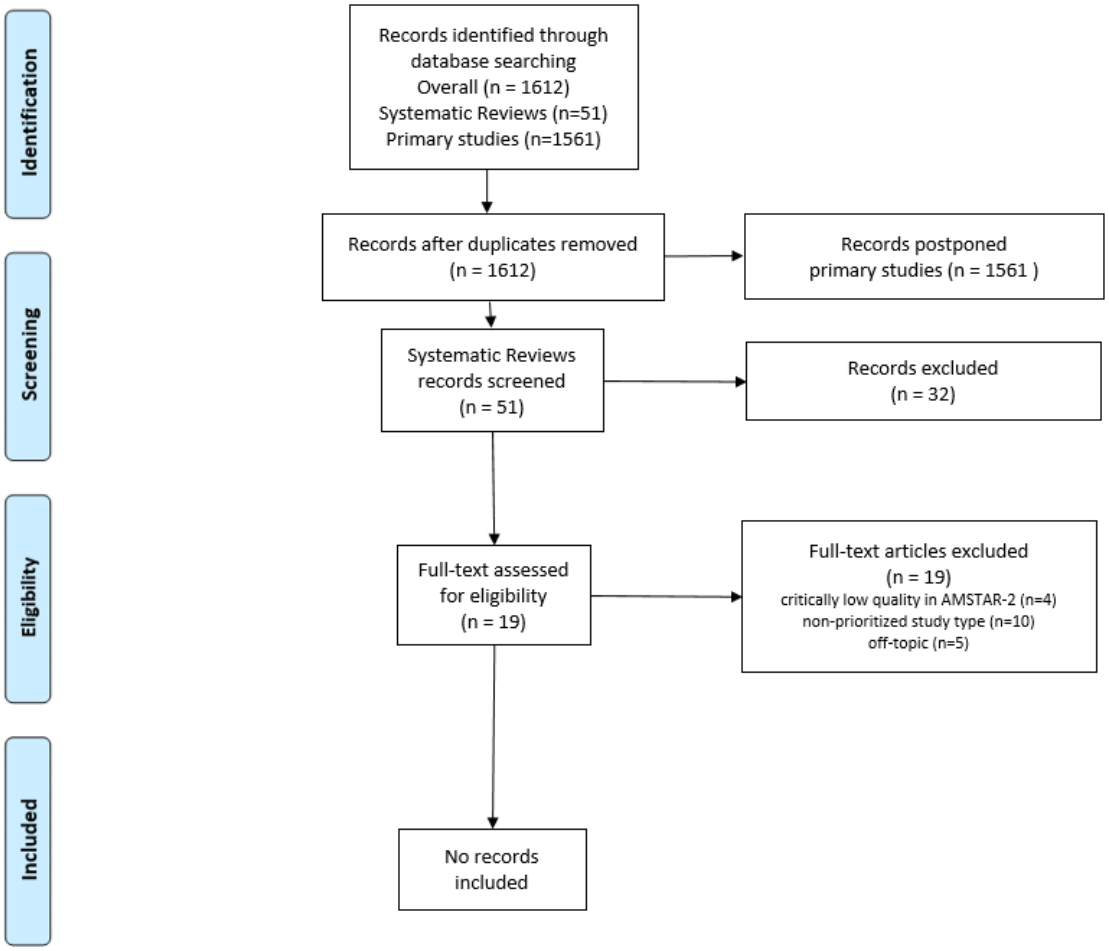
Ovid-Link:
https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=4FP9vLrBf5mn1kqAkmV2x36pXm8QJXaWSatEThFz5bNdnPa5uPaRBT6jhSVjgpAiB

Ressource: Ovid MEDLINE(R) ALL <1946 to February 27, 2023>

No.	Search term	Result
1	exp Methotrexate/	40965
2	methotrexate$.mp.	59783
3	amethopterin.mp.	401
4	mtx.ti,ab.	14675
5	exp Fumarates/	5336
6	(fumar$ and esters).mp.	471
7	dimethylfumarate.mp.	207
8	fae.ti,ab.	1026
9	dmf.ti,ab.	9775
10	fumarate$1.mp.	20919
11	Acitretin/	1291
12	acitretin.mp.	2033
13	Ustekinumab.mp.	3013
14	secukinumab.mp.	1877
15	apremilast.mp.	1037
16	guselkumab.mp.	536
17	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30204
18	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1902
19	Cyclosporine/	30502
20	(Ciclosporin* or cyclosporin*).mp.	61734
21	brodalumab.mp.	511
22	ixekizumab.mp.	949
23	tildrakizumab.mp.	249
24	bimekizumab.mp.	110
25	risankizumab.mp.	347
26	deucravacitinib.mp.	52
27	TYK2 Kinase/	615
28	(TYK2 or "tyrosine kinase 2").ti,ab.	2152
29	**or/1-28**	**188571**
30	exp Tuberculosis/	204867
31	Tuberculos*.ti,ab,kf.	234862
32	Mycobacterium tuberculosis/	56817
33	(TB or Tbc).ti,ab,kf.	72949
34	ltbi.ti,ab,kf.	2993
35	**or/30-34**	**300757**
36	cochrane database of systematic reviews.jn. or search.tw. or meta analysis.pt. or MEDLINE.tw. or systematic review.tw.	667197
37	exp animals/ not humans.sh.	5097167
38	29 and 35	2037
39	38 not 37	1612
40	**36 and 39**	**51**
41	**39 not 40**	**1561**

Results

Our update search yielded 1612 citations. No systematic reviews fulfilled the inclusion criteria. The detailed findings are presented in the PRISMA diagram provided below:



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. *J Eur Acad Dermatol Venereol*. Dec 2015;29(12):2277-94. doi:10.1111/jdv.13354
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*. 2017/12 2017;31(12):1951-1963. doi:10.1111/jdv.14454
3. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 2: specific clinical and comorbid situations. *Journal of the European Academy of Dermatology and Venereology : JEADV*. Feb 2021;35(2):281-317. doi:10.1111/jdv.16926
4. 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*. Jan 15 2017;64(2):111-115. doi:10.1093/cid/ciw778