PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines
AUTHORS	Hasan, Tasnim; Au, Eric; Chen, Sharon; Tong, Allison; Wong, Germaine

VERSION 1 – REVIEW

REVIEWER	Peter Auguste University of Warwick Warwick Medical School
REVIEW RETURNED	12-Apr-2018

GENERAL COMMENTS	The manuscript is well written and presented, and follows the best practice guidelines for reporting systematic reviews. Below are a few comments/queries:- It is unclear if the methodological quality was assessed by two reviewers independently or if one reviewer undertook the quality assessment and the other cross-checked. It would have been useful to know if any guidelines included a formal cost-effectiveness and what did these results show. Did the authors exclude guidelines that included more than one population (e.g. children and immunocompromised/immunosuppressed)? I am surprised that the search did not identify any National institute for health and care excellence (NICE) guidelines around this topic. Page 11 line 4 suggests that six guidelines supported TST. However, seven references are provided. The authors suggest that there is a clear need for the development of a comprehensive and high quality guideline. However, the evidence-based used to develop these guidelines may be scarce and of poor quality. Hence, efforts should be focused on undertaking better quality studies.

REVIEWER	Albert Nienhaus University Clinics Hamburg Eppendorf
REVIEW RETURNED	15-Apr-2018

GENERAL COMMENTS	The authors provide a review on guidelines covering LTBI management in immunosuppressed patients. In total, they identified 36 guidelines in English. 12 non-English guidelines were excluded. The quality of the guidelines was assessed using the AGREE II

	instrument. Most guidelines advocated LTBI screening in immunosuppressed using either TST or IGRA or a combination. INH was the most often mentioned treatment of LTBI. The quality of the guidelines was divers. The review is well performed and the paper is very structured. The findings are interesting and in the scope of the journal. Some minor comments might further improve the paper. 1 Is PsychINFO a relevant source? Don't they cover psychology papers mostly? 2 Prevention und prophylaxis. I am used to distinguish between prevention and prophylaxis. Prophylaxis is when you treat LTBI without knowing whether LTBI is present (small children after contact) Prevention is when you treat LTBI after a positive TST or IGRA and the exclusion of active TB. However, this might be a distinction not shared by everybody. Please consider using prevention of prophylaxis throughout the paper. 3 Strengths and Limitations. Bullet point 4 is a bit confusing. I propose to write 36 guidelines were included instead of found. And I would give the number of non-English guidelines excluded (n=12) 4 Was there a time trend for the scores in AGREE? If this information were available, it would be useful to see whether in general thinks are improving. 5 Did the guidelines discuss the problem that sensitivity of TST decreases with extent of immunosuppression? May be you could briefly comment on this. 6 Why was Taylor et al (CDC 2005) included? There population were HCW. Do they have a relevant chapter on immunosuppressed HCWs? Typos Page 5, line 43: may lead to (no comma needed) Page 13, line 41: 300 mg, line 51 10 mg/kg/day Page 16, line 30-31. Please check sentence. I think it should be "...agreed that treatment of LTBI …." Thank you for the opportunity to read this interesting paper.

REVIEWER	Judith Bruchfeld Unit of Infectious Diseases, Department of Medicine Solna, Karolinska Institutet, Stockholm Sweden
REVIEW RETURNED	15-Apr-2018

GENERAL COMMENTS	This article presents a review of published guidelines on TB screening prior to immunesuppression. The subject is timely and of clinical and public health interest given the increasing number of individuals with immunesuppresive conditions and or/treatment both in TB low and high endemic settings. Major comments: Please include in introduction and discussion a section on the nature of subjectivity in guidelines regarding TB in screening prior to/ongoing immunesuppresion. The lack of a golden standard in the diagnosis of latent TB influences both available evidence and interpretation of current diagnostic methods and therefore also subsequent mode of action. Adherence to guidelines may also be influenced due to this problem. Please discuss and recommend possible ways to improve the current evidence for screening practices. Minor comments 1. Check the commas in sentences throughout the ms, not inserted

	correctly in several sentences 2. Page 5 Line 36 Quantiferon Plus should be added line 36 3. Page 5 Line 46 Problems with indeterminate results in immunusuppressed patients are common and should be mentioned (usually due to lack of reactivity in positive control= anergy) and where IGRAs offer an advantage compared to TST as anergy can be assessed due to the inclusion of a positive control. 4. ECDC 2011 recommends a combination of TST and IGRA in immune-suppression, please check the guideline. 5. Page 13 line 10 Heading should say Latent TB infection (omit the s) 6. Page 13 Line 21 ”Indicted”, should be ”indicated” 7. Page 13 Line 43 Both interventions? (pyridoxin is not an intervention, it is given to substitue for B6 deficiency caused by INH) 8. Page 17 Line 28 ”Most screening practices recommended combinations of TST and IGRA.” Is this correct? Stated previously as recommended in 7 guidelines i e not the majority. 9. Page 17 Line 30 The sentence ”the TST is a relatively sensitive but not specific test, in particular among high risk and immunosuppressed individuals” can be misinterpreteted-as it reads now can be interpreted as the TST is less specific among immunosuppressed individuals. Is there anything to prove this statement? Furthemore sensitivity may be reduced in immunsuppression, e.g. if concomitant steroid treatment is given.This should be clarified.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
It is unclear if the methodological quality was assessed by two reviewers independently or if one reviewer undertook the quality assessment and the other cross-checked.
As stated, we have now clarified that

“The methodological quality was assessed independently by TH and EA… The Appraisal of Guidelines for Research and Evaluation (AGREE) scores were rated independently for each guideline by TH/EA and a quadratic weighted kappa (κ) score for each guideline and across all guidelines were calculated as a measure of inter-rater agreement.” (page 6-7)

It would have been useful to know if any guidelines included a formal cost-effectiveness and what did these results show.
Only the NICE guidelines provided details of a formal economic evaluation on both screening and treatment of LTBI. Very few guidelines discuss any cost implications in relation to screening and treatment for LTBI. Indeed, the lack of cost considerations is a limitation of the guidelines available, and this was discussed in the original manuscript. In addition, the following statement has been included:

“Only one guideline included a formal cost-effectiveness analysis1 which suggested that TST was more cost effective compared to the IGRA. The incremental cost-effectiveness ratio (ICER) was influenced by prevalence of disease and age of the patients.” (page 8)

Did the authors exclude guidelines that included more than one population (e.g. children and immunocompromised/immunosuppressed)? I am surprised that the search did not identify any National institute for health and care excellence (NICE) guidelines around this topic.
We have included guidelines that focussed on more than one at risk populations.2-7 We have now

also incorporated the NICE guidelines as suggested.

The authors suggest that there is a clear need for the development of a comprehensive and high quality guideline. However, the evidence-based used to develop these guidelines may be scarce and of poor quality. Hence, efforts should be focused on undertaking better quality studies.
The need for better quality studies is noted as one of the limitations of the guidelines available. As suggested, we have updated the conclusion to reflect this:

"Quality of evidence and rigor of guideline development varied. Therefore, there is a need to undertake better quality studies, with international, multidisciplinary and stakeholder involvement to consolidate current evidence. This is critical to support evidence-based clinical guidelines and patient-centred practice to improve patient outcomes." (page 19)

Reviewer: 2
Is PsychINFO a relevant source? Don't they cover psychology papers mostly?
We searched PsycINFO to be comprehensive – in the chance that the database included guidelines focussed on the psychosocial or behavioural aspects related to screening and management of TB. The search in PsycINFO did not yield any additional guidelines.

Prevention und prophylaxis. I am used to distinguish between prevention and prophylaxis. Prophylaxis is when you treat LTBI without knowing whether LTBI is present (small children after contact) Prevention is when you treat LTBI after a positive TST or IGRA and the exclusion of active TB. However, this might be a distinction not shared by everybody. Please consider using prevention of prophylaxis throughout the paper.
As suggested, we have revised the wording to 'prevention' instead of prophylaxis for the active TB infection (please see highlighted in yellow).

Was there a time trend for the scores in AGREE? If this information were available, it would be useful to see whether in general things are improving.
We have reviewed the AGREE scores and found that there was no time trend in the improvement of the AGREE scores. As suggested, we have now added the following statement:

"The AGREE scores did not improve with later guidelines and over time." (Page 9)

Did the guidelines discuss the problem that sensitivity of TST decreases with extent of immunosuppression? May be you could briefly comment on this.
The test performance characteristics of TST as a screening test for latent TB in immunosuppressed patients, was only discussed in 12 guidelines. As suggested, we have provided a sentence to describe the current evidence on the diagnostic accuracy of TST in immunosuppressed host in the discussion.

"TST generally performs poorly in immunosuppressed patients, with reported estimates of 89% and 71% for test sensitivity and specificity, respectively.5 The lower test specificity may be due to the cross-reactivity with prior BCG vaccination8,9 and infections with non-TB mycobacteria…Test sensitivity of TST and IGRA is uncertain or may be reduced among immunosuppressed hosts because of anergy.10" (page 17)

Why was Taylor et al (CDC 2005) included? There population were HCW. Do they have a relevant chapter on immunosuppressed HCWs?
The CDC guideline6 included sections that addressed patients diagnosed with HIV and also provided a discussion on the management of patients who are medically immunosuppressed.

Reviewer: 3
Please include in introduction and discussion a section on the nature of subjectivity in guidelines regarding TB in screening prior to/ongoing immunosuppression. The lack of a golden standard in the diagnosis of latent TB influences both available evidence and interpretation of current diagnostic methods and therefore also subsequent mode of action. Adherence to guidelines may also be influenced due to this problem. Please discuss and recommend possible ways to improve the current evidence for screening practices.
We agree that imperfect reference standards may lead to misclassification of patients with and without the disease and may potentially underestimate the true test sensitivity and specificity of the index tests in different settings. These uncertainties may have also resulted in the observed heterogeneity and inconsistencies of recommendations between guidelines.

In the introduction we have added the following

"There is also a lack of valid and accurate reference standard for diagnosing LTBI in immunosuppressed populations, rendering the true test performance characteristics of IGRA difficult to ascertain." (page 4-5)

We have also provided a paragraph in 'Discussion' detailing the current evidence gaps and potential ways to mitigate the problem of an imperfect gold standard in validating a diagnostic test of LTBI.

"Determining the diagnostic accuracy of the IGRA and TST are complicated because of the absence of an accurate and valid reference standard. For example, under-estimation of the true test sensitivity and specificity of the new test may occur if the imperfect reference incorrectly classify those with disease as no disease (false negative), and those without disease as disease (false positive).

Multiple diagnostic algorithms for LTBI have been proposed to overcome the shortcomings of IGRA and TST, including the use of pre-defined multiple imperfect diagnostic tests and clinical data to inform the prevalence estimates of LTBI in different settings. Despite this, prevalence of LTBI varies substantially, even in high risk patients.11 Statistical methods such as latent class and Bayesian mixture analyses may overcome this limitation.12,13" (page 17)

ECDC 2011 recommends a combination of TST and IGRA in immune-suppression, please check the guideline.
As suggested, we have amended the statement as:

"…four were IGRA specific guidelines, although, these guidelines also used TST as part of their screening strategies." (page 8)

Page 17 Line 30 The sentence "the TST is a relatively sensitive but not specific test, in particular among high risk and immunosuppressed individuals" can be misinterpreted-as it reads now can be interpreted as the TST is less specific among immunosuppressed individuals. Is there anything to prove this statement? Furthermore sensitivity may be reduced in immunosuppression, e.g. if concomitant steroid treatment is given. This should be clarified.
As suggested, we have now clarified that: (together in combination with comments from Reviewer 2)

"TST generally performs poorly in immunosuppressed patients, with reported estimates of 89% and 71% for test sensitivity and specificity, respectively.5 The lower test specificity may be due to the cross-reactivity with prior BCG vaccination8,9 and infections with non-TB mycobacteria…Test sensitivity of TST and IGRA is uncertain or may be reduced among immunosuppressed hosts because of anergy.10" (page 17)

References

1. National Collaborating Centre for Chronic Conditions (UK): Centre for Clinical Practice at NICE (UK). Tuberculosis: Prevention, diagnosis, management and service organisation. London: National Institure for Health and Clinical Excellence (UK); 2016. Availabe from: https://www.nice.org.uk/guidance/ng33
2. World Health Organization. Guidelines on the Management of Latent Tuberculosis Infection. Geneva: World Health Organization, 2015.
3. Santin M, Garcia-Garcia JM, Dominguez J, Panel of Experts from the Mycobacteria Study Group (GEIM) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Respiratory Diseases and Thoracic Surgery (SEPAR) Guidelines for the use of interferon-γ release assays in the diagnosis of tuberculosis infection. Enferm Infecc Microbiol Clin 2017; 34(5): 303.e1–303.e13.
4. Al Jahdali HH, Baharoon S, Abba AA, et al. Saudi guidelines for testing and treatment of latent tuberculosis infection. Ann Saudi Med 2010; 30(1): 38–49.
5. European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm: European Centre for Disease Prevention and Control (ECDC), 2011.
6. Taylor Z, Nolan CM, Blumberg HM. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR Morb Mortal Wkly Rep 2005; 54(Rr-12): 1–81.
7. Canadian Tuberculosis Committee. Updated recommendations on interferon gamma release assays for latent tuberculosis infection. An Advisory Committee Statement (ACS). Can Commun Dis Rep 2008; 34(Acs-6): 1–13.
8. Beglinger C, Dudler J, Mottet C, et al. Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. Swiss Medical Weekly 2007; 137(43-44): 620–2
9. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9 Suppl 3: S1–155
10. Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: A TBNET consensus statement. Eur Respir J 2012; 40(4): 990–1013.
11. Pai M, Gokhale K, Joshi R et al. Mycobacterium tuberculosis infection in health care workers in rural India: Comparison of a whole blood interferon-γ assay with tuberculin skin testing JAMA 2005; 22: 293-302.
12. Pai M, Dendukuri N, Wang L, et al. Improving the estimation of tuberculosis infection prevalence using T-cell based assay and mixture models. Int J Tuberc Lung Dis. 2008; 12(8): 895–902.
13. Doan TN, Eisen DP, Rose MT, et al. Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: A latent-class analysis. PLoS One 2017; 12(11): e0188631.

VERSION 2 – REVIEW

REVIEWER	Peter Auguste University of Warwick; United Kingdom
REVIEW RETURNED	01-Jun-2018

GENERAL COMMENTS	Many thanks for your responses. I have one comment which relate to the last sentence in paragraph one on page 15. To my knowledge adverse events (hepatotoxicity, rash, and nausea/vomiting) relating to treatment are presented in Appendix L (network meta-analyses- results and input data for

	treatment of latent TB) in the clinical guideline. If you agree, please up date this sentence.

REVIEWER	Albert Nienhaus University Clinics Hamburg-Eppendorf, Germany
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	The authors followed the suggestions of the reviewers

REVIEWER	Judith Bruchfeld Division pf Infectious Diseases, Dept of Medicine Solna, Karolinska Institutet, Stockholm Sweden
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	I am satisfied with the responses given by the authors to my previous comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
I have one comment which relate to the last sentence in paragraph one on page 15. To my knowledge adverse events (hepatotoxicity, rash, and nausea/vomiting) relating to treatment are presented in Appendix L (network meta-analyses- results and input data for treatment of latent TB) in the clinical guideline. If you agree, please up date this sentence.

We have adjusted this paragraph to clarify the side effects of treatment and also included the National Institute for Clinical Excellence (NICE) guidelines as below:

In addition, side effects associated with the treatment of LTBI, such as hepatotoxicity, neuropathy, gastrointestinal toxicity and rash, were discussed in only 50% of the guidelines.[1-19]

REFERENCES

1. Australian Rheumatology Association. Screening for latent tuberculosis infection (LTBI) prior to use of biological agents in Australia. 2010. https://rheumatology.org.au/downloads/April2010-FINAL-SCREENINGFORLATENTTUBERCULOSISINFECTION.pdf. (accessed 25th October 2016).
2. Aguado JM, Torre-Cisneros J, Fortun J, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. *Clin Infect Dis* 2009; **48**(9): 1276–84.
3. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2016. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 27 October 2016).
4. World Health Organization. Guidelines on the Management of Latent Tuberculosis Infection. Geneva: World Health Organization, 2015.
5. Duarte R, Campainha S, Cotter J, et al. Position paper on tuberculosis screening in patients with immune mediated inflammatory diseases candidates for biological therapy. *Acta Reumatologica Portuguesa* 2012; **37**(3): 253–9.
6. Fonseca JE, Lucas H, Canhao H, et al. Recommendations for the diagnosis and treatment of latent and active tuberculosis in inflammatory joint diseases candidates for therapy with tumor

necrosis factor alpha inhibitors - March 2008 update. *Revista Portuguesa de Pneumologia* 2008; **14**(2): 271–83.
7. Kavanagh PM, Gilmartin JJ, O'Donnell J, et al. Tumour necrosis factor-alpha and tuberculosis: Guidance from the National TB Advisory Committee. *Ir Med J* 2008; **101**(1): 6–7.
8. Lichauco JJT, Tankeh-Torres SA, Navarra SV, et al. Philippine guidelines on the screening for tuberculosis prior to the use of biologic agents. *APLAR Journal of Rheumatology* 2006; **9**(2): 184–92.
9. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax* 2005; **60**(10): 800–5.
10. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: A TBNET consensus statement. *Eur Respir J* 2010; **36**(5): 1185–206.
11. Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: A TBNET consensus statement. *Eur Respir J* 2012; **40**(4): 990–1013.
12. Meije Y, Piersimoni C, Torre-Cisneros J et al. Mycobacterial infections in solid organ transplant recipients. *Clin Microbiol Infect* 2014; **20 Suppl 7**: 89–101.
13. European Best Practice Guideline Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. *Nephrol Dial Transplant* 2002; **17 Suppl 4**: 1–67.
14. Subramanian AK, Morris MI. Mycobacterium tuberculosis infections in solid organ transplantation. *Am J Transplant* 2013; **13 Suppl 4**: 68–76.
15. Pozniak AL, Coyne KM, Miller RF, et al. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. *HIV Medicine* 2011; **12**(9): 51–24.
16. Republic of South Africa Department of Health. Guidelines for tuberculosis preventive therapy among HIV infected individuals in South Africa. 2010. www.who.int/hiv/pub/guidelines/south_africa_hiv_tb.pdf (Accessed 1st November 2016).
17. Al Jahdali HH, Baharoon S, Abba AA, et al. Saudi guidelines for testing and treatment of latent tuberculosis infection. *Ann Saudi Med* 2010; **30**(1): 38–49.
18. The prevention committee and the treatment committee of the Japanese society for tuberculosis. Treatment guidelines for latent tuberculosis infection. *Kekkaku* 2014;89(1):21-37.
19. National Collaborating Centre for Chronic Conditions (UK): Centre for Clinical Practice at NICE (UK). Tuberculosis: Prevention, diagnosis, management and service organisation. London: National Institure for Health and Clinical Excellence (UK); 2016. Availabe from: https://www.nice.org.uk/guidance/ng33.